CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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MEDICAL REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES

MEMORANDUM TO FILE

Date: March 5, 2014

From: Christine P. Nguyen, MD
Division Deputy Director for Safety
Division of Bone, Reproductive, and Urologic Products (DBRUP)

Through: Hylton V. Joffe, MD, MMSc
Division Director
DBRUP

To: Rachel Turow, Regulatory Counsel, Office of Regulatory Policy

Subject: Docket No. FDA-2014-P-0258, Citizen Petition Requesting that FDA Take Certain Actions with Respect to Testosterone-Containing Drugs

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On February 25, 2014, FDA received a Citizen Petition (FDA-2014-P-0258), submitted by Sidney Wolfe, MD, Founder and Senior Advisor, and Michael Carome, MD, Director, on behalf of Public Citizen's Health Research Group (Petitioner) regarding concerns about cardiovascular risks of testosterone-containing drugs (Petition). Specifically, the Petitioners request that FDA, among other things, delay the "decision date on approving a new long-acting injectable testosterone product Aveed (testosterone undecanoate, Endo) . . . because its approval, absent [a] new black box warning, would cause further harm to patients for whom this new formulation is prescribed."

This memorandum contains OND's conclusion that there is no basis to delay approval of Aveed. At this time, we are not requiring that the labeling for Aveed contain a boxed warning addressing cardiovascular (CV) risks. We have not concluded that FDA-approved testosterone products increase the risk of cardiovascular adverse events. As noted in an FDA Drug Safety Communication dated January 31, 2014, however, the agency has been monitoring the risk of stroke, heart attack, and death in men taking FDA-approved testosterone products and is undertaking a reassessment of this potential safety issue based on recent studies suggesting an increased risk of cardiovascular events among certain patient populations. The agency intends to communicate its final conclusions and recommendations when that evaluation is complete. If the agency determines that the labeling for testosterone products should be updated to include additional information regarding CV risks, or that other regulatory action is necessary, it will take appropriate action after the evaluation is complete.

FDA's assessment of cardiovascular safety risk for testosterone-containing drugs:

2010 Tracked Safety Issue Application

The Petition cites a number of studies in support of its requests, including a study by Basaria. FDA has been aware of this study since it was initially published in 2010 and evaluated it under a Tracked Safety Issue (TSI) application, an FDA-generated application created for the purpose of tracking and archiving regulatory activities associated with a significant safety issue related to a marketed prescription or over-the-counter drug.[1]

FDA opened the TSI application after learning of the premature discontinuation of the Basaria study, a randomized, placebo-controlled trial that evaluated the efficacy of testosterone gel in approximately 200 elderly men at high risk for cardiovascular disease.[2] The Data and Safety Monitoring Board for the study recommended study discontinuation due to an overall imbalance of various CV-related adverse events (e.g., peripheral edema, arrhythmias, chest pain, elevated blood pressure, myocardial infarction, and stroke) between the testosterone and placebo groups. The Division of Cardiovascular and Renal Products (DCRP) reviewed the study and concluded that it had several significant limitations that precluded a definitive assessment of the role of testosterone therapy in the CV events in the study.[3] Their review also concluded that it is questionable whether the study results were applicable to the population for whom testosterone therapy is indicated.

FDA's Division of Epidemiology (DEPI) also evaluated other data sources on CV risks of testosterone, comprising two meta-analyses of randomized, placebo-controlled clinical trials and one systematic qualitative review addressing CV risks associated with testosterone therapy in hypogonadal patients.[4] DEPI concluded that the findings from these studies did not support an association between testosterone therapy and an increased risk of adverse cardiovascular outcomes. We have appended these reviews to this memo.

In January 2011, DBRUP determined that the overall safety information informing CV risk with testosterone therapy was insufficient to support a regulatory action.

2013 Tracked Safety Issue Application

The Petition also cites several publications, including the recent Vigen and Finkle studies, in support of its requests.[5] FDA is aware of these studies and is reviewing them under the TSI

[1] See FDA Manual of Policies and Procedures 4121.2,
"Tracking of Significant Safety issues in Marketed Drugs -- Use of the DARRTS Tracked Safety Issues."

[2] S Basaria, et al., Adverse events associated with testosterone administration. N Engl J Med 2010; 363:109.

[3] See S. Grant Review dated April 8, 2010, under TSI 865 in DARRTs.

[4] See F. Kuyateh Reviews dated May 21 and December 6, 2010, OSE RCM #2010-720, under TSI 865 in DARRTs

[5] In addition to Vigen, and Finkle, the Petitions cites an April 2013 study by Xu, et al. Xu L, Testosterone therapy and cardiovascular events among men: a systematic review and meta-analysis of placebo-controlled trials. *BMC Medicine* 2013; 11:108.

application that was created in 2010 for CV safety with testosterone-containing drugs.

Publications on CV risks and testosterone therapy have reported conflicting results. For instance, the recent Vigen[6] and Finkle [7] studies found a positive association between testosterone and adverse CV outcomes. In contrast, a large observational cohort study from the Veterans' Administration reported that testosterone treatment was associated with decreased mortality compared with no treatment in men with low testosterone levels.[8] A systematic review and meta-analysis of comparative (randomized and non-randomized) studies that evaluated adverse events with testosterone did not find significant differences in mortality and CV outcomes between the testosterone and the placebo/nonintervention groups.[9]

Available evidence on the association of testosterone and CV risks generally lacks the key scientific qualities needed to reliably infer the effect of testosterone on CV outcomes. The majority of currently available data are from observational studies, which have certain inherent limitations with regard to establishing drug causality due to reasons such as uncertainty of actual drug exposure and known and unknown confounders. The controlled trials that we currently have available are limited by small sample size, lack of pre-defined and adequately adjudicated CV outcomes, short duration of treatment and follow up, and heterogeneous study population.

Safety overview and risk/benefit assessment of Aveed:

Aveed offers a benefit over currently approved injectable testosterone-containing drugs, because it is a long-acting formulation that requires substantially fewer injections and may increase the likelihood of patient compliance. The general safety profile of Aveed is comparable to other approved injectable testosterone products, with the exception of serious post-injection reactions (anaphylaxis and serious pulmonary oil microembolism (POME)). Similar to other testosterone products, the clinical program of Aveed was not designed to evaluate CV safety. The studies that support Aveed's approval are open-label, active-drug only efficacy studies with no pre-defined CV outcomes. Major cardiovascular adverse events (stroke, myocardial infarction, or deaths from these causes) were sporadically reported in the different safety databases for Aveed. Two deaths due to stroke and myocardial infarction occurred among 524 hypogonadal men treated with testosterone undecanoate in the phase 3 study for Aveed. In the same phase 3 database, 5 patients experienced nonfatal myocardial infarction and 3 patients experienced nonfatal stroke. In the database from international postmarket studies, among the 2424 patients treated with the higher dose of testosterone undecanoate (1000 mg/4 mL) approved in Europe, 2 had myocardial infarction and 1 experienced a stroke. The uncontrolled nature of these data precludes the ability to conclude that Aveed is associated with CV risk. We do not believe, at

[6] R Vigen et al. Association of testosterone therapy with mortality, myocardial infarction, and stroke in men with low testosterone levels. JAMA 2013; 310:1829.

[7] WD Finkle et al. Increased risk of non-fatal myocardial infarction following testosterone therapy prescription in men PLOS One 2014; 9:e85805.

[8] MM Shores et al. Testosterone treatment and mortality in men with low testosterone levels. J Clin Endocrinol Metab 2012; 97(6): 2050.

[9] MM Fernandez-Balsells et al. Adverse effects of testosterone therapy in adult men: a systematic review and meta-analysis. J Clin Endocrinol Metab 2010; 95(6):2560.

this time, the data suggest a CV safety signal with Aveed that warrants a warning of CV risk in the labeling.

Aveed is approved with a restricted distribution Risk Evaluation and Mitigation Strategy (REMS) with elements to assure safe use, because of the risks of serious post-injection reactions. Aveed will be distributed only to prescribers and healthcare settings that are specially certified under the REMS. Therefore, there are additional barriers to gain access to Aveed, unlike the other approved testosterone products currently on the market.

Conclusions:

As discussed above, in 2010 and 2011, FDA thoroughly considered the CV safety concern with testosterone therapy and had concluded that there were insufficient data to support a regulatory action regarding CV risk. Based on two newly published observational studies (the Vigen and Finkle studies cited in the Petition), FDA recently reopened a TSI application, and is currently updating its assessment of this safety signal. FDA also issued a Drug Safety Communication in January 2014 to alert consumers that it is assessing the results of these studies.

The agency has not yet determined that testosterone use is associated with a higher risk of heart attack, stroke, or death. As noted above, the general safety profile of Aveed is comparable to other approved injectable testosterone-containing drugs, with the exception of serious post-injection reactions. Aveed offers a benefit over currently approved injectable testosterone-containing drugs because it requires considerably fewer injections. The agency intends to conduct a thorough review of the available data and information, including those studies cited in the Petition. FDA intends to make a determination, based on that review, as to whether any regulatory action is warranted, such as invoking our authority to require safety labeling changes under section 505(o)(4) of the Federal Food, Drug, and Cosmetic Act for Aveed and other testosterone-containing drugs, as appropriate. However, at this time, FDA concludes that there is no basis to delay approval of Aveed or include a boxed warning in the labeling for Aveed regarding CV risks.

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/s/

CHRISTINE P NGUYEN
03/05/2014

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03/05/2014

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	NDA 022219
Priority or Standard	Standard
Submit Date(s)	2013-08-29
Received Date(s)	2013-08-29
PDUFA Goal Date	2014-02-28
Division / Office	DBRUP / ODE 3
Reviewer Name(s)	Guodong Fang, MD
Review Completion Date	2014-02-21
Established Name	Testosterone Undecanoate
(Proposed) Trade Name	Aveed
Therapeutic Class	Injectable Steroid Androgen
Applicant	Endo Pharmaceuticals Solutions, Inc.
Formulation(s)	$C_{30}H_{48}O_3$ (MW 456.7)
Dosing Regimen	750 mg loading regimen followed by 750 mg every 10 weeks
Indication(s)	Adult Male Hypogonadism
Intended Population(s)	Adult Men (≥ 18 years old) with Hypogonadism

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

In the opinion of this Clinical Reviewer, from a clinical perspective, the evidence presented in the original submission and three re-submissions was adequate to support the effectiveness of this product. In regard to safety, the risk related to immediate post-injection reactions, including serious pulmonary oil microembolism (POME) and anaphylaxis has been the major safety concern. In the current re-submission, the Sponsor agreed to a restricted indication and proposed a Risk Evaluation and Mitigation Strategy (REMS) with Elements to Assure Safe Use (ETASU), including restricted distribution to prescribers who are aware of the risk, who explain the risk to patients, and who observe patients in their offices for 30 minutes after each dose. In addition, the proposed REMS includes a Patient Counseling Tool based on the Medication Guide that will completely inform the patient of the risk. Therefore, with this program, this reviewer believes that the major safety concern has been put under control and is resolved for use of Aveed in the proposed population with restricted distribution and proper management in certified clinical health care settings. Therefore, this reviewer recommends an **Approval** action for this application.

1.2 Risk Benefit Assessment Based on Clinical Findings

During the last review cycle, the Clinical Review Team concluded that the postmarketing safety reports of severe post-injection reactions, including serious pulmonary oil microembolism (POME) and anaphylaxis, was a major unresolved safety issue.

After the Advisory Committee Meeting on April 19, 2013 and the Complete Response (CR) action from the Division on May 29, 2013, the Sponsor made additional efforts and resubmitted this NDA with an ETASU-based REMS designed to manage the risk of severe post-injection adverse reactions. The REMS includes measures to mitigate the risk of severe post-injection reactions, such as informing the patient of the risk, insuring the prescriber is aware of the risk, and insuring patients are observed in the office for 30 minutes after each dose. Only certified prescribers may receive Aveed for administration to patients. After careful review, this Clinical reviewer concludes that the REMS with ETASU acceptably ensures safe and effective use of the product in the indicated population.

In addition, at the Agency's request, the Sponsor agreed to include a "Black Box Warning" in the proposed labeling as well as to restrict the indicated population.

With these measures in mind, this Clinical reviewer concludes that the major risk of the product has been brought under control and that the benefits of the product outweigh the risks in the proposed population, under conditions of restricted distribution, with in-office observation for 30

minutes after each injection to allow for appropriate medical management in the event of serious POME or anaphylaxis.

1.2.1 Brief Overview of the Submission

The purpose of this third re-submission is:

- To provide an amendment (NDA Re-submission) to NDA 22-219 to provide a Complete Response to the May 29, 2013, Action Letter, and
- To respond to and to fulfill the Division's requests/requirements as described in the May 29, 2013 Action Letter.

1.2.2 Efficacy

There are no new efficacy data in the current submission. This reviewer has no new efficacy-related comments. The previous conclusion on efficacy stands.

***Reviewer's comments*: The product previously met the requirement for demonstration of efficacy for this indication.**

1.2.3 Safety

During last review circle, based on previous review of the post-marketing experience, the Sponsor was requested to submit all postmarketing safety reports of pulmonary oil microembolism (POME) and anaphylaxis, including CIOMS forms for individual cases. Reviewers from our Division (DBRUP) and from the Division of Pulmonary, Allergy and Rheumatology Products (DPARP) determined that there were 137 cases of severe post-injection adverse reactions, including cases of POME and anaphylaxis. Some of these cases were reported as severe and/or potentially life-threatening, and some required hospitalization or emergency department visitation. In some cases, patients were treated as for anaphylaxis. The pathophysiological mechanism for these post-injection reactions is believed to be: 1) lipid droplets reaching the lung from the injection site (for POME), or 2) allergic reaction, perhaps to the excipients in this product, benzyl benzoate, and/or castor oil (for anaphylaxis). There are no clinical data submitted in this re-submission that change the previous safety profile. However, the Sponsor has submitted a new REMS with ETASU.

***Reviewer's comments:* The proposed label, including Boxed Warning and narrowed indication, and the new REMS with ETASU serves to limit the potential safety risks of serious POME and anaphylaxis. Thus, this reviewer concludes that the benefits of Aveed outweigh its risks for the proposed indication.**

1.2.4 Dose Regimen and Administration

3 mL per injection (each 3 mL vial contains 750 mg testosterone, 1500 mg of benzyl benzoate and 885 mg of refined castor oil), to be injected intramuscularly at initiation, at 4 weeks, and every 10 weeks thereafter.

1.2.5 Special Populations

No new data regarding special populations are included in this re-submission.

1.2.6 Drug Abuse and Dependence

Aveed (testosterone undecanoate injection) is a Schedule III controlled substance because it contains testosterone.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies (REMS)

The Division previously recommended a Black Box Warning for the risk of serious POME and anaphylaxis, and a narrowed indication, for example:

> Aveed should only be used in patients who require testosterone replacement therapy and in whom the benefits of the product outweigh the serious risks of pulmonary oil microembolism and anaphylaxis.

The Division also recommended a restricted distribution program for Aveed, to be operationalized under a formal REMS with ETASU. The ETASU would include the following items:

- Healthcare providers who prescribe Aveed must be certified with the REMS program before ordering or dispensing Aveed.
- Healthcare settings must be certified with the REMS program and have healthcare providers who are certified before ordering or dispensing Aveed. Healthcare settings must have on-site access to equipment and personnel trained to manage serious POME and anaphylaxis.
- Distributors that distribute Aveed must be enrolled in the program and distribute only to certified prescribers and healthcare settings.

Reviewer's comment: The Sponsor has accepted and complied with all of the Division's recommendations, including all labeling elements (e.g., black box warning, narrowed indication), and all aspects of the REMS with ETASU.

1.4 Recommendations for Postmarket Requirements and Commitments

In addition to standard REMS assessments at (b) (4) 3 years, and 7 years from the date of the approval of the application, the Sponsor will conduct "enhanced" pharmacovigilance to promptly report cases of serious POME and anaphylaxis, to seek additional information on those cases, and to summarize those cases in quarterly reports.

2 Introduction and Regulatory Background

2.1 Product Information

AVEED (testosterone undecanoate IM injection) is a clear, yellowish, sterile, oily solution containing testosterone undecanoate, a testosterone ester, for intramuscular injection. Each single use vial contains 3 mL of 250 mg/mL testosterone undecanoate solution in a mixture of refined castor oil and benzyl benzoate. There is 885 ng per vial of refined castor oil and 1500 mg per vial of benzyl benzoate.

Testosterone undecanoate (17β-undecanoyloxy-4-androsten-3-one) is an ester of the androgen, testosterone. The active form, testosterone, is formed by cleavage of the side chain.

Table 2.1 Components of Aveed (testosterone undecanoate injection)

Manufacturer	Endo Pharmaceuticals Solutions, Inc.
Drug Name	Aveed (testosterone undecanoate intramuscular injection)
Active Ingredient	Testosterone, USP (750 mg in 3 mL)
Inactive Ingredient(s)	Refined castor oil (885 ng in 3 mL) Benzyl benzoate (1500 mg in 3 mL)
Route of Administration	Intramuscular injection
Dosage Form Strength	Vial (3 mL)

2.2 Currently Available Treatments for Proposed Indications

Testosterone replacement therapy is used to treat men for conditions associated with a deficiency or absence of endogenous testosterone. FDA-approved testosterone products are shown in Table 2.2, accompanied by their dose and drawbacks/potential risks.

Table 2.2 Currently Available Testosterone Products in the United States

Formulation	Formula / Trade name	Dose§	Potential Drawbacks/Potential Risks
Oral	Methyltestosterone (Testred) Fluoxymestrone	10-50 mg/day	Hepatotoxicity
Parental	T cypionate (Depo–T) T enanthate (Delatestryl) T propionate	50-400 mg IM (every 2-4 wks)	Supraphysiologic peaks, low trough concentration,
Transdermal Patch	Testoderm (scrotal) *** Testoderm TTS Androderm	4-6 mg/day 5 mg/day 5-7.5 mg/day	Can requires skin shaving Application site irritation.
Transdermal Gel	Androgel (1%) Androgel (1.62%) Testim (1%) Axiron (2%)	50-100 mg/day 20.25-81 mg/day 50-100 mg/day 30-120 mg/day	Interpersonal transferability to partners and children
Transbuccal	Striant	30 mg buccal tablet (BID)	Gum or mouth irritation
Implant	Testosterone (Testopel Pellets)	75 mg pellet; subcutaneous	Need for insertion procedure, pellet extrusion

*** Discontinued
Source: Clinical Reviewer.

Limitations of the currently available products include the following:

- Injectable depot solutions may be associated with pain at the injection site. Peak concentrations are often supratherapeutic and trough concentrations may be supratherapeutic. Mood swings are possible due to fluctuations in testosterone levels. Current formulation allow for 2-4 week dosing intervals.
- High dose, oral, methyltestosterone formulations have been associated with an increased incidence of liver disease.
- Transdermal patches may be associated with significant application site reactions.
- Pellet implants can be expelled from the insertion site and infrequently, may result in infection.
- Testosterone gels incur the potential risk of secondary exposure to testosterone of children and women.

Currently, the goal of testosterone replacement therapy in hypogonadal men is to replace testosterone levels to normal, physiological concentrations. Clinical guidance from the Endocrine Society indicates that testosterone replacement therapy should aim to achieve testosterone levels in the mid-normal range.

2.3 Important Safety Issues with Consideration to Related Drugs

Labeled risks of testosterone replacement in hypogonadal men include: worsening of clinical BPH symptoms, polycythemia, induction or exacerbation of sleep apnea, breast tenderness or enlargement, liver toxicity (with oral methyltestosterone formulations), and acne. Two major

areas of concern in older men are the unknown effects of long-term testosterone administration on the risks of prostate cancer and progression of atherosclerotic heart disease.

Topical testosterone gel preparations, which are applied directly to the skin, have been associated with a small number of events of secondary exposure of testosterone in children. Several exposed children have experienced significant clinical sequelae which prompted the FDA to mandate a Black Box Warning for all topical testosterone products.

Reviewer's comments: Aveed offers the potential for fewer injections in patients who use injectable T. The risks are clearly outlined in the label and these risks are managed by the REMS with ETASU.

2.4 Summary of Regulatory Activity since last Submission

During the last review circle, an Advisory Committee Meeting was held on April 18, 2013. Following the presentations from both the Sponsor and the Agency, the committee voted on two questions. The following table shows the voting results for these two questions:

#	Questions	Voting Results	
		Yes	No
1	Given the severe post-injection reactions that were reported with TU in clinical studies and postmarketing experience, do you believe that TU is safe for the proposed indication?	**9**	**9**
2	Whether you vote "Yes or No" to Question 1, please vote whether the Applicant's proposed instructions for use in product labeling that TU be administered using a slow (30-60 second) injection, and that patients remain in the office for 30 minutes post-injection would be sufficient to ameliorate the risk of severe post-injection reactions.	**1**	**17**

The committee recommended additional labeling and risk management activities before Aveed could be approved.

On May 29, 2013, the Division conveyed a Complete Response (CR) letter to the Sponsor, which emphasized the need for additional risk management activities for Aveed, including the following:

> Because your application cannot be approved without an approved REMS, you must revise your proposed REMS and submit it as part of your response to the deficiency cited in this letter. We will continue discussion of your revised proposed REMS after your complete response to this action letter has been submitted.
>
> Your proposed REMS must include the following:

Medication Guide: As one element of a REMS, FDA may require the development of a Medication Guide as provided for under 21 CFR 208. Pursuant to 21 CFR 208, FDA has determined that testosterone undecanoate injection poses a serious and significant public health concern requiring the distribution of a Medication Guide. The Medication Guide is necessary for patients' safe and effective use of testosterone undecanoate injection. FDA has determined that testosterone undecanoate injection is a product that has serious risks (relative to benefits) of which patients should be made aware because information concerning the risks could affect patients' decisions to use, or continue to use testosterone undecanoate injection.

Under 21 CFR 208, you are responsible for ensuring that the Medication Guide is available for distribution to patients who are dispensed testosterone undecanoate injection. The Medication Guide should be available through the REMS website.

Elements to Assure Safe Use (ETASU): We have determined that Elements to Assure Safe Use are necessary to mitigate the risks and severe complications related to post-injection reactions (POME and anaphylaxis) as will be listed in the labeling. In addition, we have determined that a Medication Guide and a communication plan alone are not sufficient to mitigate the serious risks. Your REMS must include tools to manage these risks, including at least the following:

1. Healthcare providers who prescribe or dispense testosterone undecanoate are specially certified.
    A. Develop an educational program that will train prescribers about the risk of severe post-injection reactions, measures necessary to mitigate these risks, and tools to prompt a discussion between patients and prescribers about the risks.

    B. In order for the health care providers to be certified, each prescriber must undergo an educational training program and enroll in your REMS program.

    C. Maintain a list of the prescribers who have obtained the certification.

2. Healthcare settings that dispense testosterone undecanoate injection are specially certified.

    A. In order for a health care setting to be certified, an authorized representative will complete a REMS enrollment form and agree to ensure that all health care providers who prescribe or dispense testosterone undecanoate injection are certified, that staff are properly trained and comply with all program requirements, that the health care setting is able to manage POME and anaphylaxis reactions, order testosterone undecanoate injection only from distributors enrolled in your REMS program, and have procedures in place to ensure compliance with the REMS requirements.

B. Maintain a list of the healthcare settings who have obtained the certification.

Implementation System: The REMS must include an implementation system to monitor and evaluate the implementation of the Elements to Assure Safe Use (outlined above) required under 505-1(f)(3). Include an intervention plan to address any findings of non-compliance with the elements to assure safe use and to address any findings that suggest an increase in risk.

In addition, the Division also requested the Sponsor to revise the proposed language for the **INDICATIONS** section of the label, to add the text shown in *italics* below:

"Testosterone undecanoate injection is an androgen indicated for replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous testosterone:

- Primary hypogonadism (congenital or acquired)
- Hypogonadotropic hypogonadism (congenital or acquired)

Testosterone undecanoate injection should be used in patients who require therapy and in whom the benefits (b) (4) *outweigh the serious risks of pulmonary microembolism and anaphylaxis.*"

Reviewer's comments: The Sponsor has been fully compliant with all Agency requests from the May 29, 2013, Complete Response action letter

3 Ethics and Good Clinical Practices

In previous reviews, a thorough review of the clinical study protocols, protocol amendments, and informed consent forms, as well as the approval process by either central or local IRBs, failed to identify any ethics or good clinical practice (GCP) issues.

3.1 Submission Quality and Integrity

The quality of the overall resubmission was good with the information organized and readily located. Prior submissions was similarly well organized and of high quality.

3.2 Compliance with Good Clinical Practice

No new clinical or clinical pharmacology study data was submitted in this 4th cycle re-submission. All prior studies submitted in previous submission were conducted in accordance with Good Clinical Practice (GCP) as required by the guidelines of the Agency and the International Committee on Harmonization guidelines.

3.3 Financial Disclosure

In compliance with 21 CFR part 54, the Sponsor has adequately disclosed the absence of Investigator proprietary interest in this product or Investigator participation in financial arrangements with Sponsor.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls (CMC)

The CMC review team noted that there was no new CMC information enclosed in the resubmission. During the last resubmission, the Chemistry Approvable issues were resolved. From a CMC perspective, this NDA resubmission was recommended for an approval action, pending final acceptability of the manufacturing sites from the Office of Compliance.

4.2 Clinical Microbiology

There was no new Microbiology information enclosed in the resubmission. On September 26, 2013, the microbiology reviewer stated, "No product quality microbiology issues."

4.3 Preclinical Pharmacology/Toxicology

The Pharmacology/Toxicology reviewer believes that the Applicant's nonclinical program, supplied references, available literature and general knowledge of testosterone provide reasonable assurance of the safety of testosterone undecanoate (TU) in hypogonadal men from a nonclinical perspective.

The PharmTox review team provided recommendations for nonclinical labeling edits. The nonclinical recommendations were all accepted by Sponsor.

4.4 Clinical Pharmacology

The Clinical Pharmacology review team found the application acceptable for approval, provided final agreement was reached on all labeling language.

***Reviewer's comment*: During review of last resubmission, the Clinical Pharmacology review team had noted excessive T concentrations in one patient who weighed < 65 kg. Based upon this single patient's data and concerns about potentially excessive T concentrations in light weight hypogonadal men, (b) (4) information concerning the effect of body weight and body mass index on testosterone concentrations was included in a separate**

section entitled, "Effect of Body Weight and Body Mass Index", in Section 12.3 (Pharmacokinetics).

4.5 Biostatistics

In previous memos, the Statistical Review Team recommended approval of this NDA based on their analysis of the pharmacokinetic data. For this cycle, Biometrics noted that no new efficacy data was submitted and therefore, no statistical input was needed.

4.6 Consults from Other Divisions

4.6.1 Division of Medication Errors Prevention and Analysis (DMEPA)

On October 17, 2013, in OSE Review 2013-2138, DMEPA recommended revisions to the container and carton labeling. The Sponsor implemented all of the recommended changes and the container and carton labeling was deemed acceptable by DMEPA on February 11, 2014.

DMEPA also recommended revisions to the Dosage and Administration of the PI, and these recommendations were also all implemented by the Sponsor.

4.6.2 Division of Risk Management (DRISK)

The DRISK review team provided extensive support to DBRUP in regard to the newly designed REMS with ETASU and Medication Guide. The DRISK reviewers determined that the Sponsor's original proposal for REMS with ETASU was consistent, in principle, with the REMS outlined by the Agency in the May 29, 2013, CR action letter. However, DRISK recommended a number of changes to the REMS documents, including changes to: 1) the REMS document itself, 2) the REMS Supporting Document, 3) the Healthcare Enrollment Form, 4) the Education Program for Healthcare Providers (and the other educational pieces), 5) the Healthcare Setting materials, 6) the Aveed REMS program website, and 7) the Patient Information materials, including the Patient Counseling document and the Medication Guide. DRISK also provided recommendations for improvement of the REMS Assessment Plan.

4.6.3 Office of Prescription Drug Promotion (OPDP)

In this review cycle, OPDP provided comments on the proposed product labeling (PI and PPI) from a promotional perspective. The OPDP comments were taken into consideration and revisions to product labeling were made based on the OPDP comments, as deemed appropriate and necessary by DBRUP.

4.6.4 Controlled Substance Staff (CSS)

In their original consult dated January 24, 2014, CSS made recommendations for substantial changes to the package insert, Section 9 (Drug Abuse and Dependence), as follows:

1) Introduce in Section **9 Drug Abuse and Dependence** of the label for Aveed (NDA 22-219) a description of the abuse potential of the drug product based on information in the public domain.
2) Sections 9.2 Abuse, 9.3 Dependence, should include the most current safety findings as related to abuse, misuse, overdose and dependence including withdrawal symptoms of testosterone.

CSS also recommended that DBRUP make inquiry to OSE as to the extent of information available in FDA databases regarding testosterone abuse, misuse, overdose and addiction.

Subsequent to a meeting between CSS, DBRUP and OSE on February 5, 2014, CSS issued an Addendum consult in which they stated that the proposed changes to Section 9, if instituted, would be applicable to all testosterone products and therefore, CSS would collaborate with DBRUP and OSE on a thorough assessment of all available abuse-related information for testosterone and would come to a collaborative determination as to regulatory action. CSS agreed that their current recommendations for Aveed labeling should be deferred.

4.6.5 Pediatric Review Committee (PeRC)

Pediatric studies are required based on Pediatric Research Equity Act (PREA) for the following reasons:

1) New active ingredients;
2) New indications;
3) New dosage forms;
4) New dosing regimens;
5) New routes of administration.

None of the above applies to this product of testosterone undecanoate injection, therefore, this product of testosterone undecanoate intramuscular injection is exempt from this requirement.

5 Sources of Clinical Data

5.1 Size of the clinical trial dataset

The re-submission does not include any new efficacy data from any previous completed or currently ongoing clinical trial. The only study report included was from a 2004, male contraception study entitled, "*Norethisterone enanthate (NET-EN) plus testosterone undecanoate (TU) for male contraception - a prospective, randomized, 4-arm parallel-group, controlled single-blind study*" (Study Protocol #303923) and dated December 17, 2004. The study was conducted in Italy with a sample size of 40 volunteers.

Reviewer's comment: Study 303923 is not related to the evaluation of efficacy for testosterone undecanoate for the proposed indication. Nevertheless, the safety results from this study were reviewed and are included in the safety review portion of this medical officer's review.

5.2 Review Strategy

For this resubmission, this reviewer did not conduct another efficacy review.

For safety, in the last review circle, the reviewer concentrated on the severe post-injection reactions observed in the postmarketing period. For that cycle, the reviewer conducted individual case by case reviews of the Sponsor's collection of all assumed cases of POME and anaphylaxis during the postmarketing period. For this re-submission, the reviewer conducted a review of only the newly reported assumed cases of POME and anaphylaxis from the most recent postmarketing safety update reports (PSURs) covering the 19-month period between November 25, 2011 to June 30, 2013. The reviewer also assessed the safety results from the 40 subjects in the Italian male contraception study 303923.

6 Review of Efficacy

Reviewer's comment: The Efficacy summary from the last review is unchanged and is provided herein:

Efficacy Summary

The efficacy of testosterone undecanoate injection as a TRT for conditions associated with male hypogonadism is supported by a single, open-label, pivotal study using the 750mg loading regimen (Study IP157-001, Part C, C2) in approximately 130 hypogonadal males. Different dosage strengths and different dose regimens were tested during the development program for Aveed, and the results from these additional Phase 2 and Phase 3 studies served as supporting data. In addition, a number of studies have been conducted outside the US both prior to and since the time of initial approval of testosterone undecanoate injection outside the U.S. (in 2004).

In summary,

- The Efficacy section of this review presents a qualitative integration of complete final results from Part C and Part C2 of Study IP157-001 rather than a pooled analysis of efficacy.
- Testosterone undecanoate injection 750 mg loading regimen provides acceptable replacement of testosterone, and
- The data also characterize the testosterone PK for 3 consecutive injection cycles (2nd, 3rd, and 4th) and provide support for the use of the 750 mg loading dosage regimen as the recommended therapeutic dose.

The Sponsor met the current requirement for demonstration of efficacy for this indication.

6.1 Indication

The applicant's proposed indication is replacement therapy in adult males for conditions associated with deficiency or absence of endogenous testosterone. In addition to the standard indication language, the Aveed indication includes the following special text:

Aveed should only be used in patients who require testosterone replacement therapy and in whom the benefits of the product outweigh the serious risks of pulmonary oil microembolism and anaphylaxis.

6.1.1 Overall Conclusion of Efficacy for Testosterone Undecanoate Injection

Treatment with TU 750 mg given intramuscularly at baseline, at 4 weeks, and then every 10 weeks thereafter was found to provide adequate TRT (300 to 1000 ng/dL) in hypogonadal men (as measured by testosterone C_{avg}), while not providing excessive TRT (as measured by C_{max}). Steady-state was achieved by the 3rd IM injection of TU 750 mg.

Thus, the primary efficacy objectives of the Phase 3 study were met.

7 Review of Safety

Safety Summary

Based on the Sponsor's willingness to institute an appropriate REMS with ETASU, this reviewer believes that safety risks associated with the severe post-injection adverse reactions to testosterone undecanoate 4 mL injection that were observed in the postmarketing period (n= 137 cases of severe POME and anaphylaxis) have been effectively controlled. Although the basic safety picture has not changed, the REMS with ETASU and the improved prescriber and patient labeling (including narrowed indication), has substantially mitigated the safety concerns and has improved the risk to benefit ratio. Therefore, Aveed is considered acceptably safe for the proposed indication.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

Reviewer's comment: No new integrated safety summary was submitted in this resubmission, nor was one necessary. The safety database for testosterone undecanoate injection has not changed from the last review cycle, except for the addition of safety results from a small (n = 40), 2004, male contraception study (Study 303923) and

information from updated postmarketing safety reports (November 2011 to June 2013). The additional information is reviewed herein.

7.2 Supporting Safety Results

Results from one additional study were submitted in the resubmission. This was a male contraceptive study conducted by Bayer AG, Germany. This study (Protocol 303923) is the only additional study for AVEED™ (testosterone undecanoate) injection which either was initiated or completed and not included in the November 2012 NDA Resubmission. This study is a male contraception study, conducted in healthy subjects and therefore, is not included in the review of efficacy for the proposed indication for AVEED. However, safety data from this study are relevant.

Study 303923 was a randomized, controlled, single-blind, 4-arm, parallel-group study. The study enrolled 40 healthy subjects and was conducted at 1 study center in Italy. The objective of this study was to investigate whether the combination of the progestin norethisterone enanthate (NET-EN) and the long-acting androgen testosterone undecanoate (TU) in different treatment regimens was effective for the suppression of spermatogenesis without causing major adverse effects. The study consisted of a control period lasting for 2 to 16 weeks, a treatment period lasting for 48 weeks, and a recovery period for up to week 66.

After the control period, the recruited subjects were randomly assigned to one of the following 4 treatment groups (to start treatment on day 0 after all planned examinations were performed):

- **NET-EN+TU 6/12 (Treatment Group 1)**: 3 injections of NET-EN 200 mg + TU 1000 mg on weeks 0, 6, and 12 (induction phase), followed by 2 injections of NET-EN 200 mg + TU 1000 mg on weeks 24 and 36 (maintenance phase)
- **NET-EN+TU+Placebo 6/12 (Treatment Group 2)**: 3 injections of NET-EN 200 mg + TU 1000 mg on weeks 0, 6, and 12 (induction phase), followed by 2 injections of placebo + TU 1000 mg on weeks 24 and 36 (maintenance phase)
- **NET-EN+TU 8 (Treatment Group 3)**: 6 injections of NET-EN 200 mg + TU 1000 mg every 8 weeks, on weeks 0, 8, 16, 24, 32, and 40
- **NET-EN+TU 12 (Treatment Group 4)**: 4 injections of NET-EN 200 mg + TU 1000 mg every 12 weeks, on weeks 0, 12, 24, and 36

Table 7.1: Overview of Maximum Possible Exposure in Study 303923 (n = 40)

Treatment Group	Number of Injections	Single Dose (mg)/ Number of Doses		Maximum Total Exposure (mg)	
		TU	NET-EN	TU	NET-EN
NET-EN + TU 6/12	5	1000/5	200/5	5000	1000
NET-EN + TU + Placebo 6/12	5	1000/5	200/3	5000	600
NET-EN + TU 8	6	1000/6	200/6	6000	1200
NET-EN + TU 12	4	1000/4	200/4	4000	800

NET-EN=Norethisterone enanthate; TU=Testosterone undecanoate

Table 7.2: Total Exposure in 5 Subjects Who Prematurely Discontinued from Study 303923

Subject Number[a]	Treatment Group	Injections Planned	Injections Administered	Total Exposure (mg)	
				TU	NET-EN
23	NET-EN + TU 6/12	5	2	2000	400
17	NET-EN + TU + Placebo 6/12	5	1	1000	200
30	NET-EN + TU + Placebo 6/12	5	4	4000	600
21	NET-EN + TU 12	4	3	3000	600
33	NET-EN + TU 12	4	1	1000	200

[a] Randomization number

7.2.1 Commonly Reported Adverse Events in Clinical Trials of Testosterone Undecanoate Injection

Table 7.3 Adverse Events in Study 303923 – Full Analysis Set (N = 40)

	NET-EN + TU 6/12	NET-EN + TU + Placebo 6/12	NET-EN + TU 8	NET-EN + TU 12	Total
Number of AEs	11	22	17	14	64
Number of subjects with AEs	5	6	6	8	25
Percentage of subjects with AEs	50%	60%	60%	80%	62.5%

AE=Adverse event; NET-EN=Norethisterone enanthate; TU=Testosterone undecanoate

The most frequent AEs reported in the study were acne (11 subjects), injection site pain (8 subjects), and hypercholesterolemia (4 subjects). Sore throat, sweating increased, tooth disorder, and upper respiratory infection were reported by 2 subjects each. All other AEs occurred in a single subject only.

Table 7.4 List of the Most Frequent AEs in Study 303923 (> 3.0%) – Full Analysis Set

Adverse Event Term	Number of Adverse Events	Number (%) of Subjects with Adverse Events (N = 40)	
		N	N
Acne	19	11	27.5
Injection site pain	15	8	20.0
Hypercholesterolemia	5	4	10.0
Sore throat	3	2	5.0
Sweating increased	2	2	5.0
Tooth disorder	2	2	5.0
Upper respiratory infection	2	2	5.0

The following AEs were assessed as possibly, probably, or definitely related to one of the study treatments: injection site pain (8 subjects), acne (11 subjects), sweating increased (2 subjects);

and abdomen enlarged, rash, testis disorder, and libido decreased (1 subject each). All other AEs reported were assessed as non-related or unlikely related to study treatment.

The majority of AEs were of mild or moderate intensity. Overall, 6 AEs were reported as severe intensity in 5 subjects: 5 events of injection site pain and 1 event of asthma (the subject had a medical history of allergic rhinitis and asthma). Acne was assessed either as mild (5 subjects) or moderate (6 subjects). Rash and testis disorder were of mild intensity (1 subject each). Sweating increased (2 subjects) and libido decreased (1 subject) were of moderate intensity. All 4 cases of hypercholesterolemia were of mild intensity.

7.2.2 Serious Adverse Events in Clinical Trials of Testosterone Undecanoate Injection

No cases of death were reported. There was one SAE reported: On (b) (6) (Placebo + TU 1000 mg) Subject #28 was hospitalized for further diagnostic measures after papilledema was diagnosed in the Emergency Medicine department. He was discharged on the next day. The study drug was not discontinued and the subject received the next planned study drug injection on June 27, 2002. He completely recovered. The subject belonged to treatment group NET-EN + TU + Placebo 6/12.

Narratives for Subject #28:
A 33-year old male subject was diagnosed with papilledema of the right eye on (b) (6) (suspected swelling of the optic disc) at the hospital ophthalmologic emergency room at 18:34. The patient was referred to the Emergency Medicine department for cerebral tomography (CT) and neurological interview; the patient was hospitalized at 19:03. He was administered 100 cm^3 mannitol 18%. There were no pathological neurological findings (20:24). The patient did not report any visual disturbance. The CT examination on (b) (6) (without contrast medium) was normal. The patient was discharged from observation at the Emergency Medicine department ((b) (6) 14:18) with the diagnosis papillary edema (swelling of the optic disc) of the right eye. On the next 2 days, the patient was administered 2 × 100 cm^3 mannitol 18%. The patient was to be seen again for nuclear magnetic resonance (NMR) tomography. The study treatment was not discontinued, and the patient completed the study (last contact on 17-Feb-2003). The case was followed up by the investigator with the result that the patient had recovered and in the follow-up report (from 27-Feb- 2003) the investigator did not change her assessment of the causal relationship between the SAE and the study drug (unlikely related). The Sponsor believes that "Papilledema is not an expected adverse reaction to the study drug. General edema can occur on androgenic and anabolic treatment. However, whether this is related to papilledema cannot be assessed."

Reviewer's comment: This Reviewer agrees with the Sponsor that the papilledema of the right eye in this subject was unlikely related to the treatment he received in the trial.

7.3 Major Safety Results

7.3.1 Immediate Post-injection Reactions - Regulatory History

There has been no new regulatory history since the last review circle.

7.3.2 Immediate Post-injection Reactions – Reporting Rates

Immediate Post-injection Reactions - Reporting Rates (POME and Anaphylaxis)

No new cases of pulmonary oil microembolism (POME) and/or anaphylaxis were identified in Study 303923 (n=40).

A total of 3556 subjects have received testosterone undecanoate in a total of 18 clinical trials, as shown here:

Study Pool	Study Number	Total Number of Subjects in the Pool
US IP157-001 (All Parts) and European Clinical Studies	IP157-001 Parts A, B, C, C2, and D; and JPH01495, JPH04995, ME98096, ME97029, 306605, 303934	725
Male Contraception Clinical Studies	97028, 97173, 98016, 99015, 42306	407
Postmarketing Studies	39732 (NEO601 IPASS), AWB0105, Czech NEO, NB02, TG09, and 14853	2424
Number of Subjects Included in Adverse Events of Interest Investigations		
Adverse Events of Interest (Pulmonary Oil Microembolism [POME], Anaphylaxis, and Injection Site Reactions)	IP157-001, JPH01495, JPH04995, ME98096, ME97029, 306605, 303934, 97028, 97173, 98016, 99015, 42306, 39732 (NEO601 IPASS) AWB0105, Czech NEO, NB02, TG09, and 14853	3556

Information from the Sponsor's first re-submission provides an estimate of the incidence of POME and anaphylaxis in these 18 clinical trials.

In their 2nd re-submission, in the Summary of Clinical Safety, on tables 22 and 24, the Sponsor shows data from a retrospective review that involved adjudicating all cases that met specific POME and anaphylaxis criteria. This retrospective review identified a total of 9 POME events in 8 patients and 2 events of anaphylaxis among the 3,556 patients treated with intramuscular testosterone undecanoate in these 18 clinical trials.

Tables 7.5 and 7.6 provide POME and anaphylaxis incidence rates based upon number of cases per 10,000 subject-years.

Table 7.5: Incidence Rate of Anaphylaxis in the Clinical Database (n=3556)

Total number of cases	2
Cases per 10,000 subject-years	4.7

Table 7.6: Incidence Rate of POME in the Clinical Database (n=3556)

Total number of cases	9
Cases Per 10,000 subject-years	21.3

The addition of 40 subjects from Study 303923 to this safety database has no significant impact on these estimates.

Reviewer's comment: Cases of POME and anaphylaxis were identified infrequently in clinical trials of testosterone undecanoate injection. Cases of serious POME and anaphylaxis were also identified in the postmarketing history of testosterone undecanoate injection and it is the postmarketing cases that have garnered the most FDA attention.

7.3.3 Immediate Post-injection Reactions – Case review

In this re-submission, a review of the most recent 19 months of postmarketing experience with testosterone undecanoate injection yielded an additional **43 cases** of POME and anaphylaxis. A total of 5 cases were reported as serious adverse events, 3 due to hospitalization and 2 as medically significant. Three (3) cases included the possibility of anaphylaxis. A list of these 43 cases is shown in Table 7.7. Individual narratives for the five SAE cases are also provided in this section.

Table7.7: List of Cases of POME and Anaphylaxis Identified in PSURs Submitted in the Current Submission

	Case #	Age	POME/Anaphylaxis	SAE	Relative time with injection
1	2012-123765	47	POME		immediately after
2	2012-125709	55	POME		immediately after
3	2012-125722	60	POME		immediately after
4	2012-126322	55	POME	YES	suddenly during injection
5	2012-126331	43	POME/Anaphylaxis	YES	"along injection"
6	2012-130255	45	POME/Anaphylaxis		starting 1-2 min after injection
7	2012-131584	59	POME	YES	within 2 min of administration
8	2012-134348	61	POME	YES	within 2 min of administration
9	2013-001255	50	POME		during injection
10	2013-011802	26	POME		"accompany with injection"
11	2013-016917	unk	POME		1-2 min after
12	2013-016920	unk	POME		1-2 min after
13	2013-016943	unk	POME		1-2 min after
14	2013-017902	27	POME		immediately after
15	2013-018764	unk	POME		immediately after
16	2013-025474	40-50	POME		on injection
17	2013-026008	44	POME		20 min after
18	2013-026046	56	POME		shortly after
19	2013-026047	51	POME		right after
20	2013-029155	unk	POME		not reported
21	2013-030800	unk	POME		starting 30-120s during injection
22	2013-033071	43	POME		at the end of injection
23	2013-035579	43	POME		1-2 min after injection
24	2013-037999	50	POME		when 1 mL was injected
25	2013-044162	55	POME		at the end of injection
26	2013-045839	unk	POME		"after injection"
27	2013-048291	44	POME		"after injection"
28	2013-051551	unk	POME		starting 30-120s during injection
29	2013-051572	unk	POME		starting 30-120s during injection
30	2013-052277	unk	POME		"after injection"
31	2013-053025	unk	POME		"after injection"
32	2013-053033	unk	POME		"after injection"
33	2013-053037	44	POME		"after injection"
34	2013-053519	22	POME		after 2 mL injected
35	2013-053539	55	POME		suddenly during injection
36	2013-055106	unk	POME		"after injection"
37	2013-059353	unk	POME		"after injection"
38	2013-059997	36	POME		during injection
39	2013-060557	unk	POME		during injection
40	2013-066822	54	POME		at the end of injection
41	2013-072664	39	POME X 2 episodes	YES	immediately after
42	2013-072999	48	POME		during the end of injection
43	2013-075412	69	POME		"on the occasion" of injection

Narratives for cases of POME or anaphylaxis that were reported as serious adverse events (SAEs) in the PSURs submitted in the current submission*

*Note: Unless stated, the indication for use of testosterone undecanoate was not reported.

Case 2012-126322: SAE (hospitalized)

A 55 year-old Italian male patient started Nebido 1000mg/4ml (testosterone undecanoate injectable solution) at dose 1000 mg intramuscular for male hypogonadism on 01-NOV-2011. His medical history was unknown but his concomitant medication included sertraline and levothyroxine. It was unknown whether Nebido 1000mg/4ml (soluzione injectable) was used previously. On (b) (6) during I.M. injection of Nebido the patient experienced barking cough with feeling of edema at throat and therefore the patient was hospitalized. The patient was treated with injection of betamethasone sodium phosphate solution. Nebido was not withdrawn. Monitoring of vital parameters: Arterial BP was 178/100 mmHg (elevated), HR was 104 bpm, and body temperature was 37 °C. The results of blood tests ("hemato-chemical samples") were normal. The outcome of the events, feeling of edema at throat and barking cough was recovered. The reporter did not comment on the relationship between the events and Nebido.

Reviewer's comment: The patient's symptom may be attributable to angioedema. However, the exact etiology of the case is unclear and may reflect either POME or anaphylaxis. It is notable that there was no hypotension, no description of respiratory distress, and the patient recovered fully with steroid injection.

Case 2012-126331: SAE (hospitalized)

A 43-year-old German male patient started Nebido (testosterone undecanoate) I.M. injection for Klinefelter syndrome on an unspecified date. The patient's concomitant diseases included sleep apnea syndrome treated with CPAP; allergies to early and late flowering species, and hemiplegia left side with unsteady gait. His medical history included apoplexy on (b) (6) The patient received the following concomitant medication: acetylsalicylic acid, salutec, amlodipine and simvastatin. On (b) (6) the patient received his 13th Nebido injection. The injection started on 10:15 AM, and lasted 1.5 min (standing position, into gluteus maximus muscle, done by a urologist, syringe warmed before injection). At 10:15 AM, the report states that the patient "experienced anaphylactic shock, severe, along with Nebido injection (dyspnoea along with anaphylactic reaction, cough along with anaphylactic reaction, and facial redness along with anaphylactic shock)". Therefore the patient was hospitalized. The outcome of the event was not recovered. The reporting physician considered that anaphylactic shock was probably related to Nebido injection. Therapy with Nebido was continued.

Reviewer's comment: Although reported as "anaphylactic shock", the case narrative did not include specific details, such as vital signs, to corroborate the diagnosis. It is also unusual that therapy with Nebido was continued if anaphylaxis was suspected.

Case 2012-131584: SAE (hospitalized)

A 59-year-old German male patient (physician by profession) had started Nebido injection 1.5 years before the event due to testosterone deficiency. The Q3-month injections had been without problem until (b) (6) The injections had been performed by experienced personnel. Minutes after his last injection of Nebido (testosterone undecanoate 1000 mg) on (b) (6) the patient experienced bilateral visual impairment and was unable to read the computer print, therefore he went to a hospital. Microembolism was suspected. A cerebral CT proved negative. The visual impairment was reversible and the patient fully recovered as per date of report on (b) (6) No additional information was provided.

Reviewer's comment: Based on the temporal relationship, a causal association of Nebido with the reported event cannot be excluded. The etiology of the patient's transient visual impairment is unclear. The mechanism for a suspected microembolism is also unclear.

Case 2012-134348: SAE (medically significant)

A 61 year-old British male patient was switched from Sustanon to intramuscular Nebido in 2010 for testosterone deficiency post-orchidectomy. He was administered 1 g Q3 month. The patient had had reaction to the injection. The doctor suspected possible POME or allergic reaction may have been the cause of the patient's reaction. The patient's medical history included allergic to crayfish and diabetes mellitus. The patient's drug history included Sustanon (testosterone). The patient was receiving the following concomitant medication: hydroxocobalamin, triamcinolone acetonide, lidocaine, sustanon (testosterone), bendro-flumethiazide, metformin, losartan, levothyroxine sodium and omeprazole.

On 19-DEC-2012, within 2 minutes of administration of Nebido, the patient experienced bronchospasm and tightness of the throat. He was treated with epinephrine (adrenaline) and his symptoms resolved within 5 minutes. No information on vitals signs or on physical examination were provided. After administration of adrenaline administration, physical examination did not reveal any specific findings. Nebido was withdrawn on 19-DEC-2012, with no rechallenge. Patient did not want to receive another injection. Time from the patient's first dose to the onset of this event was reported as 22 months.

Reviewer's comment: The case was considered as medically significant due to the severity and need for treatment with adrenaline

Case 2013-072664: SAE (medically significant-life threatening)

This is a spontaneous case received from a physician via Health Regulatory Authority in Switzerland referring to a 39-year-old Swiss male patient who received Nebido (testosterone undecanoate) and experienced two episodes of "immediate type hypersensitivity reaction grade III", one described as cough for five minutes immediately after a Nebido injection, and one

described as dyspnea after injection. The reported events were considered as serious due to reported life threatening nature (medically significant).

The patient received the following concomitant medication: Eltroxin (levothyroxine sodium), Hydrocortisone (hydrocortisone), Norditropin (somatropin) and Minirin (desmopressin acetate). On an unspecified date, the patient started Nebido (intramuscular testosterone undecanoate 1000 mg) every 10 weeks. On 12-FEB-2013, the report states that the patient experienced "immediate type hypersensitivity reaction grade III" with dyspnea. The event was categorized as serious due to life-threatening nature. On 23-APR-2013 the patient again experienced an "immediate type hypersensitivity reaction grade III" with coughing. The event was categorized as serious due to life-threatening event. Therapy with Nebido was withdrawn. The report states that the duration of the events was 5 minutes and they disappeared after application of oxygen.

Reviewer's comment: The reported events do not provide evidence in support of an anaphylactic reaction. Neither event was associated with hypotension or dermatological complaints. The only symptoms described were "dyspnea" and "coughing". Both cases resolved rapidly with oxygen only. The differential diagnosis of POME has to be considered.

7.4 Overall Safety Conclusions for Use of Testosterone Undecanoate Injection

The major Clinical concern for Aveed continues to be the potential for severe post-injection reactions; specifically, serious POME and anaphylaxis events. Such events were reported infrequently in the extensive postmarketing experience of testosterone undecanoate 4 mL injection outside of the U.S. The signs and symptoms of POME vary from mild to severe in intensity. Serious POME events can include: cough, dyspnea, sweating, flushing, throat pain and tightening, chest pain, dizziness, and syncope. In rare instances, patients were reported to experience respiratory distress, cardiovascular instability, or to lose consciousness. Some patients received emergent treatment and some were hospitalized. Although no deaths have been reported, some cases were described as being life-threatening. Episodes of anaphylaxis, including life-threatening events, has also been reported following injection of testosterone undecanoate 4 mL.

The occurrence of serious POME and anaphylaxis appears to be very infrequent. In addition, the events are known to occur during or soon after the injection. In no circumstance has a permanent disability or death been reported. In all cases, the event has resolved, either without treatment or with supportive medical care as for an allergic reaction.

Therefore, this clinical situation appears amenable to a Risk Mitigation strategy (a REMS program) that would require restriction of use to prescribers who were certified: 1) that they were aware of the risk of severe post-injection reactions, 2) that they would inform prospective patients of this risk, 3) that they would administer the drug per the labeled instructions, 4) that

they would observe patients in the healthcare setting for at least 30 minutes, and 5) that they were capable of managing the complications of serious POME and anaphylaxis.

The Sponsor was asked to provide such a REMS program and they complied fully with the Agency's request. The Aveed REMS Program with Elements to Assure Safe Use (EATSU) has been scrutinized by the Agency and has been optimized to every extent possible in order to provide for safe use of testosterone undecanoate. In addition, the labeling will contain a Black Box Warning and a restricted indication.

With the insertion of the ETASU into the REMS, and the clear labeling with a restricted indication, this reviewer concludes that the benefits of Aveed outweigh the risks,

8 Postmarket Requirement

The Sponsor provided a timetable for assessment of the REMS at (b) (4) 3 years and 7 years, as well as a proposed survey methodology. The Agency reviewed the Sponsor's proposed REMS assessments and provided recommendations for improvement and enhancement.

The Sponsor will also conduct "enhanced" pharmacovigilance to promptly report cases of serious POME and anaphylaxis, to seek additional information on those cases, and to summarize those cases for FDA in quarterly reports.

9 Labeling

As mentioned previously in this review, the Sponsor has agreed to include a Black Box Warning and restricted indication in labeling. The labeling also discusses the mandatory restricted distribution program under the Aveed REMS. In this section, the Black Box Warning, restricted indication, and basic components of the REMS are shown:

9.1 Black Box Warning

WARNING: SERIOUS PULMONARY OIL MICROEMBOLISM (POME) REACTIONS AND ANAPHYLAXIS

- **Serious POME reactions, involving urge to cough, dyspnea, throat tightening, chest pain, dizziness, and syncope; and episodes of anaphylaxis, including life-threatening reactions, have been reported to occur during or immediately after the administration of testosterone undecanoate injection. These reactions can occur after any injection of testosterone undecanoate during the course of therapy, including after the first dose *[see Warnings and Precautions (5.1)]*.**
- **Following each injection of Aveed, observe patients in the healthcare setting for 30 minutes in order to provide appropriate medical treatment in the event of serious POME reactions or anaphylaxis *[see Warnings and Precautions (5.1)]*.**
- **Because of the risks of serious POME reactions and anaphylaxis, AVEED is available only through a restricted program (b) (4) called the AVEED REMS Program *[see Warnings and Precautions (5.2)]*.**

9.2 Restricted Indication

Aveed is indicated for testosterone replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous testosterone.

- Primary hypogonadism (congenital or acquired): testicular failure due to cryptorchidism, bilateral torsion, orchitis, vanishing testis syndrome, orchiectomy, Klinefelter's syndrome, chemotherapy, or toxic damage from alcohol or heavy metals. These men usually have low serum testosterone concentrations and gonadotropins (follicle-stimulating hormone [FSH], luteinizing hormone [LH]) above the normal range.

- Hypogonadotropic hypogonadism (congenital or acquired): idiopathic gonadotropin or luteinizing hormone-releasing hormone (LHRH) deficiency or pituitary-hypothalamic injury from tumors, trauma, or radiation. These men have low testosterone serum concentrations but have gonadotropins in the normal or low range.

Aveed should only be used in patients who require testosterone replacement therapy and in whom the benefits of the product outweigh the serious risks of pulmonary oil microembolism and anaphylaxis.

Reviewer's comment: The narrowed indication is shown in *italicized bolded* font.

9.3 REMS

The Agency advised the Sponsor that the Aveed REMS must include the following:

A Medication Guide: The Medication Guide is necessary for patients' safe and effective use of testosterone undecanoate injection. The Agency determined that testosterone undecanoate injection is a product that has serious risks (relative to benefits) of which

patients should be made aware because information concerning the risks could affect patients' decisions to use, or continue to use testosterone undecanoate injection.

Under 21 CFR 208, the Sponsor is responsible for ensuring that the Medication Guide is available for distribution to patients who are dispensed testosterone undecanoate injection. The Medication Guide should be available through the REMS website.

Details of the Aveed REMS Program and the Med Guide will be available through: (1) the REMS website, (2) the REMS program call center, (3) the Sponsor's medical information line, and (4) from sales and/or medical representatives.

Reviewer's comment: In addition to a thorough Medication Guide, the Sponsor has created a Patient Counseling document that is focused and clear. The requirement for informing the patient is satisfied.

Elements to Assure Safe Use (ETASU): The Agency determined that Elements to Assure Safe use were necessary to mitigate the risks and severe complications related to post-injection reactions (serious POME and anaphylaxis) as listed in the labeling. In addition, we determined that a Medication Guide and a communication plan alone would not be sufficient to mitigate those serious risks. Therefore, we requested that the Aveed REMS must include tools to manage these risks, including at least the following:

- Healthcare providers who prescribe or dispense testosterone undecanoate are specially certified.
    - An educational program would be developed to train prescribers about the risk of severe post-injection reactions, measures necessary to mitigate these risks, and tools to prompt a discussion between patients and prescribers about the risks.
    - In order for the health care providers to be certified, each prescriber would be required to undergo the educational training program and to enroll in the Aveed REMS program.
    - The Sponsor would maintain a list of the prescribers who obtained the certification.
- Healthcare settings that dispense testosterone undecanoate injection would also be specially certified.
    - In order for a health care setting to be certified, an authorized representative would complete a REMS enrollment form and would agree to ensure that all health care providers who prescribe or dispense testosterone undecanoate injection are certified, that staff are properly trained and comply with all program requirements, that the health care

setting is able to manage POME and anaphylaxis reactions, order testosterone undecanoate injection only from distributors enrolled in your REMS program, and have procedures in place to ensure compliance with the REMS requirements.

- The Sponsor would maintain a list of the healthcare settings who obtained the certification.

- The REMS would include an implementation system to monitor and evaluate the implementation of the Elements to Assure Safe Use (outlined above). There would be an intervention plan to address any findings of non-compliance with the Elements to Assure Safe Use and to address any findings that suggest an increase in risk.

Reviewer's comment: The Sponsor has submitted a REMS with ETASU that satisfies all the Agency's requests.

10 Appendices

There are no Appendices in this review.

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/s/

GUODONG FANG
02/21/2014

MARK S HIRSCH
02/21/2014
I concur.

SUMMARY MEMORANDUM

Date:	**May 28, 2013**
Application Number:	**NDA 22-219**
Established Name:	**Testosterone undecanoate injection**
Proposed Tradename:	**Aveed**
Applicant:	**Endo Pharmaceuticals Solutions, Inc.**
Indication:	**Treatment of male hypogonadism**
Received Date:	**November 29, 2012**
PDUFA Goal Date:	**May 29, 2013**
From:	**Audrey Gassman, MD** **Deputy Director, Division of Bone, Reproductive and Urologic Products, Office of New Drugs, CDER, FDA**

Introduction

In this Application, Endo Pharmaceuticals Solutions, Inc. is seeking the approval of testosterone undecanoate injection (proposed tradename, Aveed) for replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous testosterone. Testosterone undecanoate (TU) will be administered at an initial dose of 750 mg via intramuscular injection of 3 mLs of solution, followed by a repeat dose of 750 mg after 4 weeks, and then maintenance dose of 750 mg every 10 weeks thereafter.

This NDA was originally submitted by another applicant (Indevus Pharmaceuticals) in August 2007. Efficacy of TU was demonstrated in the pivotal study IP157-001, Part C. However, during the initial review cycle, severe post-injection reactions reported with testosterone undecanoate injection were identified that led to a Complete Response action on June 27, 2008. The Applicant submitted the first Complete Response on March 2, 2009, to address the deficiencies in the June 2008 letter. The Division, however, determined that the risks of post-injection reactions continued to outweigh the benefits of testosterone and issued a second Complete Response action on December 2, 2009. The current November 2012 Complete Response submission aimed to address the risk of these post-injection reactions outlined in the December 2009 action letter. In this submission, the Applicant formally requested an Advisory Committee Meeting to

occur as part of the review process of this resubmission.

This memorandum summarizes key approvability issues, relevant discussions of the April 2013 Advisory Committee, and the risk-benefit of testosterone undecanoate injection in this third review cycle.

Background

The Applicant seeks marketing approval of testosterone undecanoate injection for treatment of male hypogonadism. Male hypogonadism refers to a condition in which the endogenous secretion of testosterone is insufficient to maintain serum testosterone levels within the normal range and is reflected by low serum testosterone concentrations. Hypogonadism in adult men may vary with respect to the clinical presentation; some symptoms associated with this condition include decreased sexual desire and regression of male secondary sex characteristics. Causes of male hypogonadism include cryptorchidism, bilateral testicular torsion, orchitis, Klinefelter's syndrome, exposure to chemotherapy or heavy metals ("primary hypogonadism") and pituitary-hypothalamic injury secondary to radiation, trauma, tumors or other idiopathic causes ("hypogonadotropic hypogonadism"). Approved testosterone products are indicated for "testosterone replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous testosterone due to primary hypogonadism or hypogonadotropic hypogonadism."

In the U.S., approved testosterone replacement products are available in several formulations: orally administered formulations, transdermal patch, gel, and solution, a buccal bioadhesive system, an oral tablet, a subcutaneous implant, as well as two products for intramuscular injection. The subject of this NDA, testosterone undecanoate, is formulated as an intramuscular injectable that allows for a longer interval between treatments (injections every 10 weeks compared to every 2-4 weeks with the available injectable products).

Brief overview of the regulatory history for testosterone undecanoate injection

The Division of Bone, Reproductive and Urologic Products (the Division) has traditionally relied on pharmacokinetic (PK) data (serum concentrations of testosterone) from a single open-label, uncontrolled clinical study as demonstration of efficacy for a testosterone replacement therapy indicated for adult males with conditions associated with a deficiency or absence of endogenous testosterone. The primary PK efficacy endpoint is the average total serum testosterone concentration (Cavg) over the dosing interval. The desired outcome for an individual study subject is a Cavg value for total testosterone that is within the normal range (300-1000 ng/dL). To demonstrate efficacy for a testosterone product, the point estimate of the proportion of subjects achieving a testosterone Cavg within the normal range should be 75%, and the lower bound of the two-sided 95% confidence interval should not be lower than 65%.

In the original NDA submitted on August 24, 2007, the pivotal study IP157-001, Part C evaluated the efficacy of TU 750 mg dose administered at day 1, Week 4, and then every 10 weeks thereafter. Pharmacokinetic results from this study demonstrated efficacy for TU administered according to this regimen. Additional studies, including earlier studies conducted in Europe and a study conducted with a different dosing regimen, were also submitted as supportive information.

The safety profile of TU intramuscular injection was generally comparable to other approved testosterone products, except for reports of severe post-injection reactions that included anaphylaxis and pulmonary oil microembolism (POME). The occurrence of these clinically significant adverse reactions rendered the benefit-risk balance of TU unfavorable. The Division took a Complete Response action on June 27, 2008.

The Applicant provided a Complete Response on March 2, 2009, with additional safety data to address the Division's concerns regarding these severe post-injection reactions. Despite the additional safety data, the risks of these post-injection reactions remained a significant concern, and the Division issued a Complete Response letter on December 2, 2009.

Product Information

Testosterone undecanoate is a long-acting depot formulation of testosterone in castor oil and benzyl benzoate. Testosterone undecanoate is an ester of testosterone that is metabolized to active testosterone by cleavage of the undecanoic acid side chain, presumably via serum esterases. The dosage form is an oily solution of 250 mg TU/mL (equivalent to 157.9 mg testosterone/mL) intended for intramuscular injection. An injection volume of 3 mL contains 750 mg of testosterone undecanoate, 885 mg of refined castor oil, and 1500 mg of benzyl benzoate.

Comment: There are no outstanding CMC issues related to this Application other than labeling.

Nonclinical Pharmacology/Toxicology

The toxicology of testosterone is well understood. Testosterone is a non-mutagenic rodent carcinogen (increases cervical and uterine tumors and liver tumors), and a teratogen which causes masculinization of female fetuses, female animals, and adult females with acceleration of pubertal changes in juvenile males. Because of the extensive clinical and nonclinical data available on testosterone, nonclinical evaluation of TU was limited to assessing binding affinity for the human androgen receptor, ADE (absorption, distribution and elimination) in rats, local toxicity after a single intramuscular injection in pigs, potential for toxicity after repeated intramuscular dosing in rats, and genotoxicity.

Preclinical findings for TU included: little potential for pharmacologic activity without being metabolized, a long half-life at the injection site with expected ADE, toxicities

after repeated dosing generally related to expected pharmacology or the result of large injection volumes, and negative results for *in vitro* and *in vivo* genotoxicity assays. In summary, no significant safety concerns associated with TU administration were identified in the nonclinical program, other than toxicities related to expected pharmacology and injection site trauma.

Comment: There are no outstanding Pharmacology/Toxicology issues related to this Application other than labeling.

Brief Overview of the Clinical Program

The clinical development program for TU injection was similar to those of other testosterone products seeking an indication of testosterone replacement therapy. The Applicant conducted a single Phase 3 U.S. study (Study IP157-001, Part C) to confirm the efficacy of TU injection at a dose of 750 mg for testosterone replacement therapy in adult men with a deficiency or absence of endogenous testosterone. Efficacy of the 750 mg dose was also supported by the findings from two additional pharmacokinetic studies (Study IP157-001, Parts A and B) and 5 other small studies (n=14-96 per study) conducted in Europe.

Efficacy Overview

The single phase 3 trial was a multi-center, open-label, single-arm, uncontrolled clinical study (Study IP157-001, Part C) that enrolled 130 adult male patients with hypogonadism at 31 US clinical sites. Patients received 750 mg (3 mL) of TU by IM injection at initiation of treatment, at Week 4, and every 10 weeks thereafter. Of the 130 patients, 116 (89%) received 4 injections and completed through the 4th injection visit (Week 24)[1]. The primary efficacy endpoint was the proportion of patients that had an average serum concentration of total testosterone within the normal range (300–1000 ng/dL) at the 2nd injection (Week 10). Ninety four percent (94%) of patients (110 of 117) had serum total testosterone Cavg values within the normal range. The 95% confidence interval around this point estimate was 90%-99%. Of the 7 patients who did not achieve Cavg within the normal range, 6 had a Cavg below 300 ng/dL, and one had a Cavg above 1000 ng/dL.

With the original 2007 NDA submission, the Agency concluded testosterone undecoanate administered according to the dosing regimen in the pivotal phase 3 study met the regulatory requirement of efficacy for a testosterone replacement indication.

Comment: There are no outstanding issues related to the determination of efficacy for this product from a Clinical Pharmacology, Statistical or Clinical perspective.

Safety Overview

[1] There was one patient who was missing a Day 70 concentration value; efficacy was analyzed using imputed data for the last value for that patient to bring the total number of subjects in this study to 117.

The current Complete Response submission contains safety data from 18 clinical and postmarketing studies conducted in 3,556 subjects treated with varying dose regimens of TU injection for testosterone replacement or male contraception. In addition, the Applicant provided postmarketing safety assessments from a worldwide database that extends back to the original approval of TU outside the US in 2003. Sold under the tradename NEBIDO in most markets, TU intramuscular injection has been approved for marketing in more than 90 countries and is marketed in 72 countries. The approved TU product in Europe is a 1000 mg dose administered via intramuscular injection of 4 mLs of solution.

In the pivotal phase 3 study IP157-001 (Part C), TU-treated patients experienced adverse events and laboratory changes consistent with an injectable testosterone replacement therapy. The most commonly reported adverse events (>2%) were acne, fatigue, cough, injection site pain, nasopharyngitis, pharyngeolaryngeal pain, arthralgia, insomnia, prostatitis and sinusitis. A total of 21.5% of patients reported at least one adverse event of interest, including: serum prostate specific antigen increased, prostate exam abnormal, prostatitis, prostate intraepithelial neoplasm, acne, urine flow decreased, nocturia, mood swings, aggression, hemoglobin/hematocrit increased, hyperlipidemia, and injection site reaction. Between 1 and 6 subjects reported each of these adverse events of interest, although none of these events were regarded as a new safety trend for testosterone undecanoate.

Severe post-injection reactions first identified in the original 2007 NDA submission have been evaluated from safety data obtained from clinical studies and the postmarketing experience with TU. These severe reactions are classified as either pulmonary oil microembolism (POME) or anaphylaxis. POME is generally attributed to the castor oil substance in the TU formulation, while anaphylaxis could be due to the excipient benzyl benzoate or to the castor oil; both are known allergens, although allergy to testosterone itself is also a possibility. These reactions have been reported to primarily during and within one hour from the time of the intramuscular injection and have occurred after administration of the 750 mg and 1000 mg doses. Clinical differentiation of anaphylactic reactions vs. POME is extremely difficult because of overlapping symptoms between the two reactions and because of the use of different criteria for diagnosing anaphylaxis. No deaths have been reported after these severe post-injection reactions, but resuscitations and hospitalizations have been required in some cases.

There was some debate between the Applicant and the Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) consultants regarding which criteria should be used to classify these severe events and how best to determine rates of occurrence of these reactions. The Clinical Review Team, in consultation with DPARP, categorized severe post-injection reactions from all post-marketing adverse events of anaphylaxis and pulmonary oil microembolism that occurred within 24 hours of injection who met specific clinical or regulatory criteria that included all cases requiring treatment or involving syncope or lowering of blood pressure. After evaluation of the post-injection adverse events, the Clinical Review Team determined that there are 137 cases of severe

post-injection adverse reactions of POME and anaphylaxis, obtained from postmarketing safety reports from approximately 8 years of safety in Europe with worldwide sales of (b) (4) ampules. The clinical team believes that although it is not possible to calculate an incidence rate of these events since the actual number of patients who received TU cannot be calculated from this data, the severity of these post-marketing adverse reactions, which included the necessity for resuscitation and hospitalization in some cases, poses a significant safety concern. Detailed discussions of how these post-injection events were classified are found in the Division's and DPARP's previous reviews.

In summary, the post-injection reactions of anaphylaxis and POME have occurred with testosterone undecanoate injection use in clinical trials and during post-marketing. From the clinical trial database, the Division of Epidemiology estimated the anaphylaxis rate with TU at 1.2 cases per 10,000 injections and the POME rate at 4.5 cases per 10,000 injections. These reactions, however infrequent, are concerning for TU. Other approved non-injectable testosterone products do not appear to have this risk. Although cases of severe post-injection reactions have been very rarely reported with other injectable testosterone products, it is not possible to directly compare reporting rates across products in a reliable manner.

Discussion at the April 2013 Advisory Committee Meeting

A joint Advisory Committee Meeting with the Advisory Committee for Reproductive Health Drugs and the Drug Safety and Risk Management Advisory Committee was held on April 18, 2013. At this meeting, the Applicant presented their data on the efficacy of testosterone undecanoate injection and also safety data on severe post-injection reactions. The Division, DPARP and the Division of Risk Management also presented their evaluations of these severe post-injection reactions.

The Committees voted on two questions:

1. Given the severe post-injection reactions that were reported with TU in clinical studies and postmarketing experience, do you believe that TU is safe for the proposed indication?
2. Whether you vote "Yes or No" to Question 1, please vote whether the Applicant's proposed instructions for use in product labeling that TU be administered using a slow (30-60 second) injection, and that patients remain in the office for 30 minutes post-injection would be sufficient to ameliorate the risk of severe post-injection reactions.

On the first question regarding safe use, the Committees voted 9-9. On the second question, the Committees voted 1-17 against the reliance on labeling as the only risk mitigation strategy for the risk of severe post-injection reactions.

Risk Management

Testosterone replacement therapies have been approved for use in adult males with conditions associated with a deficiency or absence of endogenous testosterone including products that are administered via the intramuscular route. Available data have demonstrated that testosterone undecanoate replaces serum testosterone to the normal range in adult men. The extended dosing interval of TU may increase the likelihood of patient compliance and may improve patient convenience. TU has a safety profile similar to other injectable testosterone therapies, except for the clinically significant risk of severe post-injection reactions.

The main outstanding issue for this clinical development program, therefore, was the occurrence of severe post-injection reactions and methods to adequately mitigate this risk. Various strategies to manage or mitigate this risk with the marketed use of TU were the focus of several discussions between the Applicant and the Agency and were further discussed at the April 2013 Advisory Committee meeting. The Agency and the Applicant, as well as the April 2013 Advisory Committees, discussed various strategies to manage or mitigate this risk, ranging from "labeling only" with a box warning to directives to ensure safe use contained within a Risk Evaluation and Mitigation Strategy (REMS) program.

In this Complete Response submission, the Applicant proposed a REMS with a Communication Plan consisting of a Dear Healthcare Provider letter and a timetable. The clinical review teams found this REMS proposal unacceptable, because such approach would not effectively manage or mitigate the risk of post-injection reactions.

Comment: In the DRISK review dated May 29, 2013, the DRISK reviewer noted that there is often little incentive for prescribers to review materials (such as a Dear Healthcare Provider letter) that are not required within a REMS, given the demands on their time and competing priorities. I concur that a REMS consisting solely of a Communication Plan is unacceptable to communicate the identified risk of severe post-injection reactions.

The clinical review team and the DRISK review team evaluated the Applicant's proposed REMS. The clinical review team and DRISK reviewers worked together to outline a REMS with ETASU program with a narrowed targeted population as a potential path forward for approving this product. In a review dated May 29, 2013, the DRISK reviewer aligned with the clinical review team and stated that "A REMS with ETASU as outlined above may help to reduce poor outcomes in patients who experience post-injection reactions."

Decision:

I agree with the Clinical, Clinical Pharmacology and Statistical review teams as well as the CDTL that testosterone undecanoate should receive a Complete Response action this cycle.

I also concur with the recommendations of the clinical review team that the Applicant's proposed REMS with a Communication Plan is insufficient. I believe that a REMS with Elements to Assure Safe Use (ETASUs) are necessary to ensure that the benefits outweigh the risks of patients receiving testosterone undecanoate as replacement therapy for conditions associated with a deficiency or absence of endogenous testosterone. A REMS with ETASUs provides active strategies to minimize the serious complications resulting from severe post-injection reactions associated with testosterone undecanoate.

In addition, because none of the other testosterone products appear to have the same risk of severe post-injection reactions, the intended population for TU should be limited to patients who require therapy and in whom the benefit of less frequent injections outweighs the risks of severe post-injection reactions. I believe these two modifications to the TU program would allow a favorable benefit-risk balance for TU. Such approach is consistent with the Advisory Committees' overall recommendations regarding allowing access to this product for select patients who require long-term injectable therapy.

The clinical reviewer and CDTL also recommended in their reviews dated May 20 and May 28, 2013, respectively, that an informed consent form be incorporated into an ETASU for TU. After discussion with the clinical team and DRISK, this recommendation will be further evaluated in the next review cycle, as the logistics of how to incorporate and assess the informed consent form need to be further discussed.

Finally, the clinical review team recommended that the Applicant's proposed study synopsis for evaluation of POME and anaphylaxis be formalized into a postmarketing required (PMR) study. At this time, I believe that further discussions on this recommendation be held with DPARP and DEPI as well as the Applicant in the next review cycle to finalize the feasibility, goals and objectives of this study.

Risk Benefit Assessment:

Pharmacokinetic data provided in the original 2007 submission for NDA 22-219 demonstrated that testosterone undecanoate injection (750 mg) administered by IM injection at initiation of treatment, at Week 4 of treatment, and every 10 weeks thereafter for the duration of treatment met the Division's criteria for efficacy for a testosterone drug product for replacement therapy in adult men. In the pivotal Study IP157-001-Part C, 94% of TU-treated patients achieved average steady state serum testosterone concentrations within the normal adult male range of 300 - 1000 ng/dL, with a lower bound of the 95% confidence of 90%.

TU injection has a unique associated risk of severe post-injection reactions (POME and anaphylaxis) not generally observed with other testosterone replacement products. The incidence of these reactions in clinical studies was small and the frequency in the post-marketing setting is unknown. The population-based reporting rate in practice is unknown. For an individual patient, however, there are no known approaches to predict or prevent the occurrence of a severe post-injection reaction. I believe that it is unlikely

that these post-injection reactions could be adequately managed or mitigated by labeling, even with a box warning, or by the proposed REMS with a Communication Plan. It is known that health care providers are inconsistent in learning the content of the prescribing information or documents of a Communication Plan. Assuming that the healthcare providers are familiar with the prescribing information and the content of the Communication Plan, knowledge of these severe post-injection reactions alone could not ensure that the providers are prepared and able to handle a severe post-injection reaction, should a patient experience one.

Because the risk of severe post-reaction injection appears to be unique to TU, I believe that the intended population for this product should be patients who require treatment with testosterone replacement and in whom the benefits of less frequent injection outweigh the serious risks of severe post-injection reactions (pulmonary microembolism and anaphylaxis). I believe that the use of TU is justified in this narrowed target hypogonadal population.

I also conclude that to have a positive benefit-risk balance for testosterone undecanoate, a REMS with Elements to Assure Safe Use (ETASU) is necessary for this product. This REMS should include provider education of the risks and benefits that are unique to this injectable testosterone product, tools to assist the provider in educating and monitoring the patient, and limiting the dispensing of testosterone undecanoate injection to only those patients that have received the Medication Guide and are fully aware of both the benefits and risks of this product. I recognize that this REMS with ETASUs program will not totally mitigate the risks of severe post-injection reactions with TU. However, I believe that the REMS with ETASUs will help ensure that the benefits of TU outweigh its unique identified risks, and allow access of TU to patients who are appropriate candidates.

Based on the safety profile of TU with documented severe post-injection reactions, although there is adequate documentation of efficacy, I do not believe that the risk-benefit balance of TU is favorable without a defined narrowed target population and REMS with ETASUs. I also agree with the clinical team and CDTL that the feasibility and design of a postmarketing requirement should be further discussed in the next cycle to determine if the information is necessary to further define the risk of these post-injection reactions.

Summary of Remaining Deficiency to Address:

The Applicant has not proposed an approach that sufficiently addresses the deficiencies of either identifying which components contribute to the post-injection reactions or identifying a population of males in whom the potential risks are acceptable as outlined in the December 2, 2009 Complete Response letter. To address the deficiency, I believe that the indicated population for TU for the purposes of labeling should be confined to hypogonadal male patients who require testosterone replacement therapy and in whom the benefits of (b) (4) outweigh the serious risks of pulmonary microembolism and anaphylaxis.

The Applicant also needs to further confine the population of hypogonadal patients who receive TU by submitting a REMS proposal for testosterone undecanoate injection that includes the following elements:

- Medication Guide
- Elements to Assure Safe Use with the following elements:
    i. Healthcare provider certification (ETASU A)
    ii. Dispensing testosterone undecanoate injection only in healthcare setting that are certified (ETASU B)
    iii. Implementation System

These restrictive proposals generally align with the recommendations of the clinical and DRISK review teams regarding risk management for these severe post-injection reactions.

Post-Marketing Requirement/Commitments:

The Applicant proposed a synopsis of a clinical study (b) (4) The clinical reviewer and CDTL in their reviews dated May 20 and 28, 2013, respectively, recommended that this study be incorporated into a post-marketing requirement to evaluate the incidence of these severe post-marketing injections with testosterone undecanoate injection. However, I believe that this type of study could have significant difficulty in recruiting enough patients in the US as the REMS with ETASU program could significantly limit the use of this product. Therefore, I think that additional discussion between the clinical review team, DPARP, DEPI and the Applicant should occur in the next cycle to further determine the feasibility, objectives, and design of a PMR study.

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/s/

AUDREY L GASSMAN
05/29/2013

Cross-Discipline Team Leader Memo

Date	May 28, 2013
From	Mark S. Hirsch, M.D.
Subject	Cross-Discipline Team Leader Memo
NDA/BLA #	22-219
Applicant	Endo Pharmaceuticals
Date of Submission	November 29, 2012
PDUFA Goal Date	May 29, 2013
Proprietary Name / Established (USAN) names	AVEED™ testosterone undecanoate injection
Dosage forms / Strength	750 mg in 3 mL solution for deep intramuscular injection
Proposed Indication(s)	Replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous testosterone
Recommended:	***Complete Response***

1. Executive Summary

1.1 Overall Summary and Recommendation

AVEED (testosterone undecanoate) injection is intended for testosterone replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous testosterone. The active ingredient in AVEED is testosterone undecanoate, an ester of testosterone. AVEED also contains refined castor oil and benzyl benzoate. AVEED is administered as a deep intramuscular (IM) injection into the gluteus medius muscle. The dosage strength and the frequency of dosing is 750 mg in 3 mL (250 mg per mL) at start of therapy, then 4 weeks later, then every 10 weeks thereafter. In this memo, this regimen is referred to as the "750 mg LOADING regimen".

Multiple preparations of testosterone have been approved by the Agency for the same indication. These include:

- Injectable testosterone preparations, including testosterone enanthate (Delatestryl) and testosterone cypionate (Depo Testosterone).
- Transdermal testosterone preparations, including the Androderm transdermal testosterone system, AndroGel (testosterone gel) 1%, and Testim (testosterone gel) 1%.
- A buccal testosterone preparation, the Striant buccal testosterone system.
- Oral testosterone preparations, such methyltestosterone capsules (Testred).
- A subcutaneous testosterone implant, Testopel.

Each of these preparations has their own advantages and disadvantages. AVEED would be an option for testosterone replacement; its benefit over the currently approved injectable T products is fewer injections per year (6 injections per year compared to a minimum of 13 injections per year).

The efficacy of AVEED is supported by a single, open-label, pivotal study using the 750mg Loading regimen (Study IP157-001, Part C). Different dosage strengths and different dose regimens were tested during the development program for AVEED, and the results from these additional Phase 2 and Phase 3 studies were submitted for review. In addition, a number of studies have been conducted outside the United States both prior to and since the time of initial approval of testosterone undecanoate injection outside the U.S. (in 2004), and these studies have been submitted for review. The AVEED 750 mg Loading regimen provides acceptable replacement of testosterone. Thus, the Sponsor has met the current requirement for demonstration of efficacy for this indication.

In regard to safety, the adverse reactions associated with AVEED are consistent with those of all testosterone replacement therapies, except for the occurrence of severe post-injection reactions. These are sudden, sporadic and unpredictable events mainly in the postmarketing period outside the U.S. Severe reactions have been reported to occur either during, or generally within 30 minutes of testosterone undecanoate (TU) intramuscular injection. A few reactions occurred later than 30 minutes after dosing, but almost all within 1 hour. We identified a total of 137 severe post-injection reactions reported during the postmarketing period, and 11 such events (9 pulmonary oil microembolism [POME] and 2 anaphylaxis) from controlled trials. The events consist of acute respiratory, skin-related, cardiovascular and upper airway signs and symptoms. The manifestations of the immediate post-injection reactions have included: cough, urge to cough, difficulty breathing, shortness of breath, flushing, sensation of warmth, urticaria, rash, throat tightness, throat closing, tickling in the throat, fullness in the throat, dizziness, palpitations, lowering (or raising) of the blood pressure, syncope, and rarely, loss of consciousness and cardiovascular collapse. Cases have occurred after the first dose, or after subsequent doses, including after up to 4 years of previously uneventful therapy. Some patients have reported a mild reaction on one occasion followed by a severe reaction on a later occasion. Some reactions have been complicated by angina pectoris and electrocardiographic changes consistent with cardiac ischemia, others have involved symptoms in the lower and upper extremities, and in the head and neck region.

The exact mechanism for these drug-related adverse events has not been elucidated, but two etiologies are believed to be underlying:

1) Pulmonary oil microembolism (POME) – as a consequence of the castor oil in AVEED, and
2) Anaphylaxis – likely due to a reaction to the castor oil, the benzyl benzoate and/or the testosterone undecanoate in AVEED.

In regard to the severe POME events, these are highlighted by a sudden urge to cough during or soon after injection, and usually accompanied by dyspnea. In some cases of POME, severe shortness of breath and severe cough were reported, and in a few cases, respiratory distress, cardiovascular symptoms (including angina pectoris), and loss of consciousness were also reported. Some of these patients required supportive therapy, including hospitalization.

In regard to the post-injection anaphylactic reactions, the signs and symptoms have included: shortness of breath, difficulty breathing, flushing, sensation of warmth, rash, urticaria,

tightening of the throat, closing up of the throat, tickling and fullness in the throat, cardiovascular collapse, and loss of consciousness.

Since the signs and symptoms overlap, it is difficult, if not impossible, to differentiate severe POME from anaphylaxis in some of the cases. Many of the patients who were experiencing a severe post-injection reaction received treatment as if they were experiencing an anaphylactic reaction. The treatments have included epinephrine, steroids, antihistamines, and oxygen. Some patients required hospitalization.

In addition to the postmarketing experience, events of POME and anaphylaxis have been quantified in 18 clinical trials involving a total of 3,556 subjects. According to the Sponsor, and as per the Summary of Clinical Safety, after a thorough search and final Endo Pharmaceuticals internal adjudication, nine (9) POME cases were confirmed in eight (8) patients in clinical trials. This translates to an overall POME incidence rate in clinical trials of 4.6 cases per 10,000 injections, or 21.3 cases per 10,000 person-years. According to the Sponsor, and as per the Summary of Clinical Safety, after a through search and final Endo Pharmaceuticals adjudication, two (2) anaphylaxis cases were identified in clinical trials. This translates to an overall anaphylaxis incidence rate in clinical trials of 0.9 cases per 10,000 injections, or 4.7 cases per 10,000 person-years.

In large part, our review of the post-marketing experience forms the basis for our concerns that severe post-injection reactions to testosterone undecanoate injection can be life-threatening events, requiring urgent treatment and/or hospitalization. Whether this problem is worse for testosterone undecanoate injection compared to T enanthate or T cypionate injection remains unclear. While there have been rare reports of severe POME and anaphylaxis for TE and TC, the totality if the cases in FDA's voluntary adverse event reporting system (FAERS) is 33 cases over a 44 year period for all approved T injections.

In any event, these reactions have led the Clinical review team to conclude that the risk-benefit profile for this drug is unfavorable, especially when compared to the currently approved products for testosterone replacement.

Our consultants from the Division of Pulmonary, Allergy and Rheumatology Products (DPARP) concur with our conclusions in regard to severe post-injection reactions. They have stated that these reactions can be attributed to severe POME and to anaphylaxis, but irrespective of the etiology, these are severe reactions and while there have been no reported deaths, some of the events have been life-threatening. DPARP has also raised the concern of chronic, low-grade POME reactions possibly leading to long-term cardio-pulmonary dysfunction. DPARP agrees that severe POME and anaphylaxis following intramuscular TU injection cannot easily be differentiated. In most cases, attending health care personnel have reported and treated the incident as an anaphylactic reaction. The mechanisms for allergic reactions to Aveed have not been elucidated. Two of the excipients in this product, benzyl benzoate, and castor oil are known allergens and may possibly have played some role in these post-injection adverse events. In one case there was skin test documentation of an allergy to the product, and in another case, documentation of a positive skin test to benzyl benzoate..

Taken together, the totality of the evidence leads the DBRUP Clinical review team to conclude that the risk/benefit profile for Aveed is <u>not acceptable</u> for the proposed

indication. At this time, we recommend a Complete Response action. I concur with the primary medical officer, Dr. Guodong Fang, in this decision.

A potential pathway forward towards eventual product approval would be a Risk Evaluation and Mitigation Strategy (REMS) with Elements to Assure Safe Use (ETASU). We recommend that such a REMS with ETASUs should include:

- Mandatory restricted distribution to certified prescribers. These prescribers would attest to (1) an awareness of the risk of severe post-injection reactions, and (2) that they had the ability and materials necessary to manage a severe post-injection reaction, and (3) that they would keep a patient under observation for at least 1 hour after each dose.
- Certified pharmacies would distribute product only to certified prescribers
- Prospective patients would be asked to sign an Informed Consent describing the potential risk of a severe post-injection reaction and stating that they would agree to remain under observation for at least 1 hour after each dose.

In the event of product approval in the future under the terms of such a REMS with ETASU, the product labeling would need to prominently inform patients and prescribers of the risk of severe post-injection reactions, including severe POME and anaphylaxis, and the need to be observed for 1 hour after each dose. A Boxed Warning would be appropriate.

1.2 Sources of Clinical Data

The development program for testosterone undecanoate injection for TRT consisted of a single U.S. Phase 3 study (Study IP157-001), six European Phase 1, Phase 2 and Phase 3 studies, 5 European male contraception studies, and 6 International Postmarketing studies, including:

U.S. Hypogonadism Study (N=524)

- IP157-001 Parts A, B, C and C2*

(*A total of 153 subjects participated in the U.S. Study IP157-001 Parts C and C2 which employed the to-be-marketed 750 mg Loading regimen)

European Hypogonadism Studies (N=201)

- JPH01495, European hypogonadism, 1 dose, n=14
- JPH04995, European hypogonadism, multiple doses, n=14
- ME98096, European hypogonadism, multiple doses, n=26
- ME97029, European hypogonadism, multiple doses, n=36
- 306605, European hypogonadism, multiple doses, n=96
- 303934, Finland andropause (prematurely terminated), 1 dose, n=15

European Male Contraception Studies (N=407)

- 97028, Germany male contraception, 4 doses, n=28
- 97173, Italy, multiple doses, n=24
- 98016, Germany, 4 doses, n=14
- 99015, Germany, 4 doses, n=42
- 42306, 6 countries, 4 doses, n=298

International Postmarketing Studies (N=2424)

- AWB0105, Germany, 4 doses, n=869
- 39732 (NE0601 IPASS), 18 countries, 4 doses, n=1411
- 14329 (Czech NEO), Czech Republic, multiple doses, n=23
- NB02, Germany (paraplegia), 2 doses, n=20
- TG09, Germany (obesity), 4 doses, n=29
- 14853, Prematurely terminated (older men), multiple doses, n= 3

This Complete Response submission also contained 2 additional Bayer/Schering Safety Updates for the postmarketing experience outside the U.S., as well as individual reports for all cases of POME and anaphylaxis reported during the entire postmarketing experience outside of the United States, which totals approximately 8 years. These cases were identified through a search of the Bayer/Schering postmarketing safety databases, using a methodology that had been agreed upon with FDA prior to submission of the CR.

The Complete Response also contained a proposed REMS, which included patient labeling and a Communication Plan (a Dear HCP Letter).

2. Background

2.1 DESCRIPTION OF PRODUCT

Aveed contains testosterone undecanoate, an ester of testosterone. Although the esterified testosterone (T undecanoate) is itself detected in the blood following injection, the pharmacologically active androgen, testosterone, is formed by esterase cleavage of the undecanoate ester side chain. Aveed is formulated as a clear, yellowish, sterile, oily solution for intramuscular injection. It is supplied in single use vials, as 750mg testosterone undecanoate in 3mL solution. In addition to testosterone undecanoate, the product also contains refined castor oil (885mg) and benzyl benzoate (1500mg).

Aveed is intended for replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous testosterone.

2.2 REGULATORY HISTORY

On August 24, 2007, the original NDA was submitted.

On June 27, 2008, the application received an **Approvable** action based upon ***Clinical*** and ***Chemistry*** deficiencies.

The original ***Clinical*** deficiency centered on immediate post-injection reactions. The etiology of these was believed to be pulmonary oil microembolism (POME) and/or anaphylaxis. While immediate post-injection reactions were reported in just 2 patients in the original NDA in clinical trials (one serious case), such events were reported in 66 patients in the postmarketing

period outside of the United States. The postmarketing cases were described as coughing, difficulty breathing, flushing, throat-related symptoms (throat tightening/closing, throat tickling, throat fullness, lump in throat), allergic phenomenon (rash, swelling around eyes, itching, wheezing), paresthesias (burning in mouth, chest, hands and feet), and constitutional symptoms (headache, malaise, sweating, shivering, weakness, nausea, etc) in the immediate post-injection period. Of the 66 cases, 28 cases were serious adverse events, including 4 with respiratory distress and 4 with loss of consciousness. While none of the patients died, and all resolved without permanent sequelae, 12 patients required emergency treatment or hospitalization. In four of these postmarketing cases, signs and symptoms of a systemic allergic reaction were reported, including two (2) cases definitely meeting clinical criteria for anaphylaxis, and 2 possibly meeting anaphylaxis criteria, as per our consultants in DPARP. At the time of the original NDA, there were no clinical trial cases with sufficient information to diagnose systemic allergic reactions.

In the Approvable letter, the Sponsor was asked to submit additional information to further assess and mitigate the risk of these immediate post-injection adverse reactions. In this regard, the letter spelled out 3 specific requests for Clinical information.

1. *Detailed safety information from clinical studies to determine the incidence of serious post-injection POME and allergic reactions (in clinical studies).*

2. *Information from clinical investigations intended to characterize the nature and etiology of the anaphylaxis-like events with testosterone undecanoate injection.*

3. *A plan to minimize the risks associated with the clinical use of the product, namely, to reduce incidence and/or severity of the serious POME and anaphylaxis-like adverse events.*

The specific **Chemistry** deficiency came from Drug Master File (DMF) # (b) (4) The DMT deficiencies were related to the assessment of sterility of the drug product and were conveyed to the DMF holder in a regulatory letter dated June 25, 2008. The Approvable letter stated that these deficiencies must be satisfactorily resolved prior to approval. The reader is referred to Section 3 of my previous CDTL memos for details of the Chemistry deficiency and the means by which it was ultimately resolved.

On March 2, 2009, the Sponsor submitted the first Complete Response.

In this first Complete Response, the Sponsor reported 1 serious POME case and no systemic allergic reactions amongst 2,834 clinical trial subjects. The Sponsor thereby proposed an incidence of 1 serious POME in 2834 subjects, or 3.53 serious events per 10,000 subjects, or 0.035%. For systemic allergic reactions, the Sponsor proposes an incidence of 0% in clinical trials.

The Clinical review team detected 6 additional cases of interest from clinical trials. However, information from these cases was too sparse to ascribe a specific etiology to the event, but they were all immediate post-injection reactions. Of these 6 cases, the Clinical review team

believes that the former 3 events have a greater chance of being severe POME or anaphylaxis compared to the latter 3, but all 6 are notable. The former 3 cases are:

- Patient #11 in Study 97173 (convulsions)
- Patient #17 in Study 97173 (collapse),
- Patient #4 in Study JPH04995 (circulatory collapse)

The latter three cases are:

- Patient #025-4187 in Study IP157-001 Part A (pre-syncope)
- Patient #26 in Study 97029 (syncope)
- Patient #35 in Study 97029 (circulatory collapse).

If just the 3 former cases were added to the numerator, the incidence of immediate post-injection reactions in clinical trials would be 4 cases /2834 subjects, or 14 serious events per 10,000 subjects, or 0.14%.

In the Division's review of the Complete Response, the Clinical review team stated that the Postmarketing Experience outside of the United States was crucial to the understanding of the risk of testosterone undecanoate. The Clinical review team identified a total of 116 post-injection reactions (POME and anaphylaxis) in the post-marketing period outside the U.S., many of which were severe reactions.

A Risk Evaluation and Mitigation Strategy (REMS) was also submitted by the Sponsor in the first Complete Response. The REMS proposal included a Patient Package Insert (PPI), a Dear Health Care Professional (HCP) letter, and a Video for HCPs in regard to proper intramuscular injection technique (notably, slow and deep intramuscular injection with care taken to avoid intravascular injection). The Sponsor also submitted a proposal for two Phase 4 studies.

While the Sponsor had provided the information requested for the Complete Response, and a risk management plan, the Division remained uncomfortable with the occurrence of severe post-injection reactions. Based on the totality of the evidence, and taking into consideration the Sponsor's contentions and our consultants' opinions, we again found the risk/benefit profile to be unacceptable for marketing at that time.

It should be noted that the Chemistry deficiency in the original NDA had been satisfactorily resolved.

On December 2, 2009, the application received an **Approvable** action based upon a remaining ***Clinical*** deficiency. The Division expressed continuing safety concerns regarding reports of serious, immediate, life-threatening post-injection reactions and their impact on the risk/benefit profile. The proposed REMS was not considered adequate to assure that the benefits outweighed the risks associated with the use of testosterone undecanoate. The Division identified 2 potential remedial actions:

- Identify which components of the drug product may be contributing to the immediate post-injection reactions, and reformulate the product; or
- Identify a population of adult males who require testosterone replacement therapy (TRT) and in whom the additional potential risks associated with the use of TU injection as currently formulated would be acceptable.

In December 2009, at the request of the Sponsor, the Division provided the Sponsor with a list of patients from CIOMS reports who sustained postmarketing post-injection adverse reactions either immediately or soon after injection. These cases constituted, in large part, the basis for the Division's risk/benefit assessment.

On May 24, 2010, the Division met with Sponsor in a Type A meeting to discuss a potential path forward for the application. The Sponsor proposed a narrowed target population with a restricted distribution program under a REMS with ETASU. In response, the Division questioned the viability and clinical appropriateness of the narrowed target population, but stated that a restricted distribution program under a REMS with ETASU might be a possible pathway forward in this situation.

On June 27, 2011, the Division met with Sponsor in Type C meeting. After further consideration and internal FDA discussion, the Division informed the Sponsor that the proposed REMS with ETASU (restricted distribution) was not an appropriate strategy for this new drug application. The Division recommended that the Sponsor submit another CR and the application would likely be discussed at an Advisory Committee Meeting.

On January 14, 2012, the Division conveyed preliminary responses to Type C meeting questions. The Sponsor was requested to provide: (1) the exact terms to be used for searching postmarketing databases for cases of POME and anaphylaxis; and (2) specific criteria to use to define POME and anaphylaxis, as well as the specific process to use in adjudicating cases generated by the search. The Division reviewed the Sponsor's proposals in collaboration with the Office of Surveillance and Epidemiology (OSE) and the Division of Pulmonary, Allergy and Rheumatology Products (DPARP). The Division largely accepted the Sponsor's plan for analysis of postmarketing safety, but provided the following advice and recommendations:

- The MedDRA terms to be queried to cull potential cases of POME and anaphylaxis are reasonable
- FDA uses a clinical definition of anaphylaxis (Sampson Criteria) developed by NIAID and the Food Allergy and Anaphylaxis Network when evaluating potential cases of anaphylaxis
- Individual CIOMS reports should be provided for all potential cases of POME and anaphylaxis irrespective of Sponsor's medical review or adjudication.

On November 29, 2012, the second CR was submitted. The CR contained a formal request for an AC meeting as part of the review process of this submission. This second CR submission is the focus of this memo.

On April 18, 2013, an AC Meeting was held to discuss the application.

2.3 PRIMARY MEDICAL REVIEWER'S RECOMMENDATION FOR APPROVABILITY

The primary reviewer, Guodong Fang, stated in his final review dated May 20, 2013:

"Recommendation on Regulatory Action: In the opinion of this Clinical Reviewer, from a clinical perspective, the evidence presented in the original submission and two re-submissions was adequate to support the effectiveness of this product. However, the safety concerns related to the risks, risk versus benefit ratio, and proposed management of severe post-injection reactions, which led to the original "Approvable action" have not been adequately addressed in the Sponsor's Complete Response to the Agency's December 2, 2009 Action Letter.

It is recommended that until such time as these issues of severe safety concerns are resolved, the application of testosterone undenoate for intramuscular injection not be approved for the indication of replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous testosterone:

- *"Primary hypogonadism (congenital or acquired)"*
- *"Hypogonadotrophic hypogonadism (congenital or acquired)".*

In regard to the risk/benefit profile, the medical officer concluded:

"The Clinical Review Team believes that the postmarketing safety reports of severe post-injection reactions, including severe pulmonary oil microembolism (POME) and anaphylaxis, included in this NDA resubmission is a major unresolved safety issue. Sufficient evidence leads this reviewer to conclude that the risk/benefit profile for this product is not acceptable for approval."

Dr. Fang also noted the following:

"*Taken together, especially the severity and unpredictability of the severe postinjection reactions, this reviewer concludes it is not safe to authorize Aveed for marketed for the proposed indication.*"

In regard to a potential pathway forward, Dr. Fang stated:

"To address the risk of severe post-injection reactions including POME and anaphylaxis, this reviewer does not believe that it is sufficient to have a standard Medication Guide and Communication Plan. The Clinical review team envisions a mandatory restricted distribution of Aveed, under a formal Element to Assure Safe Use (ETASU). The following are proposed:

- *Prescribers should be certified. They should (1) acknowledge the risk of severe post-injection reactions (2) have sufficient supplies and the ability to treat a possible episode of severe POME or anaphylaxis, and (3) be willing to keep the patient under observation of at least 1 hour after each injection.*
- *Pharmacies should be certified. They should only distribute Aveed to certified prescribers.*
- *Potential patients should sign informed consent stating that they understand the risk of a possible severe POME and/or anaphylaxis event, and that they are willing to be observed in the office for at least 1 hour after each injection.*

In addition, for an eventual Aveed NDA approved with a restricted distribution ETASU, a Black Box Warning in product labeling is recommended for the potential risk of severe post-injection reactions, including severe POME and anaphylaxis."

I concur with Dr. Fang's overall conclusions and recommendations.

3. CMC/Device

The CMC review team (Yichun Sun and Donna Christner) noted during this review cycle that there was no new CMC information enclosed in this re-submission. During the last Complete Response submission, the Chemistry Approvable issue was resolved. From a CMC perspective, therefore, this NDA resubmission was recommended for an approval action.

4. Nonclinical Pharmacology/Toxicology

The nonclinical review team (Eric Andreason and Lynnda Reid) noted that the current re-submission contained no new nonclinical information. Previously, it had been determined that from the nonclinical perspective, references from the literature and general knowledge of testosterone provided reasonable assurance of the safety of testosterone undecanoate (TU) in hypogonadal men. A local toxicity was also conducted and non-specific tissue injury at the site of injection was observed. For this review cycle, the nonclinical reviewer made only minor changes to the original pharmacology/toxicology review. These changes did not affect the overall nonclinical conclusion. In general, from the nonclinical perspective, the safety profile of testosterone was well known. Other than expected pharmacology and injection site toxicity, no significant safety concerns associated with TU at therapeutic doses were identified in the nonclinical program

In regard to previous PharmTox review issues, there is one issue of potential clinical relevance: the potential for benzyl benzoate to act as a toxin.

> In their original Pharmacology/Toxicology review, Drs. Andreason and Reid provided results from a local tolerance study of Nebido (containing intramuscular testosterone undecanoate, refined castor oil, and benzyl benzoate) in pigs. This study is reviewed on page 47 of the final PharmTox review, dated April 18, 2008. It is stated that this study was reviewed by Dr. Leslie McKinney. The results of this study, wherein pigs were injected intramuscularly with low and high volumes of the drug product, or with vehicle alone, showed areas of gross hemorrhage and necrosis at the injection sites, with necrotic tissue, inflammation and multinucleated giant cells on histopathology. All groups showed similar effects, including the vehicle alone group. The reviewer concluded that these observations are likely due to non-specific tissue injury, and that there is no direct evidence that either of the excipients, or testosterone undecanoate itself, were directly toxic to tissues. However, Dr. McKinney noted that benzyl benzoate is itself a toxin, as shown by its use in the treatment of scabies to kill the house mite that causes scabies. The review states: "*Whether it (benzyl benzoate) could directly activate macrophages, which would explain the presence of giant cells at the*

injection site, has not been established, but has been observed for other benzoates in vitro (Choi et al., Arch Pharm Res: 28[1]:49-54 [2005])".

The reader should also be aware that AVEED contains 1500mg of benzyl benzoate per vial, a fairly large amount. I have discussed this with the primary pharmacology/toxicology reviewer, Dr. Andreasen, who has indicated that he could find no approved product containing more than 750mg of benzyl benzoate. Benzyl benzoate is the condensation product of benzyl alcohol and benzoic acid. In a final report on the safety of benzoates (benzyl alcohol, benzoic acid, and sodium benzoate) in cosmetics, the U.S. Cosmetic Ingredient Expert Panel noted that benzyl alcohol and benzoic acid can produce nonimmunologic contact urticaria and non-immunologic immediate contact reactions (Int J. Toxicology 2001; 20 Suppl 3:23-50). The Panel stated that such reactions were not a concern at concentrations up to 5% topically; that is, when bodily exposure is limited. Nonetheless, the panel stated that the clinical risks of these reactions should be considered by manufacturers when assessing topical use of products containing benzyl benzoate in infants and children; and that an inhalational route for these products could not yet be considered safe. Benzyl benzoate might have played some role in the severe post-injection reactions that have been reported in the postmarketing period outside the United States. In one case, a young man experienced an anaphylactic reaction to testosterone undecanoate injection and subsequent skin testing revealed a positive reaction to the benzyl benzoate component only.

In addition, the reader should also be aware that there have been reports of "benzyl alcohol poisoning" in neonates following repeated intravenous injections of benzyl alcohol in intravenous saline flushes (MMWR Weekly 1982: 31 [22]: 290-291). These were pre-term neonates weighing 2500 grams, with premature hepatic metabolism, in whom intravenous central catheters were flushed periodically each day with saline solutions containing 9mg/mL of benzyl alcohol. The events in these infants included the following: "gasping respirations", respiratory distress, convulsions, metabolic acidosis, intracranial hemorrhage, hypotension, cardiovascular collapse, and death. The MMRW citation states "On the basis of the animal studies, it has been estimated that rapid intravenous infusion of adult humans with as much as 30mL of 0.9% benzyl alcohol (approximately 4.5mg/kg) in saline should be safe (Kimura et al., Toxicol Appl Pharmacol 1971; 18: 60). It is not known whether this same data applies to benzyl benzoate, but this information is provided to the reader nonetheless, because: 1) there is a large amount of benzyl benzoate in each injection of Aveed (1500mg), and 2) serious POME reactions reported for Aveed have included signs and symptoms similar to these reported in the premature neonates who experienced benzyl alcohol poisoning.

5. Clinical Pharmacology/Biopharmaceutics

The Clinical Pharmacology review team (Dilara Jappar and Myong-Jin Kim) found the application acceptable for approval. All labeling issues had been adequately resolved through labeling negotiations during last reviewing cycle. The current submission contained some additional long-term data from Study IP157, Part C2, an extension study. The data confirmed

that serum total testosterone (T) trough concentrations were steady and acceptable after up to 9 injections.

In regard to prior Clinical Pharmacology review issues:

> The principal Clinical Pharmacology concern during the review of the first Complete Response was the effect of body weight on exposure; specifically, the increased exposure demonstrated in patients with lower body weight/lower body mass index, and especially the excessive exposure noted in a single patient who weighed <65 kg. (b) (4) In addition, Section 12.3 (Pharmacokinetics) describes in detail the effect of body weight on exposure, including specific data in patients weighing 60-100kg and those ≥ 100kg (b) (4)
>
> One final clinical pharmacology issue of note is the presence of testosterone undecanoate concentrations in the blood. While TU is generally converted to T, serum TU concentrations were clearly identified in all regimens tested. The concentration-time profile showed that T_{max} was approximately 4 hours for TU and serum TU concentrations were generally short-lived. The reader should also be aware that while TU may be found in the blood, nonclinical studies have shown that TU itself has little potential for clinical androgenic activity. The ability of TU to bind to the human androgen receptor was assessed and the results suggest that TU does not have significant androgenic activity since its relative binding affinity was only 1.3% of testosterone. Nonetheless, it is not know if serum TU may have played some role in the severe post-injections reactions that have been observed in the postmarketing period outside the United States.

6. Clinical Microbiology

The Clinical Microbiology review team (Vinayak Pawar and David Hussong) recommended approval of the NDA on April 29, 2009. Upon review of subsequent DMF (b) (4) amendments (amendments 9-11), the original Micro recommendation for approval of the NDA remain unchanged, as there was no new information which would alter the conclusions based upon review of data from the previous DMF (b) (4) submissions.

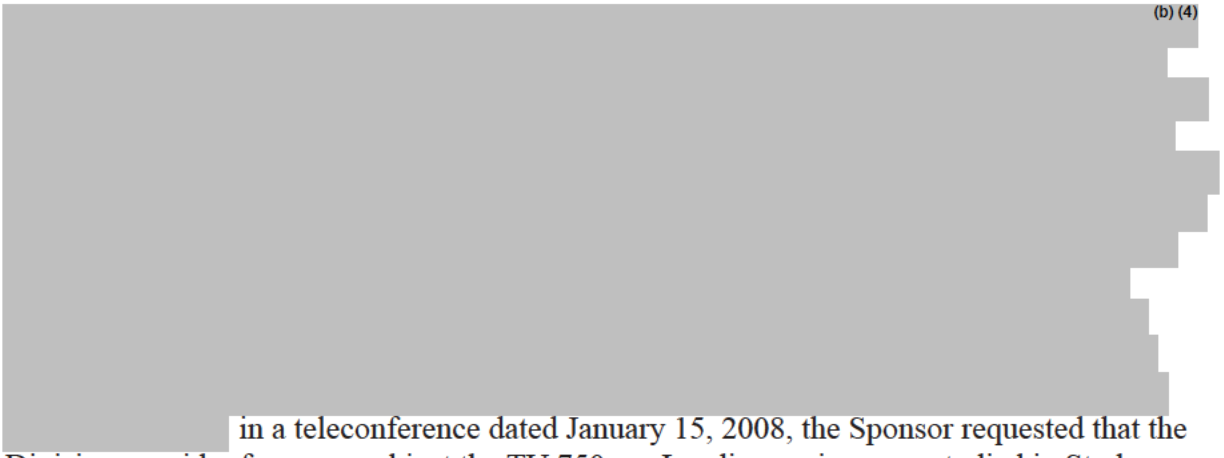
7. Clinical/Statistical - Efficacy

7.1 OVERVIEW OF CLINICAL PROGRAM

For efficacy, the NDA is supported by a single, two-part, phase 3 safety and efficacy study, referred to as Study IP157-001 - Parts C and A. Part C evaluated the 750 mg Loading regimen (n = 117) while Part A evaluated 750 mg (n=102) or 1000 mg (n=97) given every 12 weeks.

The primary endpoints in this study were average and maximum serum testosterone (T) concentrations.

Results from five (6) other European Hypogonadism studies and their extensions (including Study JPH01495, Study JPH04995, Study ME98096, Study ME97029, Study 306605 and Study 303934) were provided but were not reviewed in depth for efficacy because they employed dose regimens that were not sought for marketing. In addition, these older studies employed testosterone assay methods (radioimmunoassay or electrochemoluminescence immunoassay) that were regarded by Clinical Pharmacology as being not as accurate as the method used in Study IP157-01.



in a teleconference dated January 15, 2008, the Sponsor requested that the Division consider for approval just the TU 750 mg Loading regimen, as studied in Study IP157-001 Part C. Due to this change, data from Study IP157-001 Part C were used as the source of steady state PK. Data from Study IP157-001 Part A was used as the source of first dose PK data because Part C did not evaluate first dose PK. Part A also served as the primary source of data on serum TU and serum dihydrotestosterone undecanoate (DHTU) concentrations because these analytes were not measured in Study IP157-001 Part C.

7.2 DEMOGRAPHICS

The main diagnostic criteria for inclusion in Study IP157-001 were men at least 18 years of age with morning screening serum testosterone concentration < 300 ng/dL. Critical exclusion criteria included: 1) American Urological Association Symptoms Score ≥ 15 points, 2) Prostate symptoms or induration of the prostate (or breast) suspicious for cancer, 3) Serum prostate specific antigen level ≥ 4 ng/mL, 4) Hyperplasia of the prostate, defined as prostate size ≥ 25 cm3 on transrectal ultrasononography, 5) Past or present history of liver tumors, acute or chronic liver disease, or serum liver function tests exceeding 1.5 times upper limit of normal, 6) History of deep vein thrombosis (DVT) in the last 5 years, 7) Any history of cerebrovascular accident, 8) Severe acne, 9) Serious psychiatric disease or other uncontrolled medical illness, 10) Significant baseline hypertension (systolic BP > 160 mmHg and diastolic > 95 mm Hg), 11) Coronary artery disease not stabilized by therapy, and 12) Insulin dependent diabetes mellitus, or uncontrolled non-insulin dependent diabetes mellitus.

In brief, the demographics of the study population in Part C (n=130) were as follows:

In terms of race, the majority of subjects were White (76%), 12.3% were Black, 10.8 % were Hispanic, and 2.3% were "Other". The mean age was 54 years ± 0.9 years. The median age was 55 years. The minimum and maximum ages of subjects in the trial were 24 years and 75 years, respectively. Of the total, 23% (30/130) were between ages 40 - 50 years, 38% (50/130) were between ages 50 - 60 years, and 25% (33/130) were 60 - 70 years. The mean weight of subjects was 71 kg ± 14 kg. The median weight was 101 kg. The mean body mass index was 32 kg/m^2. Almost 60% of subjects had a body mass index over 30 kg/m^2. The average total testosterone concentration at screening was 214 ng/dL.

7.3 DISPOSITION OF SUBJECTS

For Part C, a total of 130 patients were enrolled at a total of 31 U.S. clinical sites. Of the 130 patients enrolled, 116 (89%) completed Stage 1 of Part C; that is, they completed through the 4^{th} injection visit. Of the 14 subjects who prematurely discontinued, the most common reason for premature discontinuation was adverse event (3.8%, or 5/130). Of the 5 who discontinued due to an adverse event, the adverse event was judged by the investigator to be related to treatment in 4 patients. The events in these 4 patients included: mood swings, acne, deep vein thrombosis, and estradiol increased. The fifth patients suffered a myocardial infarction, judged by the investigator as being not related to study medication. Other reasons for premature discontinuation included patient non-compliance (3 subjects), withdrawal of patient consent (1 subject), loss to follow-up (2 subjects), and "other" reasons (3 subjects). The Sponsor notes that despite the requirement for frequent blood sampling in this study, persistence on drug therapy was high.

Of note, two subjects were discontinued from the study for weighing less than 65 kg, but only after they had been enrolled.

There were 4 pre-defined criteria in the protocol for subject discontinuation. These were: hemoglobin >21 gm/dL, PSA > 10 ng/mL, PSA > 4ng/mL but ≤ 10 ng/mL unless prostate cancer was ruled out by new biopsy, and uncontrolled hypertension, defined as systolic blood pressure ≥ 160 and diastolic BP ≥ 95 mm Hg. There were no patients who terminated from the study due to any of these 4 criteria.

7.4 EFFICACY FINDINGS

7.4.1 Assessment of Efficacy

The primary efficacy variable was the percentage of patients with average T concentration at steady state within the normal range (above 300 ng/dL but below 1000 ng/dL). Testosterone undecanoate 750mg was given at baseline, week 4, and every 10 weeks thereafter. Steady state pharmacokinetic sampling occurred during the 3^{rd} injection interval. This is an acceptable primary efficacy endpoint for the proposed indication of testosterone replacement.

A total of 117 patients were included in the PK population. The majority of patients in the PK population had complete data for most efficacy outcomes. The analysis presented descriptive statistics (mean, standard errors, etc) for all patients with non-missing values. A point estimate was provided for the number (%) of subjects meeting the C_{avg} threshold, as were the 95%

confidence intervals about the point estimate. The protocol stated that in order to reject the null hypothesis (TU 750mg Loading regimen does not provide adequate T replacement) in favor of the alternate hypothesis (TU 750mg Loading regimen does provide adequate T replacement), the percentage of responders, defined as Cavg within the normal range (300-1000ng/dl), must be at least 75%, with the lower bound of the two-sided confidence interval not lower than 65%.

The protocol also stipulated that testosterone concentrations should not be excessively high outside the normal range; specifically, ≤ 1500 ng/dL in ≥ 85% of patients, 1800 – 2500 ng/dL in ≤ 5% of patients, and > 2500 ng/dL in no patients. All 3 criteria must be met to reject the null hypothesis (TU 750mg Loading regimen does result in excessively high serum T) in favor of the alternative hypothesis (TU 750mg Loading regimen does not result in excessively high serum T).

In addition, the following secondary endpoints were evaluated:

1. Other pharmacokinetic assessments of testosterone, including concentrations below the normal range (<300 ng/dL).
2. Other hormone concentrations, including free T, dihydrotestosterone (DHT), sex hormone binding globulin, estradiol (E_2) and the ratios of these hormones over time.
3. Exploratory clinical markers of testosterone replacement, including the Male Patient Global Assessment (M-PGA).
4. Body weight and BMI.
5. Correlations of T concentrations with clinical outcomes.
6. The impact of T concentrations on erythropoiesis and lipid markers.

7.4.1.1 Primary Efficacy Analysis

The mean pharmacokinetic data indicated that the serum testosterone C_{trough} values were similar at end of 2nd, 3rd, and 4th injection interval, as shown in *Figure 1*. A comparison of serum total T concentration at several time points post-injection during the 3rd and 4th injection intervals demonstrated similar concentration-time profiles (*Figure 2*). Taken together, these data indicate that steady state was achieved during the 3rd injection interval in Part C, and that this was an appropriate timepoint for assessment of the primary endpoint.

Figure 1: Mean (±SD) trough serum total T concentrations at each injection visit from pre-treatment through 5th injection – Steady state PK population, Study IP157-001 Part C

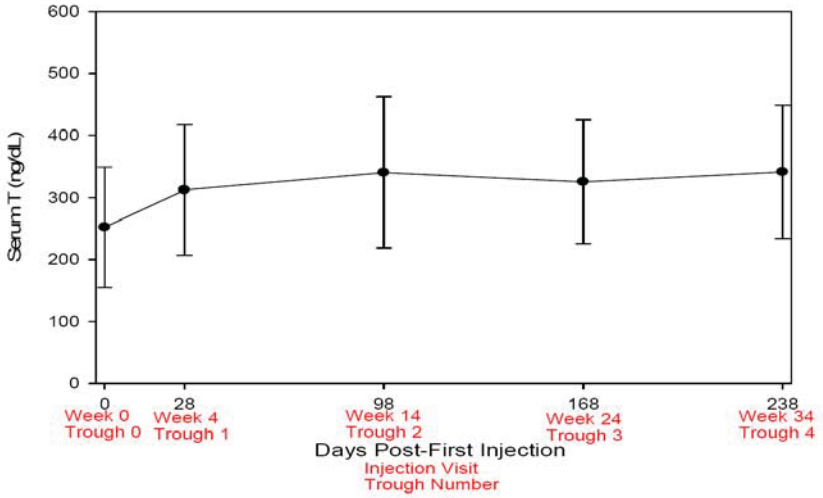
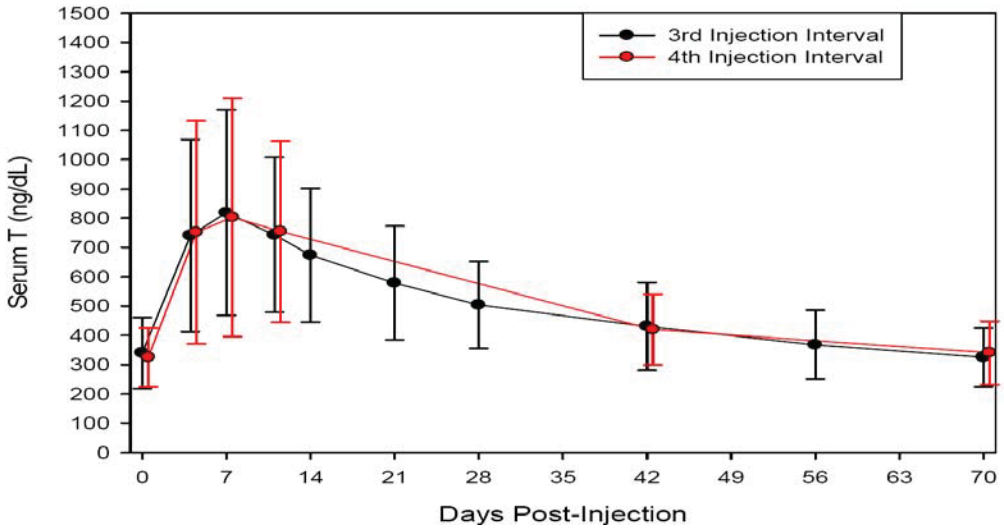


Figure 2: Comparison of serum total T concentrations between the 3rd and 4th injection intervals – Steady state PK population, Study IP157-001 Part C



Tables 1, 2 and 3 summarize the pharmacokinetic parameters of serum total T from the 3rd injection interval. The primary endpoint was $C_{average}$.

Table 1. Serum total T pharmacokinetic parameters from the 3rd injection interval, TU 750mg LOADING regimen, from Study IP157-001 Part C

PK parameter	Mean (n=117)	Standard deviation
C_{avg} (ng/dL)	495	141
C_{max} (ng/dL)	891	345
T_{max} (days)	7 (median)	4 – 42 (range)

Table 2: PK parameters of serum total T (ng/dL) following the 3rd injection interval of TU 750 mg LOADING regimen - PK population, Study IP157-001 Part C

TU Dose	Pharmacokinetic Parameter	Number Patients	Mean	Standard Deviation	Minimum	Median	Maximum	CV (%)	Geometric Mean
TU 750 mg LOADING	$AUC_{(0-70)}$ (days*ng/dl)	117	34645.6	9902.45	13755.1	33342.2	70016.9	28.6	33263.6
	C_{Trough} (Day 70)	117	323.5	99.11	138.2	316.9	611.1	30.6	309.0
	C_{max} (ng/dL)	117	890.6	345.11	311.0	813.6	1758.5	38.8	826.8
	Dose-normalized C_{max}(ng/dL)[1]	117	1.2	0.46	0.4	1.1	2.3	38.8	1.1
	T_{Last} (days)	117	70.0	0.00	70.0	70.0	70.0	0.0	70.0
	T_{max} (days)	117	10.0	7.11	4.0	7.0	42.0	71.1	8.4
	Dose-normalized $AUC_{(0-70)}$ (days*ng/dl)[1]	117	46.2	13.20	18.3	44.5	93.4	28.6	44.4
	$C_{avg, 0-70}$ (ng/dL)[2]	117	494.9	141.46	196.5	476.3	1000.2	28.6	475.2

Reference: Section 14.2 Table 9.2.1.1.1
CV = Coefficient of Variation
[1] Statistics for the dose normalized AUC were derived by dividing the mean of the original parameter ($AUC_{(0-70)}$) by the dose amount (750 mg). Thus, no measures of variability, geometric mean, or CV are presented for the dose normalized AUC.
[2] C_{avg} derived as $AUC_{(0-70)}$/70 days

Table 3: Serum total T concentrations (ng/dL) over 70 days (10 weeks) following the 3rd injection of TU 750 mg LOADING regimen - PK population, Study IP157-001 Part C

Treatment Group	Days Post-Injection	Number Patients	Mean	Standard Deviation	Minimum	Median	Maximum	CV%	Geometric Mean
TU 750 mg LOADING	0 (Pre-Injection)	117	339.5	122.69	141.4	303.0	754.1	36.1	319.8
	4	111	730.1	325.36	304.6	656.4	1715.0	44.6	662.9
	7	111	816.9	352.15	276.4	737.6	1758.5	43.1	747.5
	11	107	750.1	280.64	245.6	740.9	1757.0	37.4	697.9
	14	114	661.6	237.55	230.9	610.8	1352.3	35.9	619.2
	21	115	573.5	197.15	182.7	558.6	1350.4	34.4	541.3
	28	111	501.6	149.92	190.9	481.4	947.0	29.9	479.5
	42	109	432.3	152.16	171.3	399.8	1161.2	35.2	409.5
	56	115	367.0	120.67	144.5	349.8	780.8	32.9	348.7
	70[1]	116	323.8	99.51	138.2	317.2	611.1	30.7	309.2

Reference: Section 14.2 Table 9.2.1.2.1
[1] Note: As per the statistical analysis plan, for derivation of the PK parameters, if the concentration at the end (Day 70) of the 70-day dosing interval is missing, then the AUC was derived using λz as derived by curve-stripping. There was 1 patient who was missing a Day 70 concentration value; this table presents the data prior to the data imputation of Day 70 for this patient. However, the analysis for Table 25 was performed using the imputed data for the last value for that patient, and thus the C_{trough} value from that table will not match the Day 70 value from this table.

One patient was excluded from the PK analysis due to protocol violation. This was Patient 002-7022, who was taking concomitant DHEA, an androgenic steroid hormone prohibited in this study.

Figures 3 and 4 show the mean and individual concentration-time profiles for serum testosterone, respectively, following the 3rd injection interval.

Figure 3: Mean (±SD) serum total T concentrations following the 3rd injection interval of TU 750 mg LOADING regimen, from Study IP157-001 Part C

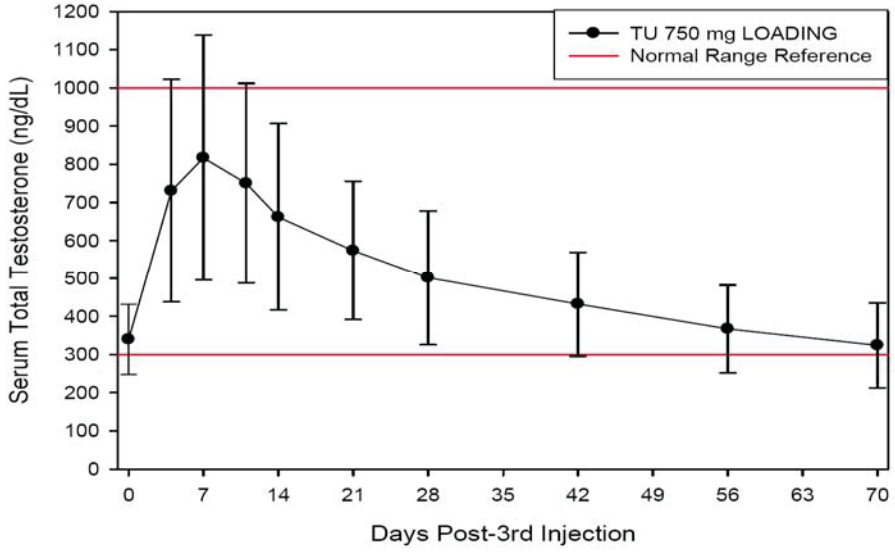
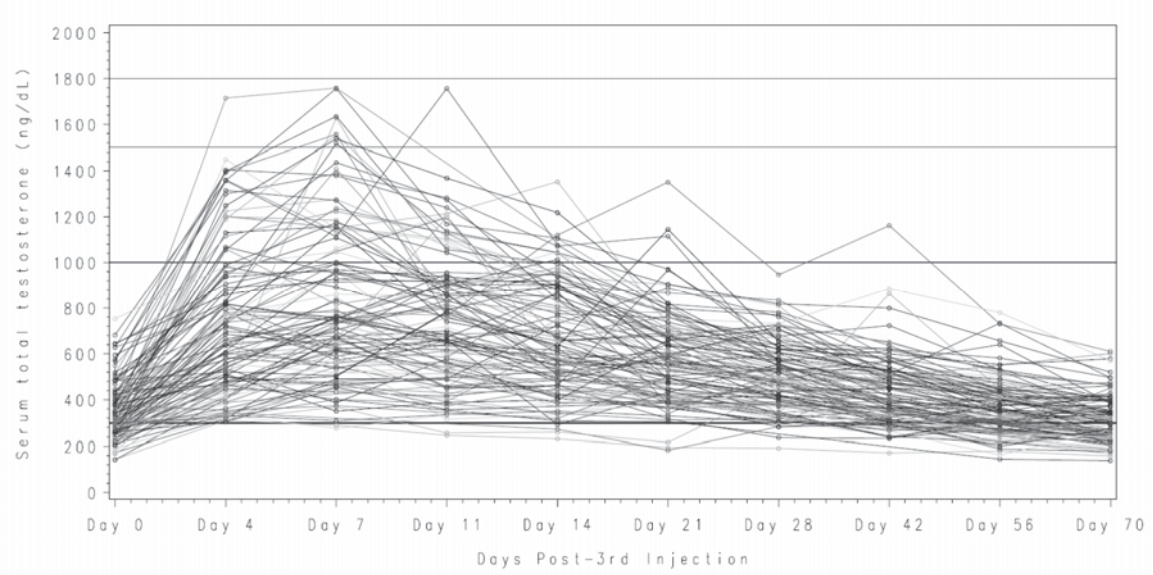


Figure 4: Composite of individual serum total T concentration following the 3rd injection of the TU 750 mg LOADING regimen – PK population, Study IP157-001 Part C



The primary efficacy endpoint in this study was the percentage of responders defined as C_{avg} within the normal range (300 – 1000 ng/dL). To meet the primary efficacy criterion, the point estimate for the pre-determined primary endpoint was set as at least 75% and the lower bound of the two-sided 95% confidence interval was set as not lower than 65%.

Ninety-four percent of patients (110 of 117) had serum total T C_{avg} within the 300 – 1000 ng/dL range. The 95% confidence interval around this point estimate was 89.6 - 98.5. Of the 7 patients who did not meet this criterion, 6 failed due to $C_{average}$ below 300ng/dL and one failed due to a $C_{average}$ above 1000ng/dL.

Therefore, the data from Part C show that the primary efficacy objective was achieved.

7.4.1.2 Secondary Efficacy Analysis

C_{max} was an important secondary efficacy endpoint in Part C. To meet the C_{max} efficacy criterion, the criteria shown in *Table 4* were pre-defined:

Table 4: Decision criteria for Cmax

Criteria for Serum Total Testosterone Maximum Concentration Observed	Criteria for Success	Not Meeting the Criteria for Success
≤ 1500 ng/dL	≥ 85% of Patients	< 85% of Patients
1800 - < 2500 ng/dL	≤ 5% of Patients	> 5% of Patients
≥ 2500 ng/dL	No Patients	At least 1 patient
All 3 criteria must be met in order to reject the null hypothesis in favor of the alternative hypothesis. If at least one of the 3 criteria is not met, the null hypothesis cannot be rejected. The time point for assessment of this secondary outcome is the post-3rd injection period (Weeks 14 - 24).		

Based upon pre-defined eligibility criteria, the Sponsor excluded from the PK analysis those patients who weighed less than 65kg. One patient (a protocol violation) fell into this category in Part C (Patient 031-7021). This patient did experience a serum testosterone concentration above 2500 ng/dL during the 3rd injection interval. Otherwise, only nine of the 117 patients (7.7%) had C_{max} > 1500 ng/dL and no patient had $C_{max} \geq$ 1800 ng/dL.

In summary, the data show that the C_{max} efficacy objective was achieved in Part C in men weighing more than 65 kg.

In addition to the increase in serum total T concentration, the serum concentrations of free T and known downstream metabolites, dihydrotestosterone and estradiol, were also increased. The increases in serum DHT and E_2 were expected. Average DHT concentrations tended to remain within the lower end of the normal range, while average E_2 concentrations tended to remain in the middle of the normal range. TU administration did not affect concentrations of sex hormone binding globulin (SHBG). With SHBG and albumin concentrations unchanged, the increase in free T concentration was also expected. The concentration versus time profiles for free T, DHT and E_2 generally paralleled the T concentration-time profile. DHT:T and E_2:T ratios were unchanged. The reader is referred to the original and subsequent medical officer's primary reviews and to the Clinical Pharmacology reviews for additional details, tables and figures for these variables.

In regard to other secondary endpoints:

- Average values of hemoglobin and hematocrit increased slightly from pre-treatment, as average T concentrations increased. The average increases in these markers of erythropoiesis were small and average values remained within the normal range.

- The improvement seen in "treatment satisfaction" appeared to correlate with higher T concentrations in some patients. Overall, 92% of patients expressed satisfaction with treatment.
- At Day 21 of the 3rd injection interval, > 80% of patients demonstrated improvements in each item of the M-PGA questionnaire.
- Changes in T concentrations were weakly inversely correlated with changes from baseline in body mass index (BMI) and weight. However, there were no notable changes in other body composition measures.

Statistician's Conclusion

In his final review of the original submission dated June 24, 2008, the Biometrics Team Leader (Mahboob Sobhan) had the following conclusion:

> "*The results support the efficacy of Nebido TU 750 mg LOADING in the treatment of hypogonadism in adult male as indicated by the attainment of steady state by the 3rd injection. The intensive sampling for PK outcomes (Cavg and Cmax) also met FDA threshold for approvability and, therefore, can be extrapolated to represent PK outcomes under extended dosing beyond 3 injections."*

In his final memo for the first Complete Response submission, dated July 21, 2009, Dr. Sobhan had the following comment:

> "*In our earlier statistical review, we concluded that testosterone undecanoate (TU) was efficacious in treating hypogonadism in adult males. There were no new efficacy data submitted for our review to further substantiate or change the efficacy data in the label. We have reviewed the new label and from a statistical perspective, our conclusions remain unchanged.*"

There were no new statistical analyses conducted as part of the review of this second CR.

7.4.2 Overall Assessment of Efficacy

The TU 750mg Loading regimen was found to provide adequate replacement of testosterone in hypogonadal men weighing >65kg (as measured by testosterone $C_{average}$), while not providing excessive testosterone (as measured by testosterone $C_{maximum}$). The dosing regimen demonstrated a C_{avg} within the normal range and a C_{max} profile that did not exceed the approvability thresholds provided. Thus, the primary efficacy objectives of the Phase 3 study were met.

8. Safety

8.1 SAFETY FINDINGS

Contents and Safety Findings From the Original NDA

The original NDA submission contained safety data from the following 6 studies:

1) The single U.S. pivotal Phase 3 study IP157-001, including Parts A, B and C.
    a. Part A included a total of **237** adult male subjects, enrolled in two dose arms: 750mg every 12 weeks (*n=120*) and 1000mg every 12 weeks (*n=117*)

    b. Part B included a total of **134** adult male subjects in two treatment groups: *112 patients* received an initial injection of TU 1000 mg, followed 8 weeks later by a loading injection of 1000 mg and then 1000 mg every 12 weeks thereafter, while *22 patients* received an initial injection of 1000 mg, followed 8 weeks later by a loading injection of 750 mg and then 750 mg every 10 weeks thereafter.

    c. Part C included a total of **117** adult male subjects enrolled in the 750mg Loading regimen. The Sponsor also submitted safety data on another **36** adult male subjects taking the 750 Loading regimen in a longer-term extension study (referred to as Part C2)

2) Five, older, European, dose-finding trials comprising a total of **185** adult male subjects (Studies JPH01495, JPH04995, ME98096, ME97029 and 306605).

When combined, a total of **709 adult male hypogonadal subjects** contributed safety data from controlled studies to the original NDA.

The original NDA also contained six (6) Bayer/Schering Periodic Safety Update Reports (PSURs) from approximately 3.5 years of worldwide postmarketing use (specifically November 25, 2003 through June 30, 2007). Bayer-Schering is the Sponsor of TU outside the US. The 120-Day Safety Update to the original NDA contained a postmarketing safety update report from Endo for the time period June 30, 2007 to October 12, 2007. Finally, the original NDA included a Summary Report entitled, "Immediate Post-Injection Reactions Suspect of Pulmonary Oil Microembolism" (report dated February 12, 2008).

In the opinion of the Clinical review team, the clinical trial safety data was consistent with an injectable androgen, except for the occurrence of immediate post-injection reactions in 2 patients. These 2 events were described as sudden and severe urge to cough, cough, and dyspnea immediately following injection. The PSURs and Summary Report of Post-Injection Reactions raised concerns related to immediate post-injection respiratory and allergic-type adverse events. While there had been only 2 such events reported in 2 patients in clinical trials, the PSURs and Summary Report of Post-Injection Reactions included 66 postmarketing cases. The 66 postmarketing cases were marked by cough, shortness of breath, throat-related symptoms (throat tickle, throat tightness, throat fullness, etc), flushing, allergic phenomenon (such as rash, pruritis, itching), tachycardia, palpitations, BP changes, and constitutional symptoms, such as headache, malaise, shivering, sweating, weakness and nausea.

Based largely on the occurrence of these post-injection reactions, the Division issued an Approvable letter for the original NDA.

Contents and Safety Findings from the First Complete Response

In the first Complete Response, the Sponsor provided safety data from an additional 11 studies; 7 completed and 4 ongoing. The data was submitted as a new Summary Report, entitled, "*Incidence of Injection-Based Pulmonary Oil Reactions and Allergic Reactions from Clinical Studies of TU*" (report dated February 12, 2009). Final or interim study reports were also provided for each of the 11 new studies. These 11 new studies comprised **a total of 2,125 additional subjects**. These studies were:

- AWB0105, Germany, 4 doses, n=870
- NE0601 (IPASS), 18 countries, 4 doses, n=763
- TG09, Germany (obesity), 4 doses, n=29
- NB02, Germany (paraplegia), 2 doses, n=19
- Czech NEO, Czechoslovakia, 4 doses, n=23
- 303934, Finland (andropause), 1 dose, n=15
- 97028, Germany, 4 doses, n=28
- 97173, Italy, 1 dose, n=24
- 99015, Germany, 4 doses, n=42
- 98016, Germany, 4 doses, n=14
- 42306, 6 countries, 4 doses, n=298

Therefore, for the first Complete Response, the overall clinical trial safety database was **2,834 subjects** in 17 trials.

The Sponsor also submitted two additional postmarketing safety updates (Bayer/Schering PSUR 7 and PSUR 8) in the first Complete Response, bringing the total duration of postmarketing experience to approximately 5.5 years:

- A Bayer/Schering PSUR for the time period November 25, 2007 through November 24, 2008
- A Final Safety Update from Endo for the time period November 25, 2008 – August 29, 2009

To briefly summarize the Safety findings from the first Complete Response:

1) In regard to the incidence of post-injection reactions in clinical trials, the Original NDA contained 2 such cases. The two Original NDA clinical trial cases were:
   - Patient #184 in Study 306605. A 54 year old male received his 10th injection of testosterone undecanoate on 3 April 2006 and shortly (1 minute) after the injection, he "experienced urge to cough associated with respiratory distress". Both symptoms lasted approximately 14-15 minutes. The event resolved without intervention and the subject continued in the study.

   - Patient #050-7006 in Study IP157-001 Part C). A 53 year old white male received his 3rd injection on 12 July 2007 and experienced a "mild and not serious coughing fit lasting 10 minutes following the injection." The narrative describes the patient's cough as not productive, without wheezing and without difficulty breathing. No intervention was given and the patient continued on-treatment without subsequent coughing event.

   In the first Complete Response, the Sponsor detected no additional cases in a total of 2125 subjects. The Sponsor therefore counted 1 serious POME case and no systemic allergic

reactions in the numerator. The denominator was totaled as 2,834 subjects. The Sponsor thereby proposed an incidence of 1 serious POME in 2834 subjects, or 3.53 serious events per 10,000 subjects, or 0.035%. For systemic allergic reactions, the Sponsor proposed an incidence of 0% in clinical trials.

The Clinical review team detected 6 additional cases of interest from clinical trials. However, information from these cases was too sparse to ascribe a specific etiology to the events, but nevertheless, they were all severe, immediate post-injection reactions. The Clinical review team believes that the former 3 events have a greater chance of being serious POME or systemic allergic reactions compared to the latter 3, but all 6 are notable. The former 3 cases are:

- Patient #11 in Study 97173 (convulsions)
- Patient #17 in Study 97173 (collapse),
- Patient #4 in Study JPH04995 (circulatory collapse)

If just these 3 cases were added to the numerator, this would result in an incidence of immediate post-injection reactions in clinical trials of 4 events in 2834 subjects (0.14%).

The latter three cases are:

- Patient #025-4187 in Study IP157-001 Part A (pre-syncope)
- Patient #26 in Study 97029 (syncope)
- Patient #35 in Study 97029 (circulatory collapse).

At the time of the first Complete Response, and again at this time, the Clinical review team believes that whether the clinical trials show 1, 2, 5 or 8 incident cases is not as critical as the overall picture, especially coupled with the findings from postmarketing reports, which show the occurrence of severe and life-threatening immediate post-injection reactions.

2) In regard to the postmarketing Safety Updates submitted in the first Complete Response, the Clinical review detected 52 new cases of immediate post-injection reactions. Of these 52 cases, almost all were severe, and approximately 20 appeared to reflect anaphylaxis. The Clinical review team also expressed concern related to a case of full-blown, post-injection anaphylaxis in a 16 year old male.

Based on the totality of the safety data in the first Complete Response, especially in light of the occurrence of severe immediate post-injection reactions in the post-marketing period outside the United States, the Division issued a Complete Response action.

Contents and Brief Safety Findings from the Current (Second) Complete Response

In this second Complete Response, the Sponsor provided safety data from one additional study, bringing the total to 18 clinical studies. These included: IP157-001 (All Parts), JPH01495, JPH04995, ME98096, ME97029, 306605, 303934, 97028, 97173, 98016, 99015, 42306, 39732 (NEO601 IPASS) AWB0105, Czech NEO, NB02, TG09, and 14853. The total number of clinical trial subjects included in the pool for analysis of adverse events of interest (POME and anaphylaxis) from this compilation of clinical trials was 3,556 subjects.

In addition to this clinical trial experience, the second CR included the results of a detailed and extensive search of the Bayer/Schering postmarketing safety databases for cases of POME and anaphylaxis for testosterone undecanoate injection. According to the Sponsor's analysis by Endo Pharmaceuticals internal assessors, this search identified a total of 307 post-injection reaction cases, including 228 cases of POME and 79 cases of anaphylaxis. A subsequent second analysis by "independent adjudicators" contracted by Endo Pharmaceuticals to conduct a similar assessment identified a total of 268 post-injection reaction cases, including 223 cases of POME and 45 cases of anaphylaxis. Consistent with FDA's request, individual CIOMS reports were included in the second CR submission for all postmarketing adverse events of interest.

The Sponsor also submitted three additional postmarketing safety updates (including Bayer/Schering PSUR 9 and PSUR 10 and a postmarketing update from Endo) in this second Complete Response, bringing the total duration of postmarketing experience to approximately 8.5 years:

- A Bayer/Schering PSUR for the time period November 25, 2009 through November 24, 2010
- A Bayer/Schering PSUR for the time period November 25, 2010 through November 24, 2011.
- A PSUR Addendum Report for the time period November 25, 2011 through April 30, 2012.

The routine safety data presented in the next two sections (Section 8.1.1 [Deaths, Serious Adverse Events and Discontinuations due to Adverse Events] and Section 8.1.2 [Other Adverse Events, including Overall Adverse Events and Adverse Events of Interest]) come from the pivotal U.S. trial IP157-001 Parts C and A. The postmarketing safety data from outside the U.S. is presented in Section 8.1.3 (Postmarketing Safety Findings). The two sets of data are considered together in the final safety section of this memo (Section 8.1.4).

8.1.1 Deaths and Serious Adverse Events

Deaths, Serious Adverse Events, and Discontinuations due to AEs in Study IP157-001 Part C

No subject died during Study IP157 Part C. Eight (6.2%) subjects experienced at least one SAE during the treatment period in Part C. No single SAE was reported in more than 1 subject. The eight SAE terms reported were: ischemic colitis, faecaloma, intervertebral disc protusion, wrist fracture, worsening spinal column stenosis, myocardial infarction, deep vein thrombosis (DVT), and urinary tract infection/prostatitis. Only one of these was judged by the investigator to be at least possibly related to treatment (Patient 018-7078, DVT, possibly related).

One additional patient who participated in Part C had an SAE of prostate cancer reported on Day 196 of treatment (during Part C2, the long-term safety extension of Part C). The investigator's judged this adverse event as "probably related" to treatment.

Study medication was permanently discontinued due to adverse events in five patients (3.8%) in Part C, for the following reasons: acne, mood swings, myocardial infarction, increased estradiol and DVT. There was no single event resulting in discontinuation that was reported in more than one subject during this study. Of these adverse events leading to discontinuation, all but myocardial infarction were judged by the investigator to be at least possibly related to study drug.

There was one patient in Part C who experienced an immediate post-injection reaction. Patient 050-7006, a 53 year old white male experienced a mild and non-serious "coughing fit" lasting approximately 10 minutes after his 3rd injection. The investigator reported that the patient's cough was non-productive, without wheezing and without difficulty breathing. No intervention was given and the patient recovered completely prior to leaving the office. That patient continued on-treatment without further cough events.

Deaths, Serious Adverse Events and Discontinuations due to AEs in Study IP157-001 Part A

There was 1 death reported in the Part A study. The cause of this patient's death was a homicide (by stabbing).

Eight (6.7%) subjects in the 750 mg group and ten (8.5%) subjects in the 1000 group experienced at least one SAE during the treatment period. Only two types of SAE were observed in more than 1 subject: atrial fibrillation in 2 subjects in the 750 mg group, and knee arthroplasty in 2 subjects in the 1000 mg group. No serious adverse events (SAEs) were judged by the investigator as being at least possibly related to study drug.

The SAE terms reported for the 750mg group were: atrial fibrillation [n=2], injury (stabbing), spinal stenosis, benign parathyroid tumor, congestive heart failure, tinnitus, acute pancreatitis, and sepsis. The SAE terms for the 1000mg group were: knee arthroplasty [n=2], spinal stenosis, arthritis, coronary artery disease, enterococcal bacteremia, malignant hepatic neoplasm, renal artery stenosis, viral gastroenteritis, prostatitis, cerebrovascular accident, and tendon rupture.

Study medication was permanently discontinued due to adverse events in 6 (5.0 %) patients in the 750 mg group and 4 (3.4 %) patients in the 1000 mg group. AEs judged by the investigator to be at least possibly related to study drug and leading to discontinuation were:

- Subject 027-4101 (TU 750 mg arm) - increased serum PSA.
- Subject 056-4077 (TU 1000 mg arm) - increased serum estradiol.
- Subject 040-4116 (TU 1000 mg arm) - increased red blood cell count.

The complete list of AE terms for the discontinuations reported for the 750mg group were: heat exhaustion, back pain, pain in extremity, PSA increased, prostatic intraepithelial neoplasia (PIN), and injury. The AE terms for the discontinuations for the 1000mg group were: estradiol

increased, red blood cell count increased, hepatic neoplasm malignant, nasal congestion, and skin ulcer.

8.1.2 Other Adverse Events

Overall Adverse Events

Overall Adverse Events in Adverse Events in Study IP157-001 Part C

In Part C, the most commonly reported adverse events, regardless of the investigator's judgment on relationship to treatment, were: acne, fatigue, cough, injection site pain, nasopharyngitis, pharyngolaryngeal pain, arthralgia, insomnia, prostatitis and sinusitis. The incidence rates are provided in Table 5 below.

A total of 7 (5.4%) patients experienced at least one severe adverse event. No event was reported as severe by more than 1 patient. The complete list of severe AE terms were: DVT, aortic aneurysm, faecaloma, urinary tract infection/prostatitis, intervertebral disc protrusion, spinal stenosis, aortic aneurysm repair, and surgery.

Table 5. Incidence of All Adverse Events Regardless of Relationship to Study Medication, Reported in at Least 2.0% of Patients in Decreasing Frequency in study IP157-001 Part C

	Number of patients (%)
MedDRA Preferred term	TU 750 mg LOADING (N=130)
Total patients with at least 1 TEAE	70 (53.8)
Acne	6 (4.6)
Fatigue	6 (4.6)
Cough	4 (3.1)
Injection Site Pain	4 (3.1)
Nasopharyngitis	4 (3.1)
Pharyngolaryngeal Pain	4 (3.1)
Arthralgia	3 (2.3)
Insomnia	3 (2.3)
Prostatitis	3 (2.3)
Sinusitis	3 (2.3)

In Part C, approximately 24% of patient experienced at least 1 adverse event *judged by the investigator to be at least possibly related to treatment*. These events were generally consistent with the known adverse reactions to testosterone replacement therapy and events commonly reported in a testosterone replacement therapy population.

The incidences of adverse events reported in Part C, without regard to attributed causality, included: acne (4.6%), fatigue (3.1%), injection site pain (3.1%), irritability (1.5%), hyperhidrosis (1.5%), hemoglobin increased (1.5%), estradiol increased (1.5%), insomnia

(1.5%), mood swings (1.5%), aggression (1.5%), PSA increased (1.5%) and disturbance in attention (1.5%).

Overall Adverse Events in Adverse Events in Study IP157-001 Part A

In Part A, for the 750mg dose, the most commonly reported adverse events (≥ 2%), regardless of the investigator's judgment on relationship to treatment, were: fatigue, bronchitis, upper respiratory tract infection, nasopharyngitis, back pain, PSA increased, urinary tract infection, weight increased, hypertension, sinusitis, insomnia, nausea, and hypercholesterolemia.

In Part A, for the 1000mg dose, the most commonly reported adverse events (≥ 2%), regardless of the investigator's judgment on relationship to treatment, were: upper respiratory tract infection, diarrhea, pain in extremity, nasopharyngitis, hypertension, sinusitis, insomnia, headache, depression, weight increased, procedural pain, arthralgia, musculoskeletal pain, urinary tract infection, rash, pain, foot fracture, muscle strain, anxiety, nasal congestion, abdominal pain, constipation, vomiting, gout, benign prostatic hyperplasia, and cough.

The incidence rates for these AEs in Part A are provided in Table 6 below.

The majority of adverse events in Part A were judged by the investigator as mild or moderate in severity. Severe AEs were reported in 8.3% of 750 mg subjects and in 7.0% of 1000 mg patients. Atrial fibrillation was reported as a severe AE in 2 subjects in the TU 750 mg group; no other single event was reported as severe in more than 1 subject per treatment group. The other severe adverse events (regardless of investigator-attributed causality) were: cardiac failure, coronary artery disease, chest discomfort, irritability, sudden hearing loss, and PSA increased.

In Part A, approximately 20% of patients in each treatment group experienced at least 1 adverse event *judged by the investigator to be at least possibly related to treatment*. These drug-related adverse events included:

> For the 750mg group: PSA increased (3.3%), insomnia (2.5%), fatigue (2.5%), injection site pain (1.7%), libido decreased (1.7%), hypercholesterolemia (1.7%), and benign prostatic hyperplasia (0.8%).
>
> For the 1000mg group: injection site pain (1.7%), benign prostatic hyperplasia (1.7%), blood cholesterol increases (1.7%), estradiol increased (1.7%), fatigue (0.9%), and insomnia (0.9%).

Table 6. Incidence of All Adverse Events Regardless of Relationship to Study Medication, Reported in at Least 2.0% of Patients in Either Treatment Group, by Preferred Term, in Decreasing Frequency in TU 1000 mg arm, from study IP157-001 Part A

MedDRA Preferred term	Number of patients (%)	
	TU 750 (N=120)	TU 1000 (N=117)
Total patients with at least 1 TEAE	70 (58.3)	73 (62.4)
Upper respiratory tract infection	5 (4.2)	5 (4.3)
Diarrhoea	2 (1.7)	5 (4.3)
Pain in extremity	2 (1.7)	4 (3.4)
Nasopharyngitis	5 (4.2)	4 (3.4)
Hypertension	3 (2.5)	4 (3.4)
Sinusitis	3 (2.5)	4 (3.4)
Insomnia	3 (2.5)	4 (3.4)
Headache	2 (1.7)	4 (3.4)
Depression	2 (1.7)	4 (3.4)
Weight increased	3 (2.5)	4 (3.4)
Procedural pain	0 (0.0)	3 (2.6)
Arthralgia	2 (1.7)	3 (2.6)
Musculoskeletal pain	1 (0.8)	3 (2.6)
Urinary tract infection	3 (2.5)	3 (2.6)
Rash	1 (0.8)	3 (2.6)
Pain	0 (0.0)	3 (2.6)
Foot fracture	0 (0.0)	3 (2.6)
Muscle strain	0 (0.0)	3 (2.6)
Anxiety	0 (0.0)	3 (2.6)
Nasal congestion	0 (0.0)	3 (2.6)
Abdominal pain	0 (0.0)	3 (2.6)
Constipation	0 (0.0)	3 (2.6)
Vomiting	1 (0.8)	3 (2.6)
Gout	0 (0.0)	3 (2.6)
Benign prostatic hyperplasia	2 (1.7)	3 (2.6)
Cough	1 (0.8)	3 (2.6)
Fatigue	7 (5.8)	2 (1.7)
Bronchitis	5 (4.2)	2 (1.7)
Back pain	4 (3.3)	2 (1.7)
Nausea	3 (2.5)	2 (1.7)
Prostatic specific antigen increased	4 (3.3)	1 (0.9)
Hypercholesterolaemia	3 (2.5)	1 (0.9)

Laboratory and vital signs data are discussed in the medical officer's reviews of the original NDA, and these data did not provide any signal of concern.

Adverse Events of Interest

"Adverse events of interest" in Part C included events related to endocrine disorders, injection site reactions, adverse lipid profiles, erythropoiesis, aggression or depression, urinary symptoms, prostate health, liver abnormalities, sleep apnea syndrome, cerebrovascular events and skin events. Such adverse events were reported in 28 subjects in Part C (21.5%) as shown in *Table 7* below.

Table 7. Adverse Events of Interest in Study IP157-001 Part C

Event Class	MedDRA System Organ Class	MedDRA Preferred term	Number of patients (%)
			TU 750 mg LOADING (N=130)
Total Patients With At Least One TEAE of Interest			28 (21.5)
Tolerability of Injection	General disorders and administration site conditions	Injection site irritation	2 (1.5)
		Injection site pain	4 (3.1)
		Injection site rash	2 (1.5)
Adverse Lipid Profiles	Investigations	Blood triglycerides increased	1 (0.8)
	Metabolism and Nutritional disorders	Hyperlipidemia	1 (0.8)
Erythropoiesis	Investigations	Haematocrit increased	1 (0.8)
		Haemoglobin increased	2 (1.5)
		Estradiol increased	2 (1.5)
Aggression or depression	Psychiatric disorders	Mood swings	2 (1.5)
		Aggression	2 (1.5)
Urinary Symptoms	Renal and urinary disorders	Urine flow decreased	1 (0.8)
		Nocturia	1 (0.8)
Prostate health	Investigations	Prostatic specific antigen increased	2 (1.5)
		Prostate examination abnormal	1 (0.8)
	Reproductive system and breast disorders	Prostatic intraepithelial neoplasia	1 (0.8)
		Prostatitis	3 (2.3)
		Paraesthesia of genital male	1 (0.8)
Skin	Skin and subcutaneous tissue disorders	Acne	6 (4.6)

"Adverse events of interest" in Part A were reported in 24 subjects treated with 750 mg (20%) and 30 subjects treated with 1000 mg (26%), as shown in *Table 8* below.

Table 8. Adverse Events of Interest in Study IP157-001 Part A

Event Class	MedDRA System Organ Class	MedDRA Preferred term	Number of patients (%)	
			TU 750 (N=120)	TU 1000 (N=117)
Total Patients With At Least One TEAE of Interest			**24 (20.0)**	**30 (25.6)**
Endocrine Disorder	Investigations	Oestradiol increased	0 (0.0)	2 (1.7)
		Glycosylated haemoglobin increased	0 (0.0)	1 (0.9)
	Metabolism and nutrition disorders	Diabetes mellitus	1 (0.8)	1 (0.9)
Tolerability of Injection	General disorders and administration site conditions	Injection site erythema	0 (0.0)	1 (0.9)
		Injection site irritation	0 (0.0)	1 (0.9)
		Injection site pruritus	1 (0.8)	1 (0.9)
		Injection site pain	2 (1.7)	2 (1.7)
		Injection site reaction	0 (0.0)	1 (0.9)
Adverse Lipid Profiles	Investigations	Blood triglycerides increased	1 (0.8)	2 (1.7)
		Blood triglycerides abnormal	0 (0.0)	1 (0.9)
		Blood cholesterol increased	0 (0.0)	2 (1.7)
		High density lipoprotein decreased	1 (0.8)	0 (0.0)
	Metabolism and Nutritional disorders	Hypercholesterolaemia	3 (2.5)	1 (0.9)
		Hyperlipidemia	1 (0.8)	1 (0.9)
Erythropoiesis	Investigations	Haematocrit increased	0 (0.0)	1 (0.9)
		Haemoglobin increased	0 (0.0)	1 (0.9)
		Red blood cell count increased	0 (0.0)	1 (0.9)
	Blood and lymphatic system disorders	Polycythaemia	1 (0.8)	1 (0.9)
Aggression or depression	Psychiatric disorders	Depression	2 (1.7)	4 (3.4)
Urinary Symptoms	Renal and urinary disorders	Pollakiuria	0 (0.0)	2 (1.7)
		Urinary hesitation	0 (0.0)	1 (0.9)
		Urinary retention	1 (0.8)	2 (1.7)
		Urine flow decreased	1 (0.8)	2 (1.7)
		Nocturia	0 (0.0)	1 (0.9)
		Dysuria	1 (0.8)	2 (1.7)
	Infections and infestations	Urinary tract infection	3 (2.5)	3 (2.6)
Prostate health	Investigations	Prostatic specific antigen increased	4 (3.3)	1 (0.9)
		Prostate examination abnormal	2 (1.7)	1 (0.9)
	Reproductive system and breast disorders	Benign prostatic hyperplasia	2 (1.7)	3 (2.6)
		Prostatic intraepithelial neoplasia	1 (0.8)	2 (1.7)
		Prostatitis	0 (0.0)	2 (1.7)
		Prostatic disorder	1 (0.8)	0 (0.0)
Liver Abnormalities	Neoplasms benign, malignant and unspecified	Hepatic neoplasm malignant	0 (0.0)	1 (0.9)
	Investigations	Aspartate aminotransferase increased	1 (0.8)	0 (0.0)
Cerebrovascular events	Nervous system disorders	Cerebrovascular accident	0 (0.0)	1 (0.9)

8.1.3 Postmarketing Safety Findings

As demonstrated in Section 8.1.1 and 8.1.2 of this memo, in the U.S. Phase 3 study IP157-001, intramuscular testosterone undecanoate was associated with the expected adverse events and laboratory changes for a testosterone replacement agent except for 1 report of an immediate, post-injection reaction. This occurred in Patient 050-7006, a 53 year old white male, who experienced a mild and non-serious "coughing fit" lasting approximately 10 minutes after his 3rd injection.

In a different clinical study (306605) conducted outside the US, another case of post-injection reaction was reported. This was Patient #184, a 54 year old male who experienced urge to cough associated with respiratory distress at 1 minute after his 10th injection. Both symptoms lasted approximately 14-15 minutes.

Additional information on post-injection reactions is available from the worldwide postmarketing experience (including postmarketing clinical trials and postmarketing voluntary reporting) and we believe that this postmarketing information is crucial to understanding the safety of testosterone undecanoate injection.

8.1.3.1 Post-Injection Reactions in Controlled Trials

As previously noted, the Sponsor submitted safety results from 12 postmarketing clinical studies conducted outside the U.S. When these safety results were pooled with the safety results from the U.S. Study IP157-001, along with the 5 European Hypogonadism studies, the total number of trials and clinical trial subjects available for analysis was 18 trials and 3,556 subjects, respectively.

As part of the review of the March 2009, Complete Response, the Clinical review team assessed all of these studies, except for Study 14853, which was submitted as part of the current CR, was prematurely terminated, and enrolled just 3 subjects.

First, the Clinical Review team made efforts to determine whether the studies had pre-defined protocols, pre-defined procedures for capturing adverse events, and valid safety results. We then investigated the safety results themselves to determine whether any immediate post-injection reactions had been reported. The reader is referred to Dr. Handelsman's medical officer's review for brief summary reviews for each of the 11 studies submitted in the March 2009, Complete Response. Some of these studies were conducted as postmarketing European surveillance studies in hypogonadal men, whereas others were conducted for different indications, including male contraception, treatment of obesity, treatment of paraplegia, and treatment of "andropause". The two largest studies were:

1) Study AWB 0105 Androgen Deficiency – Postmarketing Surveillance, Germany, n=869, and
2) Study 39732 (NE0601 IPASS) Hypogonadism – Postmarketing Surveillance, 18 countries, n=1411.

Dr. Handelsman's review concluded that the submitted studies were of generally acceptable quality for our purpose. The studies showed the expected adverse reactions for an androgen replacement product (e.g., increased serum PSA, worsening BPH, weight gain, edema, change in lipid profiles, acne, breast pain, sweating, depression, etc) and expected adverse reactions for an injection (e.g., injection site reactions). As part of the first CR, the Sponsor concluded that there was just one case of serious POME reactions among 2,834 clinical trial subjects, for an incidence of 0.035%. The Sponsor also concluded that there were no anaphylactic reactions, for an incidence of 0% in clinical trials.

At the time of the first CR, the Clinical review team did not agree with the Sponsor's conclusion about the results from the clinical studies in regard to post-injection reactions. We identified 6 additional cases of interest from clinical trials. However, information from these 6 cases was too sparse to ascribe a specific etiology to each event. Nonetheless, they were all post-injection reactions with concerning associated systemic symptomatology. The Clinical review team believes that the former 3 events have a greater chance of being serious POME or anaphylaxis compared to the latter 3, but all 6 are notable. The former 3 cases are:

- Patient #11 in Study 97173 (convulsions)
- Patient #17 in Study 97173 (collapse),
- Patient #4 in Study JPH04995 (circulatory collapse)

If just these 3 cases were added to the numerator, this would have changed the incidence of immediate post-injection reactions in clinical trials from 1 in 2834 subjects (0.035%) to 4 in 2834 subjects (0.14%).

The latter three cases are:

- Patient #025-4187 in Study IP157-001 Part A (pre-syncope)
- Patient #26 in Study 97029 (syncope)
- Patient #35 in Study 97029 (circulatory collapse).

For the review of the current submission (the second CR), Dr. Cynthia Kornegay, an epidemiologist in the Division of Epidemiology (DEPI) in the Office of Surveillance and Epidemiology (OSE) analyzed the incidence of post-injection reactions in the 18 clinical trials among the 3,556 total clinical trial subjects. She derived the data for her analysis form the Clinical Overview and Clinical Summary of Safety in the current CR. In her final review, dated March 28, 2013, Dr. Kornegay and colleagues provided the following relevant information:

1. There was one (1) POME case among the 467 men who received 750 mg TU, and eight (8) POME cases among the 3089 men who received 1000 mg TU. By dose group, this translates to 3.2 and 4.7 POME cases per 10,000 injections, respectively. For both doses combined, the incidence rate for POME is 4.5 cases per 10,000 injections, or 21.3 cases per 10,000 person-years.

2. The rates of POME in two, large, published, postmarketing studies of TU (Zitzmann et al, J Sex Med, 2013 and Gu et al, J Clin Endocrinol Metab, 2009) were similar to the rates shown in the Clinical Summary of Safety. The rates of POME shown in the Zitzman et al and the Gu et al reports were 4.8 and 5.1 POME cases per 10,000 injections, respectively

3. There were no reports of anaphylaxis among 467 men who received 750 mg TU. There were two (2) cases of anaphylaxis among 3089 men in the 1000 mg dose group, for a rate of 1.2 cases per 10,000 injections. For both doses combined, the incidence rate for anaphylaxis is 0.9 cases per 10,000 injections, or 4.7 cases per 10,000 person-years.

4. DEPI points out that published drug-related anaphylaxis rates range from 0.8 cases per 10,000 person-years to 5 cases per 10,000 person-years.

8.1.3.2 Post-Injection Reactions from Voluntary Reports

In our opinion, the number and incidence of cases of post-injection reaction (POME and anaphylaxis) in clinical trials is only one piece of information that may be gleaned from the postmarketing experience. Another part of the overall safety picture is spontaneously reported adverse events from the postmarketing period.

In collaboration with the Sponsor (Endo), as well as with our colleagues Drs Stacy Chin and Tony Durmowicz from the Division of Pulmonary, Allergy and Rheumatology Products (DPARP), we carefully evaluated all postmarketing safety updates and all potential cases of POME and anaphylaxis submitted to Endo from the entire worldwide postmarketing experience.

From our review, we identified a total of 137 cases of severe post-injection reactions, including cases of severe POME and anaphylaxis. All 137 of these reactions were reported as severe and/or potentially life-threatening, with some cases requiring hospitalization or emergency department visit and some being treated as for anaphylaxis. The occurrence of a severe post-injection reaction is sporadic and unpredictable. These reactions have occurred after the first dose, or after 4 years of otherwise trouble-free dosing. The majority of severe post-injection reactions occur either during an injection, or immediately thereafter. The clinical manifestations of the post-injection reactions have included: cough, shortness of breath, throat-related symptoms (throat tickle, throat tightness, throat fullness, etc), flushing, various allergic-type signs and symptoms (rash, pruritis, itching), tachycardia, palpitations, blood pressure changes, and general constitutional symptoms, including headache, malaise, shivering, sweating, weakness and nausea. In some cases, syncope, cyanosis, apnea and cardiovascular collapse have been reported. The spectrum of signs and symptoms of severe POME and anaphylaxis frequently overlap, making a precise diagnosis difficult in some individual cases. Even if the mechanism for these severe post-injection reactions has not been clearly elucidated, two of the excipients, benzyl benzoate, and castor oil, are known allergens, and castor oil itself is the likely etiology for the severe POME reactions.

In his final primary medical officer's review dated May 20, 2013, Dr. Guodong Fang, provided narratives for each of 137 severe post-injection reactions that were identified. The reader is referred to Dr. Fang's review for details on each case. Dr. Fang also provided commentary on some highlighted cases.

In their final consultative review, Drs. Chin and Durmowicz provided an assessment of anaphylaxis and POME among the potential POME and anaphylaxis cases. DPARP identified a total of 47 cases of anaphylaxis. DPARP also identified a total of 170-191 cases of POME, of which, a total of 55-76 met pre-defined criteria as being "severe". The DPARP memo provides a description of how cases were adjudicated as severe. DAPRP also provides case

examples for POME and anaphylaxis, as well as potential pathophysiologic mechanisms for these events.

The remainder of this section will highlight the most relevant clinical safety issues from Dr. Fang's primary medical officer review and from the DPARP consult, as it pertains to severe post-injection reactions from voluntary postmarketing adverse event reports.

1. FDA reviewed all potential postmarketing cases of POME and anaphylaxis that were included in the current resubmission. FDA elected to focus on the severe cases from the series. With this objective in mind, FDA pre-determined the following criteria to define a "case" of severe post-injection reaction to testosterone undecanoate:
   - Occurred within 24 hours of injection and met any of the following criteria:
     - Any case identified by either FDA or Sponsor as an anaphylactic reaction as a consequence of the reporter using the term "anaphylaxis" or "anaphylactic reaction"
     - Any case identified by either FDA or the Sponsor as an anaphylactic reaction by meeting the formal Sampson's criteria
     - Any case identified as a serious adverse event (SAE), based upon the FDA standard definition of an SAE
     - Any case requiring treatment
     - Any case labeled as "Serious" or "Medically Important" by the reporter or by the Sponsor
     - Any case that FDA believed to be medically significant
     - Any case involving syncope or sudden lowering of the blood pressure.

2. The complete list of all 137 cases is shown in Table 7.9 of Dr. Fang's Clinical review.

3. Most, but not all, severe post-injection reactions took place within 30 minutes of injection. A few cases occurred after 30 minutes, but within 1 hour. Of the 137 cases, 43 occurred during the injection, 51 occurred immediately after the injection, 9 occurred within 2 to 10 minutes, 3 occurred within 60 minutes, 1 occurred within 1-8 hours, and 5 occurred within 24 hours. The exact time was not specified in 25 cases, but the event was reported on the same date as the injection.

4. Of the 137 cases, 32 (23%) were either hospitalized or were seen in the emergency department, 9 (7%) were described as life-threatening, 128 (93%) were described as "medically significant", and 19 (14%) contained a statement that blood pressure dropped or syncope occurred.

5. Of the 137 cases, 60 (44%) received some form of treatment. A total of 13 (10%) received epinephrine, 38 (28%) received corticosteroids, 30 (22%) received an antihistamine, and 18 (13%) received other therapies.

6. In conducted their assessment and adjudication of cases, DPARP used the criteria set out by the National Institute of Allergy and Infectious Disease (NIAID) and Food, Allergy and Anaphylaxis Network (FAAN) to identify cases consistent with anaphylaxis (Sampson et

al, J Allergy Clin Immunol, 2006). Generally, DPARP takes the approach that anaphylaxis is identified when NIAID/FAAN criterion #1 is met; that is, acute onset of illness with involvement of the skin, mucosa or both and one of the following: respiratory compromise of reduced BP or its associated symptoms (e.g. syncope). DPARP also conducted a secondary analysis using less restrictive identification criteria (e.g., either criterion #1 or criterion #2 to identify a case of anaphylaxis) as they believed it a reasonable approach in the circumstance of TU injection where components of the products are known potential allergens.

7. DPARP reviewed case narratives for 330 potential cases of anaphylaxis. DPARP identified a total of 47 anaphylaxis cases (using just NIAID/FAAN criterion #1). If the identification criteria were less restrictive (NIAID/FAAN criteria #1 or #2), then DPARP identified a total of 68 cases. Additional anaphylaxis cases were identified in the final Safety Update to the NDA, raising the totals to 53 and 76 cases of anaphylaxis, using strict and less restrictive identification criteria, respectively.

8. Together with DBRUP, the DPARP reviewers evaluated case narratives for 533 potential cases of POME. DPARP and DBRUP identified 170-191 POME cases (the range is due to overlap as a consequence of overlap in identifying anaphylaxis using either the strict or less restrictive NIAID/FAAN criteria and thus, greater or fewer POME cases). Of these, 55-76 cases were identified as severe POME. Another 6-8 POME cases were identified in the applications final Safety Update.

   Additional comments and conclusions from DPARP consult are shown in Section 11 (Other Relevant Regulatory Issues) of this review.

9. Despite the inherent challenges and weaknesses in calculating postmarketing adverse event reporting rates, the Sponsor provided estimates of the reporting rates for anaphylaxis and POME for testosterone undecanoate injection. These estimates are shown in detail in Tables 7.7 and 7.8 of Dr. Fang's review. It is notable that there were two separate adjudications conducted by Sponsor, the original adjudication conducted by Endo's own internal reviewers and a later adjudication, conducted by "Internal Adjudicators" hired by Endo to re-assess these cases. The second assessment found essentially the same number of POME cases, but fewer anaphylaxis cases, based on a different identification criteria strategy.

   - Based on the Endo original adjudication, 79 cases of anaphylaxis were identified. With (b) (4) ampoules of TU injection sold, the reporting rate comes to (b) (4) anaphylaxis cases per 10,000 ampoules sold, or (b) (4) anaphylaxis cases per 10,000 treatment-years, assuming all ampoules sold were used in treatment.

   - Based on the "independent" adjudication, 45 cases of anaphylaxis were identified. With (b) (4) ampoules of TU injection sold, the reporting rate comes to (b) (4) anaphylaxis cases per 10,000 ampoules sold, or (b) (4) anaphylaxis cases per 10,000 treatment-years, assuming all ampoules sold were used in treatment.

- Based on the Endo original adjudication, 228 cases of POME were identified. With (b) (4) ampoules of TU injection sold, the reporting rate comes to (b) (4) POME cases per 10,000 ampoules sold, or (b) (4) POME cases per 10,000 treatment-years, assuming all ampoules sold were used in treatment.

8.1.4 Overall Assessment of Safety Findings

My overall assessment of these safety findings is essentially the same as it has been at the time of the original NDA review and at the time of the first CR. The evidence demonstrates that intramuscular testosterone undecanoate is associated with severe post-injection reactions, which are both severe POME and anaphylaxis. While there has yet to be a death reported, and no evidence of permanent disability, the characteristics of these post-injection reactions, with sudden difficulty breathing, throat tightening/fullness, cough, flushing, and cardiovascular, allergic and constitutional symptoms are quite impressive. Respiratory distress and cardiovascular collapse with loss of consciousness have been reported, albeit infrequently. Patients have been treated as if for anaphylaxis. Some patients have been hospitalized or had a concerning presentation which resulted in a visitation to the emergency department. Severe post-injection reactions are acute events that may occur after any dose of the product. In some cases, mild events have been followed by severe events. In some cases, trouble-free dosing has been interrupted by a severe post-injection reaction only after years have passed.

Aside from the severe post-injection reaction, the remainder of the safety results from clinical trials of testosterone undecanoate injection revealed the expected adverse reactions associated with the pharmacological action of testosterone (e.g., increased serum PSA, worsening BPH, weight gain, edema, change in lipid profiles, acne, breast pain, sweating, depression, etc) and expected adverse reactions for an injection (e.g., injection site reactions)

Overall, I agree with Dr. Fang, the safety data I have reviewed continues to be concerning for this product for testosterone replacement therapy.

9. Advisory Committee Meeting

On April 18, 2013, a joint meeting of the Reproductive Health Drugs and Drug Safety and Risk Management Advisory Committees was held to discuss the efficacy and safety of the new drug application for testosterone undecanoate intramuscular injection. The safety discussion focused on postmarketing reports of oil microembolism in the lungs and anaphylaxis.

During the Advisory Committee Meeting on April 18, 2013, the committee voted on the following two questions:

#	Questions	Voting Results	
		Yes	No
1	Given the severe post-injection reactions that were reported with TU in clinical studies and postmarketing experience, do you believe that TU is safe for the proposed indication?	**9**	**9**
2	Whether you vote "Yes or No" to Question 1, please vote whether the Applicant's proposed instructions for use in product labeling that TU be administered using a slow (30-60 second) injection, and that patients remain in the office for 30 minutes post-injection would be sufficient to ameliorate the risk of severe post-injection reactions.	**1**	**17**

Overall, for Question #1, the voting results did not indicate a majority decision whether testosterone undecanoate (TU) was safe for the proposed indication.

Those who voted "Yes" expressed their concerns that the sponsor, Endo Pharmaceuticals, was being evaluated at a higher standard, and that the Agency set forth very challenging remediation criteria, such as change in formulation. Those who voted "Yes" remarked that this drug has been used in Europe for many years and there have been no reported deaths. It was also stated that there is a clear indication for treatment and a long-acting, injectable testosterone replacement would be a welcome option for treatment. In terms of the risk, including anaphylaxis and pulmonary oil microembolism (POME), the panel members who voted "Yes" remarked that these incidents have been reported as complications from the use of other medications. It was also stated that it is impossible to prevent all risks with all medications. It was also noted that indeed there is a potential improvement in compliance with this formulation.

For those who voted "No", some stated that the risks of TU injection outweighed the benefits. Those who voted "No" remarked that the product may have some potential benefit, but it also can pose potential harm. There was concern that once this is product is marketed in the U.S., the possible increase in usage could markedly increase the number of adverse events. It was also noted that the Agency was persuasive in communicating their concerns.

The members recognized that although both POME and anaphylaxis reactions cannot be predicted, there is concern that the use of this medication can increase the risk of unpredictable events. In addition, if the drug product was approved by the Agency, it was noted that the FDA should consider including a black box warning as part of the labeling and patient package insert while continuing to monitor for safety and follow up as appropriate.

For Question #2, all but one member voted "No". For those who voted "No", it was stated that the risk is very difficult to predict. Therefore, the 30 minute time frame to wait in the healthcare provider's office may not be of sufficient value. There was a general consensus to strengthen the REMS proposal from the Sponsor (A Communication Plan only) to assure that the educational material is readable and usable by prescribers and patients. In addition, there should be a training program for physicians who are going to administer this medication. There could be limitations in terms of the sites where the training is offered to assure ability to

provide resuscitation should a severe post-injection reaction occur. In addition to a Black Box warning, some of the panel members recommended that the indication be narrowed. It was discussed that TU injection not be a medication of first choice and there should be efforts to define and narrow its use. A guideline on limiting use for those without cardiovascular and pulmonary disease was suggested, but no clear recommendation was put forth by the panel.

In addition, it was emphasized that early reporting of pharmacovigilance efforts was necessary to determine how this information is being communicated to patients and physicians. It was discussed that it is critical to make sure that education is effective and that physicians have a network that allows them to look at the outcomes of this REMS.

10. Pediatrics

The Applicant requested a full waiver of the requirement to conduct assessments in pediatric patients. The Sponsor stated that it is not likely to be used in a substantial number of pediatric patients. On April 29, 2009, the Division recommended to the Pediatric Review Committee (PeRC) that the Sponsor's request be granted. The PeRC agreed with the request but asked that the Sponsor confirm that it does not intend to apply for pediatric exclusivity in future submissions. On June 15, 2009, the Sponsor submitted a formal letter confirming that they had no intent to seek pediatric exclusivity. On July 2, 2009, George Greely of the Pediatric and Maternal Health Staff provided an eMAIL to DRUP stating:

> "*The Aveed (testosterone undecanoate) full waiver was reviewed by the PeRC PREA Subcommittee on April 29, 2009. The Division recommended a full waiver because too few children with the disease/condition to study. The PeRC agreed with the Division to grant a full waiver for this product.*"

11. Other Relevant Regulatory Issues

Office of Prescription Drug Promotion (OPDP)

A consultation regarding labeling for the new indication was requested and completed by OPDP. In her final consult report dated July 15, 2009, Janice Maniwang provided comments on various sections of the label, including the PI and the original Patient Package Insert (PPI), although the Patient Package Insert was subsequently withdrawn and replaced with a proposed Medication Guide.

Although we do not recommend approval at this time, nor have we engaged in any further labeling discussions with Sponsor, it should be noted that each of the original OPDP comments was considered. During the review of the original NDA (cycle 1), the review team did engage in discussions with Sponsor relevant to labeling and whatever OPDP comments appeared appropriate and useful were conveyed to Sponsor.

Division of Scientific Investigation (DSI)

Site inspections by the Division of Scientific Investigation were not requested. Clinical site inspections were not required as this was not a new molecular entity and the primary endpoint was a strict laboratory value (testosterone concentrations), not liable to subjective bias. Further, the Office of Clinical Pharmacology found that the assay methodology for measurement of testosterone was valid. In addition, no sites appeared unusual in terms of efficacy or adverse event reporting.

Financial Disclosure

All of the clinical investigators in the United States pivotal Phase 3 Study IP157-001 (42 out of 42 investigators at the U.S. clinical sites [only 31 sites actually enrolled subjects]) responded to request for financial disclosure and none had any relevant financial disclosure information to declare. There were no investigators with a proprietary interest in the product and none with significant equity in the Sponsor as defined in 21 CFR 54.2 (b). No investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(b).

Office of Surveillance and Epidemiology: Division of Epidemiology (DEPI)

Cynthia Kornegay and Rita Ouellet-Hellstrom of DEPI provided consultative support throughout this third cycle review. In their final consult dated May 28, 2013, DEPI provided insight on the relevance, validity, and applicability of postmarketing reporting rates for POME and anaphylaxis. DEPI also conducted the principal review of the POME and anaphylaxis incidence rates from controlled trials. This memo provides details of the DEPI consult in previous sections, which will not be repeated here.

Office of Surveillance and Epidemiology: Division of Pharmacovigilance (DPV)

Teresa Rubio and Adrienne Rothstein of DPV provided consultative support to DBRUP during this third cycle review. In their final consult dated February 14, 2013, DPV provided the results of a FAERS search for POME and anaphylaxis for all approved injectable testosterone products from the time of their approval to the current date. Subsequent to the search and adjudication, a total of 33 cases were identified over a 44 year period.

Office of Surveillance and Epidemiology: Division of Risk Management (DRISK)

DRISK has provided consultative support and input throughout the second and third CR reviews in regard to a REMS, and during the second cycle, in regard to a proposed Medication Guide.

In regard to the Risk Evaluation and Mitigation Strategy (REMS), the Sponsor's proposal in the first CR is not significantly different than their current proposal in this, the second CR. The REMS consisted simply of the Medication Guide, a Dear HCP communication to prescribers, and a timetable for assessments. During the first CR, a video education piece and prescriber brochure had been proposed by Sponsor, but these components were later removed at the recommendation of DRISK. The video and brochure dealt with intramuscular injection

technique and DRISK believed that this was adequately described in the prescriber labeling and generally well known to clinical practitioners.

During this third cycle review, Suzanne Robottom, Cynthia LaCivita and Claudia Manzo provide extensive support in regard to potential REMS strategies, including recommendations regarding Elements to Assure Safe Use (ETASU). DRISK provided a preliminary report for the April 18, 2013, FDA Advisory Committee backgrounder delineating the potential options available for risk management in regard to severe post-injection reactions for TU injection. DRISK also spearheaded presentations to the Risk Management Oversight Committee (ROC) as part of advice-seeking by DBRUP for potential REMS strategies for this application during this cycle and during the previous review cycle.

In their written materials and statements, DRISK remarked that no REMS, not even one with a restricted distribution program under an ETASU, could prevent the occurrence of severe post-injection reactions. Further, DRISK noted that a REMS with ETASU, such as a restriction to certified prescribers and pharmacists who were aware of the risk and were able, willing and adequately supplied to handle such an event medically, could pose a burden on the health care community. Nonetheless, DRISK was willing to assist in the development of a REMS strategy that would suit the clinical situation (e.g., with ETASU) if the review Division believed that the product offered benefit to an underserved patient population.

Office of Surveillance and Epidemiology: Division of Medication Error Prevention and Analysis (DMEPA)

During all three review cycles, DMEPA provided input on 1) the product tradename, and 2) the container/carton, Full Prescribing Information (FPI), and Medication Guide labeling, with regard to potential medication errors.

In regard to the tradename, DDMAC objected to the tradename (b) (4) In this regard, on January 7, 2008, Amy Toscano of DDMAC wrote:

(b) (4)

In response to this concern raised by DDMAC, on May 5, 2009, DRUP conveyed a regulatory letter to Sponsor concluding that the tradename (b) (4) was unacceptable. The letter noted that the re-submission included a "back-up" tradename, Aveed, and if the Sponsor would like to seek approval of the tradename "Aveed", then they would need to submit a new request for proprietary tradename review. On May 12, 2009, Sponsor submitted a new request for review of the tradename, Aveed.

On July 29, 2009, in their final consult report, Carlos Mena-Grillasca, Denise Toyer and Carol Holquist, provided the following final recommendation on the tradename Aveed:

> "*…DMEPA find the proposed proprietary name Aveed conditionally acceptable for this product. DMEPA considers this a final review; however, if approval of the NDA is delayed beyond 90 days from the date of this review, the proposed proprietary name, Aveed, must be re-evaluated.*"

In their final review of the tradename dated March 14, 2013, Alison Park and Zach Oleszczuk confirmed that the tradename, Aveed, was acceptable.

In regard to the carton/container (as well as FPI and Medication Guide) labeling, at the time of the Original NDA review (cycle 1), Carlos Mena-Grillasca and Denise Toyer, provided several recommendations for revisions and these were all instituted. Perhaps the most relevant of these recommendations was that presentation of the Medication Guide statement on the container was quite small and could be overlooked by the reader. DMEPA advised that this be made more prominent and in response, the Sponsor enlarged and emboldened the font for the Medication Guide statement. Subsequently, DMEPA requested and Sponsor agreed to delete certain other carton information to make the Medication Guide statement even more conspicuous.

In their final review of the revised product labeling, including revised container/carton labeling, dated April 30, 2013, Alison Park and Carol Holquist provided several additional recommendations for changes that would minimize the potential for medication errors. Since there were no labeling discussions held with Sponsor during this cycle, these comments were not conveyed to Sponsor at this time.

Office of Compliance

The July 7, 2009 final Chemistry review states:

> *"The Office of Compliance has given an overall acceptable recommendation for the manufacturing facilities."*

The Establishment Evaluation Report is attached to the Chemistry review (pages 27 and 28 of 28) showing the overall acceptable recommendations (on June 26, 2008 and again on March 26, 2009).

Controlled Substances Staff (CSS)

During review of the Original NDA (cycle 1), DRUP requested a consult from CSS to verify the scheduling status of Aveed and to assess the labeling as it applies to Abuse and Dependence.

In their final consult report, dated August 19, 2009, James Tolliver, Silvia Calderon, and Michael Klein, stated that testosterone undecanoate (and thus Aveed) is in Schedule III of the Controlled Substances Act. They also provided recommendations for revisions to Section 9 (Drug Abuse and Dependence) of the label. Although labeling discussions have ceased based upon safety concerns, the CSS labeling recommendations had been wholly incorporated into the proposed Aveed labeling during the first cycle review.

Division of Pulmonary, Allergy and Rheumatology Products (DPARP)

The Division of Pulmonary, Allergy and Rheumatology Products (DPARP) has provided consultative support to DBRUP on each of the previous review cycles and again for this third cycle review. DPARP has been asked to provide comment and guidance on the events of post-injection pulmonary oil microembolism (POME) and anaphylaxis.

It may be useful to the reader to provide a brief overview of DPARP's previous consultative involvement with this application before describing the current DPARP consult remarks.

Original NDA DPAP Consult

In their original consult to the Division (Dr. Charles Lee, final consult dated April 14, 2008), DPAP concluded that there had been 4 reports of anaphylaxis in the postmarketing period for intramuscular testosterone undecanoate, with two of these events meeting the currently accepted diagnostic criteria for anaphylaxis. The reader should be aware that at the time of the original NDA review and at the time of first CR review, the Sponsor disagreed that these cases reflected anaphylaxis. In concluding their first consult, DPAP made the following relevant comments:

- DPAP noted that IgE-mediated sensitivity to castor bean allergen in castor bean extract and castor wax extract had been reported in patients with occupational hypersensitivity to castor beans. Anaphylaxis had also been reported with use of polyethoxylated castor oil (Cremophor EL) when used as a solubilizing vehicle for various drugs.

- After considering the severity of some of the post-injection POME reactions and allergic reactions, DPAP noted that the decision to approve the product would be a risk versus benefit decision, and should be made in light of the degree of efficacy, the seriousness of the indication, the availability of alternative products for that indication, and the extent of the safety data.

- DPAP expressed the opinion that it would be appropriate to characterize the frequency of the POME and POME-like events prior to, not after, approval.

- DPAP stated that given the unclear mechanism of the allergic reactions, they would also recommend that Sponsor characterize the nature of the anaphylaxis events. In this regard, DPAP proposed avenues for additional investigations:
    - Ask the Sponsor to develop an in vitro test for specific IgE and IgG antibody to the drug, including the active ingredient and the inactive excipients, and to evaluate the presence of antibodies in patients who have had anaphylaxis events associated with the drug, in those who have been exposed to the drug but who have not had anaphylaxis, and in unexposed controls.

    - Ask the Sponsor to develop a skin testing procedure to the product and its excipients to evaluate the same populations as recommended for the in vitro testing above.

Following the Approvable action on the Original NDA, DPAP continued to assist in the review of this application. The Sponsor proposed a (b) (4) study protocol (b) (4)

(b) (4)

DPAP felt that the study protocol was insufficient and proposed several modifications. Of importance, DPAP emphasized the limitations of the proposed study (b) (4)

On September 24, 2008, the Division met with Sponsor in a Type A (End of Review) Meeting. At this meeting, DRUP stated that while we would continue to encourage the Sponsor to conduct the skin prick testing/re-challenge study, we would not require it as part of the Complete Response.

Nonetheless, the Sponsor submitted a revised study protocol and DRUP again consulted DPAP. DPAP again voiced that the study was largely insufficient and that the modifications that they had advised were not made. More importantly, they reiterated the following:

> *"Overall, DPAP maintains its previous position that the clinical criteria of anaphylaxis has been met after injection of the Aveed product and that if the product is to be approved, the risk of anaphylaxis should be stated in the labeling and that an appropriate risk management plan be developed for the product. The likelihood of the proposed re-challenge study to yield useful information regarding the mechanism through which the reactions occur is low. However, if the sponsor decides to conduct the study, we continue to recommend the study design changes previously conveyed to the sponsor which were outlined in the previous DPAP consult dated September 18, 2008."*

First CR (Second cycle) DPAP Review

In the later part of the second cycle review, DPAP was re-consulted to review 52 postmarketing adverse event cases culled from the most recent Bayer/Schering and Endo Safety Updates. The Clinical review team asked DPAP to adjudicate the cases as POME or as anaphylaxis. DPAP categorized the cases as follows:

- Anaphylaxis 11 cases
- Possible anaphylaxis 9 cases
- Allergic reactions 4 cases
- Possible POME 8 cases
- Injection site problem 1 case
- Cases with too little information 13 cases
- Cases with non-specific symptoms 6 cases

DPAP provided the following additional insights and comments:

- For categorization of the cases, DPAP used the same criteria that FDA has generally used; specifically, the criteria determined by the National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network Symposium in 2005 (Sampson, HA, Second Symposium on the Definition and Management of Anaphylaxis: Summary Report – Second National Institute of Allergy and Infectious

Disease/Food Allergy and Anaphylaxis Network Symposium; Annals of Emergency Medicine, Volume 47, Number 4, pages 373-380).

- Skin flushing and throat tightening can reflect anaphylaxis. Cutaneous and mucosal signs and symptoms such as generalized flushing, pruritis, hives, swollen lips, tongue and throat are commonly seen in anaphylaxis.
- POME generally lacks cutaneous/mucosal symptoms.
- Benzyl benzoate is known to cause Type XX (cell-mediated) hypersensitivity reactions when applied topically. It is known to be a possible source of contact dermatitis. It is also a component of several products with reported cases of anaphylaxis. Benzyl benzoate can cause hypersensitivity reactions, but not necessarily IgE mediated reactions. When delivered parenterally, its allergic profile could be different. Note, however, that any component of Aveed can be a possible allergen.
- DPAP believes that whether the immediate adverse events following injection can be classified as meeting the clinical definition of anaphylaxis is not the main concern, but any immediate severe adverse event following injection of Aveed requiring treatment should be considered a safety concern.
- The long-term cardiopulmonary consequences of repeated POME events, even if mild, are unknown.
- As previously conveyed, the decision on whether to approve the product will be a risk benefit decision that should take into consideration the seriousness of the indication, the availability of alternative products for that indication, and the extent of the safety data.

Second CR (third cycle) DPARP Review

For this third cycle review, DPARP was again asked to adjudicate potential cases of POME and anaphylaxis in the postmarketing period. For this period, the number of cases was substantially greater than in prior cycles.

As discussed earlier in this memo (Section 8.1.3.2), DPARP reviewed case narratives for 330 potential cases of anaphylaxis. DPARP identified a total of 47 anaphylaxis cases (using just NIAID/FAAN criterion #1). If the identification criteria were less restrictive ((NAIAID/FAAN criteria #1 or #2), then DPARP identified a total of 68 cases. Additional anaphylaxis cases were identified in the final Endo Safety Update to the NDA, raising the totals to 53 and 76 cases of anaphylaxis, using strict and less restrictive identification criteria, respectively.

DPARP reviewers also assisted DBRUP in the evaluation of 533 potential cases of POME. DPARP and DBRUP identified 170-191 POME cases (the range is due to overlap as a consequence of overlap in identifying anaphylaxis using either the strict or less restrictive criteria and thus, resulting in greater or fewer POME cases). Of these, 55-76 cases were identified as severe POME. Another 6-8 POME cases were identified in the application's final Endo Safety Update.

Based on these findings, the final conclusions and recommendations offered by DPARP (Stacy Chin, Tony Durmowicz, and Badrul Chowdhury) were consistent with their conclusions and recommendation from their prior consults:

- The safety signals of anaphylaxis and severe POME identified in previous submissions were confirmed.
- No less than 53 cases of anaphylaxis were identified in this review.
- No less than 170 cases of POME were identified, and of those at least 55 (to 76) cases were severe POME.
- The severity of the episodes are due, at least in part to decreased cardiac output as a result of acute pulmonary hypertension resulting in dyspnea, dizziness and collapse.
- It is likely that POME also results in pulmonary inflammatory changes with a similar pathology to that observed in patients and in animals models of fat embolism.
- The long-term consequence of POME events, including repeated "low-grade POME" is unknown. POME that doesn't manifest as an acute event may nonetheless be harmful to lung tissue.
- As in prior consults, DPARP concluded: "Ultimately, the decision to approve or not approve TU is a risk versus benefit decision and should be made in light of the degree of efficacy, the seriousness of the indication, the availability of alternative products for that indication, and the extent of the safety data."

12. Labeling

Labeling discussions were held during the original NDA review. Revised labeling was proposed by Sponsor as part of the March 2009, Complete Response. The revised labeling (b) (4) recommended that patients wait for 30 minutes in a medical facility after being injected with the product, in the event of a severe, immediate post-injection reaction. The proposed labeling included a Patient Package Insert, which was subsequently converted to a Medication Guide. Container/carton labeling was also subsequently revised to emphasize the existence of the Medication Guide. Labeling discussions were not held as part of the second cycle review.

Revised labeling was submitted with this second Complete Response. It included a Medication Guide and again referred to "potential" anaphylactic reactions. Subsequent to the April 18, 2013 Advisory Committee, wherein several members recommended a Black Box Warning, the Sponsor submitted a labeling revision to incorporate a Black Box warning for severe post-injection reactions, including severe POME and anaphylaxis. Labeling discussions were not held during this third cycle review.

13. Recommendations/Risk Benefit Assessment

13.1 Recommended Regulatory Action

I recommend that the product not be approved at this time. Like the medical officer, I remain concerned by the risk of severe post-injection reactions, which include cases of severe POME and anaphylaxis. I am not yet convinced that the demonstrated benefits of the product are sufficient to outweigh this demonstrated risk. I recommend that the application should receive a "Complete Response" action. The Sponsor should be informed that a potential pathway to approval would be a mandatory restricted distribution program under a formal REMA with ETASU. The product would be available only to certified prescribers through certified pharmacies. Prescribers would attest to their awareness of the risk of severe post-injection reactions, their ability to mange the potential severe post-injection events, their willingness to keep the patient under observation for at least 1 hour, and that they have sufficient supplies on hand in the event of a severe reaction. Patients would be asked to sign an informed consent (at the start of therapy) attesting that they have been made aware of the risk of a severe post-injection reaction.

13.2 Risk Benefit Assessment

I find the risk benefit profile for this product to be currently unfavorable. The product conveys a serious risk: the occurrence of severe post-injection reactions. These reactions were reported in clinical trials and spontaneously in the postmarketing period. They are characterized by difficulty breathing, throat tightening, throat closing, throat fullness, cough, flushing, paresthesias (burning in hands, feet, chest and mouth), other allergic phenomenon (rash, itching, bronchospasm, wheezing, flushing, angioedema), and constitutional symptoms (sweating, dizziness, weakness, headache, chest pain, ECG changes, etc). In some cases, syncope, collapse, apnea, cyanosis and cardiovascular collapse have been reported. Many of the cases that I have reviewed were treated as for anaphylactic reactions, with the use of oxygen, epinephrine, steroid and antihistamine. In some of the cases, the event was clearly life-threatening. Some required hospitalization or emergency resuscitation. The etiology for these events appears to be both allergic (anaphylaxis) and respiratory (POME). Allergic reactions may be related to any of the three components: testosterone undecanoate, refined castor oil, or benzyl benzoate. Castor oil may contain toxins, allergic components or contaminants that may be responsible for at least some of these events. Benzyl benzoate is known to be associated with contact dermatitis, and in at least one case, there was a clear anaphylactic reaction to TU injection in a 16 year old boy who showed a postive skin test to the benzyl benzoate component only. Regardless of the etiology, though, these events can be severe, life-threatening and some require medical intervention including hospitalization. There is currently no known way to predict or to prevent them from occurring. They may occur after any dose and may follow a long period of trouble-free dosing. They may initiate as a mild reaction and subsequently manifest as a severe reaction.

While the product does confer the expected benefit for a testosterone replacement therapy (TRT), with the need for fewer injections per year compared to other injectable TRT products,

I do not currently find this benefit sufficient to outweigh the life-threatening risk of severe, immediate, post-injection reactions. Like the primary MO, I do not find the Sponsor's proposed Medication Guide and Communication Plan sufficient as a risk management strategy for severe post-injection reactions (severe POME and anaphylaxis).

The reader is referred to previous sections of this memo, including the Executive Summary and Safety Summary sections for additional discussion and detail.

13.3 Recommendation for Postmarketing Risk Management Activities

Like the primary MO, I believe that the Sponsor's proposed Medication Guide and Communication Plan are not sufficient.

We acknowledge that no REMS will be capable of preventing the occurrence of severe post-injection reactions. These events are sporadic and unpredictable. We also acknowledge that no REMS will reduce the acute severity of the reactions. However, it might be possible to reduce the overall number of such events and to lessen their clinical impact by instituting a mandatory restricted distribution program as a formal Element to Assure Safe Use (ETASU). We currently envision a restricted distribution program that would include the following:

- Prescribers would need to be certified that they (1) acknowledge the risk of a severe post-injection reaction and (2) have sufficient supplies and ability to treat an episode of severe POME or anaphylaxis, and (3) are willing to keep the patient under observation for 1 hour after each injection.
- Pharmacies would need to certify that they will distribute Aveed only to certified prescribers.
- Potential patients would need to sign an informed consent at the start of treatment that they understand the risk of a severe post-injection reaction, they will remain in the office for the mandated time after each injection, and they are willing to proceed.

13.4 Recommendation for other Postmarketing Study Commitments

Following successful collaboration on a REMS with ETASU, we recommend that the Sponsor be asked to conduct a Phase 4 study to further evaluate and quantify the risk of severe postinjection reactions, including severe POME and anaphylaxis, of 750 mg Aveed (testosterone undecanoate intramuscular injection) in hypogonadal men, with the number of clinical investigative site locations, the number of subjects to be enrolled, and the number of injections to be administered to be further determined.

13.5 Recommended Comments to Applicant

I recommend issuing a CR letter to Sponsor, describing the Clinical deficiency, as summarized in Sections 13.1 and 13.2. The letter should delineate a potential pathway forward (REMS with ETASUs, mandatory restricted distribution), as described in Section 13.3.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MARK S HIRSCH
05/28/2013

AUDREY L GASSMAN
05/28/2013
I concur with the regulatory recommendation in Dr. Hirsch's CDTL review.

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	NDA 022219
Priority or Standard	Standard
Submit Date(s)	2012-11-29
Received Date(s)	2012-11-29
PDUFA Goal Date	2013-05-29
Division / Office	DBRUP / ODE 3
Reviewer Name(s)	Guodong Fang, MD
Review Completion Date	2013-05-08 (draft)
Established Name	Testosterone Undecanoate
(Proposed) Trade Name	Aveed
Therapeutic Class	Injectable Steroid Androgen
Applicant	Endo Pharmaceuticals Solutions, Inc.
Formulation(s)	$C_{30}H_{48}O_3$ (MW 456.7)
Dosing Regimen	750 mg loading regimen followed by 750 mg every 10 weeks
Indication(s)	Adult Male Hypogonadism
Intended Population(s)	Adult Men (≥ 18 years old) with Hypogonadism

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

In the opinion of this Clinical Reviewer, from a clinical perspective, the evidence presented in the original submission and two re-submissions was adequate to support the effectiveness of this product. However, the safety concerns related to the risks, risk versus benefit ratio, and proposed management of severe post-injection reactions, which led to the original "Approvable action" have not been adequately addressed in the Sponsor's Complete Response to the Agency's December 2, 2009 Action Letter.

It is recommended that until such time as these issues of severe safety concerns are resolved the application of testosterone undenoate for intramuscular injection, **not be approved** for the indication of replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous testosterone:

- "Primary hypogonadism (congenital or acquired)"
- "Hypogonadotrophic hypogonadism (congenital or acquired)".

1.2 Risk Benefit Assessment Based on Clinical Findings

The Clinical Review Team believes that the postmarketing safety reports of severe post-injection reactions, including severe pulmonary oil microembolism (POME) and anaphylaxis, included in this NDA resubmission is a major unresolved safety issue. Sufficient evidence leads this reviewer to conclude that the risk/benefit profile for this product is not acceptable for approval.

1.2.1 Brief Overview of the basis for the Third Resubmission

The purposes of this second re-submission are:

- To provide an amendment (NDA Resubmission) to NDA 22219 to provide a Complete Response to the December 2, 2009 Action Letter, and
- To formally requesting an Advisory Committee Meeting to occur as part of the review process of this resubmission

1.2.2 Efficacy

The difference for efficacy between this submission and previous submissions is inclusion of the results from Study IP157-001, Part C2. Combining Part C and Part C2, which used the 750mg loading regimen of testosterone undecanoate injection, approximately 130 hypogonadal males

enrolled in this single, open-label, pivotal study and the results showed an acceptable replacement of testosterone.

***Reviewer's comments*: The Sponsor met the current requirement for demonstration of efficacy for this indication.**

1.2.3 Safety

Based on previous review of the post-marketing experience, the Sponsor was requested to submit all postmarketing safety reports of pulmonary oil microembolism (POME) and anaphylaxis with CIOMS forms. DBRUP and DPARP review teams determined 137 cases of severe postinjection adverse reactions including both POME and anaphylaxis. The spectrum of signs and symptoms of these post-injection reactions frequently overlap, and all 137 of these reactions were reported as severe and/or potentially life-threatening, with some cases requiring hospitalization or emergency department visitation and some being treated as for anaphylaxis. Even if the mechanism for these severe postinjection reactions have not been clearly elucidated, two of the excipients in this product, benzyl benzoate, and castor oil are known allergens, and may possibly play roles in anaphylaxis and castor oil itself is the likely etiology for the severe POME reactions.

***Reviewer's comments:* Taken together, especially the severity and unpredictability of the severe postinjection reactions, this reviewer concludes it is not safe to authorize Aveed for marketed for the proposed indication.**

1.2.4 Dose Regimen and Administration

3 mL per injection (each 3 mL vial contains 750 mg testosterone, 1500 mg of benzyl benzoate and 885 mg of refined castor oil), to be injected intramuscularly at initiation, at 4 weeks, and every 10 weeks thereafter.

1.2.5 Special Populations

No new data regarding special populations are included in this re-submission.

1.2.6 Drug Abuse and Dependence

Aveed (testosterone undecanoate injection) is a Schedule III controlled substance because it contains testosterone.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies (REMS)

A REMS, including a Medication Guide and a Communication Plan, have been included in this resubmission.

To address the risk of severe postinjection reactions including POMEs and anaphylaxis, this reviewer does not believe that it is sufficient to have a standard Medication Guide and

Communication Plan. The Clinical review team envisions a mandatory restricted distribution of Aveed, under a formal Element to Assure Safe Use (ETASU). The following are proposed:

- Prescribers should be certified. They should (1) acknowledge the risk of severe post-injection reactions (2) having sufficient supplies and the ability to treat a possible episode of severe POME or anaphylaxis, and (3) be willing to keep the patient under observation of at least 1 hour after each injection.
- Pharmacies should be certified. They should only distribute Aveed to certified prescribers.
- Potential patients should sign informed consent stating that they understand the risk of a possible severe POME and/or anaphylaxis event, and that they are willing to be observed in the office for at least 1 hour after each injection.

In addition, for an eventual Aveed NDA approved with a restricted distribution ETASU, a Black Box Warning in product labeling is recommended for the potential risk of severe post-injection reactions, including severe POME and anaphylaxis.

1.4 Recommendations for Postmarket Requirements and Commitments

As a postmarketing requirement besides the standard REMS assessments at (b) (4) 3 years , and 7 years from the date of the approval of the REMS, this reviewer recommends the Sponsor to conduct a Phase 4 study to evaluate the safety of Aveed (testosterone undecanoate) , including specific monitoring for severe post-injection reactions (severe POME and anaphylaxis). The number of clinical investigative site locations, the number of subjects to be enrolled, and the number of injections to be administered are to be determined.

2 Introduction and Regulatory Background

2.1 Product Information

AVEED (testosterone undecanoate IM injection) is a clear, yellowish, sterile, oily solution containing testosterone undecanoate, a testosterone ester, for intramuscular injection. Each single use vial contains 3 mL of 250 mg/mL testosterone undecanoate solution in a mixture of refined castor oil and benzyl benzoate. There is 885 ng per vial of refined castor oil and 1500 mg per vial of benzyl benzoate.

Testosterone undecanoate (17β-undecanoyloxy-4-androsten-3-one) is an ester of the androgen, testosterone. The active form, testosterone, is formed by cleavage of the side chain.

Table 2.1 Components of Aveed (testosterone undecanoate injection)

Manufacturer	Endo Pharmaceuticals Solutions, Inc.
Drug Name	Aveed (testosterone undecanoate intramuscular injection)
Active Ingredient	Testosterone, USP (750 mg in 3 mL)
Inactive Ingredient(s)	Refined castor oil (885 ng in 3 mL) Benzyl benzoate (1500 mg in 3 mL)
Route of Administration	Intramuscular injection
Dosage Form Strength	Vial (3 mL)

2.2 Currently Available Treatments for Proposed Indications

Testosterone replacement therapy is used to treat conditions associated with a deficiency or absence of endogenous testosterone. FDA-approved testosterone products are shown in Table 2.2, accompanied by their dose and drawbacks/potential risks.

Table 2.2 Currently Available Testosterone Products in the United States

Formulation	Formula / Trade name	Dose§	Potential Drawbacks/Potenial Risks
Oral	Methyltestosterone (Testred) Fluoxymestrone	10-50 mg/day	Hepatotoxicity
Parental	T cypionate (Depo–T) # T enanthate (Delatestryl)** T propionate***	50-400 mg IM (every 2-4 wks)	Supraphysiologic peaks, low trough concentration,
Transdermal Patch	Testoderm (scrotal) Testoderm TTS Androderm	4-6 mg/day 5 mg/day 5-7.5 mg/day	Can requires skin shaving Application site irritation.
Transdermal Gel	Androgel (1%) Androgel (1.62%) Testim (1%) Axiron (2%)	50-100 mg/day 20.25-81 mg/day 50-100 mg/day 30-120 mg/day	Interpersonal transferability to partners and children
Transbuccal	Striant	30 mg buccal tablet (BID)	Gum or mouth irritation
Implant	Testosterone (Testopel Pellets)*	75 mg pellet; subcutaneous	

* Prescribing information available from Slate: (www.slatepharma.com/wp-content/uploads/2008/12/testopelpi.pdf)
\# Prescribing information available from Pfizer (www.pfizer.com/files/products/uspi_depo_testosterone.pdf)
** Prescribing information available from Indevus (www.indevus.com/site/images/PDF/delatestryluspi.pdf)
§ Dose information available from Drug Facts and Comparisons, 4.0 (Wolters Kluwer Health, Inc; 2008)
*** Discontinued
Source: Clinical Reviewer.

Limitations of the currently available products include the following:

- Injectable depot solutions may be associated with pain at the injection site. Peak concentrations are often supratherapeutic and trough concentrations may be subtherapuetic. Mood swings are possible due to fluctuations in testosterone levels.
- High dose, oral, methyltestosterone formulations have been associated with an increased incidence of liver disease.
- Transdermal patches may be associated with significant application site reactions.
- Pellet implants can be expelled from the insertion site and infrequently, may result in infection.
- Testosterone gels incur the potential risk of secondary exposure to testosterone of children and women.

Currently, the goal of testosterone replacement therapy in hypogonadal men is to replace testosterone levels at close to physiological concentrations. Clinical guidance from the Endocrine Society indicates that testosterone replacement therapy should aim to achieve testosterone levels in the mid-normal range.

2.3 Important Safety Issues with Consideration to Related Drugs

Labeled risks of testosterone administration in hypogonadal men include worsening of clinical BPH symptoms, polycythmia, induction or exacerbation of sleep apnea, breast tenderness or enlargement, liver toxicity (with oral methyltestosterone formulations), and acne. Two major areas of concern in older men are the unknown effects of long-term testosterone administration on the risks of prostate cancer and progression of atherosclerotic heart disease.

Topical testosterone gel preparations, which are applied directly to the skin, have been associated with a small number of events of secondary exposure of testosterone in children. Several exposed children have experienced significant clinical sequelae which prompted the FDA to mandate a Black Box Warning for all topical testosterone products.

***Reviewer's comments*: For testosterone undecanoate IM injection, life-threatening sevrre post-injection reaction events (including severe POME and anaphylaxis) associated with the use of Aveed leads to an unacceptable risk-benefit ratio for Aveed.**

2.4 Summary of Presubmission Regulatory Activity Related to Submission

Table 2.3 Regulatory History of NDA 022-219 (Aveed)

	Sponsor	FDA
Original NDA Submission in 2007-2008	**Original NDA submitted on August 24, 2007** Pulmonary oil micro-embolism (**POME**)**:** reported in 2 patients in clinical trials: these 2 events were described as sudden (and in one case, severe) urge to cough, cough, and dyspnea immediately following injection. In post-marketing safety update reports (PSURs), the 120-day Safety Update, and a Summary Report of "cough fits", a total of 66 European postmarketing cases were detected.	**"Approvable" action taken on June 7, 2008 with Chemistry, Manufacturing, and Clinical deficiencies.** • "There are reports of serious, immediate post-injection AEs in men who have received TU intramuscular injections." • "These reports, although the exact etiology has yet to be determined, are consistent with anaphylaxis and POME." The Applicant was requested to provide additional safety information to determine the incidence of serious post-injection POME and allergic reactions and to characterize the nature and etiology of the anaphylaxis-like events.
Complete Response (CR) Submitted on March 2, 2009	**Complete Response submitted on March 2, 2009** Safety data submitted from 2,834 subjects who had received 16,191 injections in 12 completed and 5 ongoing clinical trials. There was just 1 report of serious POME (0.035%) and no reports of systemic allergic reaction. Approximately 125 cases of post-injection reactions (POME and anaphylaxis) were reported in postmarketing experience. A proposed Risk Evaluation and Mitigation Strategy (REMS), consisting of a Medication Guide and a Communication Plan, was included.	**CR action taken on Dec. 2, 2009, with Clinical deficiency of continuing safety concerns regarding reports of serious, immediate, life-threatening post-injection reactions and their impact on the risk/benefit profile.** The proposed REMS was considered not sufficient to ensure that the benefits of Aveed injection outweighed the risks associated with use of Aveed. The Division identified 2 potential remedial actions: • Identify which components of the drug product may be contributing to the immediate post-injection reactions, and reformulate the product; or • Identify a population of adult males who require testosterone replacement therapy (TRT) and in whom the additional potential risks associated with the use of TU injection as currently formulated would be acceptable. In addition, a safety update including worldwide postmarketing safety reports was requested.
From 2009 CR through 2010	Subsequent to the December 2009, CR action, the **Sponsor requested that FDA provide a list of cases** of post-injection reaction that led to the CR action. In April 2010, the Sponsor requested a **Type A meeting** to discuss a potential path forward. The Sponsor proposed to narrow the target population and restrict distribution of Aveed.	In December 2009, **DRUP provided a list** of patients from CIOMS reports who sustained postmarketing post-injection adverse reactions either immediately or soon after injection. On May 24, 2010, **FDA met with Sponsor in Type A meeting** to discuss potential path forward (narrowed target population with restricted distribution).
2011	February 16, 2011 & May 26, 2011 – The sponsor requested a **Type C**	On June 27, 2011, **FDA met with Sponsor in Type C meeting**. After

	meeting and submitted a briefing package, respectively, which included a revised, proposed REMS with Elements To Assure Safe Use (ETASU). The REMS was specifically designed to restrict the distribution of Aveed to certain populations.	further consideration and internal FDA discussion, the Agency determined that the proposed REMS with ETASU was not appropriate for Aveed. DRUP recommended that the Sponsor resubmit the NDA and the application would likely be discussed at an Advisory Committee Meeting.
2012 prior to second Complete Response (CR)	In November 2011, the Sponsor requested another **Type C meeting** to receive feedback on preparing the resubmission. A major issue was identification and analysis of postmarketing reports of POME and anaphylactic reaction. The meeting was granted but was **cancelled by the Sponsor after receiving FDA response**. The Sponsor provided proposals for case identification and classification: • Exact terms were provided for searching the postmarketing database for cases of POME and anaphylaxis • Anaphylaxis will be defined using the "Rüggeberg" definition of anaphylaxis developed in Europe from the Brighton Collaboration Anaphylaxis Working Group	On January 14, 2012, **FDA conveyed preliminary responses to the Type C meeting questions**. The Sponsor was requested to provide: (1) the exact terms to be used for searching postmarketing databases for cases of POME and anaphylaxis; (2) specific criteria to use to define POME and anaphylaxis, as well as the specific process to use adjudicating cases generated by search. DRUP reviewed the Sponsor's proposals in collaboration with the Office of Surveillance and Epidemiology (OSE) and Division of Pulmonary, Allergy and Rheumatology Products (DPARP). DRUP stated: • The MedDRA terms to be queried to cull potential cases of POME and anaphylaxis are reasonable • FDA uses a clinical definition of anaphylaxis (Sampson Criteria) developed by NIAID and the Food Allergy and Anaphylaxis Network when evaluating potential cases of anaphylaxis • Individual CIOMS reports should be provided for all potential cases of POME and anaphylaxis irrespective of Sponsor's medical review or adjudication.
Second CR Submitted on November 29, 2012	**Second CR submitted on November 29, 2012** Sponsor formally requested an AC meeting as part of the review process of this submission	**AC Meeting scheduled for April 18, 2013**

3 Ethics and Good Clinical Practices

Through a thorough review of the clinical study protocols, protocol amendments, and informed consent forms, as well as the approval process by either central or local IRBs, no ethics or good clinical practice (GCP) issues have been identified.

3.1 Submission Quality and Integrity

The quality of the overall this resubmission was good with the information organized and readily located. Additional information was received from Sponsor on November 29, 2012 concerning an "independent adjudication" of the severe post-injection reactions collected during the postmarketing period.

3.2 Compliance with Good Clinical Practice

Part C2 of the pivotal Study IP157-001 was completed after the last resubmission and the study was conducted in accordance with Good Clinical Practice as required by the guidelines of the Agency and the International Committee on Harmonization guidelines. The Clinical and Clinical Pharmacology teams decided that DSI inspections were not needed for Part C2.

3.3 Financial Disclosure

In compliance with 21 CFR part 54, the Sponsor has adequately disclosed the absence of Investigator proprietary interest in this product or Investigator participation in financial arrangements with Sponsor.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls (CMC)

The CMC review team notes during this review cycle, there were no new CMC information enclosed in the resubmission. During the last resubmission, the Chemistry Approvable issues were resolved. From a CMC perspective, this NDA resubmission was recommended for an approval action.

4.2 Clinical Microbiology

The original NDA 22219 submission was recommended for approval on April 29, 2009, based on adequate product quality microbiology information referenced in DMF (b) (4) (amendments

5-8). Upon review of subsequent DMF (b) (4) amendments (amendments 9-11), the original recommendation for approval stands as there was no value-added information which would enhance the data reviewed from the prior DMF (b) (4) submissions.

4.3 Preclinical Pharmacology/Toxicology

The application type was changed from a 505(b)(1) to a 505(b)(2) due to changes in regulatory interpretation (applicant's letter December 11, 2012). This does not alter the nonclinical conclusions regarding approval. The nonclinical information used to support approval of this product is complete as presented in previous reviews.

The current resubmission contains no new nonclinical information. The Applicant's nonclinical program, consisting of references, available literature and general knowledge of testosterone, provide reasonable assurance of the safety of testosterone undecanoate (TU) in hypogonadal men from a nonclinical perspective. The nonclinical reviewer made some changes and corrections to the original pharmacology/toxicology review, but the changes do not affect the overall conclusion. In general, the safety profile of testosterone is well known. Other than expected pharmacology and injection site toxicity, no significant safety concerns associated with TU at therapeutic doses were identified in the nonclinical program.

4.4 Clinical Pharmacology

The Clinical Pharmacology review team found the application acceptable for approval. All labeling issues had been adequately resolved through labeling negotiations during last reviewing cycle.

***Reviewer's comment*: During review of last resubmission, the Clinical Pharmacology review team had noted excessive T concentrations in one patient who weighed < 65 kg.** (b) (4) **the Office of Clinical Pharmacology had determined the NDA was acceptable.**

4.5 Biostatistics

According to their final memo based on the analysis of clinical pharmacology data, the Statistical Review Team recommended approval of this NDA.

4.6 Consults from Other Divisions

4.6.1 Division of Medication Errors Prevention and Analysis (DMEPA)

The DMEPA reviewer concludes that the proposed proprietary name of Aveed is acceptable from both a promotional and safety perspective.

4.6.2 Division of Risk Management (DRISK) under Office of Medication Error Prevention and Risk Management of OSE

The DRISK reviewer believes that the Agency has the authority to require a REMS if additional measures beyond labeling are necessary to ensure that the benefits of a drug outweigh the risks. In considering a REMS for Aveed, the primary benefit of Aveed is fewer injections in a patient population who has a variety of other treatment options available. The DRISK reviewers stated that in this circumstance, a REMS cannot prevent the potentially life-threatening reactions and safe use restrictions pose substantial burden on stakeholders.

4.6.3 Division of Drug Marketing, Advertising and Communications (DDMAC)

DDMAC was not involved in this resubmission as they are usually asked to review the proposed product labeling (PI), carton labeling and container labeling. DDMAC comments and recommendations will be addressed in the final labeling, when such becomes appropriate.

4.6.4 Office of Pharmacovigilance and Epidemiology (OPE) in the Office of Surveillance and Epidemiology (OSE)

In summary, the OPE reviewer believes that Sponsor's inability to characterize the postmarketing TU use accurately, the consistent POME and excess anaphylaxis incidence rates seen in the clinical and postmarketing databases, and Sponsor's unwillingness to acknowledge or effectively address these rates are concerning. The OPE reviewer also stated that it is unlikely that the incidence of either POME or anaphylaxis associated with TU has decreased in the postmarketing period, since these events still occurred under ideal study conditions. OPE concluded that the risk of serious and life-threatening events should be carefully weighed against the benefit of a potentially longer period between TU injections, particularly given that there are multiple alternatives to TU, including other injectable testosterone preparations and other dose forms.

4.6.5 Pediatric Review Committee (PeRC)

Pediatric studies are required based on Pediatric Research Equity Act (PREA) for the following reasons:

1) New active ingredients;
2) New indications;
3) New dosage forms;
4) New dosing regimens;
5) New routes of administration.

None of the above apply to this testosterone undecanoate injection product, therefore, this product of testosterone undecanoate intramuscular injection is exempt from this requirement.

5 Sources of Clinical Data

5.1 Size of the clinical trial dataset

The development program for testosterone undecanoate injection for TRT consisted of a single U.S. Phase 3 study (Study IP157-001), six European Phase 1, Phase 2 and Phase 3 studies, 5 European male contraception studies, and 6 International postmarketing studies (Table 1)

Table 5.1 Clinical and Postmarketing Studies of Testosterone Undecanoate Injection

	Indication Sample Size	Title	Type	Study Design	Treatment
US Clinical Study (N = 524)					
IP157-001 Part A Part B Part C Part C2 Completed	Hypogonadism (TU 750 mg, n =272; TU 1000 mg, n=252; Overall, n = 524)	A 2-arm, open-label, randomized, multicenter pharmacokinetic and long-term safety study of intra-muscular (IM) injections of testosterone undecanoate (TU) 750 mg and 1000 mg in hypogonadal men. This was a 5-part protocol that included 2 IM treatment arms in Part A, 2 IM treatment arms in Part B, a single IM treatment arm in Part C, a single IM treatment arm in Part C2 and 2 subcutaneous (SC) treatment arms in Part D.	Phase 3	Open-label, randomized, 2-arm, active-controlled, multiple-dose	**Part A:** TU 750 mg IM; TU 1000 mg IM; **Part B:** All subjects TU 1000 mg IM initial dose followed by 2-arms: TU 750 mg IM; TU 1000 mg IM; **Part C:** TU 750 mg IM; **Part C2:** TU 750 mg IM; **Part D: SC** TU 1000 mg (Part A pts) TU 750 mg (Part C pts)
European Clinical Studies (N = 201)					
JPH01495 Completed	Hypogonadism (n = 14)	Study to investigate the PK of TU after single IM injection	Phase 1	Open-label, single arm, single dose	TU 1000 mg IM
JPH04995 Completed	Hypogonadism (n = 14)	Study to investigate the PK and efficacy of TU after multiple IM injections in hypogonadal men	Phase 2/3	Open-label, single arm, multiple dose	TU 1000 mg IM
ME98096 Completed	Hypogonadism (n = 26)	Open-label study to evaluate safety and PK parameters of total and free testosterone after repeated IM administrations of TU 1000 mg (5 injections over 36 weeks) in hypogonadal male subjects	Phase 2	Open-label, single arm, multiple dose	TU 1000 mg IM
ME97029 Completed	Hypogonadism (n = 36)	Study to investigate the efficacy and safety of TU vs. testosterone enanthate (TE) after IM injection in hypogonadal men	Phase 3	Randomized, open-label, parallel-group, 2-arm, active-controlled, multiple dose	TU 1000 mg IM TE 250 mg IM
306605 Completed	Hypogonadism (n = 96)	Open-label, one-arm study to investigate safety and efficacy of IM injections of TU 1000 mg in hypogonadal men at variable intervals during a 136- to 192-week treatment including PK of TU during steady state in a subgroup of 30 subjects	Phase 3	Open-label, single arm multiple dose	TU 1000 mg IM
303934 Terminated	Male Andropause	A monocenter, prospective, randomized, double-blind, parallel-	Phase 2	Randomized, double-blind,	TU 1000 mg IM 4 mL placebo IM

Early[a]	(n = 15)	group, placebo-controlled, long term clinical trial to investigate the effects of a long-acting IM reparation of TU on andropause-related symptoms		parallel-group, 2-arm, placebo-controlled, multiple-dose	
European Male Contraception Studies (N = 407)					
97028 Completed	Male contraception in healthy males (n = 28)	Male contraception with TU vs. combined administration of TU and levonorgestrel (LNG) - a double-blind, randomized, single-center comparative study	Phase 2	Randomized, double-blind, parallel-group, 2-arm, placebo-controlled, multiple-dose	TU 1000 mg IM + oral Placebo TU 1000 mg IM +oral LNG
97173 Completed	Male contraception in healthy males (n = 25)	Male contraception with a sequential regimen of cyproterone acetate (CPA) and TU followed by a lower dose of CPA and TU in normal men	Phase 2	Randomized, double-blind, 3- arm, placebo-controlled, multiple-dose	**Induction Phase:** TU 1000 mg IM+CPA 20 mg/day oral **Maintenance Phase:** 3 Randomized Groups: TU 1000 mg IM+CPA 20 mg/day oral; or TU 1000 mg IM+CPA 2 mg/day oral; or TU 1000 mg IM+daily oral placebo.
98016 Completed	Male contraception in healthy males (n = 14)	A single-center, prospective, 1-arm, uncontrolled study to investigate the efficacy and safety of male contraception with TU and nor-ethisterone enanthate (NET-EN) over 24 weeks	Phase 2	Open-label, single arm multiple dose	TU 1000 mg IM + NET-EN 200 mg IM
99015 Completed	Male contraception in healthy males (n = 42)	Study on efficacy and safety of male contraception with TU and NET combined in different application regimens	Phase 2	Randomized, double-blind, parallel-group, 3-arm, placebo-controlled, multiple-dose	TU 1000 mg IM+NET-EN 200 mg IM TU 1000 mg IM+NET-EN 400 mg IM TU 1000 mg IM+NET-A 10 mg/day oral
42306 Completed	Male contraception in healthy males (n = 298)	A phase IIb, double blind, placebo-controlled, randomized, multicenter, multiple dose trial investigating the efficacy, safety and pharmacokinetics of a subcutaneous etonogestrel (ENG) rod combined with intramuscular TU for male fertility control	Phase 2b	Randomized, double-blind, parallel-group, 7-arm, placebo-controlled, multiple-dose	TU 750 mg IM+LR ENG Implant every 10 weeks TU 750 mg IM+LR ENG Implant every 12 weeks TU 1000 mg IM+LR ENG Implant every 12 weeks TU 750 mg IM+HR ENG Implant every 10 weeks TU 750 mg IM+HR ENG Implant every 12 weeks TU 1000 mg IM+HR ENG Implant every 12 weeks Placebo IM+Placebo Implant
International Postmarketing Studies (N = 2424)					
AWB 0105 Completed	Androgen Deficiency in Men (n = 869)	Efficacy and tolerability of Nebido®	Post-marketing surveillance: prospective, non-interventional	Open-label, single-arm, multiple-dose	TU 1000 mg IM
39732	Hypogonadism	International, multicenter post	Post-	Open-label,	TU 1000 mg IM

(NE0601 IPASS) Completed	(n = 1411)	authorization surveillance study on the use of Nebido® to assess tolerability and treatment outcomes in daily clinical practice	marketing surveillance: prospective, non-interventional observational	single-arm, multiple-dose	
14329 (Czech NEO) Completed	Hypogonadism (n = 23)	NEO; Observational post-marketing study (Nebido)	Post-marketing surveillance: prospective, non-interventional observational	Open-label, single-arm, multiple-dose	TU 1000 mg IM
NB02 Completed	Hypogonadism (n = 20)	NEBIDO Therapy in Hypogonadal Male Patients With Paraplegia With Osteoporosis Compared With Conventional Osteoporosis	Post-marketing surveillance: prospective, non-interventional observational	Open-label, 3-arm, multiple dose, single center	TU 1000 mg IM
TG09 Completed	Hypogonadism (n = 29)	Efficacy and tolerability of Testogel/Nebido in combination with a standardized exercise and diet programme in hypogonadal male patients with abdominal obesity compared with exercise and diet programme	Post-marketing surveillance: non-interventional observational	Open-label, 2-arm, multiple-dose, single center	TU 1000 mg, Testogel
14853 Terminated Early[b]	Hypogonadism (n = 3)	Effect of exercise alone or in combination with testosterone replacement on muscle strength and quality of life in older men with low testosterone concentrations; a randomized double-blind, placebo controlled study	Post-marketing surveillance: interventional	Randomized, Double blind, parallel-group, 2-arm, placebo controlled, multiple-dose	TU 1000 mg, Placebo

[a] terminated early by Sponsor.
[b] terminated early due to slow recruitment rate.
CPA=Cyproterone acetate; ENG=Etonogestrel; IM=Intramuscular; LNG=Levonorgestrel; NET-A= Norethisterone acetate; NET-EN=Norethisterone enanthate; SC=Subcutaneous; TE=Testosterone enanthate; TU=Testosterone undecanoate.
Source: Integrated Safety Summary

Overview of Clinical Studies

The Clinical review of NDA 022-219 focused on Parts C and C2 (extension) of Study IP157-001, a single, U.S., Phase 3 study. For safety, the review focused on the information from Study IP157-001, as well as safety information from 12 additional European and International Phase 1-3 studies, and finally, the relevant post-marketing safety experience.

Study IP157-001 was a phase 3, open-label, multicenter clinical trial conducted in the US to evaluate the safety and pharmacokinetics (PK) of testosterone undecanoate injection in hypogonadal men. This study was conducted in 5 parts (Parts A, B, C, C2, and D), with varying dose and treatment regimens. IP157-001 Part C and Part C2 provide pivotal data to support efficacy for U.S. approval. The study was conducted after discussions with DRUP and took into consideration FDA recommendations.

- Treatment in Part A of the study was either TU 750 mg or 1000 mg injected intramuscularly every 12 weeks. Data was presented for Stage 1, which included data through the 5th injection visit.
- Treatment in Part B of the study was TU 1000 mg given intramuscularly at baseline followed by either TU 750 mg or 1000 mg injected 8 weeks later and then every 12 weeks thereafter.
- Treatment in Part C was TU 750 mg given intramuscularly with a second injection ("loading") at 4 weeks and at 10-week intervals thereafter. This loading dosing regimen was selected to provide adequate testosterone replacement over a 10-week dosing interval and to reach steady state conditions sooner than those observed for the treatment regimens in Part A.
  - In Part C, the pivotal measurement was after the 3rd injection (e.g., Stage 1).
  - In Part C2, the pivotal measure was after the 2nd injection.
- Part D was exploratory and was intended to evaluate the PK of TU when given subcutaneously. A total of 21 patients from Part C and 22 patients from Part A crossed over into Part D. No PK parameters were derived from serum total testosterone concentrations measured after SC injections, and no efficacy analysis was performed for Part D

5.2 Review Strategy

During the current review process, this reviewer conducted an efficacy review of the pivotal study IP157-001 Part C and the newly submitted Part C2.

For safety, the reviewer particularly concentrated on the severe post-injection reactions observed in the postmarketing period. The reviewer conducted individual case by case reviews of the Sponsor's collection of all assumed cases of POME and anaphylaxis during postmarket period. The reviewer also reviewed the most recent Safety Update submitted on November 29, 2012.

In addition, the reviewer reviewed the Sponsor's addendum to the submission Section 5.3.5.3, evaluation of immediate post injection adverse reactions by the "independent adjudicators" submitted on March 4, 2013.

6 Review of Efficacy

Efficacy Summary

The efficacy of testosterone undecanoate injection as a TRT for conditions associated with male hypogonadism is supported by a single, open-label, pivotal study using the 750mg loading regimen (Study IP157-001, Part C, C2) in approximately 130 hypogonadal males. Different dosage strengths and different dose regimens were tested during the development program for

Aveed, and the results from these additional Phase 2 and Phase 3 studies served as supporting data. In addition, a number of studies have been conducted outside the US both prior to and since the time of initial approval of testosterone undecanoate injection outside the U.S. (in 2004).

In summary,

- The Efficacy section of this review presents a qualitative integration of complete final results from Part C and Part C2 of Study IP157-001 rather than a pooled analysis of efficacy.
- Testosterone undecanoate injection 750 mg loading regimen provides acceptable replacement of testosterone, and
- The data also characterize the testosterone PK for 3 consecutive injection cycles (2nd, 3rd, and 4th) and provide support for the use of the 750 mg loading dosage regimen as the recommended therapeutic dose.

The Sponsor met the current requirement for demonstration of efficacy for this indication.

6.1 Indication

The applicant's proposed indication is replacement therapy in adult males for conditions associated with deficiency or absence of endogenous testosterone. The product will be administered as the "750 mg loading regimen" with 750 mg given at initiation and at 4 weeks, followed by 750 mg every 10 weeks thereafter. The evidence from Study IP157-001 Parts C and C2 shows that adequate T replacement is achieved with the use of that regimen.

6.1.1 Methods

This reviewer used following approach for the efficacy review:

- Review the proposed indication, key protocols, and regulatory and scientific background.
- Identify and review the well-controlled studies to support the indication.
- Conduct detailed review of each key parts for efficacy.
- Generate conclusions regarding efficacy from the pivotal and supporting studies.

6.1.2 Efficacy Study Design

IP157-001 Part C

The primary objective for Part C of the study was to evaluate the PK of testosterone from TU 750 mg given intramuscularly at baseline, at 4 weeks, and then every 10 weeks thereafter, over the 10-week interval following the 3rd injection, via multiple measurements of serum total testosterone.

The secondary objectives for Part C of the study were:

- To evaluate the PK of testosterone over the 10-week interval following the 4th injection, via multiple measurements of serum total testosterone
- To compare serum levels of dihydrotestosterone (DHT), estradiol, and sex hormone binding globulin (SHBG) to simultaneous levels of serum total testosterone over the 3rd injection interval
- To evaluate safety through up to 9 injections in hypogonadal men

IP157-001 Part C2

The primary objective for Part C2 of the study was to evaluate the maximum concentration (C_{max}) of testosterone from TU 750 mg, given intramuscularly at baseline, at 4 weeks, and then every 10 weeks thereafter, over the 10-week interval following the 2nd injection, via multiple measurements of serum total testosterone, in up to approximately 20 hypogonadal men.
In order to provide a complete PK profile of TU 750 mg during the 2nd injection interval, the Day 70 measurement was included in the evaluations.

The secondary objectives for Part C2 of the study were:

- To compare serum levels of DHT, estradiol, and SHBG to simultaneous levels of serum total testosterone.
- To evaluate safety in patients treated with TU 750 mg at baseline, at 4 weeks, and then every 10 weeks thereafter, through up to 6 injections in hypogonadal men.

Part C2 replicated the dosing regimen of Part C, but focused on PK assessment during the 2nd injection interval. Approximately 20 patients were to be enrolled. The total exposure for individual patients was to be approximately 12 months (54 weeks).

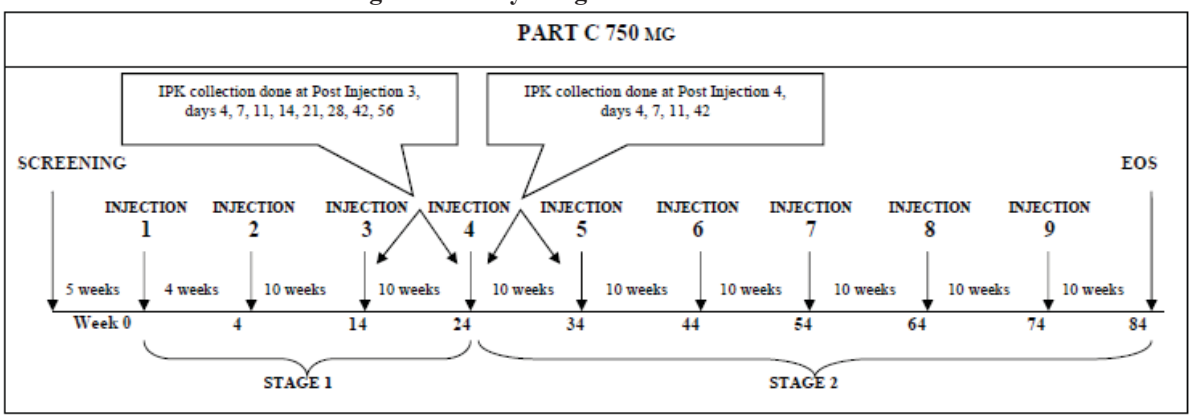
All patients were to have PK assessments during the 2nd injection interval in order to capture C_{max} in the post-loading dose interval. In addition, patients also had a trough PK assessment at the 3rd injection and continued to have trough PK captured at each 10-week dosing interval visit through the remainder of the study. Safety was assessed through 6 injections.

6.1.3 Efficacy Study Conduct

6.1.3.1 Study Schedule and Conduct

The Schedule of Events for Part C is displayed in Figure 1.

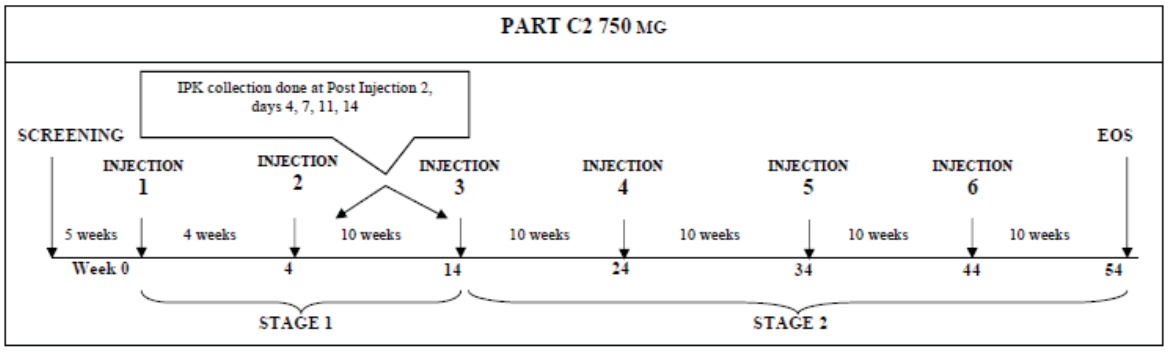
Figure 1: Study design for IP157-001 Part C



EOS = end of study; IPK = Intensive pharmacokinetics

The Schedule of Events for Part C2 is displayed in Figure 2.

Figure 2: Study design for IP157-001 Part C2



EOS = end of study; IPK = Intensive pharmacokinetics

6.1.3.2 Eligibility Criteria

Patients enrolled in both Parts C and C2 of the study were to be men at least 18 years of age with primary or secondary hypogonadism (morning screening serum testosterone concentration <300 ng/dL). They could not have an American Urological Association Symptom Score ≥15 or significant prostatic symptoms, a screening serum prostate specific antigen level above 4 ng/mL or hyperplasia of the prostate (size >75 cm^3 as measured by transrectal ultrasonography), or history or suspicion of carcinoma, tumors, or induration of the prostate or the male mammary gland. In addition, the use of any sex hormones within 28 days (e.g., injectable testosterone preparations) or 7 days (e.g., oral, gel, patch testosterone preparations) prior to the screening serum testosterone collection for PK assessment as well as at any time throughout the study was prohibited. Complete inclusion/exclusion criteria were provided in the study protocol. A lower weight threshold of 65 kg was added as an exclusion criterion in Amendment 8 to account for an inverse relationship between weight and serum testosterone concentration,

6.1.4 Efficacy Analysis Populations

The Clinical Efficacy section presents a qualitative integration of complete final results of Part C and Part C2 of Study IP157-001 rather than a pooled analysis of efficacy. Part C2 in conjunction with Part C were designed to characterize the PK of the injection intervals of an initial TU 750 mg dose, followed by TU 750 mg given at 4 weeks and then at 10-week intervals thereafter in a repeated-injection setting. In summary, the study characterized 3 consecutive injection cycles (2nd, 3rd, and 4th) of PK behavior of TU 750 mg. This data provided support for the use of this dosage regimen as the recommended therapeutic dose.

Analysis Population

Table 6.1 IP157-001 Part C Study Populations

Population	Number of Subjects	Definition
Total Patient Sample	130	All subjects who were enrolled in Part C and given at least 1 injection of study drug
PK Population[a]	117	Subjects who had a minimum of 4 serum total testosterone concentration values during the 3rd injection interval. The 4 values could include the Day 0 and/or Day 70 values from the interval. Additionally, subjects had to weigh at least 65 kg[b] in order to be included in the PK Population. Any subject found to have used other TRT during the study was excluded from the PK population.
Steady-State PK Population	104	All subjects in the PK Population with non-missing 4th and 5th injection serum total testosterone concentrations
Long-Term PK Population	98	All subjects in the Steady-State PK Population with a non-missing 8th injection serum total testosterone concentration

[a] The primary efficacy endpoint was based on the PK population.

[b] One subject with a baseline weight <65 kg enrolled in the study and was excluded from the PK Population. An additional exclusion criterion was added in Amendment 8.

Source: Summary of Clinical Efficacy, Table 3

Table 6.2 IP157-001 Part C2 Study Population

Population	Number of Subjects	Definition
Total Patient Sample	23	All subjects who were enrolled in Part C2 and given at least 1 injection of study drug

Source: Summary of Clinical Efficacy, Table 4

6.1.5 Efficacy Endpoints and Result

6.1.5.1 Primary Efficacy Endpoint Results

IP157-001 Part C Primary Efficacy Results:

TU 750 mg given intramuscularly at baseline, at 4 weeks, then at 10-week intervals thereafter provided adequate TRT (as measured by C_{avg}) while not providing excessive TRT (as measured by C_{max}). The mean C_{avg} during the pivotal interval (3rd injection) was 494.9 ng/dL (coefficient of variation [CV]: 28.6%), and was within the normal range (i.e., 300 to 1000 ng/dL), with 110 subjects (94.0% [2-sided 95% confidence interval (CI), 89.7%-98.3%]) achieving the normal range for C_{avg}. At all time points measured during the 3rd injection interval, the mean serum total testosterone concentrations remained within the normal range

Table 6.3 Part C: Descriptive Statistics for Injection 3 Serum Total Testosterone (ng/dL) Pharmacokinetic Parameters, Pharmacokinetic Population

	C-750 mg (N=117)							
	N	Mean	SD	Min	Median	Max	%CV	Geometric Mean
$AUC_{0\text{-}70days}$ (d•ng/dL)	117	34645.6	9902.45	13755.1	33342.2	70016.9	28.6	33263.6
C_{trough} (ng/dL)	117	323.5	99.11	138.2	316.9	611.1	30.6	309.0
C_{max} (ng/dL)	117	890.6	345.11	311.0	813.6	1758.5	38.8	826.8
T_{max} (days)	117	10.0	7.11	4.0	7.0	42.0	71.1	8.4
C_{avg} (ng/dL)	117	494.9	141.46	196.5	476.3	1000.2	28.6	475.2

Source: Summary of Clinical Efficacy

A total of 110 subjects (94.0% [2-sided 95% CI, 89.7%-98.3%]) had C_{avg} between 300 and 1000 ng/dL and were considered responders, and 7 subjects were considered non-responders. Of the 7 subjects who were non-responders, 6 subjects (5.1% [2-sided 95% CI, 1.1%-9.1%]) had a C_{avg} <300 ng/dL (range: 196.5 to 296.9 ng/dL) and 1 subject (0.9% [2-sided 95% CI, 0.0%-2.5%]) had a C_{avg} of 1000.2 ng/dL.

Table 6.4 Study IP157-001 Part C: Number (%) of Patients (and Two-Sided 95% Confidence Interval) Meeting Serum Total Testosterone C_{avg} Criteria for a Responder During the 3rd Injection Interval, Pharmacokinetic Population

Serum Total Testosterone C_{avg} Criteria	C-750 mg (N=117)	
	N (%)	95% CI
Responder		
C_{avg} within 300-1000 ng/dL	110 (94.0%)	(89.7%, 98.3%)
Not a Responder		
C_{avg} <300 ng/dL	6 (5.1%)	(1.1%, 9.1%)
C_{avg} >1000 ng/dL	1 (0.9%)	(0.0%, 2.5%)

Source: Summary of Clinical Efficacy

IP157-001 Part C2 Primary Efficacy Results:

Table 6.5 Study IP157-001 Part C2: Descriptive Statistics for Serum Total Testosterone (ng/dL) Pharmacokinetic Parameters after Injection 2, Total Patient Sample/Pharmacokinetic Sample

	C2-750 mg (N=23)

	N	Mean	SD	Min	Median	Max	%CV	Geometric Mean
$AUC_{0\text{-}70days}$ (d•ng/dL)	23	31475.2	10990.41	17114.4	30436.2	68092.8	34.9	29910.2
C_{trough} (ng/dL)	23	317.4	105.31	135.8	298.9	487.5	33.2	299.1
C_{max} (ng/dL)	23	689.0	266.94	338.6	657.2	1576.3	38.7	646.6
T_{max} (days)	23	8.0	3.27	4.0	7.0	14.0	41.1	7.3
C_{avg} (ng/dL)	23	449.6	157.01	244.5	434.8	972.8	34.9	427.3

$AUC_{0\text{-}70days}$=Area under curve from Day 0 through Day 70; C_{avg}=Average concentration; C_{max}=Maximum concentration; C_{trough}=Day 70 concentration; CV=Coefficient of variation; T_{max}=Time of maximum concentration.
Note: C2-750 mg refers to TU 750 mg.
Source: Summary of Clinical Efficacy

Table 6.6 Study IP157-001 Part C2: Number (%) of Patients Meeting Serum Total Testosterone C_{max} Criteria for Success During the 2nd Injection Interval, Total Patient Sample / Pharmacokinetic Sample

Serum Total Testosterone C_{max} Observed During 2nd Injection Interval	Criteria for Success[a]	C2-750 mg (N=23) N (%)
≤1500 ng/dL	≥85% of patients	22 (95.7%)
>1500 to <1800 ng/dL	--	1 (4.3%)
1800-2500 ng/dL	≤5% of patients	0
>2500 ng/dL	No patients	0

[a] All 3 criteria for success must have been met in order to reject the null hypothesis in favor of the alternate hypothesis. If any of the 3 criteria did not meet its criteria for success, the null hypothesis could not be rejected.
Note: Percentages based on non-missing data. C2-750 mg refers to TU 750 mg.
Source: Summary of Clinical Efficacy

Comparison of Efficacy Endpoints

In Part C of the study, percentages of "responders", defined as patients with C_{avg} within the normal, was comparable between the 3rd and 4th injection intervals (94.0% and 96.2%, respectively) (Table 6.7). A maximum serum T concentration (C_{max}) <1500 mg/dL was achieved in 92.3% of the PK Population and in 92.3% of the Steady-State PK Population (Table 6.8).

In Part C2, prior to steady state, Cmax was <1500 mg/dL in 95.7% of the Total Patient Sample/PK Sample (Table 6.8).

Table 6.7 Study IP157-001 Part C: Number (%) of Patients Meeting Serum Total Testosterone C_{avg} Criteria for Success During the 3rd and 4th Injection Intervals, Pharmacokinetic and Steady-State PK Populations

Serum Total Testosterone	C-750 mg (N=117) 3rd Injection Interval, PK Population		C-750 mg (N=104) 4th Injection Interval, SS PK Population	
	N (%)	95% CI	N (%)	95% CI
Responder				
C_{avg} within 300-1000 ng/dL	110 (94.0%)	(89.7%; 98.3%)	100 (96.2%)	(92.5%; 99.8)
Not a Responder				
C_{avg} <300 ng/dL	6 (5.1%)	(1.1%; 9.1%)	4 (3.8%)	(0.2%; 7.5%)
C_{avg} >1000 ng/dL	1 (0.9%)	(0.0%; 2.5%)	0	

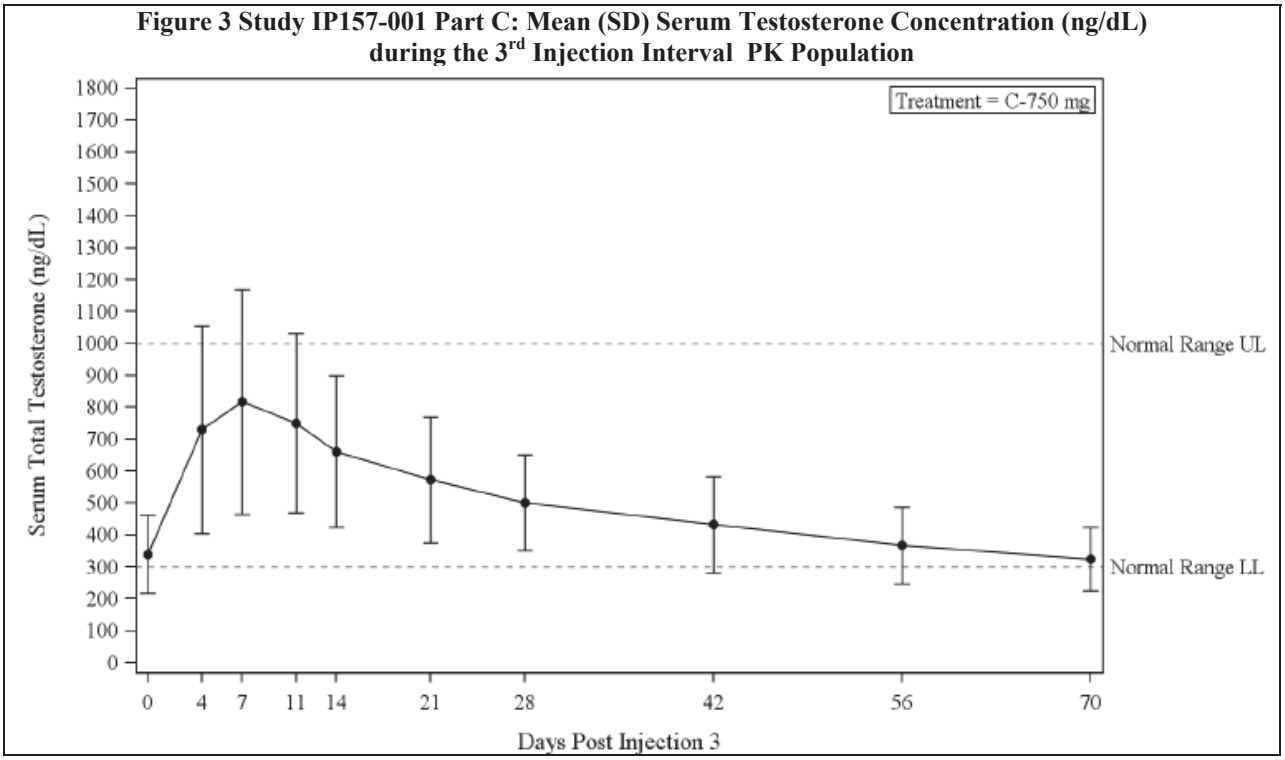
PK=Pharmacokinetic; SS=Steady-state.
Note: Percentages based on non-missing data. C-750 mg refers to TU 750 mg.
Source: Summary of clinical Efficacy

Table 6.8 Study IP157-001 Part C, Part C2: Number (%) of Patients Meeting Serum Total Testosterone C_{max} Criteria for Success, Pharmacokinetic Population, Steady-State PK Population and Total Patient Sample/Pharmacokinetic Sample

Serum Total Testosterone C_{max} Observed	Criteria for Success[a]	C-750 mg (N=117) 3rd Injection Interval, PK Population	C-750 mg (N=104) 4th Injection Interval, SS PK Population	C2-750 mg (N=23) 2nd Injection Interval, TPS/PK Sample
		N (%)	N (%)	N (%)
≤1500 ng/dL	≥85% of patients	108 (92.3%)	96 (92.3%)	22 (95.7%)
>1500 to <1800 ng/dL	--	9 (7.7%)	4 (3.8%)	1 (4.3%)
1800-2500 ng/dL	≤5% of patients	0	4 (3.8%)	0
>2500 ng/dL	No patients	0	0	0

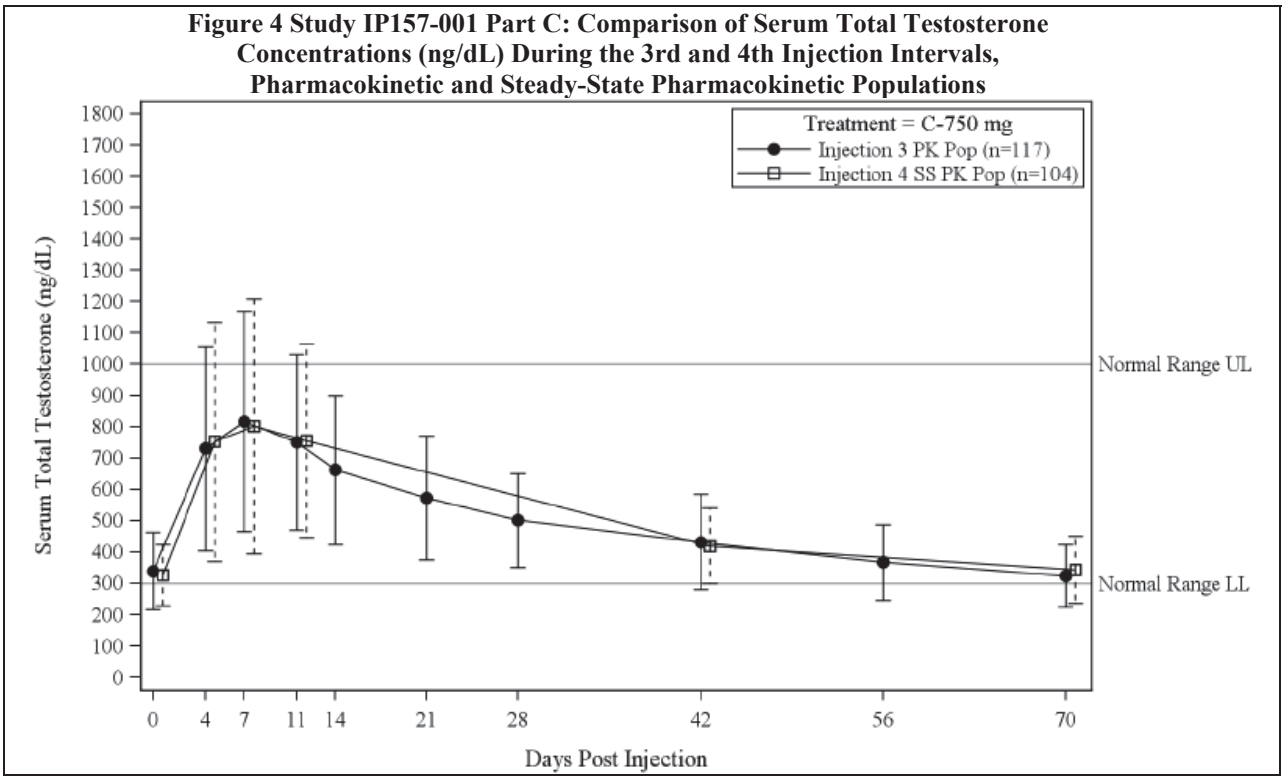
[a] All 3 criteria must have been met in order to reject the null hypothesis in favor of the alternate hypothesis. If any of the 3 criteria did not meet its Criteria for Success, the null hypothesis could not be rejected.
PK=Pharmacokinetic; SS=Steady-state; TPS=Total Patient Sample.
Note: Percentages based on non-missing data. C-750 mg refers to TU 750 mg. C2-750 mg refers to TU 750 mg.
Source: Summary of clinical Efficacy

Figure 3 Study IP157-001 Part C: Mean (SD) Serum Testosterone Concentration (ng/dL) during the 3rd Injection Interval PK Population



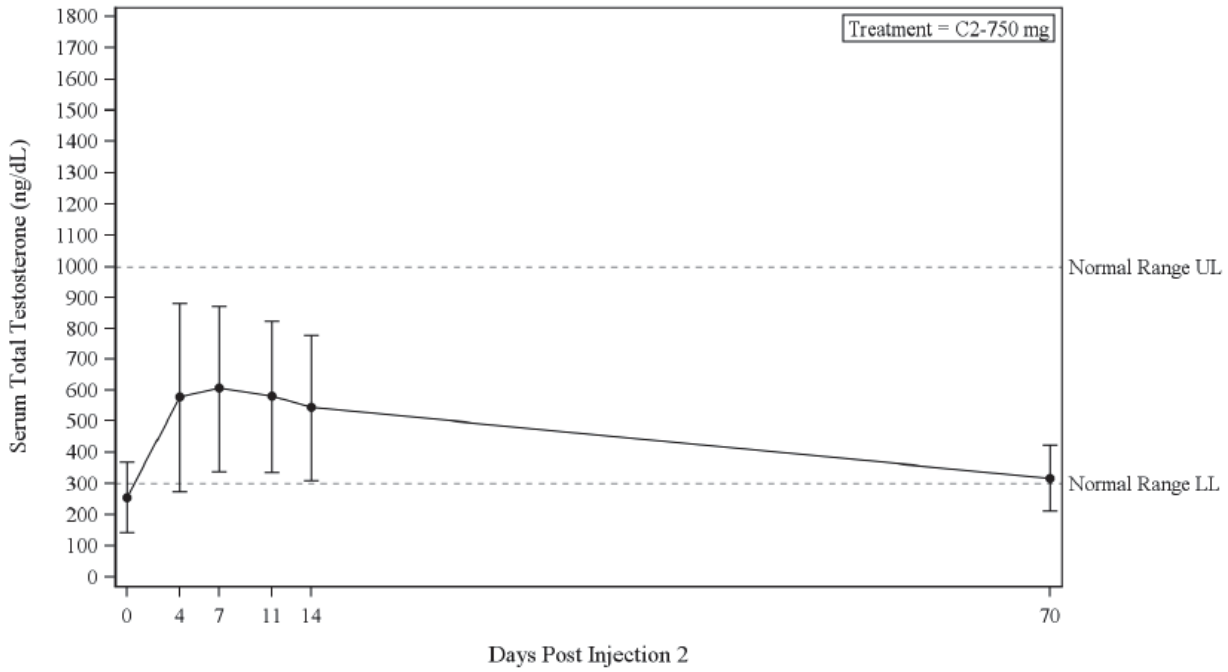
Source: Summary of Clinical Efficacy

Figure 4 Study IP157-001 Part C: Comparison of Serum Total Testosterone Concentrations (ng/dL) During the 3rd and 4th Injection Intervals, Pharmacokinetic and Steady-State Pharmacokinetic Populations



Source: Summary of Clinical Efficacy

Figure 5 Study IP157-001 Part C2: Mean (SD) Serum Testosterone Concentration (ng/dL) during the 2nd Injection Interval PK Population

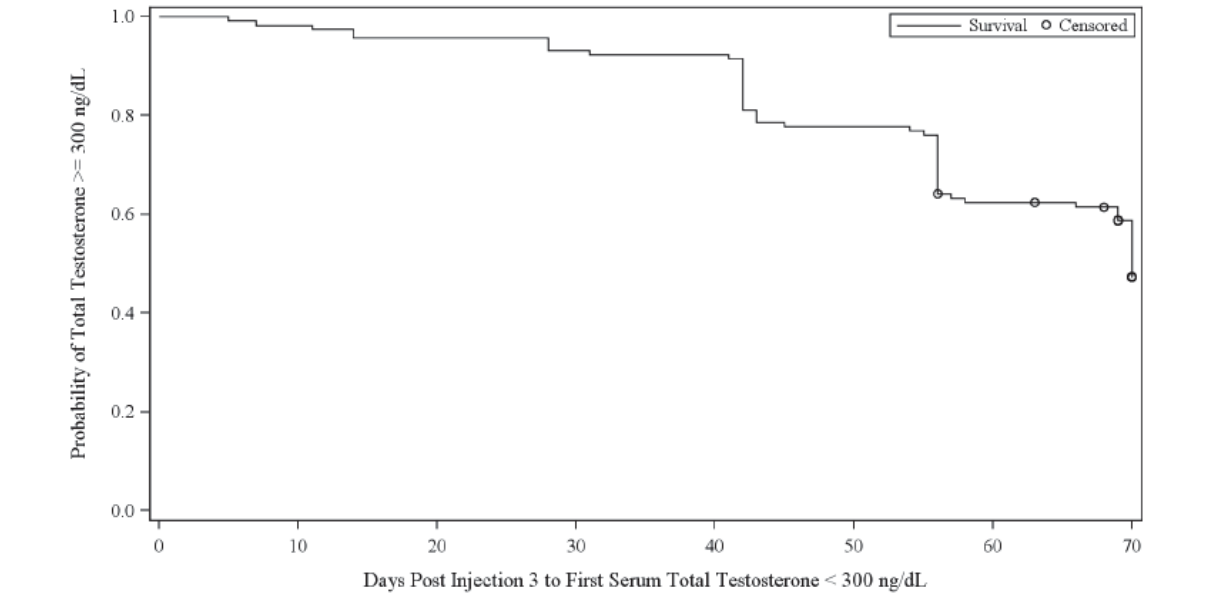


Source: Summary of Clinical Efficacy

6.1.5.2 Secondary Efficacy Endpoint Results

For the PK Population, the overall median time to the first serum total testosterone concentration <300 ng/dL based on a Kaplan-Meier estimate was 70 days.

Figure 6 Study IP157-001 Part C: Kaplan-Meier Estimate of the Probability of the First Serum Total Testosterone Concentrations < 300 ng/dL During the 3rd Injection Interval, Pharmacokinetic Population



Source: Summary of Clinical Efficacy

In regard to other secondary endpoints:

Table 6.9 Other Secondary Efficacy Endpoints

PK	Part C	Part C2
C_{avg} $AUC_{0\text{-}70days}$ C_{trough}	During the 3rd injection interval mean C_{avg} was 494.9 ng/dL and was within the normal range (i.e., 300 to 1000 ng/dL) with 110 subjects (94.0%) achieving this range; mean $AUC_{0\text{-}70days}$ = 34645.6 d•ng/dL, and mean C_{trough} = 323.5 ng/dL. During the 4th injection interval mean C_{avg} was 514.3 ng/dL and was within the normal range (i.e., 300 to 1000 ng/dL) with 100 subjects (96.2%) achieving this range; mean $AUC_{0\text{-}70days}$ = 35999.5 d•ng/dL, and mean C_{trough} = 342.8 ng/dL.	During the 2nd injection interval mean C_{avg} (prior to steady state) = 449.6 ng/dL and was within the normal range (300 to 1000 ng/dL); mean $AUC_{0\text{-}70days}$ = 31475.2 d•ng/dL, and mean C_{trough} = 317.4 ng/dL.
C_{max}	During the 3rd injection interval mean C_{max} was 890.6 ng/dL; no subjects had a C_{max} value >2500 ng/dL or between 1800 and 2500 ng/dL; 108 subjects (92.3%) had a C_{max} value ≤1500 ng/dL. During the 4th injection interval, mean C_{max} was 837.6 ng/dL; no subjects had a C_{max} value >2500 ng/dL; 4 subjects (3.8%) had a C_{max} value between 1800 and 2500 ng/dL; and 96 subjects (92.3%) had a C_{max} value ≤1500 ng/dL.	Prior to steady-state, mean C_{max} was 689.0 ng/dL following the initial dose at Week 4. The 2nd injection interval was investigated to confirm that the loading dose did not result in high C_{max} values. No subject had a C_{max} value >2500 ng/dL or between 1800 and 2500 ng/dL; and 22 subjects (95.7%) had a C_{max} value ≤1500 ng/dL during the 2nd injection interval.
C_{trough}	Mean trough concentration of serum total testosterone was within the normal range (300 to 1000 ng/dL) at Week 4 and remained within the normal range at each trough time point through Week 74 after the first injection.	Mean trough concentrations of serum total testosterone were within the normal range at Week 14 and remained within the normal range at each subsequent trough time point through Week 44 after the 1st injection.

In an analysis by subgroup, adequate TRT was provided by IM injection of TU 750 mg regardless of age, race, body mass index (BMI), and prior TRT use.

For Part C and Part C2, the post-baseline mean serum concentrations of DHT and estradiol closely paralleled those for total testosterone.

6.1.6 Overall Conclusion of Efficacy for Testosterone Undecanoate Injection

Treatment with TU 750 mg given intramuscularly at baseline, at 4 weeks, and then every 10 weeks thereafter was found to provide adequate TRT (300 to 1000 ng/dL) in hypogonadal men weighing >65kg (as measured by testosterone C_{avg}), while not providing excessive TRT (as measured by C_{max}). Steady-state was achieved by the 3rd IM injection of TU 750 mg.

Thus, the primary efficacy objectives of the Phase 3 study were met.

7 Review of Safety

Safety Summary

Based on review of severe postinjection adverse reactions in the postmarketing period (n= 137 cases of severe POME and anaphylaxis), Aveed is not considered as safe for the proposed indication. The risk to benefit ratio is not favorable.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

Overview of the Safety Database for Testosterone Undecanoate injection

The safety database for testosterone undecanoate injection consists of clinical trials for testosterone replacement as well as TU injection as part of male contraception studies. Additional data was obtained from overseas postmarketing studies and postmarketing experience. An overview of the available safety information is outlined in the table below:

Table 7.1 Safety Data Integration of Clinical and Postmarketing Studies

Study Pool	Study Number	Total Number of Subjects in the Pool
US Study IP157-001 Parts C and C2	IP157-001 Parts C and C2	153
US Study IP157-001 All Parts	IP157-001 Parts A, B, C, C2 and D	524
European Clinical Studies	JPH01495, JPH04995, ME98096, ME97029, 306605, 303934	201
Male Contraception Clinical Studies	97028, 97173, 98016, 99015, 42306	407
International Postmarketing Studies	39732 (NEO601 IPASS), AWB0105, Czech NEO, NB02, TG09, and 14853	2424
Number of Subjects Included in Adverse Events of Interest Investigations		
Adverse Events of Interest (Pulmonary Oil Microembolism [POME], Anaphylaxis, and Injection Site Reactions)	IP157-001 (All Parts), JPH01495, JPH04995, ME98096, ME97029, 306605, 303934, 97028, 97173, 98016, 99015, 42306, 39732 (NEO601 IPASS) AWB0105, Czech NEO, NB02, TG09, and 14853	3556

Source: Integrated Safety summary

Reviewer's comment: During this review cycle, the postmarket experience based on the entirety of the postmarketing adverse reaction case reports was the main focus of the evaluation. Specifically, the immediate postinjection reactions were each evaluated in depth.

7.2 Supporting Safety Results

7.2.1 Commonly Reported Adverse Events in Clinical Trials of Testosterone Undecanoate Injection

7.2.1.1 U.S. Study IP157-001 Parts C and C2:

In IP157-001 Parts C and C2, most TEAEs were attributable to the system organ class (SOC) of Infections and Infestations (47 subjects [30.7%]). The most commonly reported TEAEs (occurring in ≥5% of subjects) were sinusitis (11 subjects [7.2%]), PSA increased (10 subjects [6.5%]), prostatitis (10 subjects [6.5%]), arthralgia (9 subjects [5.9%]), insomnia (9 subjects [5.9%]), and acne (8 subjects [5.2%]).

Table 7.2 Incidence of Treatment-Emergent Adverse Events that Occurred in ≥ 3% of the Population, Subjects Treated with TU in Study IP157-001 Part C and Part C2

MedDRA SOC (Body System)/ Preferred Term	Number (%) of Subjects TU-750 mg (N=153)
At Least One Treatment-Emergent Adverse Event	104 (68.0%)
Infections and Infestations	**47 (30.7%)**
Sinusitis	11 (7.2%)
Nasopharyngitis	7 (4.6%)
Bronchitis	6 (3.9%)
Upper Respiratory Tract Infection	6 (3.9%)
General Disorders and Administration Site Conditions	**31 (20.3%)**
Fatigue	7 (4.6%)
Injection Site Pain	7 (4.6%)
Musculoskeletal and Connective Tissue Disorders	**30 (19.6%)**
Arthralgia	9 (5.9%)
Back Pain	6 (3.9%)
Pain In Extremity	5 (3.3%)
Investigations	**24 (15.7%)**
Prostatic Specific Antigen Increased	10 (6.5%)
Reproductive System and Breast Disorders	**20 (13.1%)**
Prostatitis	10 (6.5%)
Psychiatric Disorders	**19 (12.4%)**
Insomnia	9 (5.9%)
Anxiety	5 (3.3%)
Injury, Poisoning and Procedural Complications	**18 (11.8%)**
Muscle Strain	5 (3.3%)
Skin and Subcutaneous Tissue Disorders	**15 (9.8%)**
Acne	8 (5.2%)
Vascular Disorders	**11 (7.2%)**
Hypertension	5 (3.3%)

Note: Subjects are counted once within each SOC (Body System) and Preferred Term. Treatment-emergent adverse events occurred on or after the date of first injection of TU. Adverse events were coded with MedDRA version 14.0. Source: Summary of Clinical Safety

7.2.1.2 U.S. Study IP157-001 All Parts:

In IP157-001, all parts combined, most TEAEs in both treatment groups were attributable to the SOC of Infections and Infestations (TU 750 mg, 84 subjects [30.9%]; TU 1000 mg, 83 subjects [32.9%]); the other most commonly reported TEAEs included: prostatic specific antigen increased (TU 750 mg, 20 subjects [7.4%]; TU 1000 mg, 10 subjects [4.0%])

Table 7.3 Incidence of Treatment-Emergent Adverse Events that Occurred in ≥ 3% of the Population, Subjects Treated with TU in IP157-001 All Parts Combined, By Dose

MedDRA SOC (Body System)/ Preferred Term	Number (%) of Subjects		
	TU-750 mg (N=272)	TU-1000 mg (N=252)	Overall (N=524)
At Least One Treatment-Emergent Adverse Event	198 (72.8%)	195 (77.4%)	393 (75.0%)
Infections and Infestations	**84 (30.9%)**	**83 (32.9%)**	**167 (31.9%)**
Sinusitis	19 (7.0%)	13 (5.2%)	32 (6.1%)
Upper Respiratory Tract Infection	15 (5.5%)	15 (6.0%)	30 (5.7%)
Nasopharyngitis	14 (5.1%)	14 (5.6%)	28 (5.3%)
Bronchitis	12 (4.4%)	8 (3.2%)	20 (3.8%)
Urinary Tract Infection	6 (2.2%)	10 (4.0%)	16 (3.1%)
Musculoskeletal and Connective Tissue Disorders	**53 (19.5%)**	**69 (27.4%)**	**122 (23.3%)**
Arthralgia	12 (4.4%)	11 (4.4%)	23 (4.4%)
Back Pain	13 (4.8%)	10 (4.0%)	23 (4.4%)
Musculoskeletal Pain	6 (2.2%)	12 (4.8%)	18 (3.4%)
Pain In Extremity	9 (3.3%)	9 (3.6%)	18 (3.4%)
Osteoarthritis	2 (0.7%)	8 (3.2%)	10 (1.9%)
Investigations	**51 (18.8%)**	**56 (22.2%)**	**107 (20.4%)**
Prostatic Specific Antigen Increased	20 (7.4%)	10 (4.0%)	30 (5.7%)
General Disorders and Administ. Site Conditions	**50 (18.4%)**	**39 (15.5%)**	**89 (17.0%)**
Fatigue	17 (6.3%)	8 (3.2%)	25 (4.8%)
Injection Site Pain	10 (3.7%)	15 (6.0%)	25 (4.8%)
Reproductive System and Breast Disorders	**43 (15.8%)**	**42 (16.7%)**	**85 (16.2%)**
Prostatitis	15 (5.5%)	14 (5.6%)	29 (5.5%)
Erectile Dysfunction	4 (1.5%)	10 (4.0%)	14 (2.7%)
Gastrointestinal Disorders	**32 (11.8%)**	**46 (18.3%)**	**78 (14.9%)**
Diarrhoea	4 (1.5%)	11 (4.4%)	15 (2.9%)
Nausea	4 (1.5%)	8 (3.2%)	12 (2.3%)
Psychiatric Disorders	**34 (12.5%)**	**35 (13.9%)**	**69 (13.2%)**
Insomnia	12 (4.4%)	12 (4.8%)	24 (4.6%)
Depression	8 (2.9%)	8 (3.2%)	16 (3.1%)
Anxiety	6 (2.2%)	8 (3.2%)	14 (2.7%)
Nervous System Disorders	**28 (10.3%)**	**34 (13.5%)**	**62 (11.8%)**
Headache	6 (2.2%)	8 (3.2%)	14 (2.7%)

Renal and Urinary Disorders	**24 (8.8%)**	**36 (14.3%)**	**60 (11.5%)**
Dysuria	3 (1.1%)	8 (3.2%)	11 (2.1%)
Nephrolithiasis	3 (1.1%)	8 (3.2%)	11 (2.1%)
Skin and Subcutaneous Tissue Disorders	**29 (10.7%)**	**30 (11.9%)**	**59 (11.3%)**
Acne	9 (3.3%)	4 (1.6%)	13 (2.5%)
Respiratory, Thoracic and Mediastinal Disorders	**29 (10.7%)**	**21 (8.3%)**	**50 (9.5%)**
Sleep Apnea Syndrome	10 (3.7%)	4 (1.6%)	14 (2.7%)
Vascular Disorders	**23 (8.5%)**	**18 (7.1%)**	**41 (7.8%)**
Hypertension	16 (5.9%)	10 (4.0%)	26 (5.0%)

Note: Subjects are counted once within each SOC (Body System) and Preferred Term. Treatment-emergent adverse events occurred on or after the date of first injection of TU. Adverse events were coded with MedDRA version 14.0. The events are listed in descending order based on the Overall column SOC. Source: Summary of Clinical Safety.

Reviewer's comment: **Although it is not uncommon to observe cases of upper respiratory infection, sinusitis and bronchitis in clinical trials, especially trials with a treatment duration of 1 year, it is possible that some pulmonary oil microembolism-related cough could be interpreted as bronchitis or other respiratory tract -related symptomatology.**

7.2.1.3 U.S. Study IP157-001 and European Clinical Studies:

In Study IP157-001 and 5 European clinical studies combined, all TEAEs (by preferred term) which occurred in <3% of hypogonadal subjects treated with TU in all pools of studies are shown in Table 14.

Table 7.4 Overall Incidence of Treatment-Emergent Adverse Events That Occurred in ≥ 3% of the Population in Any Pool of Study, Subjects Treated with TU in US and European Clinical Studies

MedDRA Preferred Term	Number(%) of Subjects (Overall)			
	IP157-001 Parts C and C2 (N=153)	IP157-001 (All Parts) (N=524)	EU Clinical Studies (N=201)	IP157-001 (All Parts) and EU Clinical Studies (N=725)
At Least One TEAE	104 (68.0%)	393 (75.0%)	145 (72.1%)	538 (74.2%)
At Least One Severe TEAE	22 (14.4%)	80 (15.3%)	27 (13.4%)	107 (14.8%)
Sinusitis	11 (7.2%)	32 (6.1%)	2 (1.0%)	34 (4.7%)
Prostatic Specific Antigen Increased	10 (6.5%)	30 (5.7%)	5 (2.5%)	35 (4.8%)
Prostatitis	10 (6.5%)	29 (5.5%)	5 (2.5%)	34 (4.7%)
Arthralgia	9 (5.9%)	23 (4.4%)	8 (4.0%)	31 (4.3%)
Insomnia	9 (5.9%)	24 (4.6%)	1 (0.5%)	25 (3.4%)
Acne	8 (5.2%)	13 (2.5%)	11 (5.5%)	24 (3.3%)
Nasopharyngitis	7 (4.6%)	28 (5.3%)	34 (16.9%)	62 (8.6%)
Fatigue	7 (4.6%)	25 (4.8%)	0	25 (3.4%)
Injection Site Pain	7 (4.6%)	25 (4.8%)	8 (4.0%)	33 (4.6%)
Upper Respiratory Tract Infection	6 (3.9%)	30 (5.7%)	5 (2.5%)	35 (4.8%)

Bronchitis	6 (3.9%)	20 (3.8%)	7 (3.5%)	27 (3.7%)
Back Pain	6 (3.9%)	23 (4.4%)	9 (4.5%)	32 (4.4%)
Pain In Extremity	5 (3.3%)	18 (3.4%)	2 (1.0%)	20 (2.8%)
Anxiety	5 (3.3%)	14 (2.7%)	1 (0.5%)	15 (2.1%)
Muscle Strain	5 (3.3%)	11 (2.1%)	1 (0.5%)	12 (1.7%)
Hypertension	5 (3.3%)	26 (5.0%)	10 (5.0%)	36 (5.0%)
Diarrhoea	3 (2.0%)	15 (2.9%)	8 (4.0%)	23 (3.2%)
Musculoskeletal Pain	3 (2.0%)	18 (3.4%)	2 (1.0%)	20 (2.8%)
Urinary Tract Infection	3 (2.0%)	16 (3.1%)	4 (2.0%)	20 (2.8%)
Depression	3 (2.0%)	16 (3.1%)	3 (1.5%)	19 (2.6%)
Headache	2 (1.3%)	14 (2.7%)	16 (8.0%)	30 (4.1%)
Blood Triglycerides Increased	2 (1.3%)	8 (1.5%)	7 (3.5%)	15 (2.1%)
Respiratory Tract Infection Viral	1 (0.7%)	5 (1.0%)	12 (6.0%)	12 (1.7%)

Note: TEAEs are listed in descending order for Study157-001 Parts C and C2. Subjects in IP157-001 Parts C and C2 were treated with TU 750 mg (N=153); Subjects in IP157-001 (All Parts) were treated with TU 750 mg (N=272) or TU 1000 mg (N=252); Subjects in EU Clinical Studies (JPH01495, JPH04995, ME98096, ME97029, 306605, 303934) were treated with TU 1000 mg (N=201); and Subjects in IP157-001 (All Parts) and EU Clinical Studies (JPH01495, JPH04995, ME98096, ME97029, 306605, 303934) were treated with TU 750 mg (N=272) or TU 1000 mg (N=453). Subjects are counted once within each Preferred Term. TEAEs occurred on or after the date of first injection of TU. Adverse events were coded with MedDRA version 14.0.
Source: Summary of Clinical Safety.

7.2.1.4 International Postmarketing Studies

All reported adverse events in the 6 International Postmarketing studies (n=2424) are presented in Table 25 below.

Table 7.5 Incidence of All Treatment-Emergent Adverse Events, Subjects Treated with TU in International Postmarketing Studies (39732 [NEO601 IPASS], AWB0105, Czech NEO, NB02, TG09, and 14853)

MedDRA Preferred Term	Number (%) of Subjects with TU 1000 mg (N=2424)	MedDRA Preferred Term	Number (%) of Subjects with TU 1000 mg (N=2424)
At Least 1 TEAE	197 (8.1%)	Dizziness	2 (0.1%)
At Least 1 Severe TEAE	27 (1.1%)	**Sciatica**	2 (0.1%)
PSA Increased	14 (0.6%)	Nipple Swelling	2 (0.1%)
Haematocrit Increased	13 (0.5%)	**Musculoskeletal Pain**	2 (0.1%)
Injection Site Pain	11 (0.5%)	**Aggression**	2 (0.1%)
Headache	7 (0.3%)	**Anxiety**	2 (0.1%)
Acne	6 (0.2%)	Confusional State	2 (0.1%)
Hyperhidrosis	5 (0.2%)	**Depression**	2 (0.1%)
Pruritus	4 (0.2%)	**Hot Flush**	2 (0.1%)
Influenza	4 (0.2%)	Anaemia	2 (0.1%)
BPH	4 (0.2%)	**Atrial Fibrillation**	2 (0.1%)
Myalgia	4 (0.2%)	**Myocardial Infarction**	2 (0.1%)

Hypertension	4 (0.2%)	**Hypertriglyceridaemia**	2 (0.1%)
Cough	4 (0.2%)	Blood Cholesterol Increased	1 (<0.1%)
Haemoglobin Increased	3 (0.1%)	Blood Creatinine Increased	1 (<0.1%)
Weight Increased	3 (0.1%)	**Blood Glucose Increased**	1 (<0.1%)
Chest Pain	3 (0.1%)	Blood Test Abnormal	1 (<0.1%)
Fatigue	3 (0.1%)	Blood Testosterone Increased	1 (<0.1%)
Injection Site Discomfort	3 (0.1%)	**Blood Triglycerides Increased**	1 (<0.1%)
Rash	3 (0.1%)	Haematocrit Abnormal	1 (<0.1%)
Upper Respir. Tract Infection	3 (0.1%)	Haemoglobin Abnormal	1 (<0.1%)
Diarrhoea	3 (0.1%)	**Oestradiol Increased**	1 (<0.1%)
Nausea	3 (0.1%)	Sperm Concentration Decreased	1 (<0.1%)
Gynaecomastia	3 (0.1%)	Weight Decreased	1 (<0.1%)
Pain In Extremity	3 (0.1%)	WBC Count Abnormal	1 (<0.1%)
Oropharyngeal Pain	3 (0.1%)	Hernia	1 (<0.1%)
Polycythaemia	3 (0.1%)	Immedi. Postinjection Reaction	1 (<0.1%)
Hypercholesterolaemia	3 (0.1%)	**Influenza Like Illness**	1 (<0.1%)
Blood Testosterone Decreased	2 (0.1%)	Injection Site Extravasation	1 (<0.1%)
Hematology Test Abnormal	2 (0.1%)	Injection Site Pruritus	1 (<0.1%)
Laboratory Test Abnormal	2 (0.1%)	**Injection Site Rash**	1 (<0.1%)
Injection Site Reaction	2 (0.1%)	Multi-Organ Failure	1 (<0.1%)
Irritability	2 (0.1%)	Oedema	1 (<0.1%)
Malaise	2 (0.1%)	Sluggishness	1 (<0.1%)
Oedema Peripheral	2 (0.1%)	**Unevaluable Event**[a]	1 (<0.1%)
Pain	2 (0.1%)	Dermatitis	1 (<0.1%)
Pyrexia	2 (0.1%)	Dermatitis Acneiform	1 (<0.1%)
Alopecia	2 (0.1%)	Dermatosis	1 (<0.1%)
Bronchitis	2 (0.1%)	Prurigo	1 (<0.1%)
Pharyngitis	2 (0.1%)	Seborrhoea	1 (<0.1%)
Sinusitis	2 (0.1%)	Eye Infection	1 (<0.1%)
GERD	2 (0.1%)	Hepatitis C	1 (<0.1%)
Infected Bites	1 (<0.1%)	**Insomnia**	1 (<0.1%)
Injection Site Abscess	1 (<0.1%)	Sleep Disorder	1 (<0.1%)
Lower Resp Tract Infection	1 (<0.1%)	Flushing	1 (<0.1%)
Onychomycosis	1 (<0.1%)	**Hypotension**	1 (<0.1%)
Osteomyelitis	1 (<0.1%)	Lymphoedema	1 (<0.1%)
Pharyngotonsillitis	1 (<0.1%)	Peripheral Vascular Disorder	1 (<0.1%)
Staphylococcal Sepsis	1 (<0.1%)	Phlebitis	1 (<0.1%)
Syphilis	1 (<0.1%)	Raynaud's Phenomenon	1 (<0.1%)
Tooth Abscess	1 (<0.1%)	Dyspnoea	1 (<0.1%)
Abdominal Distension	1 (<0.1%)	Productive Cough	1 (<0.1%)
Abdominal Pain	1 (<0.1%)	**Sleep Apnoea Syndrome**	1 (<0.1%)
Dyspepsia	1 (<0.1%)	Haemoconcentration	1 (<0.1%)
Dysphagia	1 (<0.1%)	Lymphadenopathy	1 (<0.1%)
Gastritis	1 (<0.1%)	**Bradycardia**	1 (<0.1%)

Hyperchlorhydria	1 (<0.1%)	**Cardiovascular Disorder**	1 (<0.1%)
Oesophagitis	1 (<0.1%)	Palpitations	1 (<0.1%)
Peritoneal Adhesions	1 (<0.1%)	Cataract Operation	1 (<0.1%)
Rectal Haemorrhage	1 (<0.1%)	Haemorrhoid Operation	1 (<0.1%)
Reflux Oesophagitis	1 (<0.1%)	Pituitary Tumour Removal	1 (<0.1%)
Tooth Disorder	1 (<0.1%)	Polypectomy	1 (<0.1%)
Carpal Tunnel Syndrome	1 (<0.1%)	Tooth Extraction	1 (<0.1%)
Cerebrovascular Accident	1 (<0.1%)	Transurethral Prostatectomy	1 (<0.1%)
Dementia	1 (<0.1%)	Varicocele Repair	1 (<0.1%)
Paraesthesia	1 (<0.1%)	**Hyperuricaemia**	1 (<0.1%)
Paralysis	1 (<0.1%)	**Contusion**	1 (<0.1%)
Radiculopathy	1 (<0.1%)	**Muscle Strain**	1 (<0.1%)
Somnolence	1 (<0.1%)	Tibia Fracture	1 (<0.1%)
Syncope	1 (<0.1%)	Wrist Fracture	1 (<0.1%)
Breast Tenderness	1 (<0.1%)	Lymphoma Cutis	1 (<0.1%)
Erectile Dysfunction	1 (<0.1%)	**Prostate Cancer**	1 (<0.1%)
Nipple Pain	1 (<0.1%)	Prostatic Adenoma	1 (<0.1%)
Prostatic Disorder	1 (<0.1%)	Skin Papilloma	1 (<0.1%)
Prostatitis	1 (<0.1%)	Adrenal Insufficiency	1 (<0.1%)
Prostatomegaly	1 (<0.1%)	Growth Hormone Deficiency	1 (<0.1%)
Spontaneous Penile Erection	1 (<0.1%)	Hypothyroidism	1 (<0.1%)
Arthralgia	1 (<0.1%)	**Nephrolithiasis**	1 (<0.1%)
Back Pain	1 (<0.1%)	**Nocturia**	1 (<0.1%)
Musculoskeletal Discomfort	1 (<0.1%)	**Urinary Retention**	1 (<0.1%)
Neck Pain	1 (<0.1%)	Tinnitus	1 (<0.1%)
Polymyalgia Rheumatica	1 (<0.1%)	Blepharitis	1 (<0.1%)
Completed Suicide	1 (<0.1%)	Drug Hypersensitivity	1 (<0.1%)
Depressed Mood	1 (<0.1%)		1 (<0.1%)

Note: Subjects are counted once within each Preferred Term. Treatment-Emergent Adverse Events occurred on or after the date of first injection of TU. Adverse events were coded with MedDRA version 14.0.
TEAEs in bold typeface also occurred in hypogonadal subjects treated with TU in the U.S. and European Clinical Studies. Source: Summary of Clinical Safety

Reviewer's comments: **The incidence of adverse events reported in the European postmarketing studies is considerably lower than in the U.S. clinical study IP157-001.**

7.3 Major Safety Results

7.3.1 Immediate Post-injection Reactions - Regulatory History / Important Clinical Issues

The **original NDA** contained safety data from a total of 709 male subjects who received testosterone undecanoate injection in 7 controlled clinical studies (including the U.S. Study IP157-001 Parts A, B, C and D; and six European Phase 1-3 studies).

The original NDA also contained 6 periodic safety update reports (PSURs) from Bayer/Schering, the current marketer of testosterone undecanoate injection, that included all spontaneously reported adverse events from approximately 3.5 years of worldwide postmarketing use of testosterone undecanoate injection (specifically November 25, 2003 through June 30, 2007).

The 120-Day Safety Update to the original NDA contained another Bayer/ Schering PSUR (for the time period June 30, 2007 to October 12, 2007), which brought the total duration of postmarketing experience up to 4 years.

An additional Sponsor report was submitted approximately 6 months after NDA submission. The report was included in the NDA materials for FDA review and was entitled "*Immediate Post-Injection Reactions Suspect of Pulmonary Oil Microembolism*".

After reviewing the original NDA, the Division concluded that the clinical trial safety data was consistent with an injectable androgen, except for the occurrence of immediate post-injection reactions in 2 patients. These 2 events were described by the Sponsor as sudden urge to cough, cough, and dyspnea immediately following injection. These two cases, included in original NDA, were:

> **Patient #184 in Study 306605**. A 54-year-old male received his 10th injection of testosterone undecanoate on 3-April-2006 and shortly (1 minute) after the injection, he "experienced urge to cough associated with respiratory distress". Both symptoms lasted approximately 14-15 minutes. The event resolved without intervention and the subject continued in the study. The investigator and Sponsor both attributed the event to "pulmonary lipid (oil) microembolism" and cited the following possible reason: either too fast administration of the study drug or accidental intravascular placement of the study drug.
>
> **Patient #050-7006 in Study IP157-001 Part C**: A 53-year-old white male received his 3rd injection on 12-July-2007 and experienced a "mild and not serious coughing fit lasting 10 minutes following the injection." The narrative describes the patient's cough as not productive, without wheezing and without difficulty breathing. No intervention was given and the patient continued on-treatment without subsequent coughing event.

After reviewing the PSURs and the Summary Report in the original NDA, the Division identified additional clinical trial and postmarketing cases, leading to serious concerns related to the occurrence of immediate post-injection reactions.

Although there were only 2 patients in the original clinical trials with a clear post-injection reactions, the Division's review of the clinical studies submitted with the CR yielded another 6 possible cases, as well as sixty-six (66) postmarketing cases derived from the submitted PSURs and Summary Report. The additional clinical trials cases, identified in the International Postmarketing studies, were listed as post-injection "syncope", "convulsions" and "circulatory collapse" (and three other events) without further detail.

A brief regulatory history associated with the review of these post-injection reactions is provided in Table 7.6.

Table 7.6 Regulatory History Related to Immediate Post-Injection Reactions

	Sponsor	FDA
Original submission in 2007-2008	2 patients in clinical trials with reported adverse events of sudden urge to cough, cough, and dyspnea (POME) immediately following injection. PSURs and Summary Reports of "cough fit" included 66 European postmarketing cases	6 additional clinical trials cases of "immediate post-injection reactions" possible (e.g., post-injection convulsions, syncope, cardiovascular collapse, etc). Of the 66 postmarketing cases (April 2004 to Jan 2007), 28 serious cases (42%), 12 hospitalized (18%). After Pulmonary/Allergy (DPARP) consultation, 2 cases deemed to reflect anaphylaxis and 2 other cases, possible anaphylaxis.
Resubmission in 2009	1 serious POME in 2,834 subjects (0.035%) and no systemic allergic reaction events reported. Total number of injections = 16,191 injections in 12 completed and 5 ongoing trials. *Sponsor's analysis:* POME: 5/3905 subjects (0.1425%); Serious POME: 1/3905 subjects (0.0285%); Anaphylaxis: 0	3 additional possible cases from clinical trials: (postinjection "convulsions", "syncope" and "circulatory collapse", respectively). 3 other cases not included. *FDA analysis* 4/2834, 0.14%. Additional PSUR (25-Nov-2007 to 24-Nov-2008) and final Safety Update yielded 52 more postmarketing cases (total >100 cases). Of the new 52 cases, almost all severe and about 20 consistent with anaphylactic reactions.
After 2009 resubmission to 2010	In the postmarketing period 106 total post-injection reactions: POME: 68 cases; Anaphylaxis: 38 cases.	FDA review also yields a final total of 106 post-injection reactions in the postmarketing period - case list conveyed to Sponsor.
2011	Sponsor informed FDA of a total of **400** post-injection reaction reports (160 POME and 240 anaphylaxis). The Sponsor agreed that all 160 POME cases should be included in the analysis, but only 23 of the 240 anaphylactic reactions should be included.	FDA requested the Sponsor provide individual CIOMS reports for all potential cases of POME and anaphylaxis after searching the entire postmarketing safety database irrespective of medical review or adjudication by the Sponsor.

In the clinical review of the 66 postmarketing cases obtained from the original NDA, the manifestations of the events that were evident included: cough, shortness of breath, throat-related symptoms (throat tickle, throat tightness, throat fullness, etc), flushing, various allergic-type signs and symptoms (rash, pruritis, itching), tachycardia, palpitations, blood pressure changes, and general constitutional symptoms, including headache, malaise, shivering, sweating, weakness and nausea.

The spectrum of signs and symptoms of severe post-injection reactions after testosterone undecanoate injection frequently overlap between anaphylaxis and POME, making a precise diagnosis difficult in some cases.

Although the Sponsor acknowledges a number of postmarketing cases as anaphylactic reactions, the Sponsor continues to believe that most of the post-injection reactions are POME. Our consultants from the Division of Pulmonary and Allergy Products (DPAP) have conducted an extensive review and despite the inherent limitations of retrospective case review, have categorized the severe post-injection reactions cases as either anaphylactic reaction or POME. The criteria used to defined severe post-injection reactions are delineated in Section 4.4.2 below.

The mechanisms for allergic reactions to Aveed have not been fully elucidated. Two of the excipients in this product, benzyl benzoate and castor oil, appear to have played a role in post-injection adverse reactions: benzyl benzoate as an allergen and castor oil as both a potential allergen and an oily carrier. In one case, there was skin test documentation of an allergy to the product, and in another case, documentation of a positive skin test to benzyl benzoate. The role played by testosterone undecanoate itself is unknown but some role as an allergen remains possible. In addition, an injectable estrogen receptor antagonist approved for the treatment of advanced breast cancer, and an approved injectable estrogen replacement product, both of which contain the same excipients as Aveed were associated with post-injection reactions virtually identical to those associated with Aveed (FDA Adverse Events Reporting System; accessed September 25, 2009), and these events are reported in both these products labeling as "anaphylactic or anaphylactoid reactions".

Regardless of the specific mechanism for these post-injection events, and despite difficulty in categorizing them, many of these reactions were reported as severe, and some life-threatening. Severe POME and anaphylactic reactions following intramuscular TU injection cannot easily be differentiated by a health care provider. In most cases, attending health care personnel have reported and treated the incident as an anaphylactic reaction.

Finally, on September 21, 2009, FDA received a report of a full-blown post-injection anaphylactic reaction in a 16 year old male***1***. The Sponsor finds this to be "*the first instance of true anaphylaxis*". We requested another consult from the Division of Pulmonary and Allergy Products (DPAP) and in their draft consult dated November 16, 2009 (and final consult of

1 Ong GS, Somerville CP, Jones TW, Walsh JP.: Anaphylaxis triggered by benzyl benzoate in a preparation of depot testosterone undecanoate. Case Reports in Medicine 2012; Vol. 2012: Article ID

November 25, 2009), DPAP concluded that 20 cases of these new 52 cases were either anaphylaxis (n=11) or possible anaphylaxis (n=9). Another 4 cases were described as "allergic reactions". DPAP also stated that POME generally lacks cutaneous and mucosal symptoms, such as generalized flushing and swollen throat, as reflected in many of the post-injection reaction cases.

7.3.2 Immediate Post-injection Reactions –Reporting Rates

Immediate Post-injection Reactions - Reporting Rates (POME and Anaphylaxis)

The postmarketing reporting rates of POME and anaphylaxis cases were analyzed by the Sponsor in the recent re-submission. The Sponsor's first analysis was conducted by internal Endo Pharmaceuticals reviewers and was submitted in the CR on November 29, 2012. The Sponsor's second analysis was conducted by independent adjudicators who were consulted by Sponsor, and this second analysis was submitted on March 5, 2013. Results of the two analyses and comparison of the results are shown in the next two tables.

Table 7.7 Comparison of Postmarketing Reporting Rates of POME Identified by Sponsor's "Independent Adjudicators" versus Postmarketing Reporting Rates Identified by the Sponsor's Internal Reviewers (shown in parentheses)

	11/25/03-11/24/07	11/25/07-11/24/08	11/25/08-11/24/09	11/25/09-11/21/10	11/22/10-11/24/11	Total Over All Time Periods
Number of Potential POME Cases	143 (137)	75 (75)	120 (117)	89 (89)	116 (115)	543 (533)
Number of POME Cases Identified as Yes or Indeterminate	49 (49)	26 (27)	48 (49)	43 (45)	57 (58)	223 (228)
Number of Ampoules Sold	(b) (4)					
Number of Treatment Years	142927.0	108469.5	136621.9	156201.9	178489.5	722709.8
Rate of Cases of POME Identified as Yes or Indeterminate Per 10,000 Ampoules Sold	0.797 (0.797)	0.557 (0.579)	0.817 (0.834)	0.640 (0.670)	0.743 (0.756)	0.718 (0.734)
Rate of Cases of POME Identified as Yes or Indeterminate Per 10,000 Treatment Years	3.428 (3.428)	2.397 (2.489)	3.513 (3.587)	2.753 (2.881)	3.193 (3.249)	3.086 (3.155)

Source: Integrated Summary of Safety (ISS) page 248, Table 88, Submission #10 (November 29, 2012)
Addendum to ISS, page 19, Table 8, Submission #019 (March 05, 2013)

Table 7.8 Comparison of Postmarketing Reporting Rates of Anaphylactic Reactions Identified by Sponsor's "Independent Adjudicators" versus Postmarketing Reporting Rates Identified by the Sponsor's Internal Reviewers (shown in parentheses)

	11/25/03-11/24/07	11/25/07-11/24/08	11/25/08-11/24/09	11/25/09-11/21/10	11/22/10-11/24/11	Total Over All Time Periods
Number of Potential Anaphylactic Reaction Cases	78 (78)	39 (39)	76 (76)	59 (59)	78 (78)	330 (330)
Number of Anaphylactic Reaction Cases Identified as Yes or Indeterminate[a]	9 (24)	7 (9)	7 (11)	10 (16)	12 (19)	45 (79)
Number of Ampoules Sold	(b) (4)					
Number of Treatment Years	142927.0	108469.5	136621.9	156201.9	178489.5	722709.8
Rate of Cases of Anaphylaxis Identified as Yes or Indeterminate Per 10,000 Ampoules Sold	0.146 (0.391)	0.150 (0.193)	0.119 (0.187)	0.149 (0.238)	0.156 (0.248)	0.145 (0.254)
Rate of Cases of Anaphylaxis Identified as Yes or Indeterminate Per 10,000 Treatment Years	0.630 (1.679)	0.645 (0.830)	0.512 (0.805)	0.640 (1.024)	0.672 (1.064)	0.623 (1.093)

[a] The independent adjudicators used Sampson criteria 1; the Sponsor's internal reviewers used a combination of Sampson criteria, Rueggeburg criteria and special terms.

Source: Integrated Summary of Safety (ISS) page 259, Table 92, Submission #10 (November 29, 2012)
Addendum to ISS, page 22, Table 11, Submission #019 (March 05, 2013)

As part of the second resubmission of November 29, 2012, the Sponsor submitted an Addendum relevant to immediate postinjection reactions on March 5, 2013, based on an evaluation conducted by two independent adjudicators who were consulting to Endo Pharmaceuticals.

The independent adjudicators identified 223 cases of POME compared to 228 cases identified by the internal reviewers. Thus, the most recent adjudication had little impact (–2%) on POME cases.

However, for anaphylactic reactions, the new adjudication had more of an impact. The independent adjudicators identified 45 cases of anaphylactic reaction compared to 79 cases identified by the internal reviewers. The reason for the difference is that the independent adjudicators
qualified a case of anaphylactic reaction only if it met Sampson's criteria number 1, while the Sponsor's internal review in their most recent CR used a combination of Sampson's criteria, Rueggeburg's criteria and other special terms.

Thus, the analysis of postmarketing reporting rate based upon the consultants' adjudication reduced the rates of anaphylactic reaction per 10,000 ampoules sold and per 10,000 treatment years by 43%.

Overall, however, the total number of severe post-injection reactions, both POME and anaphylactic reaction, was not markedly different between sets of adjudicators.

7.3.3 Immediate Post-injection Reactions – Case Narratives

FDA reviewed all potential postmarketing cases of POME and anaphylaxis that were included in the current resubmission. FDA elected to focus on the severe cases from the series. With this objective in mind, FDA pre-determined the following criteria to define a "case" of severe post-injection reaction to testosterone undecanoate:

Criteria for Defining Severe Post-Injection Reactions to Testosterone Undecanoate:

We categorized any case as a severe post-injection reaction if it occurred within 24 hours of injection and if any of the following criteria were met:

- Any case identified by either FDA or Sponsor as an anaphylactic reaction as a consequence of the reporter using the term "anaphylaxis" or "anaphylactic reaction"
- Any case identified by either FDA or the Sponsor as an anaphylactic reaction by meeting the formal Sampson's criteria
- Any case identified as a serious adverse event (SAE), based upon the FDA standard definition of an SAE
- Any case requiring treatment
- Any case labeled as "Serious" or "Medically Important" by the reporter or by the Sponsor (any case that had a check in box 8-12 of the CIOMS form)
- Any case that FDA believed to be medically significant
- Any case involving syncope or sudden lowering of the blood pressure

In this section of the review, all FDA-adjudicated severe cases are presented (Table 15) and provide narratives for each severe postmarketing post-injection reaction in the testosterone undecanoate series, whether a case of POME, of anaphylaxis, or of either POME or anaphylaxis if a differentiation was not possible. Due to difficulty in distinguishing severe POME from anaphylaxis, the list includes some overlapping cases where POME or anaphylaxis could not be differentiated. The list shows a total of **137 cases**.

Table 7.9 137 Cases of Severe Postmarketing Post-injection Reactions to TU Injections

	Case #		Case #		Case #
1	200711268BNE	48	201034191GPV	95	2011108338
2	200711270BNE	49	201034195GPV	96	2011110321
3	200711462BNE	50	201034605GPV	97	2011110671
4	200718455GPV	51	201035276GPV	98	2011124098
5	200811461BNE	52	201036559GPV	99	2012004307
6	200812881BNE	53	201037659GPV	100	2012004532
7	200812947GPV	54	201038945GPV	101	2012005684
8	200815181GPV	55	201040373GPV	102	2012005853
9	200815625LA	56	201040508GPV	103	2012007253
10	200818230LA	57	201041966GPV	104	2012014074
11	200818257LA	58	201042008GPV	105	2012014975
12	200819842GPV	59	201045017GPV	106	2012015311
13	200820307GPV	60	201046647GPV	107	2012019653
14	200821519GPV	61	201047159GPV	108	2012020873
15	200821776GPV	62	201047285GPV	109	2012025807
16	200826527GPV	63	2011002167	110	2012025864
17	200826556GPV	64	2011007367	111	2012032972
18	200828604GPV	65	2011009542	112	AT-2007-035468
19	200832838GPV	66	2011011368	113	AU-2007-014016
20	200910048BNE	67	2011014093	114	BR-2007-005496
21	200910221BNE	68	2011014662	115	CH-2007-042227
22	200912079BNE	69	2011016767	116	DE-2004-037302
23	200912293BNE	70	2011018006	117	DE-2005-004016
24	200912294BNE	71	2011022738	118	DE-2005-005199
25	200916799LA	72	2011024048	119	**DE-2005-008140**
26	200919013LA	73	2011025652	120	DE-2005-008181
27	200919765LA	74	2011025755	121	DE-2005-009283
28	200924735GPV	75	2011039522	122	DE-2005-015256
29	200929719GPV	76	2011040546	123	DE-2006-002815
30	200930704GPV	77	2011044214	124	DE-2006-003298
31	200932012GPV	78	2011046164	125	DE-2006-008415
32	200933178GPV	79	2011046482	126	DE-2007-004747
33	200940006GPV	80	2011048218	127	DE-2007-023890
34	200940275GPV	81	2011050730	128	DE-2007-030464
35	200940933GPV	82	2011052409	129	GB-2007-006197
36	201010793GPV	83	2011052410	130	GB-2007-000740
37	201014170GPV	84	2011056865	131	GB-2007-023826
38	201018709GPV	85	2011063184	132	NO-2007-008557
39	201019083GPV	86	2011065559	133	SE-2006-004192
40	201020041GPV	87	2011071329	134	SE-2006-017516
41	201020446LA	88	2011074882	135	SE-2006-022330
42	201021482GPV	89	2011083027	136	SE-2007-002541
43	201025167GPV	90	2011087892	137	ZA-2007-035469

44	201028214GPV	91	2011095240		
45	201029358GPV	92	2011090820		
46	201033158GPV	93	2011102083		
47	201034100GPV	94	2011105544		

*Note: Single case in **bold** typeface denotes the only case picked up by the Sponsor's adjudicators, but not by the Sponsor and FDA during previous evaluations.*

Narratives for Cases of Severe Postmarketing Post-injection Reactions to Testosterone Undecanoate Injection*

*Note: Unless stated, the indication for use of testosterone undecanoate was not reported.

Case 200711268BNE: A UK male patient of unknown age was given Nebido injection by his wife, a practicing nurse. He began coughing immediately afterward and was unable to get his breath, and also experienced a burning sensation in his mouth and chest. The patient required urgent hospitalization for 2 days with presumed embolism. The patient recovered.

Case 200711270BNE: A UK male patient with unknown age was given Nebido injection in a general practitioner's (GP's) office and began to cough immediately. He was unable to get his breath, he felt a burning sensation in his mouth and chest, and he collapsed. He was hospitalized for 2 days, and recovered. The Sponsor's analysis included that the injection was given whilst the patient was standing, the drug not warmed, and the drug was also given quickly.

Case 200711462BNE: On 30-Nov-2007, immediately after an injection, a 44-year-old UK male patient experienced cough, shortness of breath, and flushing, considering serious due to it being an important medical event. The patient recovered after 1 day.

Case 200718455GPV: On 25-Sep-2007, during Nebido injection, a 68-year-old German male patient showed symptoms of an allergic reaction including tingling sensation and sensation of numbness in his lips and mouth. This was considered severe as a medically important event. He was treated with H1 and H2-blocking agents and stayed in the doctor's office for 3 hours under observation. The complaints resolved within 6 hours after administration of Nebido.

Case 200811461BNE: On an unknown date, a 55-year-old UK male patient was given his 3rd injection of Nebido, he immediately complained of a metallic taste in his mouth, and he began to sweat profusely and experienced a "burning up" sensation. His blood pressure soared to 275/175 mmHg during the event, but 30 minutes after the injection, the patient's BP stabilized at a normal level. Due to a sharp increase in the patient's blood pressure for about 30 minutes after the injection, the event was considered as serious by the reporter due to medical significance.

Case 200812881BNE: On 01-Oct-2008, 2 months after an initial injection of testosterone undecanoate for Noonan syndrome (primary testicular failure) and immediately after a second injection of Nebido, a 27-year-old UK male patient experienced bronchospasm, cough, wheeze, and flushing. The patient was treated with salbutamol nebulizer and recovered after 20 minutes. The Sponsor's analysis was that the event constellation may be indicative of POME or of a hypersensitivity reaction.

Case 200812947GPV: A 38-year-old Swedish male patient with lack of testosterone due to radiotherapy received Nebido twice. After his first injection, the patient experienced a mild allergic reaction. Six months later (b) (6) another injection was given in a hospital and the patient developed a "severe allergic reaction" (severe throat swelling) and "potential heart failure". These events were reported to be life-threatening. The patient recovered shortly after treatment but information about treatment was not given. Nebido therapy was discontinued.

Reviewer's comment: **This case demonstrates that a single patient may suffer a mild reaction on one occasion followed by a more severe reaction sometime thereafter.**

Case 200815181GPV: A 52-year-old German male patient of unknown age was given Nebido on (b) (6), and he experienced heat sensation in the neck and tickling in the throat, severe dyspnea, and muscle twitching. Later, the patient lost consciousness for about 20 seconds. Shock positioning and intravenous fluids were administered. The patient was admitted for "clarification". The next day, about 28 hours later, the patient was discharged with a light headache.

Case 200815625LA: The 60-year-old male from Brazil started receiving Nebido at 4mL every 3 months beginning in July 2007. On (b) (6), instantaneously after Nebido's injection, the consumer experienced "anaphylactic reaction" including throat itching followed by cough, glottis spasm and glottis edema. The patient was treated with adrenaline and intravenous corticosteroids, oxygen and an antihistamine orally. He stayed in a hospital under observation, and after 6 hours he recovered and was discharged.

Case 200818230LA: This 58-year-old male from Brazil has been receiving Nebido for an unknown amount of time when he experienced an "anaphylactic reaction" and was hospitalized. No other information was provided.

Case 200818257LA: This 53-year-old male from Brazil (b) (6) experienced profuse sweating, arterial blood pressure decreased, nausea and pain at injection site during Nebido injection. He recovered from these events 4 hours after injection. During the same period, the patient experienced heaviness of head. He did not recover from this event.

Case 2008-19842GPV: During an injection with Nebido, this 67-year-old Swedish male patient experienced a "light fall" in his blood pressure (from 140/80 to 125/70 mmHg) and sweating. The BP regressed spontaneously within a few minutes. The patient received one additional Nebido injection after this event without experiencing any problems.

Case 200820307GPV: This 72-year-old male patient from Malaysia experienced non-stop coughing for about 10 minutes, and his face turned blue (cyanosis) immediately following an injection of Nebido. He also reported suffering from dizziness and numbness of his face. The patient's symptoms of cough and cyanosis recovered after 10 minutes; dizziness and numbness of the face recovered on an unspecified date.

Case 200821519GPV: On (b) (6), after half a dose of Nebido injection had been given, this 21-year-old Swedish male patient experienced severe chest pain radiating towards his throat and neck, cold sweating and coughing. The injection was stopped. Since the discomfort did not disappear, the patient was given 0.5 mL adrenaline, betamethasone and oxygen. The event was reported as serious as chest pain was considered a medically important event. The condition improved gradually and the patient recovered without sequelae, and he was transferred to the ER for observation.

Case 200821776GPV: This 33-year-old Denmark male patient had undergone a unilateral orchiectomy and also had received radiotherapy to the other testicle. In July 2006 he started treatment with Nebido. On 08-May-2008, directly after an injection of Nebido, the patient experienced a life-threatening allergic reaction with symptoms of breathing problems and cough. The patient was treated with salbutamol inhalation treatment and an antihistamine (cetirizine). After one hour, all of the patient's symptoms disappeared. The patient's initial blood pressure of 147/89 decreased to 124/73 mmHg.

Case 200826527GPV: This 72-year-old German male patient experienced severe coughing, choking fit, facial dysesthesia, and temporary palsy of mouth (7^{th} nerve paralysis) and face musculature during the injection of Nebido on 15-Sep-2008. After injection of half a vial, the administration of Nebido was discontinued. The complaints persisted over 25 minutes after the injection. The patient recovered within 30 minutes. This reported event was considered serious by the reporter due to medical importance.

Case 200826556GPV: This 76-year-old German male patient with a history of diabetes, hypertension, dyslipidemia and longtime metabolic syndrome received Nebido. During the injection, the patient developed severe coughing, dyspnea, and a choking fit. The injection was

discontinued after half a vial. Within 10 minutes after the injection, the patient recovered. The reporting attending urologist stated that the patient had already developed similar events in the context of Nebido administration on 08-Dec-2006. In 2006, the patient had experienced dyspnea, urge to cough and cyanosis.

Reviewer's comment: **This case demonstrates the occurrence of severe POME on two occasions in the same patient.**

Case 200828604GPV: This 41-year-old German male patient had been under treatment with Nebido for six years for Klinefelter's syndrome. In Aug-2008, during a Nebido injection, the patient developed a tingling sensation which started in the lungs and ascended to the nose. Furthermore, he suffered from feeling of tightness in the region of the thorax, dry cough, burning eyes, and flushing symptoms, considering a possible anaphylactic reaction. Thirty minutes after treatment with prednisone, an antihistamine (dimethindene maleate) and ranitidine, the patient recovered. A testosterone cypionate prick test was performed on 09-Oct-2008 and was negative after 20 minutes and also negative after 24 hours. In addition, a dermatological test (prick test) was performed in Nov-2008, using the single ingredients provided by the company (testosterone undecanoate, castor oil and benzyl benzoate). The *in vivo* diagnostic did not show any signs of type I sensitization.

Case 200832838GPV: On 08-Dec-2008, after 2.6 mL of Nebido was injected slowly, this 58-year-old South Korean male patient experienced moderate chest pain, cough, dyspnea, and dizziness. The patient recovered with treatment (no further specified) on the same day.

Case 200810048BNE: This 39-year-old UK male patient had been given Nebido for 1 year and 4 months. On (b) (6), when 2 mL from a 4 mL Nebido vial was just being injected, the patient suddenly complained of throat closing, coughing, tingling tongue, and difficulty breathing. Facial swelling, tongue swelling, shortness of breath and tremor were observed. The injection was stopped and needle removed. Adrenaline 0.5 mg was administered IM. The patient's BP was monitored and oxygen was given whilst awaiting the ambulance. On arrival at hospital, the patient was asked to sit to transfer to a chair, but on doing so started with tremors. Adrenaline was repeated (20 min after the first dose). Whilst in hospital, he remained symptom free and no further treatment was given.

Reviewer's comment: **This case illustrates the occurrence of a severe post-injection reaction after 1 year and 4 months of otherwise safe use.**

Case 200910221BNE: A 44-year-old UK male patient was given Nebido for low testosterone on 08-Jan-2009. After the injection, he experienced chest tightness, cough, sweatiness, and throat

tightness. The event was considering serious by the reporter as it was an important medical event. Nebido was withdrawn and the patient recovered the same day.

Case 200912079BNE: This UK male patient with unknown age received Nebido injection on unspecified date. One hour after the injection, the patient felt funny and experienced cough fits. He was treated with antihistamines, and improved.

Case 200912293BNE: This 53-year-old UK male patient started Nebido treatment in Dec-2007. After receiving his 6th dose in 2009 (12 weeks ago), the patient experienced a "mild anaphylactic shock". He felt burning in his throat and couldn't breathe very well. He recovered. In early (b) (6), after receiving another Nebido injection, this time at the hospital, the patient experienced closed throat, tight burning throat, dyspnea, feeling hot and sweaty, red face. The nurse reported "*pulse rate thready, irregular – quickly returned to normal, bronchospasm and SOB, range from 68 to 90 SBP fluctuating from normal ranges very briefly then settling at 142/87." The reporter thinks the event may be treated with hydrocortisone. The situation was steadily worsening some 5 – 30 minutes then eased.*" The nurse also reported that the patient was positioned and calmed and recovered 45 to 60 minutes later with supervision.

Reviewer comment: **This is another case in which a patient sustained a less severe post-injection reaction followed by a more severe post-injection reaction.**

Case 200912294BNE: This 32-year-old UK male patient received Nebido for 2 years. On (b) (6), the patient's mother who is a nurse administered the injection to the patient. Having received the injection, the patient immediately felt odd, experienced a tightening of the throat, shortening of breath, and flushing. His mother reported that it was a bit like a panic attack. The patient was admitted for observation on that day. The event of anaphylactic shock (SOB, flushing and bronchospasm) lasted 1 hour. It is unclear what treatment, if any, the patient received.

Case 200916799LA: This male patient from Ecuador of unknown age reported symptoms of skin rash and difficulty breathing immediately after administration of Nebido by a pharmacist. The patient was treated with intravenous hydrocortisone and recovered. The patient had received Nebido for 3 months prior to this injection. No other information was given. The reporting physician considered the event possible anaphylactic shock.

Case 200919013LA: This 75-year-old male patient from Brazil had been receiving Nebido for male hormone replacement due to his benign pituitary tumor. On (b) (6), the consumer received a Nebido injection in a pharmacy and a few minutes later, he experienced bad taste in mouth, malaise, cough, hot feeling in body, body formication, pain between his fingers, redness

on his face and burning sensation on his skin. He was taken to a hospital and received parenteral adrenaline, corticosteroid and an anti-allergic drug. The consumer recovered on the same day.

Case 200919765LA: This 33-year-old man from Honduras received Nebido for male hypogonadism. In Jun-2009, patient had his first application of Nebido. Nebido was still being administered IM (there was approximately 1 mL left in the syringe) when the patient started complaining about difficulty to breath. This difficulty intensified and the patient became cyanotic so the treating physician stopped the administration and started administering hydrocortisone IV and an antihistamine (chlorpheniramine). The condition of the patient improved within minutes and then the patient said he needed to cry, started crying and he said he did not known why. Minutes later this need to cry had stopped and the patient left physician's office. Patient also experienced cough and vomiting during the event. That night, at 8 pm, the patient called saying he was having fever (40 Celsius degrees) which was treated with unspecified NSAIDs. The fever had disappeared by midnight. The events (difficulty breathing, cyanosis, crying, vomiting, cough and fever) were considered as allergic reaction. Patient fully recovered from the event.

Case 200924735GPV: This 22-year-old male patient from Sweden with Klinefelter's syndrome started Nebido treatment in Feb-2006. On (b) (6), the patient received an injection from his sister-in-law. During the ongoing injection, the patient suddenly developed dyspnea and his throat became swollen when approximate 1 mL of the drug was left in the syringe. The patient became scared and he shivered with his whole body. The needle was drawn and the injection was stopped. The patient was sent to a hospital and was treated with a corticosteroid, salbutamol, an antihistamine (clemastine), adrenaline intravenously, and ipratropium. The patient stayed in the hospital and recovered.

Case 200929719GPV: This Spanish male patient of unknown age received testosterone undecanoate (Reandron) injection on an unspecified date and experienced hypotension, and was not treated. Patient recovered.

Case 200930704GPV: This 43-year-old German male patient with Klinefelter's syndrome had been treated with Nebido since Aug-2005. On 02-Jun-2009, during a Nebido injection, the patient experienced sensation of heat, urticaria and dyspnea. He was treated with an injection of an intravenous corticosteroid immediately after the occurrence of the adverse reaction. The symptoms started to subside within 30 minutes. After 1 hour, the event was resolved.

Case 200932012GPV: This 16-year-old Australia male with testicular agenesis received two injections of testosterone undecanoate (Reandron) without problems. On an unspecified date, an IM injection of Reandron was administered as his 3rd dose by a general practitioner. Within 3

minutes, the patient experienced itching of his palms, groin, and feet followed by widespread/ generalized urticaria, tightening in the throat, sweatiness, facial and lips swelling, shortness of breath, constriction of the chest, hypotension, cough and dizziness. The patient was given IV adrenaline, hydrocortisone, antihistamines and IV fluids. The patient recovered without sequelae. The case was described as life-threatening by the reporter. The patient had a history of eczema, asthma, food allergies and other drug allergies. Prior to switching to Reandron, the patient had received a testosterone ester preparation. The patient was referred to the allergist who performed skin prick testing with Reandron, which showed a very positive reaction (type I reaction).

> **Addendum**: In this patient, skin prick testing found a definite reaction to Reandron with a 10×8 mm wheal, but no reaction to testosterone esters gel or saline solution control. Testing of the individual components of Reandron found that non-skin-irritating concentrations of benzyl benzoate resulted in a 10×10 mm wheal and smaller peripheral lesions. Neither castor oil nor TU induced a response.

Reviewer's comment: **This case clearly documents benzyl benzoate as an allergen.**

Case 200933178GPV: This 34-year-old UK male patient was injected with Nebido for transgender hormonal therapy in Dec-2007. On 13-Aug-2009, the patient experienced fat embolism, considered serious by the reporter due to important medical event. No further information is available.

Case 200940006GPV: On 03-Sep-2009, this 70-year-old UK male patient developed shortness of breath, cough, and instant chest pains immediately after injection of Nebido. The symptoms lasted 1-2 minutes. He recovered after 1-2 days. This event was considered serious by the reporter due to medical significance.

Case 200940275GPV: On (b) (6), directly after an injection of Nebido, this 68 year-old German male patient experienced a severe cough attack and dyspnea followed by vomiting and tightness of chest. He was hospitalized. Once in the hospital, the patient was treated with nitroglycerine and his condition improved, but he developed nausea and vomited once. The reported events lasted approximately 4 hours. The patient was admitted due to a suspicion of acute coronary syndrome (ACS, sub-type of unstable angina pectoris). An ECG on (b) (6) revealed horizontal ST depression. An ECG performed 6-hr later showed regression of ST depression. Cardiac enzymes were normal.

Reviewer's comment: **This case illustrates the occurrence of unstable angina pectoris in a geriatric patient who sustained a severe post-injection reaction.**

Case 200940933GPV: This 37-year-old German male patient with Klinefelter's syndrome started treatment with Nebido in Jul-2008. On 12-Oct-2009, four minutes after a Nebido injection, the patient was sweaty, collapsed (experienced syncope), developed nausea, an urge to

vomit, tachycardia and hypotension. The reporter states that the patient had developed an allergic reaction with shortness of breath and anxieties. The patient was immediately treated with hydrocortisone intravenously. The patient's condition improved. After 7 minutes, all symptoms disappeared.

Case 201010793LA: This 64-year-old Columbian male patient with primary hypogonadism received a Nebido injection on 09-Dec-2009. On the same day, the patient experienced facial rash and cough with expectoration considered serious by the reporter due to medically important event. The patient improved after 1 day.

Case 201014170LA: This 84-year-old male patient from Mexico received his 2nd Nebido injection on 25-Apr-2010. On an unknown date (the case report was received on 29-Apr-2010), the consumer experienced dyspnea and high arterial blood pressure (up to 190 mmHg). The outcome was unknown. The event was considered serious by the reporter as a consequence of medical significance.

Case 201018709GPV: This 40-year-old Austrian male patient started treatment with Nebido for testosterone substitution after orchidectomy. On 25-Feb-2010, following 1 year of Nebido treatment, the patient received a Nebido injection, and 20 seconds later experienced circulatory collapse with a fall in his blood pressure lasting 30 minutes. In addition, he suffered from cough and dyspnea, also lasting 30 minutes. The report does not describe whether any treatment was administered. The outcome was event was reported as improved. The events were considered serious by the reporter due to medical importance.

Reviewer's comment: **The previous two cases illustrate the potential for both increased and decreased blood pressure as part of a severe post-injection reaction.**

Case 201019083GPV: A report received on 08-Mar-2010 described a 46-year-old Swiss male patient who on an unknown date experienced pulmonary fat embolism with fits of cough, and rising warmth of the body after an injection of Nebido. The patient recovered after 10 minutes. No further information was available. The event was considered serious by the reporter due to its medical importance.

Case 201020041GPV: This 58 year-old German male patient with prostate adenoma started receiving Nebido injections on Aug-2005. On 21-Jul-2009, during a Nebido injection, the patient experienced tickle of the throat, mild nausea, weakness and cold sweat. No treatment was given, the patient recovered spontaneously after 10 minutes. The event of suspected POME was considered serious by the reporter due to medical importance.

Case 201020446LA: This 60-year-old Mexican male patient started Nebido therapy for panhypopituitarism in 2007. In Jul-2010, 10 seconds after a Nebido administration, the patient experienced a hypersensitivity reaction, including taste of oil in the throat, dyspnea, malaise, drowsiness, and dry cough. He recovered after 1 hour without treatment. On 25-Oct-2010, approximately 3 months later, the patient received another Nebido injection and during the administration, he experienced persistent dry cough, feeling of irritation (like burning) that started in the throat and spread to the face, nose, ears, mouth and eyes, intense dyspnea, and numbness of the mouth. The event was very intense until about 45 minutes after injection, and gradually resolved spontaneously within 15 minutes. Both episodes of the event were considered serious by the reporter due to medical importance.

Case 201021482GPV: This 63-year-old South African male patient received Nebido treatment for hypogonadism. On 19-Mar-2010, while his 3rd or4th dose of Nebido was being injected into the right gluteus muscle, he experienced cough and dyspnea, became anxious, and wanted to faint (pre-syncope). In addition, he also suffered from tachycardia and a drop in blood pressure. He was given oxygen and hydrocortisone intramuscularly. The patient was not hospitalized, and recovered. This serious event was considered an anaphylactic reaction by the reporter.

Case 201025167GPV: This 51-year-old German male patient with a history of ablation of the right testes due to seminoma experienced cough after his first and 3rd Nebido injections. On 25-Nov-2009, approximately 10 seconds into the injection of Nebido, the patient developed heat sensation in the head, tingling in the fingertips, headache, and attacks of asthma-like cough. The BP was measured at 125/90 mmHg. After IV administration of hydrocortisol, the symptoms subsided with 20 minutes. The event was considered severe POME or hypersensitivity by the reporter.

Case 201028214GPV: This 46-year-old UK male patient received Nebido for testicular hypogonadism starting 2-3 year prior to the event. On 10-Mar-2010, immediately after an injection of Nebido, the patient experienced a mild anaphylactic reaction where he had breathing difficulties, sweating, a cough fit 2 minutes after the injection, felt hot and sick, felt faint and had to lie flat. No adrenaline was given but the physician gave him prednisone tablets 5 mg, 6 times daily for a total 42 tablets. The patient eventually recovered, but felt very “unwell” after the incident.

Case 201029358GPV: This 52-year-old German male patient used Nebido for the treatment of hypogonadism. On an unspecified date (4 weeks before the report that was received 07-Jul-2010) immediately after a Nebido injection, the patient developed cough, tingling sensation, malaise, sensation of constriction of the chest and redness of the facial skin. The patient recovered after 30 minutes. The event was considered serious by the reporter due to medical significance.

Case 201033158GPV: This German male patient of unknown age experienced cough and taste disturbance at the end of a Nebido injection on a unspecified date. The injection was administered in a standing position. The symptoms abated. The patient was not hospitalized. The event was considered serious by the reporter due to medical significance, but no further information was available.

Case 201034100GPV: This 70-year-old German male patient received Nebido treatment for androgen deficiency syndrome since Aug-2007. On 04-Jan-2010, during slow injection of Nebido, the patient experienced severe "unpleasant" cough and dyspnea. The event lasted about 20 minutes, and subsided. The patient received no remedial therapy. The event was considered serious by the reporter due to medical significance.

Case 201034191GPV: This 45-year-old German male patient received Nebido therapy for hypogonadism. On 05-Jul-2010, upon slow Nebido injection, the patient developed severe cough attacks with dyspnea after injection of just 2 mL. The symptoms improved after approximately 20 minutes. Patient received no remedial therapy. The event was considered serious by the reporter due to medical significance.

Case 201034195GPV: This German male patient of unknown age experienced unpleasant cough and dyspnea. The patient received no remedial therapy. No further information was available. The event was considered serious by the reporter due to medical significance. The injection was given over four minutes, with the patient in lying position. During the injection aspiration had been performed several times.

Reviewer's comment: **The prior three cases illustrate that severe post-injection reaction can occur even when testosterone undecanoate is injected slowly.**

Case 201034605GPV: This 60-year-old German male patient received Nebido injections for **androgen deficiency syndrome. On an unspecified date, the patient experienced a severe cough** attack with initial dyspnea, followed by a sweating attack and malaise. Duration of the events was reported as about 15 hours. The next morning, the patient recovered. The patient received no remedial therapy. The event was considered serious by the reporter due to medical significance.

The next 4 cases (201034100GPV, 201034191GPV, 201034195GPV, and 201034605GPV) were reported by the same urologist.

Case 201035276GPV: This 45-year-old UK male patient received Nebido for pituitary adenoma starting in 2006. On 15-Jul-2010, the patient experienced an anaphylactic reaction. Nebido was withdrawn, and the patient recovered.

Case 2010 36559GPV: This Swiss male patient of unknown age had a history of orchidectomies for seminoma of both testes for which he received treatment with Nebido. On 12-Aug-2010, at 3 to 5 minutes after the Nebido injection, the patient experienced feeling of heat, cough and dyspnea. The patient received methylprednisolone, an antihistamine (clemastine), and intravenous ranitidine, and he felt quickly better without problems. Allergy tests to the Nebido ingredients turned out to be negative. The Sponsor determined this event was a case of severe POME.

Case 201037659GPV: This 61-year-old Danish male patient with a testicular disorder received Nebido therapy since 22-Jun-2006. On (b) (6), the patient experienced breathing difficulty and coughing after the injection. The patient was hospitalized and recovered.

Case 201038945GPV: This 63-year-old Belgian male patient with a hypophyseal tumor, hypophysectomy and prostatectomy received Nebido therapy for hypogonadism. On (b) (6), one minute after a Nebido injection, the patient experienced shortness of breath. He was transferred to an emergency room and received cortisol intravenously. He stayed in observation for 1 hour and recovered completely.

Case 201040373GPV: This 53-year-old UK male patient received Nebido injection on an unknown date. He experienced an odd taste at the back of his mouth whilst Nebido was still being injected. Almost immediately thereafter, this patient began to cough, developed difficulty breathing, became sweaty, and turned pale. No rash was reported. The patient was given intramuscular adrenaline and he started feeling better after a couple of minutes. An anaphylactic reaction was assumed by the reporter.

> **Addendum**: The patient was skin tested to benzyl benzoate, Nebido and also to "Virormone". A skin prick test and intradermal tests up to 1:10 concentration were performed. There was no evidence of reaction and therefore, symptoms were considered as not suggestive of a type I allergy. The AE term Anaphylactic Reaction was amended to Suspicion of POME.

Case 201040508GPV: This German male patient of unknown age was enrolled in an investigator-sponsored study to evaluate the allergic potential of Nebido (*Study IP157-003, a phase 1, double-blind study to evaluate the allergic potential of Nebido and formulation components in patients who have exhibited anaphylactic-like reactions following intramuscular*

injection of Nebido). After the 1st injection of Nebido, the subject developed reddening of the skin, increase in BP, a feeling of flushing, and dyspnea. The severity was mild. The subject was treated with corticosteroids and recovered. A re-challenge was reported as positive. The event was considered serious due to its medical significance. The investigator determined that the reaction in this patient was clearly not POME, but rather a perfect example of a non-allergic hypersensitivity reaction, which was most likely specifically related to study drug.

Case 201041966GPV: On an unspecified date, this 42-year-old Denmark male patient started treatment with Nebido. On an unspecified date, he experienced an anaphylactic shock. The temporal relationship between the event and Nebido was unclear in the report.

Case 201042008GPV: This 61-year-old Swedish male patient received Nebido for hypogonadism on 05-Oct-2010. Approximately one minute after completion of injection, the patient experienced coughing and swollen throat, which were originally considered non-serious. However, the patient kept suffering from coughing and swollen throat with an unchanged intensity for the next 10 days until the symptoms decreased on 19-Oct-2010. After receiving his 2nd Nebido injection on 10-Nov-2010 (about 5 weeks after the 1st injection), the patient experienced a similar reaction to the one he experienced after the initial injection was given. Approximately 1.5 hours after injection, the patient was still suffering from the reaction of coughing and swollen throat. However, no breathing difficulty occurred. The event of swollen throat was upgraded to serious by the reporter due to medical importance.

Case 201045017GPV: This 51-year-old Swiss male patient with testicular hypofunction, essential hypertension, HIV disease, and opioid dependence syndrome received Nebido treatment. On 11-Oct-2010, after his 2nd injection of 0.75 mL Nebido, the patient experienced cough and dyspnea, reported as medically important events. The injection was stopped after 1 mL, and he was treated with 100 mg prednisone 100 mg orally and two tablets of an antihistamine (desloratadine). After 10 minutes the patient recovered.

Case 201046647GPV: This 38-year-old Italian male patient experienced chest pain, respiratory symptoms, arthralgia, and syncope. No additional details were provided. The time frame between the injection and the occurrence of events was not reported.

Case 201047159GPV: This 63-year-old German male patient was treated with Nebido for testosterone deficiency syndrome. On 21-Sep-2010, the patient received his 2nd Nebido injection, and experienced a life-threatening, immediate hypersensitivity reaction with symptoms of feeling hot (flushing), an irritative cough, and bronchospasm that lasted for 20 minutes. He was treated with IV anaphylaxis therapy, and quickly improved afterwards. Nebido was discontinued.

Case 201047285GPV: This 54-year-old German male patient received Nebido for trans-sexualism. On 26-Jan-2010, the patient experienced irritative cough, a generalized hot feeling, and palpitations that lasted for 20 minutes. It was not reported whether the events occurred during or shortly after injection or later, but the report did mention that Nebido was withdrawn. The event was considered serious by the reporter due to medical importance.

Case 2011-002167: This Ghanaian male patient of unknown age had been using Nebido for about 3 years as part of his hormone replacement therapy for panhypopituitarism. A few seconds after starting his injection of Nebido on 04-Jan-2011, he experienced an overwhelming need to cough, followed by a constriction in his airway and serious difficulty in breathing. This episode of coughing and impaired breathing lasted for about 10 minutes, and was extremely frightening for him. No treatment was performed. The case was considered serious by the reporter due to medical importance (constriction of airway and serious difficulty in breathing).

Case 2011007367: This 58-year-old Austrian male patient received Nebido for testosterone deficiency syndrome. During the injection on 01-Jun-2010, the patient experienced cough, dyspnea, anxiety, attack of sweating, and a "feeling of constriction in chest", which lasted few seconds. The window was opened, and the patient was laid down on the bed under observation. He recovered after 5 minutes. The events were considered serious by the reporter due to medical significance.

Case 2011009542: On unknown date, after his 3rd Nebido injection, this 62-year-old South Korean male patient experienced POME with a symptom of cough. After his 1st POME episode, the patient took three more Nebido injections, which were followed by the new POME episodes. According to reporter, the patient did not recovered from the last episode yet. The event was considered serious by the reporter due to medical significance.

Case 2011011368: This 41-year-old UK male patient received Nebido for an unknown indication. On 21-Jan-2011, the patient experienced an anaphylactic reaction with symptoms of dyspnea, rash, and throat tightness. The event was considered life-threatening. The event was treated with oxygen, adrenaline, an antihistamine (chlorphenamine), and hydrocortisone. The patient recovered.

Case 2011014093: This German male patient of unknown age received Nebido for an unknown indication. On an unknown date, the patient received an injection that was probably less than 2 mL, and during the injection the patient developed marked symptoms of POME, which was considered serious by the reporter due to medical importance.

Case 2011-014662: This 33-year-old Spanish male patient was prescribed Reandron for androgenic insufficiency two years prior to this event. On 20-Jan-2011, he experienced bronchospasm. He was treated with corticosteroid therapy. Reandron was discontinued and the patient recovered from the event.

Case 2011016767: This 42-year-old UK male patient had been on Nebido for 3 years for testicular cancer. In (b) (6), the patient had an anaphylactic reaction immediately after the 2nd injection. He felt his throat closing, cough, difficult breathing, and had an erythematous rash. He received oxygen, an antihistamine, hydrocortisone, adrenaline and prednisolone. The breathing improved with adrenaline. The patient was hospitalized and he recovered. He was discharged home on prednisolone and the antihistamine. Nebido therapy was discontinued.

Case 2011018006: On 19-Apr-2010, after his 3rd injection of Nebido, this 61-year-old Swiss male patient experienced an immediate type hypersensitivity reaction, grade III, coughing, dyspnea, wheezes, face edema, rash erythematous, and blood pressure increased. The events lasted for 30 minutes. The patient was treated with an antihistamine (clemastine), hydrocortisone intravenously, and salbutamol. The events were considered serious by the reporter due to medical significance.

Case 2011022738: This 57-year-old German male patient received Nebido on 14-Mar-2011. After a Nebido injection, the patient experienced urge to cough, burning sensation of eyes, breathing difficulties, and pressure on trachea. The patient did not receive any treatment and recovered after 30 minutes. The event was considered serious by the reporter due to medical significance.

Case 2011024048: On 16-Mar-2011, 30 seconds after starting his 3rd injection of Nebido (about 0.5 mL being injected), this 69-year-old Brazilian male patient experienced cough during injection, dizziness, chest pain, profuse sweating, and increased blood pressure. The events lasted about 5 to 7 minutes. The patient recovered from all events. The events were considered serious by the reporter due to medical significance.

Case 2011025652: This Swedish male patient of unknown age received Nebido for a unknown indication and experienced POME. This event was considered serious by the reporter due to medical importance.

Case 2011025755: This 65-year-old male German patient received Nebido for hypogonadism. On 24-Feb-2011, immediately after a Nebido injection, the patient experienced chest pain,

dizziness, tingling and burning sensation, increased sweating, malaise, dyspnea and cough. He did not receive any medication to treat the event. Actual symptoms abated after one hour, however, dry cough after athletic activity remained for three weeks after the injection. The events were considered serious by the reporter due to medical significance.

Case 2011039522: This German male patient of unknown age received Nebido injection and experienced bronchospasm, cold sweat, and dry cough. It was not reported whether these symptoms appeared directly after the injection. The patient's outcome was not reported. The event was considered serious by the reporter due to medical significance.

Case 2011040546: This Brazilian male patient of unknown age received a Nebido injection at a drug store. On 12-Mar-2011, approximately 1 to 2 minutes after injection, the patient experienced reduced breathing capacity followed by increased difficulty of breathing (he could not inflate the chest with air). As a consequence of difficulty breathing, the patient experienced dizziness, vertigo, darkness of vision (he saw alternate points of light like an off TV), joint pain (with more intensity in the lower limbs), intense sudoresis in his whole body, weakness, pallor, decreased body temperature, and "total absence of autonomy" (he remained sitting for 15 to 20 minutes). The outcome of the events was reported as recovered /resolved. According to the consumer, during the episode of the adverse events, he thought he would die as a result of these events. The events were considered serious by the reporter due to medical significance.

Case 2011044214: This unknown-aged male UK patient used Nebido since 2007 for unknown indication. On an unspecified date, after a Nebido injection by a general practitioner, the patient experienced coughing and wheezing. He went to an allergy clinic and the physician suggested it was POME. The symptoms were resolved within hours after the reaction occurred. The event was considered serious by the reporter due to medical significance.

Case 2011046164: This 34-year-old Spanish male patient had received Reandron for years. On (b) (6), after an IM injection, the patient experienced dyspnea, cough, depressed level of consciousness, muscular weakness, excessive sweating, and pallor. Adrenaline and oxygen were administered and he improved. However, after 30-40 minutes, the symptoms started again and the patient was taken to the hospital where he remained for observation. He recovered the next day and was discharged from the hospital.

Case 2011046482: This 49-year-old male UK patient started Nebido injection (indication for use not reported). After his 1st injection on 07-Jan-2011, the patient reported fatigue and flu-like symptoms. The reaction that occurred after his 2nd injection on 16-Feb-2011 (6 weeks apart) was more severe, with severe flu-like symptoms, headache, dizziness, hot flushes, sweating, aching joints, feeling of faintness, weakness, wheezing, sneezing, chest pain and heart palpitations. The

patient sought care from a specialist, who informed the patient of "blood pressure through the roof". The patient felt very poorly for 2 weeks, then quite poorly for 8 weeks. He decided to discontinue Nebido treatment. The events were considered serious by the reporter due to medical significance.

Case 2011048218: This 48-year-old Italian male patient started Nebido for primary male hypogonadism on 31-May-2011. On 31-May-2011, the consumer experienced dry cough, mild dyspnea, malaise, hyperhidrosis and mild dizziness in the afternoon after a slow injection of Nebido that was self-administered. Nebido injection was discontinued immediately. The event was considered serious by the reporter due to medical significance.

Case 2011050730, **Case 2011052409**, **Case 2011052410**: These 3 case reports were submitted by a single physician and concerned three Singaporian male patients of unknown age who started Nebido treatment for unknown indications about 3 years ago. During the injection all 3 patients experienced cough. The physician was aware of the possibility of POME. All three cases were considered serious by the reporter due to medical significance.

Case 2011056865: This unknown-aged male German patient started Nebido treatment on an unspecified date. On an unspecified date, the patient experienced allergic reaction and suspicion of POME. The outcome for this event was not reported. The event was considered serious by the reporter due to medical significance.

Case 2011063184: This 28-year-old South African male patient had been on Nebido treatment for the past 2-3 years for primary hypogonadism. On (b) (6), about 30 seconds after a Nebido injection, the patient complained about a burning sensation in his throat and he started coughing. After about 5 minutes, the patient felt pins and needles on his tongue. He was referred to ER and hospitalized for observation. The outcome of this event was not reported.

Reviewer's comment: **This case highlights the occurrence of paresthesia of the tongue. In other cases, tingling sensations in the lips, face, and throat have also been reported.**

Case 2011065559: This 67-year-old Russian male patient started Nebido treatment for age-related androgenic deficit on 27-Jul-2011. On 27-Jul-2011, during a regular injection of Nebido, the patient experienced cough. Nebido treatment was continued and the patient experiencing bronchospasm during the following injection (dyspnea and difficulty breathing) and cyanosis. The injection was stopped. The patient also experienced small bleeding at the injection site. The physician considered that Nebido could have been injected directly into a blood vessel. The events resolved on the same day without treatment.

Case 2011071329: On (b) (6), a few minutes after an injection of Nebido, a 49-year-old Swedish male patient experienced a feeling of pressure on his chest centrally and a slight feeling of cough. The patient was hospitalized with telemetry monitoring and received aspirin. An ECG approximately 10 minutes post-hospitalization showed 0.5-1 mm ST segment elevation in V2-V4. The physician diagnosed POME. The patient felt well and was discharged the same day. Nebido treatment was discontinued.

Reviewer's comment: **This case again highlights the potential for angina pectoris/ cardiac ischemia in middle aged men as a consequence of a severe post-injection reaction.**

Case 2011074882: This 60-year-old Brazilian male patient started Nebido treatment on 10-Jun-2008 for androgenic deficiency. On 08-Aug-2011, after a Nebido injection, the consumer experienced dizziness, vertigo, feeling of disappearing, confusion, disorientation, inability to stand, sensitivity alterations, gastrointestinal disorders (peppery taste on mouth, nausea, diarrhea), tiredness, general malaise and hypotension. The physician stated that the patient also experienced injection site bleeding on the buttock, which was believe to reflect unsuccessful and rapid injection. The events were considered serious by the reporter due to medical significance.

Case 2011083027: This male Russian patient of unknown age took hormonal replacement therapy by testosterone during last 10 years and used Nebido during the last several years. On 07-Sep-2011, the patient experienced a "strange wish to cough" after the 1st mL of Nebido was injected, then severe cough and difficulty breathing after the 2nd mL Nebido was injected. The patient experienced itching after the 3rd mL was injected. Finally, the patient experienced loss of consciousness after the 4th mL was injected. The patient was administered liquid ammonia as corrective therapy. The patient's BP was 100/90 mmHg after the injection. The event was considered serious by the reporter and the patient was recommended to discontinue Nebido.

Reviewer's comment: **This case illustrates 3 postive re-challenges in the same patient with increasing severity of the post-injection reactions.**

Case 2011087892: This 50-year-old UK male patient started Nebido for impotence on 12-Apr-2009. On (b) (6), he experienced shortness of breath immediately after an injection of Nebido. He also had burning in his hands and feet, burning in the roof of his mouth, severe pain in his right shoulder and extremity, and was clammy and pale. He lay down and ambulance was called. He was given an antihistamine with little effect, and then he was transferred to a hospital. The patient experienced syncope and received aspirin and glycerol trinitrate (GTN) as treatment for this event. The outcome of these events were not specified. The events were considered serious and life-threatening by the reporter.

Reviewer's comment: **This case illustrates the occurrence of a severe post-injection reaction after the first dose. It also raises the potential for cardiac ischemia in a middle aged man, as right shoulder pain was reported and nitroglycerin was administered.**

Case 2011095240: This 72-year-old Austrian male patient began coughing during a Nebido injection about 2-5 seconds after starting the injection. The cough was long-lasting and occurred twice after Nebido injections despite reporting a correct injection technique. After 2 hours, the patient recovered. Nebido injection was discontinued after the 3rd occurrence of cough and patient was switched to a testosterone gel product. The events were considered serious by the reporter due to medical significance.

Case 2011090820: On an unspecified date in 2007, after an injection with Nebido, this German male patient of unknown age experienced an anaphylactic shock. No additional information was reported.

Case 2011102083: One minute following injection of Nebido, this 47-year-old UK male patient began to cough fairly immediately, then described some tightening of the throat but no swelling noted, some difficulty breathing but mostly due to cough, also then felt very hot and sweaty. His BP was taken showing 170/105 mmHg. The events lasted 10 minutes. The events were not treated and resolved the same day. The events were considered serious by the reporter due to medical significance.

Case 2011105544: This 68-year-old German male patient with a medical history of multiple allergies (to bees, wasps, peanuts, unspecified food) initiated Nebido therapy for hypogonadism on 06-Dec-2007. On 27-Oct-2011, the patient experienced anaphylactic reaction during a Nebido injection, with symptoms of cough, dyspnea, flushes, taste disorders in mouth, and pronounced spasticity. He was treated with glucocorticoids and antihistamine medications. The patient's symptoms lasted for over one hour and slowly improved. His blood pressure remained stable, and no skin irritation was reported. Nebido was discontinued on the same date and the patient recovered after 1 hour.

Case 2011108338: This 42-year-old UK male patient started Nebido treatment on 17-Oct-2011 and experienced acute shortness of breath at the time of the first dose administration. The event resolved within several minutes. The reported event was considered serious by the reporter due to medical significance.

Case 2011110321: This male patient of unknown age from Malta with a medical history of hypopituitarism after brain cancer received Nebido treatment since 2008. His concomitant medications included thyroxine, hydrocortisone. On 30-Sep-2011, the patient experienced violent cough during intramuscular injection of Nebido and was close to collapsing. He also developed a generalized maculopapular rash. Due to their severity, these events were considered

life-threatening for the patient by the reporter. He recovered from the events and Nebido was discontinued the same day.

Reviewer's comment: **In this case, the patient had "violent cough" consistent with severe POME as well as "generalized maculopapular rash" consistent with a systemic hypersensitivity reaction.**

Case 2011110671: This 64-year-old German male patient received Nebido treatment for hypogonadism post orchidectomy. On 15-Nov-2011, 2 minutes after an injection of Nebido, the patient developed dry cough, mild dizziness, nausea, and dyspnea. These symptoms improved after approximately 5 – 10 minutes, and the patient recovered after approximately 20 minutes. No skin reactions occurred, and no treatment was necessary. The event was considered serious by the reporter due to medical significance.

Case 2011124098: This 56-year-old Finnish male patient received Nebido treatment for hypogonadism for many years. In 2011, the patient experienced cough, and strange feeling in the throat and mouth after a Nebido injection. One hour later, he recovered. The event was reported as POME and considered serious by the reporter due to medical importance.

Case 2012004307: This 50-year-old male patient started using Nebido for hypogonadism. During a Nebido injection on 12-Jan-2012, he experienced cough, furry feeling on tongue, tingling sensation, red eyes, sweating, rash on whole body, and ear pressure. The cough fully recovered shortly after the occurrence, while all other symptoms improved but were reported to have not fully recovered.

Case 2012004532: This Austrian male patient of unknown age experienced dry cough, dyspnea, and hypertensive crisis during an injection of Nebido. The patient's condition recovered 30 minutes later. The event was reported as POME and considered serious by the reporter due to medical importance.

Case 2012005684: This 58-year-old Australian male patient started Reandron therapy on 19-Jan-2012. Shortly after the 1st injection, he experienced postural hypotension and presyncope. The patient was reported to have recovered.

Case 2012005853: This 25-year-old German male patient received Nebido. On 27-Jun-2011, he received an injection over 30 seconds and experienced severe cough, sweating and dizziness. He was symptomatically treated and recovered after 25 minutes. The event was considered serious by the reporter due to medical significance.

Case 2012007253: This 53-year-old German male patient received several injections of Nebido. On 07-Oct-2011, during an injection that lasted 30 seconds, the patient experienced severe cough, sweating, and dizziness, lasting about 25 minutes. Symptoms were symptomatically treated. The patient recovered. The event was considered serious by the reporter due to medical significance.

Case 2012014074: This Austrian male patient of unknown age received Nebido injection for lack of testosterone/hypogonadism. During the injection, the patient experienced dyspnea, hypertensive crisis, paresthesia of the upper limbs, and dry cough. The event led to hospitalization.

Case 2012-014975: This 71-year-old male patient from South Africa received Nebido at a pharmacy, and afterward, he experienced a feeling of faintness, throat tightness (constriction of throat), and cough. He also experienced numbness in the leg for approximately three days.

Case 2012015311: Immediately after his 3rd injection of Nebido, this 76-year-old Nicaraguan male patient with androgenic hypogonadism experienced 2 minutes of cough. Subsequently, he complained of itching in the interscapular region, and a macular papular reaction of the skin. The patient was diagnosed with an allergic reaction and treated with antihistamines. The symptoms resolved. The event was considered serious by the reporter due to medical significance.

Case 2012019653: This Austrian male patient of unknown age received Nebido injection for low testosterone/hypogonadism. On an unspecified date, during the injection, the patient experienced hypertensive crisis, paresthesia of his upper limbs, dry cough, and dyspnea for 30 minutes. Therefore, the patient was hospitalized. His condition recovered and Nebido was discontinued. The event was considered serious by the reporter due to medical significance and hospitalization.

Reviewer's comment: **This is one of several cases that illustrate paresthesias of the upper and lower extremities as part of a severe post-injection reaction.**

Case 2012020873: This 68-year-old Brazilian male patient received Nebido injection on 29-Dec-2011 for hormone replacement. On an unspecified date after the product was administered, the patient developed an allergic reaction, and was hospitalized for 8 days and treated with unspecified medication. He had not recovered at the time of the report.

Case 2012025807: This unknown-aged German male patient had been using Nebido for several years due to insufficiency of the adenohypophysis. On an unspecified date, the patient

experienced anaphylactic reaction with symptoms of cough, dyspnea, swelling of face and eyelids, dizziness, dry throat and mouth which appeared within seconds after an injection and lasted approximately 30 - 60 minutes. The patient was treated with dexamethasone and an antihistamine (clemastine) and subsequently hospitalized. At admission, his complaints resolved. Skin allergy testing was planned. The patient had history of rash and general skin redness of unclear etiology.

Reviewer's comment: **This patient experienced a severe post-injection reaction with signs of hypersensitivity even after years of prior use.**

Case 2012025864: This 59-year-old Brazilian male patient started Nebido treatment for testosterone replacement on an unspecified date. On 15-Mar-2012, at the end of an injection, the consumer experienced pain in middle of the chest, continuous cough crisis, cold sweating, itching on his scalp, difficulty breathing, redness, malaise, burning in the side of his nose, burning in the buccal and lip mucosa, and itching eyes. The events of pain in the middle of chest, continuous cough crisis, cold sweating, itching on his scalp, difficulty breathing, redness and malaise resolved around 15 to 20 minutes after injection. The other events resolved after 30 minutes. Patient reported that he had never had these events before. He denied hospitalization and remedial therapy. The patient also reported that on previous injections, he had experienced a bad taste in mouth and slight somnolence. Of note, the box for hospitalization in the CIOMS form was checked.

Case 2012032972: This 47-year-old Swiss male patient received Nebido injections since Nov-2005. On 29-Mar-2012, 5 minutes after starting an injection of Nebido, the patient experienced progressive dry cough, followed by symptoms of a low grade Quincke's edema (angioedema). He also experienced generalized rash, intensive sweating, dyspnea, and dizziness. The symptoms lasted for 15 minutes. The patient was treated with an antihistamine (clemastine) and a corticosteroid. The patient recovered after 12 hours.

AT-2007-035468: On 13-Jun-2007, approximately 30 seconds after receiving Nebido injection, this 46-year-old Austrian male patient presented with anaphylactic reaction, a gagging throat irritation and a tickle of the throat. The patient was treated with an antihistamine. The patient recovered after 15 minutes.

AU-2007-014016: On 23-Apr-2007, during the 2nd injection of Reandron, this Australian male patient of unknown age developed severe coughing, as well as bodily shivering shortly after the injection. The injection was stopped approximately halfway and the patient was treated with oxygen, antihistamines and cortisone. The symptoms subsided. The patient was observed for one and a half hours prior to going home.

BR-2007-005496: This 57-year-old Brazilian male patient received his 1st Nebido injection on 05-Feb-2007 for hormone replacement therapy. On 05-Feb-2007, immediately after the Nebido injection, the patient experienced anaphylactic shock with symptoms of glottis edema, breathlessness, and malaise. The patient's breathlessness became worse 30 minutes after injection and he was lying down and treated with corticosteroids, and ventilated with oxygen. The patient experienced malaise during next 3 days. Nebido was withdrawn the same day.

CH-2007-042227: This 60-year-old Swiss male patient received Nebido injection on 07-Sep-2007. During the slow injection, the patient developed cough and respiratory distress. He recovered after 30 minutes. The event was considered serious by the reporter due to medical significance.

DE-2004-037302: On 21-Dec-2004, this 38-year-old German male patient received his first dose of Nebido injection for transexualism. During the injection, the patient experienced hyperventilation followed by pronounced redness in the face, malaise, and shivers. The patient's BP and HR increased. He was treated with prednisolone intravenously and an antihistamine, and kept in the clinic for observation. He left in a relatively recovered state. On the next day (22-Dec-2004), the patient still had late allergic symptoms like feeling of heat in the thighs and upper arms, malaise, and a feeling of fever, but no skin reactions or urticaria. The patient recovered.

DE-2007-004016: This unknown-aged German male patient received his 2nd dose of Nebido injection on an unspecified date. Approximately 15 seconds after the injection, the patient experienced circulatory collapse with unconsciousness for several minutes, nausea, tickling cough, and encopresis.

Reviewer's comment: **This case illustrates the extent of severity of a post-injection reaction (unconsciousness for several minutes).**

DE-2005-005199: This 30-year-old German male patient received Nebido treatment for Klinefelter's syndrome. On 31-May-2005, immediately after his 2nd dose of Nebido, the patient experienced medically significant stenocardia (angina), as well as tickle of the throat, shortness of breath, and sweating. The patient was reported to have recovered after 0.5 hours. The events were considered serious by the reporter due to medical significance.

Case DE-2005-008140: On 13-May-2005, this 56-year-old male German patient received his 1st injection of Nebido. He developed tickling of the throat immediately after removal of the needle, and was diagnosed as having a non-serious allergic reaction. The patient was treated with an antihistamine, clemastine.

Reviewer's comment: It is notable that neither the Sponsor nor FDA picked up the preceding case, but it was counted by the independent adjudicators.

DE-2005-008181: On an unspecified date, after receiving an injection of Nebido, this 67-year-old German male patient experienced circulatory collapse with decrease in BP, nausea, retching and fever attacks. The event was regarded as a hypersensitivity reaction. The outcome of the reaction was not reported.

DE-2005-009283: This 54-year-old German male patient received a dose of Nebido injection for hypogonadism. Immediately after the injection, the patient developed cough, flushing, sweating attacks, restlessness, tremor, dizziness, cold sweats, and increased blood pressure up to 150/95 mmHg. The symptoms lasted longer than 20 minutes. The patient was treated with cortisone in the office practice setting and transferred to a hospital. In hospital, he received ranitidine and an antihistamine. After observation, he was discharged the same evening.

DE-2005-015256: After his 2nd Nebido injection, this 61-year-old German male patient experienced a severe cough attack. The event subsided after 10 minutes. The event was considered serious by the reporter due to medical significance.

DE-2006-002815: This 15-year-old German male patient received Nebido treatment for hypogonadism due to Kallmann's syndrome. On 14-Feb-2006, immediately after his 2nd injection of Nebido, the patient developed extremely severe urge to cough, retrosternal pain and mild dyspnea, redness of the eyes and tachycardia. Blood pressure was normal. The patient was treated with an antihistamine, (dimetindene), and prednisolone. The patient recovered. The injection was administered in a reclining position but within less than a minute. The reporting physician suspected a type 1 hypersensitivity reaction.

DE-2006-003298: This 42-year-old German male patient received Nebido injection quarterly on 3 occasions for hypogonadotropic azoospermia and androgen deficiency after radiation. On an unspecified date, 3 minutes after his 4th Nebido injection, the patient experienced a hot flush, paresthesia in the area of his mouth and head, increasing dyspnea, cough, and an episode of apnea lasting 1-2 minutes. After 10 minutes, stable cardiovascular conditions returned. The patient recovered in the course of another 10 minutes. The events were considered serious by the reporter due to medical significance.

Reviewer's comment: **This case illustrates apnea for 1-2 minutes as part of a severe post-injection reaction.**

DE-2006-008415: This 54-year-old German male patient was enrolled in Study 306605 and received his 1st dose of testosterone undecanoate on 15-Mar-2004 for hypogonadism. On 03-Apr-2006, the patient received the 10th dose. Shortly (1 minute) after the injection of the study medication, the patient experienced cough with dyspnea. The event lasted about 15 minutes. The patient recovered without treatment. The investigator confirmed that he considered the event "cough after injection" as serious.

DE-2007-004747: This 74-year-old German male patient started Nebido treatment on 14-Jan-2005 for hypogonadism and erectile dysfunction (ED). On 08-Dec-2006, starting at 3 minutes after the slow injection of Nebido, the patient developed pronounced urge to cough, dyspnea and cyanosis. The event lasted for 20 min. The event of cyanosis was reported as life-threatening. The patient recovered. Allergic reaction (hypersensitivity) was suspected by the reporter.

DE-2007-023890: This 57-year-old German male patient received the 1st dose of Nebido injection on (b) (6) for hypogonadism due to pituitary tumor. During the injection, the patient complained that everything turned black and he experienced a headache, sweating and tickling of the palms of the hands and soles of feet. After the injection, the patient developed dizziness, tingling sensation of the upper part of the body and on hands and feet, a sensation of weakness and pressure in head. The patient was treated with 8 mg of an antihistamine (dimetindene maleate) and prednisolone in the ER. In the ER, the patient developed dry mouth, a numbness sensation in his fingers and toes, continued dizzy, the sensation of warmth at the injection site (which was hot, hard, sensitive to pressure and reddened). Cardiac, pulmonary and abdominal examinations were unremarkable. Blood pressure was normal (128/88 mmHg). The patient received an infusion of intravenous fluids E153, ranitidine and cooling of the injection site. The patient's outcome was not reported.

> **Addendum**: In this patient, all skin testing with Nebido, testosterone undecanoate, benzyl benzoate, caster oil, a testosterone gel product, and latex were negative. Total Ig E was 16 kU/L (normal range < 100 kU/L) and Immuno CAP specific Ig E was 0 kU/L for caster oil and 0.07 kU/L for latex on 19 Jul 2007.

DE-2007-030464: This 47-year-old German male patient started Nebido treatment for hypogonadism after orchidectomy. On unspecified dates, twice during his Nebido treatment course, the patient experienced cough after injection. During the last injection (b) (6) the patient developed severe dyspnea which was interpreted as laryngospasm. The emergency physician was called but the patient recovered spontaneously within a few minutes. Nebido was discontinued. The event was considered serious by the reporter due to medical significance.

GB-2007-006197: On (b) (6) just minutes after his 2nd Nebido injection, this 67-year-old UK male patient who was post-orchidectomy, experienced an acute anaphylactic reaction with a

coughing fit and tightness in the throat. There was no cardiovascular deficit and no wheezing. The patient was treated with an antihistamine (chlorpheniramine) and epinephrine (adrenaline). The event was considered life threatening and involved hospitalization. The patient was reported to have recovered from the event after treatment.

GB-2007-000740: This 54-year-old UK male patient received his 2nd dose of Nebido injection on (b) (6) for the indication of testicular hypogonadism and osteopenia. Approximately halfway through the injection, the patient began coughing, and began to get progressively worse with difficulty breathing and sweating. His pulse was 48 bpm during the episode and the patient was near respiratory arrest. The event was considered to reflect acute laryngeal edema and was life-threatening. The patient was administered two adrenaline injections and high concentration oxygen by face mask with re-breathing bag. The patient was transferred to the hospital via ambulance. The event was considered immediately life-threatening. The patient was reported to have recovered on (b) (6)

GB-2007-023826: This 45-year-old UK male patient started Nebido treatment as a growth hormone in Apr-2005. On (b) (6), after the 2nd dose, the patient suffered respiratory distress and couldn't breathe. In addition, the patient experienced the urge to cough, coughing, inspiratory wheezing, tightening of his throat, a rash on his abdomen with the feeling of itching, and closing of his airway. The event was considered to be a life-threatening anaphylactic reaction. The patient was hospitalized and treated with epinephrine (adrenaline) and an antihistamine (chlorphenamine). At the time of the report, the patient was recovering and the event was resolving.

> **Addendum**: The patient had no known drug allergies, but was allergic to a testosterone gel product (Testogel) and a testosterone patch (Andropatch). The patient took Andropatch in 1996 but discontinued the product due to local irritation and allergic skin reaction. The patient took Testogel in Aug 2003 and the dose was doubled in Mar 2004. The patient then developed a skin allergy to Testogel in Mar 2005.

NO-2007-008557: On 29-May-2006, just before an injection of Nebido was finished (2.5mL were given instead of 3mL), this 35-year-old Norwegian male patient developed dry coughing, itching, and a tingling sensation in his throat, then in his face and head. These events resolved after 5 minutes.

SE-2006-004192: On (b) (6) just one minute after starting the 3rd injection of Nebido, this 44-year-old Swedish male patient with Klinefelter's syndrome experienced burning pain over the lower part of his sternum radiating up to the chin with dyspnea. The administration of Nebido was discontinued and the events lasted for 2-3 minutes. The patient was hospitalized for further observation. No new episodes of chest pain occurred. The patient recovered and Nebido was

discontinued on (b) (6). The patient underwent an EKG which showed non-specific ST changes probably of ischemic character. The reporting physician's assessment was that Nebido might have been administrated intravascularly. The event was considered serious by the reporter due to medical significance and hospitalization.

Reviewer's comment: **This is another case in which the patient experienced chest pain and electrocardiographic changes consistent with cardiac ischemia as part of a severe post-injection reaction.**

SE-2006-017516: This 47-year-old Swedish male patient received his 1st dose of Nebido injection for unknown indication on 24-Jan-2006. After the injection, he experienced a swelling sensation in his throat, difficulty breathing and palpitations. The patient's discomfort disappeared spontaneously after 5 minutes. On 30-Mar-2006, immediately after his 2nd injection, the patient again experienced difficulty breathing for a duration of approximately 5 minutes. In addition, he experienced fatigue and cough for several hours. The reporting Swedish health authority assigned the MedDRA code "angioedema" to these symptoms. The event was considered serious by the reporter due to medical significance.

SE-2006-022330: This 38-year-old Swedish male patient received his 1st dose of Nebido injection on (b) (6) During the injection, the patient developed angioedema and pruritus. In addition, the patient experienced nausea, malaise, swelling around the eyes and itching of the throat. The patient was treated with hydrocortisone and antihistamine (clemastine). He was discharged home after observation for a few hours. The patient recovered without sequelae from the angioedema and pruritus. In this case, the Sponsor concluded that differentiation between angioedema, hypersensitivity reaction, and POME could not be done conclusively for this report.

SE-2007-002541: On an unspecified date, at the end of his 4th injection of Nebido, this 64-year-old Swedish male patient experienced a feeling of warmth over his chest and head, coughing and reddening of his face. These events lasted for 5 minutes and resolved spontaneously. Nebido was discontinued and therapy was switched to another testosterone injectable product.

ZA-2007-035469: This 29 year-old South African male who was prescribed Nebido presented with an allergic reaction and life-threatening bronchospasm on (b) (6). The event was reported as anaphylaxis. The patient's BP dropped and he collapsed within a minute of receiving Nebido. His BP was 111/74 mmHg, his HR was 100, and his oxygen saturation was 94%. He recovered after treatment with hydrocortisone and an adrenaline nebulizer. He was observed for 2 hours and was well when discharged the same day (with oxygen saturation of 99%). The patient had received one prior dose of Nebido, 3 months before. He was reported to have fainted after his first dose and was very pale afterwards.

Reviewer's comment: **This is another case in which the patient collapsed as part of a severe post-injection reaction.**

7.3.4 Analysis of 137 Cases with Severe Post-Injection Reactions

Reviewer's comment: **For additional details and expert evaluation of these cases, the reader is referred to the consultative review provided by DPARP.**

Temporal relationship between reactions and the injections

Table 7.10 Temporal Relationship between Reactions and Injection of TU in Cases with Severe POME/Anaphylaxis (N=137)

Temporal Relationship between Reactions and Injection of TU						
During Injection	Immediately After	2'-10'* After	Within 60 Min	1-8 hr After	Within 24 hrs	Not Specified
43	51	9	3	1	5	25
94 (68.6%)		12 (8.8%)		31 (22.6%)		

* ' = minute(s)

Reviewer's comment: **Most, but not all, severe post-injection reactions took place within 30 minutes of the injection. A few cases occurred after 30 minutes and in approximately 20% of cases, no specific time was provided but the event occurred on the same day as the injection.**

Case severity analysis

Table 7.11 Severity of Cases with Severe POME/Anaphylaxis (N=137)

Hospitalized /ER	Life-Threatening	Medically Significant*	Syncope /BP Dropped
32 (23%)	9 (7%)	128 (93%)	19 (14%)

* "Medically significant" as indicated on the report form.

Treatment received for cases with POME/Anaphylaxis

Table 7.12 Treatments in Cases with Severe POME/Anaphylaxis (N=137)

Subjects Who Underwent Treatments (n=60, 44%)			
Epinephrine	**Cortico-Steroids**	**Anti-Histamines**	**Other Therapies**
13 (10%)	**38 (28%)**	**30 (22%)**	**18 (13%)**

Case Severity List by Case Number

Table 7.13 Case Severity Category by Case numbers

Severity of POME/Anaphylaxis		
Hospitalized/ER	**Life-threatening**	**Syncope/BP drop**
200711268BNE	200812947GPV	200711270BNE
200711270BNE	200932012GPV	200815181GPV
200815181GPV	2011-011368	200818257LA
200815625LA	2011-016767	200819842GPV
200818230LA	2011-087892	200912079BNE
200821519GPV	DE-2007-004747	200929719GPV
200910048BNE	GB-2006-006197	200932012GPV
200912293BNE	GB-2007-000740	200940933GPV
200912294BNE	GB-2007-023826	201018709GPV
200919013LA		201021482GPV
200924735GPV		201046647GPV
200940275GPV		2011-074882
201021482GPV		2011-083027
201037659GPV		2011-087892
201038945GPV		2012-005684
2011-016767		DE-2005-004016
2011-046164		DE-2005-008181
2011-063184		GB-2007-000740
2011-071329		ZA-2007-035469
2011-087892		
2012-014074		
2012-019653		
2012-020873		
2012-025807		
2012-025864		
DE-2004-037302		
DE-2005-009283		
DE-2007-023890		
GB-2007-006197		
GB-2007-000740		
GB-2007-023826		
SE-2006-004192		

Analysis of Treatment Received

Table 7.14 Treatment Received by Individual Patients with Severe Postinjection Reactions

Treatment			
Adrenaline	**Steroids**	**Anti-Histamine**	**Other Treat**
200815625LA	200815625LA	200718455GPV	200812947GPV
200821519GPV	200821519GPV	200812881BNE	200815181GPV
200910048BNE	200828604GPV	200815625LA	200821776GPV
200919013LA	200912293BNE	200821776GPV	200832838GPV
200932012GPV	200916799LA	200828604GPV	200924735GPV
201047159GPV	200919013LA	200912079BNE	200940275GPV
2011-011368	200919765LA	200919013LA	201036559GPV
2011-016767	200924735GPV	200919765LA	2011-011368
2011-046164	200930704GPV	200924735GPV	2011-018006
GB-2006-006197	200932012GPV	200932012GPV	2011-046164
GB-2007-000740	200940933GPV	200940006GPV	2011-083027
GB-2007-023826	201021482GPV	201036559GPV	2011-087892
ZA-2007-035469	201025167GPV	201045017GPV	2012-005853
	201028214GPV	2011-011368	2012-020873
	201036559GPV	2011-016767	AU-2007-014016
	201038945GPV	2011-018006	BR-2007-005496
	201040373GPV	2011-087892	DE-2005-009283
	201040508GPV	2011-105544	GB-2007-000740
	201045017GPV	2012-015311	
	201047159GPV	2012-025807	
	2011-011368	2012-032972	
	2011-014662	AT-2007-035468	
	2011-016767	AU-2007-014016	
	2011-018006	DE-2004-037302	
	2011-048218	**DE-2005-008140**	
	2011-105544	DE-2005-009283	
	2012-025807	DE-2006-002815	
	2012-032972	DE-2007-032890	
	AU-2007-014016	GB-2007-023826	
	BR-2007-005496	SE-2006-022330	
	DE-2004-037302		
	DE-2005-009283		
	DE-2006-002815		
	DE-2007-032890		
	GB-2007-000740		
	SE-2006-022330		
	SE-2007-002541		
	ZA-2007-035469		

7.4 Summary of Differences between the Sponsor's Internal Review and More Recent Review by the Sponsor's "Independent Adjudicators"

7.4.1 For Cases in Clinical Trials

Table 7.15 Independent Adjudicator Results Compared with Endo Clinical Review for POME and Anaphylaxis in the Clinical Studies

	Anaphylaxis		POME	
	Yes	Indeterminate	Yes	Indeterminate
Number of Cases Identified by Independent Adjudicators	0	8	3	23
Endo Results of Cases				
Yes	0	2	2	6
No	0	6	1	15
Not Reviewed	0	0	0	2
Number of Cases Identified by Endo	2	NA	9	NA
Independent Adjudicator Results of Cases				
Yes	0	NA	2	NA
Indeterminate	2	NA	6	NA
No	0	NA	0	NA
Not Reviewed	0	NA	1	NA

Thus, for the analysis of clinical trial cases, there were minor differences between the original Sponsor's internal review and the more recent report of a case review by the Sponsor's "independent adjudicators". The only difference of note is that Endo concluded "yes" for 2 cases of anaphylaxis and the internal adjudicators concluded "Yes" for zero (0) cases and "Indeterminate" for 8 cases.

The difference between Endo evaluators and the independent adjudicators for postmarket cases is also relatively minor. The internal reviewers identified 228 cases of POME, while the independent adjudicators identified 223 cases. The differences in the analyses for postmarket cases are summarized in Table 7.16.

7.4.2 For Cases from Postmarket Experience

Table 7.16 Independent Adjudicator Results Compared with Endo Clinical Review for POME and Anaphylaxis in the Postmarketing Surveillance

	Anaphylaxis		POME	
	Yes	Indeterminate	Yes	Indeterminate
Number of Cases Identified by Independent Adjudicators	19	26	141	82
Endo Results of Cases				
Yes	17	24	141	68
No	2	2	0	14
Number of Cases Identified by Endo	79	NA	228	NA
Independent Adjudicator Results of Cases				
Yes	17	NA	141	NA
Indeterminate	24	NA	68	NA
No	38	NA	19	NA

The only difference of note is that Endo's evaluators indentified 79 cases of anaphylaxis, while the independent adjudicators indentified 45. This difference is based on the independent adjudicators' use of Sampson's criterion #1 only for case definition. The 34 anaphylaxis cases that were excluded through this process were nonetheless rolled into the POME category.

7.4.3 Further Analysis of Sponsor's Adjudication on Cases of POME and Anaphylaxis and Reviewer's Comments

For POME

Table 7.17 Sponsor's Adjudication of Cases of POME

19 Cases Not in Concordance within 228 POME			14 IND Cases Not in Concordance out of 228 POME		
Case Number	Independent Adjudication	Sponsor Adjudication	Case Number	Independent Adjudication	Sponsor Adjudication
200811257GPV	No	Yes	200818230LA	Indeterminate	No
200816518LA	No	Yes	200818754GPV	Indeterminate	No
200824903GPV	No	Yes	201030488GPV	Indeterminate	No
200918244LA	No	Yes	201035276GPV	Indeterminate	No
201014170LA	No	Yes	201041966GPV	Indeterminate	No
201019729GPV	No	Yes	2011-016420	Indeterminate	No
201022548GPV	No	Yes	2011-090820	Indeterminate	No
201043202GPV	No	Yes	2011-105941	Indeterminate	No
201046647GPV	No	Yes	AT-2007-035468	Indeterminate	No
2011-036255	No	Yes	BR-2006-019257	Indeterminate	No
2011-046482	No	Yes	DE-2004-037302	Indeterminate	No
2011-063096	No	Yes	DE-2005-008140	Indeterminate	No
2011-074882	No	Yes	DE-2005-008154	Indeterminate	No
AR-2006-007565	No	Yes	ZA-2007-035469	Indeterminate	No
AT-2006-001317	No	Yes			

BR-2007-015689	No	Yes			
DE-2005-011567	No	Yes			
DE-2007-023890	No	Yes			
SE-2006-022330	No	Yes			

Table 7.18 presents a summary of the 19 POME cases that were not counted by the Sponsor's independent adjudicators but were counted by the Sponsor's original internal reviewers. Table 22 presents a summary of the 14 POME cases that were not counted by the Sponsor's internal reviewers but were counted by the independent adjudicators

Table 7.18 19 Cases Not in Concordance of 228 cases of POME assessed by the Sponsor's internal review and cited in the CR of Nov-29-2012

Case Number	Independent Adjudication	Sponsor Adjudication	Clinical manifestation
200811257GPV	No	Yes	dizzy, sweating, rhinitis
200816518LA	No	Yes	weakness, malaise, sudoresis
200824903GPV	No	Yes	shivering, sweating, red + pustules
200918244LA	No	Yes	shortness of breath
201014170LA	No	Yes	dyspnea and BP high
201019729GPV	No	Yes	difficulty breathing dyspnea
201022548GPV	No	Yes	cough, hoarseness
201043202GPV	No	Yes	shortness of breath
201046647GPV	No	Yes	chest pain, syncope, arthralgia
2011-036255	No	Yes	chest pain, cough
2011-046482	No	Yes	flu-like symptoms, headache, severe fluey, dizziness, hot flush, sweating feeling faint,
2011-063096	No	Yes	difficulty breathing, dyspnea, and had a grand mal seizure
2011-074882	No	Yes	dizziness, diarrhea, hypotension
AR-2006-007565	No	Yes	dyspnea
AT-2006-001317	No	Yes	Dyspnea, anxiety, fatigue depress
BR-2007-015689	No	Yes	Emotional disorder, burning in chest, dizziness sweating in hands
DE-2005-011567	No	Yes	feeling of a lump in his throat
DE-2007-023890	No	Yes	things turned black, sweating, tingling sensation; headache dizziness, weakness ER
SE-2006-022330	No	Yes	angioedema and pruritus, nausea, malaise, swelling around the eyes and itching of the throat.

Table 7.19 14 "IND" Cases Not in Concordance of 228 cases of POME assessed by the Sponsor's internal review and cited in the CR of Nov-29-2012

Case Number	Independent Adjudication	Sponsor Adjudication	Clinical Manifestation
200818230LA	Indeterminate	No	"anaphylactic reaction", hospitalized.
200818754GPV	Indeterminate	No	"recurrent pulmonary embolism"
201030488GPV	Indeterminate	No	tickle of the throat
201035276GPV	Indeterminate	No	"anaphylactic reaction", drug withdrawn
201041966GPV	Indeterminate	No	"anaphylactic shock", no details
2011-016420	Indeterminate	No	"allergic reaction"
2011-090820	Indeterminate	No	"anaphylactic shock", no details
2011-105941	Indeterminate	No	"allergic reaction"
AT-2007-035468	Indeterminate	No	tickle in throat, gag irritation
BR-2006-019257	Indeterminate	No	"allergic reaction"
DE-2004-037302	Indeterminate	No	hyperventilation, erythema, shivering
DE-2005-008140	Indeterminate	No	tickling of the throat
DE-2005-008154	Indeterminate	No	"experienced pressing complaints"
ZA-2007-035469	Indeterminate	No	bronchospasm, BP decreased

IND = Indeterminate

For Anaphylactic Reactions

In the analysis of anaphylactic reactions, there were differences between the Sponsor's original internal review and the more recent review by the Sponsor's independent adjudicators that led to 35 fewer anaphylactic reaction cases overall (from 78 original cases to 45 cases).

The internal reviewers identified 79 cases of anaphylactic reaction, while the independent adjudicators identified 45 cases. The differences in the analyses are summarized in Table 7.20.

Table 7.20 Sponsor's Adjudication of Cases of Anaphylactic Reaction

38 Cases Not in Concordance of 79 Anaphylaxis in CR (29-Nov-2012)			2 Yes / 2 IND Cases Not in Concordance out of 79 Anaphylaxis in CR (29-Nov-2012)		
Case Number	Independent Adjudication	Sponsor Adjudication	Case Number	Independent Adjudication	Sponsor Adjudication
200813805LA	No	Yes	200812881BNE	Yes	No
200818257LA	No	Yes	200942732GPV	Indeterminate	No
200821776GPV	No	Yes	2011-002167	Indeterminate	No
200832838GPV	No	Yes	AT-2006-001317	Yes	No
200919765LA	No	Yes			
200939969GPV	No	Yes			
200940006GPV	No	Yes			
2010-000541	No	Yes			
201018386GPV	No	Yes			
201018670GPV	No	Yes			
201020446LA	No	Yes			
201025167GPV	No	Yes			

201028214GPV	No	Yes			
201036559GPV	No	Yes			
201040744GPV	No	Yes			
2011-016426	No	Yes			
2011-030349	No	Yes			
2011-048218	No	Yes			
2011-063184	No	Yes			
2011-070247	No	Yes			
2011-074882	No	Yes			
2011-110671	No	Yes			
AU-2007-014016	No	Yes			
DE-2004-037302	No	Yes			
DE-2005-009283	No	Yes			
DE-2005-011567	No	Yes			
DE-2006-002815	No	Yes			
DE-2007-004747	No	Yes			
DE-2007-004748	No	Yes			
DE-2007-023890	No	Yes			
DE-2007-030464	No	Yes			
GB-2006-006197	No	Yes			
GB-2007-000740	No	Yes			
NO-2007-008557	No	Yes			
SE-2006-017518	No	Yes			
SE-2006-022330	No	Yes			
SE-2007-002515	No	Yes			
SE-2007-002541	No	Yes			

Table 7.21 presents a summary of the 38 anaphylactic reaction cases that were not counted by the Sponsor's independent adjudicators but were counted by the Sponsor's original internal reviewers. Table 7.22 presents a summary of the 4 anaphylactic reaction cases that were not counted by the Sponsor's internal reviewers but were counted by the independent adjudicators

Tables 7.21 and 7.22 also include reviewer's comments.

Table 7.21 38 Cases Not in Concordance of 79 cases of Anaphylactic Reaction assessed by the Sponsor's internal review and cited in the CR of 9-Nov-2012

Case Number	Independent Adjudication	Sponsor Adjudication	Clinical Manifestation
200813805LA	No	Yes (ST)	Injection site pain, itching, induration
200818257LA	No	Yes	BP decreased, nausea, sudoresis
200821776GPV	No	Yes (ST)	Cough, dyspnea, BP increased; treated
200832838GPV	No	Yes	Cough, dyspnea, dizziness, treated
200919765LA	No	Yes	dyspnea, cough vomiting, treated
200939969GPV	No	Yes (ST)	Skin erythema, pruritis, treated
200940006GPV	No	Yes (ST)	Cough, dyspnea, chest pain
2010-000541	No	Yes	Cough, face erythema
201018386GPV	No	Yes (ST)	Swollen eyes, tongue, gritty sensation
201018670GPV	No	Yes	cough/dyspnea, BP decreased, dizziness
201020446LA	No	Yes	cough/dyspnea, throat irritation, numbness

201025167GPV	No	Yes (ST)	Asthma-like cough, heat sensation, tingling
201028214GPV	No	Yes	cough, dyspnea, dizziness, sweating
201036559GPV	No	Yes (ST)	cough, dyspnea, feeling of hear
201040744GPV	No	Yes	cough, dizziness, perspiration, dyspnea
2011-016426	No	Yes (ST)	allergic reaction dyspnea, cough attacks
2011-030349	No	Yes (ST)	generalized, mouth, tongue itching
2011-048218	No	Yes	cough, dyspnea, dizziness, sweating
2011-063184	No	Yes (ST)	cough, throat irritation
2011-070247	No	Yes	nausea, erythema, malaise
2011-074882	No	Yes	dizziness,, diarrhea, hypotension,
2011-110671	No	Yes	cough, dyspnea, dizziness, nausea
AU-2007-014016	No	Yes	cough, shivering
DE-2004-037302	No	Yes	hyperventilation, erythema, shivering
DE-2005-009283	No	Yes	cough, flushing, sweat, tremor, dizziness,
DE-2005-011567	No	Yes (ST)	throat irritation, vertigo, tachycardia
DE-2006-002815	No	Yes (ST)	cough, chest pain, dyspnea, eye redness
DE-2007-004747	No	Yes	cough, dyspnea, cyanosis
DE-2007-004748	No	Yes	cough, dyspnea,
DE-2007-023890	No	Yes (ST)	dizziness, tingling, numbness sensation
DE-2007-030464	No	Yes	laryngospasm, dyspnea, cough
GB-2006-006197	No	Yes (ST)	cough, tightness in throat
GB-2007-000740	No	Yes	laryngeal edema, cough, dyspnea,
NO-2007-008557	No	Yes	cough, pruritis, tingling sensation
SE-2006-017518	No	Yes (ST)	itching
SE-2006-022330	No	Yes	angioedema, pruritis, nausea, eye swelling
SE-2007-002515	No	Yes (ST)	urticaria generalized, pruritis
SE-2007-002541	No	Yes	cough, erythema

ST: Special Term only, SII = meets Sampson Criterion Number 2 only

Table 7.22 2 Yes / 2 IND Cases Not in Concordance out of 79 Anaphylaxis in CR (29-Nov-2012)

Case Number	Independent Adjudication	Sponsor Adjudication	Clinical Manifestation
200812881BNE	Yes	No	bronchospasm, cough, wheeze, "flushed"
200942732GPV	Indeterminate	No	Malaise, feel hot, cough, stridor
2011-002167	Indeterminate	No	cough, dyspnea, airway constriction
AT-2006-001317	Yes	No	dyspnea, anxiety

Reviewer's comment: **The difference in case number for immediate post-injection reactions generated through evaluation by the independent adjudicators as compared to the Sponsor's original case number does not significantly change the whole picture of immediate post-injection reactions, including severe POME and anaphylaxis**

7.5 Summary of Search Results and Analysis of the FDA's Adverse Event Reporting System (FAERS) for Immediate Post-injection Reactions with U.S. Approved Injectable Testosterone Products from January 1, 1969 through January 29, 2013

Using the same criteria as was used for identifying cases of severe post-injection reactions (severe POME and anaphylactic reactions) for testosterone undecanoate, FDA conducted a

search and analysis of the FDA Adverse Event Reporting System 2 (FAERS) for cases of severe POME and anaphylaxis that occurred immediately post-injection with the U.S. approved injectable testosterone products, testosterone enanthate and testosterone cypionate. The search encompassed the dates January 1, 19693 to January 29, 2013.

The search and analysis identified a total of 33 cases of severe post-injection reaction for the 44-year period January 1969 to January 2013. The Clinical review team's analysis determined that 19 of these cases reflected severe POME and 14 were anaphylactic reactions.

Among the identified cases, 4 patients were hospitalized, and 3 patients were reported to experience a life-threatening event.

The 33 individual cases are outlined in brief in Table 7.23 below.

Table 7.23 Cases of Severe Post-injection Reactions Identified from A Search of FAERS for U.S. Approved Injectable Testosterone Products - January 1, 1969 through January 29, 2013

Case #	Receipt	Age	Sex	Event Date	Clinical manifestation
1	1982	63	M	1982	Dermatitis, eczema, dyspepsia, bronchospasm and obstruction
2	1983	50	M	Oct. 1983	Cough, chest pain, discomfort
3	1986	70	M	05/01/1985	Cough, tongue swelling
4	1990	31	M	4/1/1989	Ulticaria, anaphylactic reaction, bronchospasm and obstruction
5	1991	63	M	3/29/1991	Tongue edema, hypersensitivity, malaise, palpitations
6	1991	33	M	1/1/1991	Laryngeal spasm, edema and obstruction, angioedema, anaphylactic reaction, ulticaria
7	1993	42	F	2/19/1993	Anaphylactic reaction, laryngeal spasm+edema, obstruction, diarrhea, sweating
8	1993	40	M	6/24/1993	Dermatitis, eczema, anaphylactic reaction, bronchospasm+obstruction,
9	1993	47	M	12/3/1992	Anaphylactic reaction. Breathing abnormalities, dyspnea, vasodilation
10	1994	55	M	12/1/1993	Dermatitis, eczema, anaphylactic reaction, angioedema
11	1994	40	M	7/1/1993	Anaphylactic reaction, laryngeal spasm + edema, obstruction, bronchospasm, obstruction, urticaria
12	1994	Unk	M	July 1994	Wheeze, urticaria, difficulty breathing
13	1994	35	M	6/29/1993	Dizzy within a few minutes of injection
14	1995	41	M	2/21/1995	SOB, disoriented POME/Anaphylaxis
15	1995	66	M	10/03/1994	Heaviness in chest 10 min after injection
16	1995	38	M	09/13/1994	Laryngeal spasm and edema, obstruction, anaphylactic

2 FAERS is a database designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. FAERS data do have limitations (e.g., variable quality and quantity of information provided, cannot determine causality, voluntary reporting system, reporting biases). Additionally, FAERS cannot be used to calculate the incidence of an adverse event in the U.S. population. FDA implemented FAERS on September 10, 2012, and migrated all the data from the previous reporting system (AERS) to FAERS. Differences may exist when comparing case counts in AERS and FAERS. FDA validated and recoded product information as the AERS reports were migrated to FAERS. In addition, FDA implemented new search functionality based on the date FDA initially received the case to more accurately portray the follow up cases that have multiple receive dates.
3 AERS implementation date

					reaction, dyspnea, pain
17	1996	Unk	M	1996	SOB, palpitations
18	1997	45	M	8/13/1996	Cough, dizziness, hypertension, tachycardia
19	1997	Unk	M	1997	Respiratory difficulty
20	1998	Unk	M	1998	Cough
21	1998	Unk	Unk	1998	Bronchospasm, obstruction, coughing
22	2000	32	M	7/1/1998	Cough, throat irritation
23	2000	48	M	6/1/1999	Laryngeal spasm, edema obstruction
24	2000	47	M	7/7/1999	Coughing, chills
25	2000	47	M	7/14/1999	Cough, chest pain and discomfort
26	2000	62	M	08/16/2000	Syncope upon injection
27	2007	50	M	05/27/2007	Throat swelling, dyspnea, feeling hot, injection site erythema+pain
28	2008	71	M	12/04/2008	Dyspnea, cough, nausea
29	2010	63	M	08/01/2010	Pain, not breathing right, feeling terrible
30	2011	52	M	3/1/2011	Anaphylactic reaction, pharyngeal edema
31	2012	69	M	04/01/2012	Edema, dyspnea
32	2012	53	M	03/15/2012	Difficulty breathing, hives, facial and peripheral edema
33	2012	20	M	11/19/2012	Paresthesia, tingling, wooziness in head, SOB, dyspnea, malaise, dizziness

7.6 Overall Safety Conclusions for Use of Testosterone Undecanoate Injection

The overall assessment based on the above safety findings from clinical trials and postmarketing reports is that testosterone undecanoate intramuscular injection product is associated with severe immediate post-injection adverse reactions, which appear to be both anaphylactic reactions and severe POME. The clinical concern is based largely on the immediacy and severity of these reactions, in particular, the anaphylactic reactions and POME reactions accompanied by throat tightening, dyspnea, cardiovascular changes, and loss of consciousness. While there are a series of lesser symptomologies, such as cough, throat irritation, flushing, nausea, GI disorders, sweating, etc., it is the cases of anaphylactic reaction and severe POME reactions that constitute our major concern. The characteristics of the above 137 cases of serious post-injection reactions, with their sudden onset of difficulty breathing, throat tightness/fullness, cough, flushing, cardiovascular, allergic, and constitutional symptoms are clinically impressive. In some cases, patients have reported feeling that they would not survive the event, some became apneic or lost consciousness, some required hospitalization, some received emergent treatment, and some cases were described as life-threatening. Respiratory distress and cardiovascular collapse with loss of consciousness were also reported. Some patients also required resuscitation for a catastrophic event, including treatment for anaphylaxis.

Other than the severe post-injection adverse reactions, the remainder of the safety results from clinical studies as well as the International Postmarketing studies of testosterone undecanoate injection reveals expected adverse reactions associated with the pharmacological action of testosterone (e.g., increasing serum PSA, worsening BPH, increasing hematocrit, weight gain,

peripheral edema, change in lipid profiles, acne, breast pain, sweating, depression, etc.), and expected local adverse reactions at the injection site (e.g., injection site reactions).

Overall, the safety data associated with the use of this testosterone undecanoate product continue to be very concerning based upon the occurrence of severe post-injection reactions.

8 Postmarket Requirement

In the current resubmission, the Sponsor included a Risk Evaluation and Mitigation Strategy (REMS) for Aveed. In detail, the goals of proposed REMS are:

- Healthcare professionals and patients understand the risks of an injection-based pulmonary oil microembolism reaction and an anaphylactic reaction following the administration of AVEED.
- Patients remain at the healthcare facility or doctor's office for 30 minutes to allow early recognition and management of an injection-based pulmonary oil microembolism reaction or an anaphylactic reaction following the administration of AVEED.

The proposed REMS does not include Elements to Assure Safe Use (ETASU). Under the proposed REMS, the distribition of product would not be restricted by formal REMS mandate. To support the proposed REMS elements, a Medication Guide and Communication Plan for Healthcare Providers (HCPs) are included.

Finally, the Sponsor provides a timetable for assessment of the REMS at (b) (4) 3 years and 7 years, as well as a proposed survey methodology.

Reviewer's comment:
This reviewer and the Clinical review team believe that the proposed REMS and supporting information are not adequate to assure that the benefits of Aveed outweigh its potential risks. We acknowledge that no REMS will be capable of preventing the occurrence of severe post-injection reactions, some of which are indeed life-threatening events. These events are sporadic and unpredictable. We also acknowledge that no REMS will reduce the acute severity of the reactions. However, it might be possible to reduce the overall number of such events and to lessen their clinical impact by instituting a mandatory restricted distribution program as a formal Element to Assure Safe Use (ETASU). We currently envision a restricted distribution program that would include the following:

- **Prescribers would need to be certified that they (1) acknowledge the risk of a severe post-injection reaction and (2) having sufficient supplies and ability to treat an episode of severe POME or anaphylaxis, and (3) will keep the patient under observation for 1 hour after each injection.**

- **Pharmacies would need to certify that they will distribute Aveed only to certified prescribers.**
- **Potential patients would need to sign an informed consent at the start of treatment that they understand the risk of a severe post-injection reaction, they will remain in the office for the mandated time after each injection, and they are willing to proceed.**

In addition, we recommend that the Sponsor conduct a Phase 4 study to further evaluate the risk of severe postinjection reactions, including POME and anaphylaxis, of 750 mg Aveed (testosterone undecanoate intramuscular injection) in hypogonadal men, with the number of clinical investigative site locations, the number of subjects to be enrolled, and the number of injections to be administered to be further determined.

9 Labeling

No labeling discussions were held during this cycle. Should the application be approved eventually with a restricted distribution program ETASU, the reviewer highly recommends that a Black Box Warning of the potential for severe post-injection reactions, including POME and anaphylaxis, be included in the labeling.

10 Appendices

There are no Appendices in this review.

Addendum

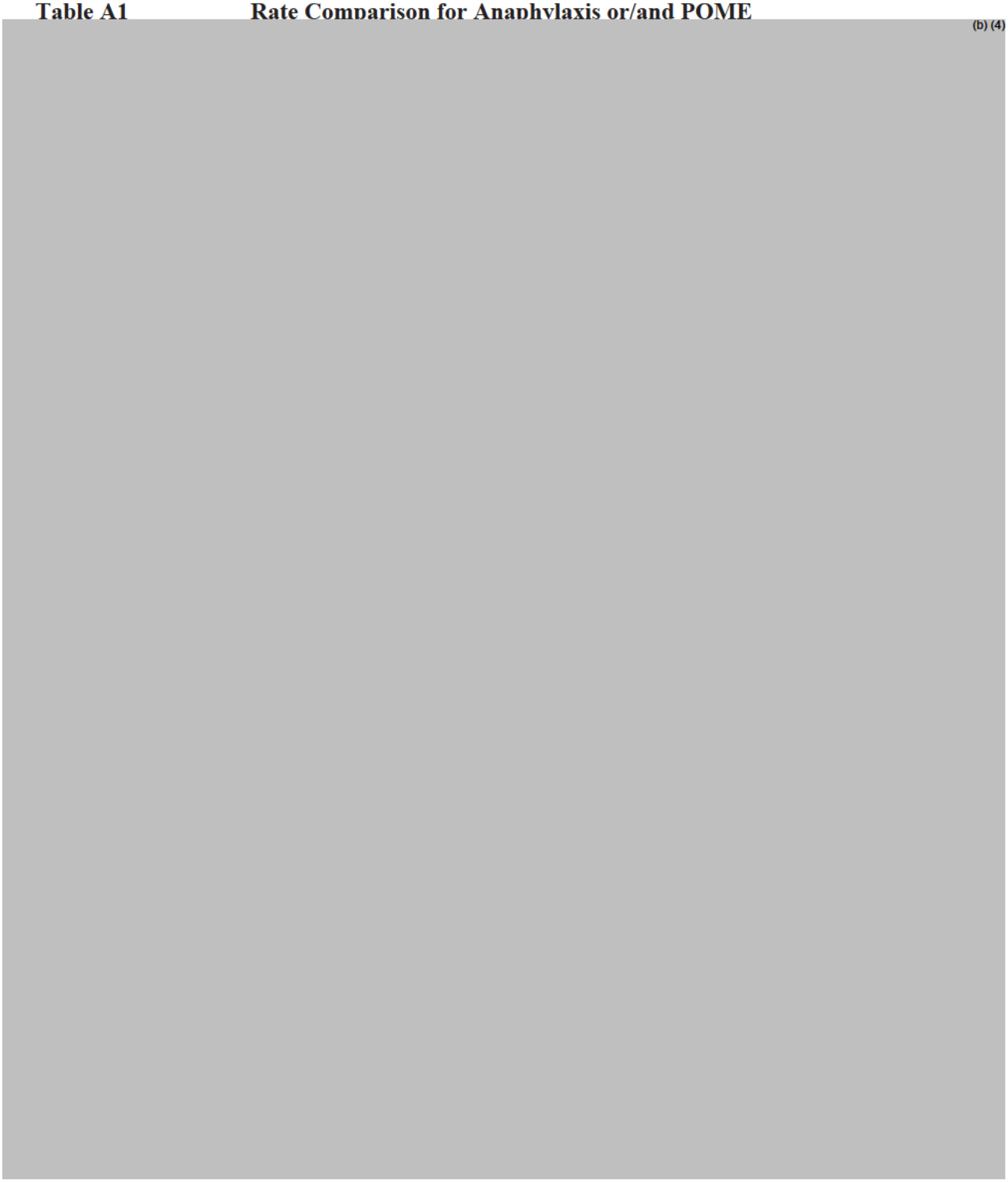
During the Advisory Committee Meeting on April 18, 2013, the committee voted on the following two questions:

#	Questions	Voting Results	
		Yes	No
1	Given the severe post-injection reactions that were reported with TU in clinical studies and postmarketing experience, do you believe that TU is safe for the proposed indication?	**9**	**9**
2	Whether you vote "Yes or No" to Question 1, please vote whether the Applicant's proposed instructions for use in product labeling that TU be administered using a slow (30-60 second) injection, and that patients remain in the office for 30 minutes post-injection would be sufficient to ameliorate the risk of severe post-injection reactions.	**1**	**17**

Another issue that was raised at the AC meeting was the occurrence of severe post-injection reactions with the two, U.S., marketed, injectable testosterone products, testosterone cypionate (TC) and testosterone enanthate (TE). The FDA presented data showing a total of 33 cases for both products over the course of 44 years, with very few cases reported over the last 10 years. The Sponsor provided an analysis of data (b) (4) An overview of the relevant data that the Sponsor provided to the AC and again as a 5-page amendment to the NDA after the AC meeting, is shown in Table A1 below.

Table A1 Rate Comparison for Anaphylaxis or/and POME

(b) (4)



Reviewer's comment:

(b) (4)

[redacted]

Based on differences (b) (4) [redacted] **it is difficult to use this information to make informed decisions comparing TC and TE to TU. We can not validate the Sponsor's claim that** (b) (4) [redacted] **We can not make any statement concerning severe POME. This information does not affect the Clinical review team's overall risk/benefit analysis of Aveed for the proposed indication.**

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

GUODONG FANG
05/20/2013

MARK S HIRSCH
05/20/2013
I concur.

DIVISION OF PULMONARY, ALLERGY, AND RHEUMATOLOGY PRODUCTS (DPARP) MEDICAL OFFICER CONSULTATION

Date:	March 22, 2013
To:	Mark Hirsch, MD, Cross Disciplinary Team Leader Division of Reproductive and Urologic Products
From:	Stacy Chin, MD, Medical Reviewer, DPARP
Through:	Anthony Durmowicz, MD, Team Leader, DPARP
Through:	Badrul A. Chowdhury, MD, PhD, Director, DPARP
Subject:	Aveed (testosterone undecanoate) for intramuscular injection

General Information

NDA#:	NDA# 22-219
Sponsor:	Endo Pharmaceuticals
Drug Product:	Aveed (testosterone undecanoate) for intramuscular injection
Request From:	Jeannie Roule, Project Manager, Division of Reproductive and Urologic Products
Date of Request:	December 11, 2012
Date Received:	December 19, 2012
Materials Reviewed:	NDA 22-219 Resubmission, DPARP Medical Officer Consultations (4/14/08, 5/27/08, 9/18/08, 5/4/09, 11/24/09, 6/9/11)

Introduction

This Division of Pulmonary, Allergy, and Rheumatology (DPARP) medical officer review outlines the safety concerns of serious post-injection reactions observed with testosterone undecanoate (NDA 22-219) under development for marketing in the United States as an androgen indicated for replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous testosterone. The Division of Reproductive and Urologic Products (DRUP) requested this consult to help identify and adjudicate reported cases of anaphylaxis and pulmonary oil microembolism [(POME), an adverse respiratory and systemic reaction to the embolization of the oil used in the drug product into the pulmonary microcirculation] events associated with this product's use in the post-marketing setting. The following review covers a brief regulatory history of testosterone undecanoate (also known by tradenames Aveed, Nebido, and Reandron), a discussion of anaphylaxis and POME with case examples of each, and results from the review of spontaneous post-marketing reports for testosterone undecanoate outside of the U.S. For consistency, unless specifically identified otherwise, such as in case reports, the testosterone drug product will be referred by its chemical name, testosterone undecanoate (TU).

Background

TU is an androgen for IM injection indicated for replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous testosterone such as congenital or acquired primary hypogonadism and hypogonadotropic hypogonadism. The TU drug product contains testosterone undecanoate, 250 mg/mL, in a solution of castor oil and benzyl benzoate. The proposed dose is 750 mg (3 mL) by intramuscular injection (IM) at initiation, 4 weeks, and every 10 weeks thereafter. TU has been approved and marketed in Europe under the trade names Nebido and Reandron since market authorization was granted in November 2003, albeit at a higher recommended dose of 1000 mg (4 mL IM). Its proposed tradename for the US market is Aveed.

The original NDA was submitted on August 24, 2007 by Indevus Pharmaceuticals, Inc. Although TU demonstrated adequate efficacy in terms of serum testosterone parameters, post-marketing reports of medically significant post-injection "coughing fits" and allergic reactions in countries where TU had been approved raised concern. Adverse events characterized by sudden onset of cough, dyspnea, and respiratory distress occurring shortly after injection were also noted in clinical trials. In the total clinical trial population at that time used to support US approval (approximately 600 subjects and 4,000 injections), there were 2 acute post-injection reactions reported. The Applicant had also submitted 66 post-marketing adverse event reports from outside the US of which 28 were categorized as serious adverse events, 12 required emergency medical care (treated with epinephrine, antihistamines, steroids), and 6 required hospitalization. DRUP consulted the Division of Pulmonary and Allergy Products [now the Division of Pulmonary, Allergy and Rheumatology Products, (DPARP)] in April 2008 to review these post-marketing reports identified by the Applicant as POME events to determine if any of the cases might actually be allergic reactions. That review as well as an independent review by FDA-commissioned outside experts determined that 2 of the 66 adverse reactions reported definitely met the clinical criteria for anaphylaxis (further described in a subsequent section of this consultation). Because of the uncertainty surrounding the incidence and etiology of these post-injection reactions, the original NDA application received an "approvable" letter with clinical deficiencies in June 2008. DRUP has maintained that the primary reason for lack of approval was and continues to be the failure to demonstrate that benefits of TU, taken in light of the availability of alternative products for the indication, outweigh the potential risks, namely the serious post-injection reactions due to either anaphylaxis or POME events. Alternatively, the Applicant, while acknowledging that anaphylaxis can and does occur, contends that immediate post-injection reactions are rare and have yet to result in death or permanent disability. In addition, they assert that careful and slow IM injection, as well as a lower injection volume (3 mL compared to the 4 mL dose approved in the rest of the world) are adequate measures to mitigate these reactions. In order to attempt to resolve what was felt to be an impasse between DRUP and the Applicant regarding the risk/benefit profile for TU, DRUP recommended resubmission of the NDA with additional safety data in order to bring the risk/benefit discussion to an Advisory Committee.

For the current NDA submission, the Applicant searched their database of spontaneous post-marketing reports over an 8 year period (November 25, 2003 to November 24, 2011) using agreed-upon search terms for anaphylaxis (Appendix 1) and POME (Appendix 2). The search resulted in the identification of 330 potential anaphylaxis events and 533 potential POME events.

Because the search terms for anaphylaxis were a subset of the search terms for POME, virtually all potential anaphylaxis reports are contained within the 533 potential POME population.

Following is DPARPs evaluation of the post-marketing reports of potential anaphylaxis and POME submitted by the Applicant with a focus on evaluating serious and/or medically important adverse reactions consistent with anaphylaxis or POME. While in most cases, a reasonable determination can be made as to whether an adverse reaction is due to anaphylaxis or severe POME, it should be noted that the similarity of the clinical presentation makes it difficult to distinguish between an allergic or hypersensitivity reaction versus a pulmonary oil embolism in some cases. However, the severity or seriousness of the adverse reaction is not diminished by the lack of an exact etiology.

Anaphylaxis – definition/case identification

Although anaphylaxis has always been regarded as a severe, potentially fatal, systemic allergic reaction that occurs suddenly after contact with an allergy-causing substance, there has been no universal agreement on the clinical definition of anaphylaxis or the criteria for diagnosis. Because the lack of specific diagnostic criteria hampered research, created confusion among health care providers, and led to inconsistent diagnosis and treatment of patients, the National Institute of Allergy and Infectious Disease (NIAID) and the Food Allergy and Anaphylaxis Network (FAAN) convened meetings in 2004 and 2005 to address this need. The symposia involved over 18 physician, patient advocate, regulatory, and scientific organizations including the American Academy of Allergy, Asthma and Immunology; the American College of Allergy, Asthma and Immunology; the Centers for Disease Control and Prevention; the Food Allergy Initiative; the US Food and Drug Administration; the European Academy of Allergy and Clinical Immunology; the Australasian Society of Clinical Immunology and Allergy. The symposia defined anaphylaxis as a clinical syndrome characterized by acute onset of illness with involvement of skin, mucosal tissue, and respiratory and/or cardiovascular systems.[1] It is worth noting that the NIAID/FAAN diagnostic criteria do not grade the severity of anaphylaxis. By virtue of multi-organ, multi-system involvement and the unpredictable nature of anaphylaxis, all anaphylactic reactions are considered severe and potentially life-threatening.

The three recommended diagnostic criteria are as follows:

Anaphylaxis is highly likely when any one of the following 3 criteria is fulfilled:

1) Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (e.g., generalized hives, pruritus or flushing, swollen lips-tongue- uvula), and at least one of the following:
   a) Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
   b) Reduced BP or associated symptoms of end-organ dysfunction (e.g., hypotonia (collapse), syncope, incontinence)
2) Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):
   a) Involvement of the skin-mucosal tissue (e.g., generalized hives, itch-flush, swollen lips-tongue-uvula)
   b) Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)

c) Reduced BP or associated symptoms (e.g., hypotonia (collapse), syncope, incontinence)
d) Persistent gastrointestinal symptoms (e.g., crampy abdominal pain, vomiting)

3) Reduced BP after exposure to known allergen for that patient (minutes to several hours):
   a) Infants and children: low systolic BP (age specific) or greater than 30% decrease in systolic BP
   b) Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that person's baseline

Since their inception, DPARP has used the NIAID/FAAN criteria to review all adverse reaction case reports to identify cases consistent with anaphylaxis. DPARP has usually taken a conservative approach in the determination of anaphylaxis by limiting the identification to cases fulfilling criterion 1 above in which skin and/or mucosal involvement must be present and accompanied by respiratory compromise and/or reduced blood pressure or accompanying end organ dysfunction such as collapse, syncope, or incontinence. However, based on the knowledge that the components of TU have already been associated with anaphylaxis and/or allergic reactions, one could potentially justify using both criteria 1 and 2 to identify cases of anaphylaxis.

To identify cases of anaphylaxis culled from spontaneous post-marketing reports over an 8 year period (2003-2011) by the use of the agreed-upon anaphylaxis search terms, DPARP reviewed the case narratives of the 330 potential cases of anaphylaxis that resulted from the Applicant's search. When we used the most conservative method for identifying anaphylaxis cases by using only NIAID/FAAN criterion #1 and including cases that reported the adverse reaction as either "anaphylaxis" or "anaphylactoid reaction", we identified 47 cases of anaphylaxis. This number increased to 68 when less restrictive criteria (NIAID/FAAN criteria 1 and 2) were used to identify anaphylaxis. While use of criteria 1 and 2 was more inclusive, a risk is the inclusion of severe adverse reactions that failed to have skin manifestations, which could also represent severe POME as well as anaphylaxis. However, whether these severe adverse reactions are categorized as anaphylaxis or POME does not make them any less severe. The overall number of anaphylaxis cases identified by DPARP is less than the 79 cases of anaphylaxis identified during the Applicant's internal review and reported in the NDA Complete Response submission. There could be several reasons for the discrepancy. The most apparent appears to be our conservative approach in defining anaphylaxis using NIAID/FAAN criterion 1 only while the Applicant seems to have been more liberal in applying the criteria. Additionally, in reaching their overall number, the Applicant appears to have accepted reports of adverse reactions that were broader in nature and included terms such as "hypersensitivity" or "allergic reaction" as reports of anaphylaxis. The interpretation of clinical symptoms in light of NIAID/FAAN criteria can also be somewhat subjective. For example, the presence of throat tightening could be interpreted as a mucocutaneous symptom indicative of edema or, alternatively, as a respiratory symptom. Again, as mentioned above, whether categorized as anaphylaxis or POME does not make the adverse reactions any less severe.

In addition to the post-marketing reports from 2003 through 2011 that were reviewed for anaphylaxis, additional safety data were submitted to the TU NDA in a periodic safety update report covering the time period from November 25, 2011 through April 30, 2012. This report contained adverse reactions reported after the Applicant's data lock and thus were not included

in the post-marketing surveillance database search. Review of adverse reaction case reports in this submission identified an additional 6 (NIAID/FAAN criterion 1) or 8 (NIAID/FAAN criteria 1+2) cases of anaphylaxis bringing the total number of anaphylaxis cases to 53 and 76, respectively.

For the cases of anaphylaxis DPARP identified, 9-14 of the reactions (depending on the criteria used) occurred upon the first exposure to TU. The mechanism for reaction with first exposure is unclear, but might be explained by nonspecific histamine release from drug, complement activation from the drug, or prior sensitization to a component of the TU drug product or another cross-reactive agent. It should be noted that drugs may cause anaphylaxis due to both IgE-mediated and non-IgE mediated etiologies. An example is vancomycin, which may produce both IgE-mediated and non-specific mast cell degranulation and anaphylaxis. Whether IgE-mediated or not, the underlying mechanism does not alter the clinical diagnosis of anaphylaxis and the risk for serious injury or even death.

Following are several representative case narratives for anaphylaxis.

Case 200815625LA (Brazil): After his fifth injection of Nebido (1000 mg/4 mL), this 60 year old male instantaneously experienced an anaphylactic reaction (considered life-threatening) involving throat itching, cough, glottis spasm, and edema. He was treated with serum physiological, adrenalin, Solu-cortef intravenously, and oxygen supplementation for 2 hours and oral Talerc (antihistamine). He was hospitalized under observation and discharged home after 12 hours fully recovered. After the reaction, he discontinued Nebido and started treatment with testosterone dipropionate gel.

Case 200910048BNE (Great Britain): Approximately 1 year and 4 months after initiating treatment with Nebido (1000 mg/4 mL), this 39 year old male experienced anaphylactic shock (considered life-threatening) during Nebido injection. After 2 mL from a 4 mL vial of Nebido had been administered intramuscularly, the patient suddenly complained of throat closing, coughing, and difficulty breathing as well as facial and tongue swelling. The injection was stopped and 0.5 mcg adrenalin was given along with oxygen. Upon arrival to the hospital, adrenalin was repeated (20 minutes following the first dose). He was admitted for further observation and discharged 24 hours later fully recovered. Following this reaction, he discontinued treatment with Nebido.

Case 2011-016767 (Great Britain): Immediately after the second Nebido injection (1000 mg/4 mL), this 42 year old male experienced anaphylactic shock (considered life-threatening). Symptoms included throat tightness, difficulty breathing, cough, and erythematous rash. He received adrenalin, oxygen, Piriton, Efcortesol, and prednisolone. He fully recovered during hospitalization and was discharged home on prednisolone and Piriton.

Case GB-2007-000740 (Great Britain): During the second dose of Nebido (1000 mg/4 mL), this 54 year old male experienced an anaphylactic reaction (considered life-threatening). Halfway through the injection, he developed cough which worsened as the injection continued. Although he was given water, his symptoms progressed to involve difficulty breathing, laryngeal edema, diaphoresis, and near respiratory arrest. His pulse was 48 bpm during the episode. He was given two 0.5 mL doses of adrenalin 1:1000 and oxygen via a re-breathing bag before hospital transfer. He recovered the same day and received no further doses of Nebido.

Potential Anaphylaxis-inciting Agents

When a safety signal for anaphylaxis or hypersensitivity to a drug becomes apparent, one must consider the allergenicity of the individual components of the drug product. As such, DPARP examined the potential for each of the individual components of TU to trigger clinical symptoms consistent with anaphylaxis. TU contains one active ingredient, testosterone undecanoate, and two excipients, castor oil and benzyl benzoate. While no studies have been undertaken to attempt to systematically differentiate the potential cause(s) of anaphylaxis for the specific TU product, both evidence from the literature and individual adverse reaction case reports support the notion that several of the components of TU, including excipients, may be responsible for the cases of anaphylaxis observed.

Testosterone undecanoate

Testosterone undecanoate, the drug substance and active ingredient, is a testosterone ester which forms active testosterone by cleavage of the ester side chain. From review of the literature, we are not aware of reports that the specific testosterone ester, testosterone undecanoate, is associated with immediate hypersensitivity reactions. However, the case report below suggests that testosterone itself (the only common ingredient between the TU injectable product and the Testogel and Andropatch topical testosterone products) may be capable of eliciting an anaphylactic reaction.

Case GB-2007-023826 (Great Britian)

Immediately after TU injection, a 46 year old male experienced anaphylaxis (considered life-threatening) with cough, inspiratory wheeze, tightening of throat, rash on abdomen, and closing of airways. The patient was treated with adrenalin and oral antihistamine. He had no history of asthma, eczema, or atopy, but reported past allergic skin reactions to Testogel and Andropatch requiring discontinuation of both.

Castor oil

Castor oil is derived from the castor seed *(Ricinus communis*). The castor seeds are cold pressed to extract the oil which is then clarified by heat. Although castor seed contains the toxic protein ricin, this protein is denatured and removed during the oil extraction process. The oil itself is a triglyceride composed primarily of ricinoleic acid and is frequently used as a skin-conditioning agent, emulsion stabilizer, and surfactant in cosmetics. In the food industry, food grade castor oil is used in food additives, flavorings, and in packaging. The FDA considers castor oil as "generally recognized as safe and effective" when administered enterally as a laxative. As with the TU product, depot formulations of IM injectable drugs sometimes use vegetable oil vehicles, such as castor oil, to increase storage in fatty tissues of the body and thus prolong drug half-life.

With regard to allergenicity and the potential to cause anaphylaxis, the ricinoleic acid of which castor oil is composed has been implicated as the causative allergen in allergic contact dermatitis case reports.[2-5] Three proteins known to be potent allergens have also been identified as well from the castor seed: Ric c 1, Ric c 2, and allergen 3.[6] The presence of castor seed allergen in castor oil depends upon the purity of the oil and thus the extraction process. A castor oil derivative, polyethoxylated castor oil is also an excipient in many drugs and has been implicated in anaphylactic reactions following cyclosporin and paclitaxel administration.[7-10]

In addition to the allergens noted above, the ricinoleic acid component of castor oil shares similarity in structure with salicylic acid (both are hydroxy acids) and ricinoleic acid has been demonstrated to act on the prostanoid system as well, which suggests the possibility of cross-reaction in persons who are salicylate allergic/sensitive[11]. Following is a case report of a severe adverse reaction and subsequent evaluation in a subject who was later discovered to have aspirin hypersensitivity that may support the concept of such a cross-reaction.

Case DE-2004-037302 and 201040508GPV (Germany): During injection of the first dose of Nebido (1000 mg/4 mL), a 38 year old male developed hyperventilation, hypertension, and pronounced facial erythema without urticaria. In addition, he complained of malaise and shivers. He was treated with prednisolone and cetirizine. He gradually recovered and was discharged home. The following day he continued to feel a sensation of heat in his extremities, malaise, and "fevers", but no rash or urticaria.

As a result of the reaction, he was enrolled in an Applicant-sponsored clinical trial (study IP157-003) designed to assess immediate hypersensitivity reactions in a controlled manner. On evaluation, he had no reaction to skin prick testing with either diluted or undiluted TU (Nebido). He received blinded intramuscular injections of saline placebo and Nebido. He had no reaction to placebo, but upon re-exposure to 0.4 mL of Nebido (1/10th dose), he developed reddening of the skin, hypertension, dyspnea, and flushed feeling. He received corticosteroids and antihistamines according to protocol, and his symptoms resolved within 20 minutes. The patient reported similar hypersensitivity reactions to aspirin in the past leading the allergist involved in the case to believe the reaction was neither IgE-mediated anaphylaxis nor POME, but rather a non-allergic hypersensitivity reaction.

Benzyl benzoate

Benzyl benzoate is a colorless, oily liquid that is rapidly metabolized to benzoic acid and benzyl alcohol. It is widely used as a preservative, a solvent in perfumes, and a component of insecticides and insect repellents in topically applied products and as a flavoring agent in foods and medications. In oil-based vehicles meant for IM depot steroid preparations, it lowers viscosity to improve ease of administration and prevents crystallization of steroids during storage. As a class (benzyl alcohol, benzoic acid, and sodium benzoate), benzoates are recognized to produce "nonimmunologic" contact urticaria and immediate reactions.[12] Following is a well-described published case report of an anaphylactic reaction in an adolescent patient who received the TU product (Reandron) and subsequent evaluation that directly implicates benzyl benzoate as the cause.[13]

Case 200932012GPV (Australia)

A 16-year-old boy with primary hypogonadism due to bilaterally absent testes, but otherwise unremarkable medical history, was converted from monthly intramuscular injections of testosterone esters (Sustanon, Schering-Plough) to depot testosterone undecanoate (Reandron 1000, Bayer). He had significant improvement in his mood fluctuations and energy levels on the depot preparation.

Less than 3 minutes after the third dose administration, he experienced a life-threatening anaphylactic reaction involving generalized urticaria and pruritus, tightening in the throat,

angioedema of the lips and face, shortness of breath, constriction of the chest, hypotension, cough, and dizziness. He was treated with adrenalin, intravenous promethazine, prednisolone, oxygen, and intravenous fluids. He was taken to an emergency department, but was not hospitalized overnight.

Upon further evaluation, skin prick testing revealed a 10x8 mm wheal to Reandron and no reaction to testosterone esters gel, or saline solution control. Skin prick testing to the Reandron components revealed a 10x10 mm wheal to benzyl benzoate and no reaction to either castor oil or testosterone undecanoate alone.

Pulmonary oil microembolism (POME) – definition/case identification

POME is an adverse reaction as a result of direct vascular or lymphovascular delivery of oil-based preparations to the pulmonary microvasculature. It was initially described coincident with procedures which involved large injection volumes of oil such as during lymphangiography, and hysterosalpingography but has also been noted to occur during or immediately after IM injections of oil-based depot injections including other oil-based testosterone preparations (testosterone enanthate).[14-15]

Both the presenting symptoms and severity can be variable, but cough and some degree of dyspnea seem to virtually always be present. POME can be severe; in these cases symptoms such as chest pain, dizziness, profuse sweating, paresthesias, syncope, and circulatory collapse have been noted.

The pathophysiology underlying this phenomenon is postulated to be similar to that observed with the more widely-recognized fat embolism syndrome. Pulmonary oil microembolization leads to transient acute pulmonary hypertension related to mechanical vascular occlusion and immediate respiratory symptoms such as cough and dyspnea. More severe microembolism is likely to result in decreased cardiac output with syncope and collapse. As with fat embolism, release of free fatty acids by the action of pulmonary lipases may also cause an inflammatory reaction and result in lung injury. This may explain why symptoms with severe oil/fat microembolism may be biphasic, initial acute symptoms such as cough dyspnea which resolve relatively quickly followed by return of symptoms later due to the inflammatory effect of free fatty acids to lung microvasculature.[16-18] Although not extensively studied, the management of POME would be the same as that for fat embolism, supportive care until symptoms resolve.

As with the evaluation of anaphylaxis adverse reactions, to identify cases of POME culled from spontaneous post-marketing reports over the 8 year period (2003-2011) by the use of the agreed-upon POME search terms, DPARP and DRUP together reviewed the case narratives of the 533 potential cases of POME that resulted from the Applicant's search. During the review we noted overlap of potential POME with potential anaphylaxis cases. This was likely due to the fact the anaphylaxis search terms were also included in the larger group of search terms used for POME.

The criteria used to identify POME cases were very similar to those of the Applicant except that POME cases were also reviewed for severity. To be categorized as severe, the reaction must have been identified as POME and must have met at least one of the following criteria:

- reported as an serious adverse event

- required hospitalization or emergency department care
- required medical treatment
- involved syncope or decreased blood pressure
- labeled medically important, serious, or life-threatening by the reporter or Sponsor

Using the POME identification and severity grading criteria, of the 533 potential case of POME from the data-base search, we identified 170-191 cases of POME (the range is due to whether the severe reactions meeting NIAID criteria 1 and 2 are classified as anaphylaxis or POME) of which 55-76 met the criteria for being severe. As with the anaphylaxis reports, an additional 6-8 adverse reaction reports of severe POME were identified in the periodic safety update report covering the time period from November 25, 2011 through April 30, 2012, that wasnot included in the Applicant's post-marketing surveillance database search.

Following are several case narratives of what DPARP believes are of severe POME.

Case 201018709GPV (Austria): This 40 year old male experienced circulatory collapse with a fall in blood pressure, cough, and dyspnea (considered serious) immediately after Nebido injection (1000 mg/4 mL). Onset of symptoms occurred 20 seconds after injection and lasted for 30 minutes. He did not suffer from urticaria. He recovered and did not receive medical treatment. The patient started Nebido one year prior to the reaction and had never experienced similar signs or symptoms previously. The treating physician stated that the injection was applied intramuscularly while the patient was in a horizontal position.

Case DE-2005-004016 (Germany): A male patient of unknown age experienced circulatory collapse with several minutes of unconsciousness, nausea, cough, and encopresis (defecation) (considered serious) 15 seconds following Nebido injection (1000 mg/4 mL). The patient had been treated with Nebido once previously but it is unknown if it was tolerated. He recovered but it is unknown over what time frame or if treatment was given. Attempts to contact the involved practice to obtain additional information were unsuccessful.

Case 2011-040546 (Brazil): Approximately 1-2 minutes after Nebido injection (1000 mg/4 mL), this male patient of unknown age experienced adverse reactions considered serious consisting of reduced breathing capacity and increased difficulty breathing, dizziness, vertigo, darkened vision, joint pain, weakness, pallor, profuse sweating, decreased body temperature, and total absence of autonomy (he remained sitting for 15-20 minutes as a result). During the episode the patient thought that he would die as a result of these events. It is not known if any treatment was given. The patient recovered after an unspecified duration. It was not reported if Nebido was used previously.

Case 200919765LA (Honduras): While his first dose of Nebido (1000 mg/4 mL) was still being administered intramuscularly, this 33 year old male started to complain of difficulty breathing which progressed to cyanosis (considered serious). The treating physician stopped the injection and immediately administered intravenous hydrocortisone and chlorpheniramine. Within minutes, the patient improved then began to cry as well as cough and vomit. That evening the patient called the physician and informed him that he was having fever to 40°C which was treated with unspecified NSAIDs and resolved. The treating physician reported that the injection

had been applied slowly and intramuscularly following aspiration. The patient received an additional two doses without problems.

Case 200815181GPV (Germany): Following Nebido injection (1000 mg/4 mL), this 52 year old male developed a heat sensation in his neck, tickle in his throat, severe dyspnea, headache, muscle twitching, and 20 second loss of consciousness (considered serious). He was placed in shock positioning and given normal saline intravenous fluid resuscitation. The patient was hospitalized and underwent intensive care therapy without artificial ventilation. A CCT did not reveal pathological findings. Infarction was excluded and no bleeding was detectable. The next day, about 28 hours later, the patient was discharged. A physician assumed micro fat embolism retrospectively and stated a possible relation to Nebido. He had been on Nebido for 4 years prior to this reaction and has received it subsequently without problem.

Summary

In summary, the potential safety signals (anaphylaxis and severe POME) identified in the original NDA submission and early post-marketing experience of TU are confirmed upon review of additional post-marketing reports.

Review of potential anaphylaxis cases culled from the Applicant's set of search criteria and submitted with the NDA has resulted in the identification of from 47 to 68 cases of anaphylaxis as defined by the NIAID/FAAN criteria, a clinical definition of anaphylaxis that FDA has adopted to assess for anaphylaxis in clinical trials and post-marketing reports since their publication in 2006. The range in the number of cases identified is the result of using the most conservative application of the NIAID/FAAN definition (criterion1 only) or a more inclusive estimate that employs both criteria 1 and 2 to define anaphylaxis, but since there is overlap in the signs and symptoms of anaphylaxis and POME, likely includes a substantial number of severe cases that represent POME. An additional 6-8 cases of anaphylaxis were identified in a periodic safety update report covering the time period from November 25, 2011 through April 30, 2012 that occurred after the Applicant's data lock bringing the total number of anaphylaxis cases to 53 to 76 using NIAID/FAAN 1 or NIAID/FAAN 1+2 criteria, respectively.

In addition to the cases defined as anaphylaxis, there may be additional cases consistent with hypersensitivity reactions that do not meet the anaphylaxis criteria and cannot be distinguished from POME and are classified as such.

Review of potential cases of POME has resulted in the identification of 170-191 total cases of which we consider 55-76 cases to be severe adverse reactions as a result of pulmonary oil embolism. As with anaphylaxis reports, an additional 6-8 adverse reaction reports of severe POME were identified in the periodic safety update report covering the time period from November 25, 2011 through April 30, 2012, that occurred after the Applicant's data lock, which further increases the number of POME cases reported.

The severity of the episodes is, at least in part, due to decreased cardiac output as a result of acute pulmonary hypertension resulting in dizziness, dyspnea and collapse. Because the symptoms associated with POME observed in the TU post-marketing reports have lasted up to

several days and the protracted clinical course reported in patients who have been inadvertently been administered testosterone products intravascularly, it is likely that POME also results in pulmonary inflammatory changes with a similar pathology to that observed in patients with and animal models of fat embolism.

The occurrence of POME events may be dependent on the overall volume of the oil-based injection received. The Applicant has proposed a lower volume (3mL) and therefore, lower dose (750 mg) of TU in the US NDA application than the dose approved elsewhere in the world (4 mL/1000 mg), at least in part, as an attempt to reduce the incidence of and alleviate concern over POME events. However, because only the 4 mL dose is used around the world where TU is approved, there is not enough clinical information to be able to discern if the 3 mL dose may be associated with reduced POME events.

Because the reports of POME events in the literature are sparse and only describe the acute event, the long-term consequences are largely unknown. POME events encompass a wide range of severity from mild cough to severe dyspnea, cyanosis, and loss of consciousness. As mentioned above, pulmonary oil microembolization leads to transient acute pulmonary hypertension related to mechanical pulmonary vascular occlusion and immediate symptoms. More severe microembolism is likely to result in decreased cardiac output with syncope and collapse. Subsequent release of fatty acids in the lung by the action of pulmonary lipases may result in pulmonary inflammation and injury which becomes apparent hours after the initial insult. In cases of a severe POME event, many patients might choose to discontinue treatment. However, many POME events may be less severe in nature and, because they are not severe enough to cause drug discontinuation, might occur repeatedly over time with subsequent exposures. The “harmless” nature of these milder cases of POME is largely speculative since there is no data in the literature to suggest what the long-term cardiopulmonary consequences might be of repeated POME over time. The effects of POME, whether severe acute episodes or mild repeated ones, in patients with concomitant cardiac disease or risk factors are also unknown.

The decision to approve or not approve TU is a risk versus benefit decision, and should be made in light of the degree of efficacy, the seriousness of the indication, the availability of alternative products for that indication, and the extent of the safety data. The identification of cases of anaphylaxis and POME from post-marketing reports is, by definition, a qualitative analysis since anaphylaxis and severe POME do undoubtedly occur. If a quantitative determination is necessary in order to inform the risk-benefit decision for TU, a large safety study, specifically designed to assess the incidence of anaphylaxis and POME would need to be conducted.

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/s/

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NDA #22-219 **General Correspondence** (SDN 009)

Medical Officer's Memorandum: Sponsor's Proposal for Analysis of Data in Complete Response (CR) Submission

Date Submitted: March 21, 2012
Date Received: March 21, 2012
Date Review Completed: July 12, 2012

Drug: Aveed™ (testosterone undecanoate)
Dose and route: 750 mg via intramuscular injection
Indication: Replacement of testosterone in hypogonadal men

Sponsor: Endo Pharmaceuticals
Chadds Ford, Pennsylvania

1. Background

On November 27, 2011, Endo Pharmaceuticals requested a Type C meeting to discuss the content and format of their planned NDA re-submission for Aveed (testosterone undecanoate). A major issue in the planned re-submission is identification and analysis of postmarketing reports of anaphylactic reaction and pulmonary oil microembolism (POME).

On January 14, 2012, the Division conveyed preliminary responses to questions posed in the meeting brochure.

On January 17, 2012, the Sponsor cancelled the teleconference meeting.

In the preliminary responses (on page 6), the Division requested that Sponsor provide the following information prior to the NDA re-submission, so that the Division could provide additional recommendations for the planned analyses of postmarketing data:

1. "*Provide the exact terms you plan to use to search your post-marketing data bases for cases of POME and anaphylaxis*", and

2. "*Provide specific criteria you plan to use to define POME and anaphylaxis, as well as the specific process you plan to use to adjudicate cases generated by post-marketing database search*".

On February 21, 2012, the Division conveyed final responses to the meeting brochure questions.

On March 21, 2012, the Sponsor submitted a response to the Division's two requests. The Sponsor's submission included:

1. A 4-page document entitled "*Pulmonary Oil Microembolism and Anaphylaxis: Case Identification and Classification*".

2. A list of exact search terms for the postmarketing databases for cases of POME and anaphylaxis.

3. Four references, including three published articles from the scientific literature and one from the MedDRA Maintenance and Support Services Organization.

On May 11, 2012, these documents were sent for comment to the Division of Pharmacovigilance (DPV1) in the Office of Surveillance and Epidemiology (OSE), and on the same day, a formal consultation was requested from the Division of Pulmonary, Allergy, and Rheumatology Products (DPARP).

2. Consultants' Comments and Recommendations

2.1 Comments from DPV1 in OSE

On May 15, 2012, Adrienne Rothstein of DPV1 provided the following comments:

1. It is recommended that Sponsor provide CIOMS line listings as a separate Excel spreadsheet that would facilitate organizing the reports. The Excel spreadsheet should include a special code or flag for cases Sponsor deems POME or anaphylaxis following adjudication. The Excel spreadsheet should also include both the lower level term (LLT) and the preferred term (PT) for each listing.

2. In Step 1 of the Sponsor's identification and classification process, clarify whether adjudicators are blind to the drug used.

3. In Step 2 of the process, clarify how events with an onset greater than 30 minutes are classified.

4. In Step 2 of the process, clarify what is meant by a "medically qualified reporter'.

5. The occurrence of POME following injection of Aveed could itself be viewed as a medication error.

2.2 Consultation from DPARP

On June 5, 2012, DPARP completed a consultation report, containing the following comments:

1. Overall, the MedDRA terms to be queried to cull potential cases of POME and anaphylaxis are reasonable.

2. With regard to identifying cases of anaphylaxis, DPARP noted that the criteria proposed by the Sponsor to define episodes of anaphylaxis is the so-called "Rüggeberg" definition of anaphylaxis developed in Europe from the Brighton Collaboration Anaphylaxis Working Group as a standardized method to evaluate immunization safety data. While the Sponsor is free to conduct their own analyses of anaphylaxis, the FDA uses a different, clinical definition of anaphylaxis developed in 2004 and 2005 by the National Institute of Allergy and Infectious Disease and the Food Allergy and Anaphylaxis Network when evaluating potential cases of anaphylaxis[1,2], and will base its safety assessment on cases of anaphylaxis defined by criteria specified in that definition.

3. DPARP does not believe that cases of anaphylaxis should be limited to those reactions which occur within 30 minutes of injection of Aveed.

4. For both the POME and anaphylaxis identification criteria where the temporal relationship between injection of Aveed and event onset is unknown, DPARP does not agree that for a case to be defined as POME or anaphylaxis that the adverse reaction must be reported as related to study drug (in clinical trials) or that Aveed should be stated as the suspected product (in postmarketing spontaneous reports).

5. As conveyed to the Sponsor in the DRUP preliminary responses, and final minutes dated February 21, 2012, in order to allow for independent analyses of potential cases of POME and anaphylaxis, individual CIOMS reports should be provided for all potential cases of POME and anaphylaxis irrespective of medical review or adjudication by the Sponsor.

6. Because of the marked variability in the quality of data in spontaneous postmarketing adverse event reports, it is possible that some cases may not be classified as POME or anaphylaxis by the Sponsor's criteria, yet these cases would still represent a severe, potentially life-threatening adverse reaction.

References

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Reviewer's Comments:

a. Regarding the issue of timing of the onset of post-injection adverse reactions (POME or anaphylaxis) to injection of Aveed, the experience to date has been that these events have generally occurred within minutes after injection. However, delayed anaphylactic reactions to a variety of compounds have been reported to occur hours after intake. These facts support OSE's comment # 3 and DPARP's comment # 3.

b. *It should be noted that there continues to be an absence of universal agreement on both the definition and criteria for the diagnosis of anaphylaxis.*

c. *Regarding Sponsor's proposed use of the "Rüggeberg" definition of anaphylaxis for reporting to the FDA, and recognizing that the FDA uses a different clinical definition, the "Sampson" criteria, DRUP requests that Sponsor provide its primary analysis using the "Sampson" criteria for the primary analyses, and in addition, if they wish, Sponsor may provide an additional analysis using the "Rüggeberg" criteria.*

3. Conclusion

This reviewer concurs with all comments from OSE and DPARP in response to the Sponsor's March 21, 2012, proposal for identification and categorization of cases of anaphylaxis and POME. All OSE and DPARP comments should be conveyed to Sponsor (see next section).

Of particular note is DPARP's recommendation that the anaphylaxis reports be analyzed using the "Sampson" criteria as the primary analyses, rather than the "Rüggeberg" criteria. If the Sponsor wishes, an additional analysis using the "Rüggeberg" criteria may be provided.

4. Recommended Regulatory Action

The following should be conveyed to Sponsor via a regulatory letter:

"We have completed our review of your March 21, 2012, submission, containing a proposal for case identification and classification of anaphylaxis and pulmonary oil microembolism (POME). In consultation with the Division of Pulmonary and Allergy Products (DPARP) and the Division of Pharmacovigilance (DPV) in the Office of Surveillance and Epidemiology (OSE), we have the following comments and recommendations:

1. Provide CIOMS line listings as a separate Excel spreadsheet to facilitate organizing the reports. The Excel spreadsheet should include a special code or flag for cases deemed POME or anaphylaxis by adjudication. The Excel spreadsheet should also include both the lower level term (LLT) and the preferred term (PT) for each listing.

2. In Step 1 of the proposed identification and classification process, clarify whether adjudicators are blinded to the drugs used.

3. In Step 2 of the process, clarify how events with an onset greater than 30 minutes are classified. Be aware that we do not agree that cases of anaphylaxis should be limited to reactions occurring within 30 minutes of injection.

4. In Step 2 of the process, clarify what is meant by "medically qualified reporter'.

5. With regard to identifying cases of anaphylaxis, you propose to use the "Rüggeberg" definition, as developed by the Brighton Collaboration Anaphylaxis Working Group to evaluate immunization safety data. In contrast, the Agency currently uses the "Sampson" clinical definition of anaphylaxis developed in 2004 and 2005 by the National Institute of Allergy and Infectious Disease and the Food Allergy and Anaphylaxis Network to evaluate potential anaphylaxis cases (Sampson HA, Journal of Clinical Immunology 2005 and 2006). We request that the primary analysis of anaphylaxis in your submission be based on the Sampson definition. If you wish, you may provide a secondary analysis using the Rüggeberg definition.

6. Where the temporal relationship between injection of Aveed and POME/ anaphylaxis onset is unknown, we do not agree that an adjudicated case must be reported as related to study drug or that Aveed must be stated as the suspect product.

7. We remind you that individual CIOMS reports should be provided for all potential cases of POME and anaphylaxis, irrespective of medical review or adjudication.

8. We remind you that because of the marked variability in the quality of data in spontaneous postmarketing adverse event reports, it is possible that some cases not classified as POME or anaphylaxis by your criteria may still represent severe, potentially life-threatening adverse reactions."

Harry Handelsman, DO
Medical Officer, DRUP

Mark S. Hirsch, MD
Medical Team Leader, DRUP

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/s/

HARRY HANDELSMAN
07/12/2012

MARK S HIRSCH
07/12/2012
I concur

DIVISION OF PULMONARY, ALLERGY, AND RHEUMATOLOGY PRODUCTS (DPARP) MEDICAL OFFICER CONSULTATION

Date:	May 29, 2012
To:	Jeannie Roule, Project Manager Division of Reproductive and Urologic Products
Through:	Anthony Durmowicz, MD, Team Leader, DPARP
Through:	Lydia Gilbert-McClain, MD, Deputy Director, DPARP
Subject:	Aveed (testosterone undecanoate) for intramuscular injection

General Information

NDA/IND#:	NDA# 22-219
Sponsor:	Endo Pharmaceuticals, Inc.
Drug Product:	Aveed (testosterone undecanoate) for intramuscular injection
Request From:	Jeannie Roule, Project Manager, Division of Reproductive and Urologic Products
Date of Request:	May 11, 2012
Date Received:	May 11, 2012
Materials Reviewed:	Aveed submission dated March 21, 2012 and previous DPARP consults

INTRODUCTION/BACKGROUND

DPARP has been a consultant to the Division of Reproductive and Urologic Products (DRUP) for Aveed (previously Nebido) (NDA 22-219) for evaluation of post injection anaphylaxis and pulmonary oil microembolism (POME) events since April 2008. Aveed contains testosterone undecanoate in castor oil and benzyl benozate and is administered as an IM injection for testosterone replacement in hypogonadal men with testosterone deficiency. In a Complete Response action on December 2, 2009, DRUP expressed concerns regarding reports of serious, immediate, potentially life-threatening post-injection adverse reactions and felt that the Applicant had not demonstrated the benefits of the drug outweighed the additional potential risks associated with the use of testosterone undecanoate for injection (compared with various other formulations, including topical gel). There have been several subsequent meetings between DRUP and the Applicant in order to discuss a path forward for the application, namely, the type and amount of additional safety data required to support the safety of Aveed as well as the possibility of an indication in a population of adult males who require testosterone replacement therapy in whom the additional potential risks associated with the use of Aveed (anaphylaxis and POME) would be acceptable. For this consult, DPARP has been asked to review a submission by the Applicant dated March 21, 2012, which outlines case identification and classification criteria for post-marketing POME and anaphylaxis events and search terms to be used to cull for potential POME and anaphylaxis

events. The submission is based on previous DRUP responses dated February 21, 2012 to the Applicant's January 14, 2012 submission.

As the submission asks no specific questions regarding the Applicant's proposed case identification criteria, following is a brief summary of the POME and anaphylaxis case identification processes followed by DPARP comments for DRUP to consider in their future interactions with the Applicant.

Case identification and classification criteria for post-marketing POME and anaphylaxis events

POME Case Identification: The Applicant proposes to utilize a POME-specific MedRA query, developed by Bayer AG, Germany, to retrieve cases with one or more symptoms and signs suggestive of POME. Such symptoms include cough and dyspnea, throat irritation, malaise, chest pain, dizziness, paraesthesia, and syncope, among others. After retrieval of adverse reaction reports containing the designated terms, a manual review and adjudication of possible POME identified cases will be performed by 2 independent clinicians with possible involvement of a third independent clinician if agreement cannot be reached. Cases will be categorized as POME if:

1. The reported event(s) occurred during or shortly after (within about 30 minutes) the injection, and the symptoms are
   a. cough or dyspnoea (with or without any other symptoms), or
   b. 2 or more symptoms suggestive of POME including throat irritation, malaise, hyperhydrosis, chest pain, dizziness, paraesthesia, or syncope, or
   c. the medically qualified reporter referred to the event using the MedDRA Lowest Level Term (LLT) "pulmonary oil microembolism".

   or
2. No temporal relationship between the injection and the event onset is known, and the event contains a combination of symptoms highly suggestive of POME (defined as meeting 1a and 1b or meeting 1c), and one of the following:
   a. if the reported event is from a clinical trial and considered possibly or probably related to study drug, or
   b. if the reported event is from the postmarketing spontaneous reports and AVEED was the suspected product.

Anaphylaxis Case Identification: To facilitate identification of potential anaphylaxis cases, the Applicant will utilize SMQs developed by MedRA for anaphylactic reactions and an anaphylactic/anaphylactoid shock conditions. Because the cases identified by the MedRA SMQs will likely capture some reports that will not represent anaphylaxis, a manual review and adjudication of SMQ-identified cases will be conducted. For adjudication, the Applicant has chosen to use a case definition derived from the Brighton Collaboration Anaphylaxis Working Group (the Rüggeberg definition). Cases will be categorized as anaphylaxis if:

1. The reported events occurred during or shortly after (within about 30 minutes) the injection and
   a. meet Rüggeberg criteria level 1 (definite anaphylaxis), or levels 2 or 3 (possible anaphylaxis); or
   b. contain the PTs "anaphylaxis" or "anaphylactic shock" even if the case did not contain sufficient information to meet the defined Rüggeberg criteria.

   or

2. No temporal relationship between the injection and the event onset is known, and the reported event meets the Rüggeberg criteria level 1, level 2, or level 3, and one of the following:
   a. if the reported event is from a clinical trial and considered possibly or probably related to study drug, or
   b. if the reported event is from the postmarketing spontaneous reports and AVEED was the suspected product.

DPARP Comments:

1. Overall, the MedRA terms to be queried to cull potential cases of POME and anaphylaxis are reasonable.

2. With regard to identifying specific cases of anaphylaxis, we note that the criteria proposed by the Applicant to define episodes of anaphylaxis is the so-called "Rüggeberg" definition of anaphylaxis developed in Europe from the Brighton Collaboration Anaphylaxis Working Group as a standardized method to evaluate immunization safety data. While the Applicant is free to conduct their own analyses of anaphylaxis, as the Applicant is aware, the FDA uses a different, clinical definition of anaphylaxis developed in 2004 and 2005 by the National Institute of Allergy and Infectious Disease and the Food Allergy and Anaphylaxis Network when evaluating potential cases of anaphylaxis[1,2] and will base its safety assessment on cases of anaphylaxis defined by criteria specified in that definition.

3. We do not believe that cases of anaphylaxis should be limited to those reactions which occur within 30 minutes of the injection of Aveed.

4. For scenario #2, for both the POME and anaphylaxis identification criteria, we do not agree that for a case to be defined as POME or anaphylaxis that the adverse reaction must be reported as related to Aveed/study drug.

5. As conveyed to the Applicant in DRUP comments dated February 21, 2012, in order to allow for independent analyses of potential cases of POME and anaphylaxis, individual CIOMS reports should be provided for all potential cases of POME and anaphylaxis irrespective of medical review or adjudication by the Applicant.

6. Because of the marked difference of the quality of data in post-marketing adverse event reports, it is possible that some descriptions of adverse reactions may not be able

to be classified as POME or anaphylaxis by your criteria yet would still represent a severe, potentially life-threatening adverse reaction.

References

1. Sampson HA, et. al. J Allergy Clin Immunol. 115 (3):584-591, 2005.
2. Sampson HA, et. al. J Allergy Clin Immunol. 117 (2):391-397, 2006.

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/s/

ANTHONY G DURMOWICZ
05/30/2012

LYDIA I GILBERT MCCLAIN
06/05/2012

DIVISION OF PULMONARY, ALLERGY, AND RHEUMATOLOGY PRODUCTS (DPARP) MEDICAL OFFICER CONSULTATION

Date:	June 09, 2011
To:	Jeannie Roule, Project Manager Division of Reproductive and Urologic Products
Through:	Anthony Durmowicz, MD, Team Leader, DPARP
Through:	Badrul A. Chowdhury, MD, PhD, Director, DPARP
Subject:	Aveed (testosterone undecanoate) for intramuscular injection

General Information

NDA/IND#:	NDA# 22-219
Sponsor:	Endo Pharmaceuticals, Inc.
Drug Product:	Aveed (testosterone undecanoate) for intramuscular injection
Request From:	Jeannie Roule, Project Manager, Division of Reproductive and Urologic Products
Date of Request:	May 5, 2011
Date Received:	May 5, 2011
Materials Reviewed:	NDA 22-219 CDTL review, Aveed briefing document dated February 16, 2011, updated May 26, 2011, previous DPARP consults

INTRODUCTION/BACKGROUND

DPARP has been a consultant to the Division of Reproductive and Urologic Products (DRUP) for Aveed (previously Nebido) (NDA 22-219) for evaluation of post injection anaphylaxis and pulmonary oil microembolism (POME) events since April 2008. Aveed contains testosterone undecanoate in castor oil and benzyl benozate and is administered as an IM injection for testosterone replacement in hypogonadal men with testosterone deficiency. In a Complete Response action on December 2, 2009, DRUP expressed concerns regarding reports of serious, immediate, potentially life-threatening post-injection adverse reactions and felt that the Applicant had not demonstrated the benefits of the drug outweighed the additional potential risks associated with the use of testosterone undecanoate for injection (compared with various other formulations, including topical gel). Subsequently, a meeting was held between DRUP and the Applicant on May 24, 2010 to discuss a potential path forward toward approval of Aveed. At the meeting, the Sponsor proposed to pursue one of the options outlined in the Complete Response letter, to identify (and seek an indication for) a population of adult males who require testosterone replacement therapy in whom the additional potential risks associated with the use of Aveed (severe acute adverse reactions including anaphylaxis and POME) as currently formulated would be acceptable. For this consult, DPARP has been asked to review sections of a meeting package dated February 16, 2011 (updated May 26, 2011), including several adverse event reports and physician's findings, in preparation for a meeting with the Applicant on June 27, 2011 during which a future development plan for

Aveed will be discussed. Following are the questions posed by DRUP followed by DPARP responses.

Question #1: What is the clinical significance of the positive skin prick test to AVEED, and to the benzyl benzoate component in AVEED, in Case 2009 32012 GPV – a 16 year old Australian male who had experienced a previous anaphylactic reaction to AVEED? Have there been other reports of allergic reaction to benzyl benzoate or to benzyl alcohol?

DPARP Response: The summary report is that for a 16 year old Australian male with testicular agenesis who, less than 3 minutes after receiving his third intramuscular injection of Reandron [Aveed, (testosterone undecanoate, castor oil, and benzyl benzoate)] experienced an anaphylactic reaction considered as life-threatening. Symptoms included itching of his palms, groin and feet, followed by generalized urticaria, tightening in the throat, angioedema of the lips and face, shortness of breath, constriction of the chest, hypotension, cough and dizziness. He was resuscitated with IV adrenalin, antihistamines, hydrocortisone, and fluids. The patient recovered without sequelae and was referred to an allergist for evaluation. Of note is that the patient had received another testosterone replacement therapy in the past, Sustanon (testosterone esters) without any adverse reactions. An allergist evaluated the patient and felt the immediate life-threatening reaction was definitely anaphylaxis. He performed skin testing to Reandron as well as its components and to 2 other testosterone products, Testogel and Sustanon. The patient had a significant wheal reaction to Reandron and subsequently, to the benzyl benzoate component of Reandron. No reactions occurred to any of the other products. DPARP agrees that this should be considered a potentially life-threatening anaphylactic reaction.

With regard to the benzoate as the cause of the anaphylactic reaction, benzoates are recognized to produce immediate urticarial and other immediate contact reactions[1]. Some reports suggest these immediate reactions are "nonimmunologic". However, based on the clinical definition of anaphylaxis developed during a multinational symposia in 2004 and 2005 by the National Institute of Allergy and Infectious Disease and the Food Allergy and Anaphylaxis Network which the FDA uses[2,3], the issue of the reaction being of immune or nonimmune etiology does not matter and is more of a scientific discussion point (also see the Summary statement below).

Question #2: What is the clinical significance of the post-injection reaction to AVEED in Case DE-2004-037302, at the time of skin prick testing – the same reaction the patient had experienced previously? What is the clinical significance of the lack of skin prick reaction to any substance, including saline, in this patient? Do you agree with the attending physician's diagnosis of "non-allergic hypersensitivity reaction" in this case?

DPARP Response: This patient was recruited into the Nebido (Aveed) "allergy study" (Study IP157-003) in which patients who had demonstrated an immediate hypersensitivity reaction to Nebido were recruited and re-exposed to Nebido in a controlled manner. For reference, the

summary of the initial adverse reaction to Nebido included in DPAP's consult to DRUP dated November 24, 2009, is included below:

Bayer Case ID: DE 2004 037302
Country: Germany
Date that report was received: December 22, 2004
Reason for use: transsexualism.
Reporter: health care professional
On December 21, 2004 12:56 pm the patient received the first dose of Nebido at 1000mg, 1 dose via intramuscular route of administration. During the injection, the patient experienced hyperventilation followed by pronounced redness in face (blood pressure was 132/ 102 and heart rate normal). No local complaints of urticaria were seen. Afterwards, patient experienced malaise and shivers. He was treated with Prednisolone IV at 250 mg and cetirizine hydrochloride at 10 mg (1 tablet). Repeated measurement of blood pressure showed moderate increase (172/109) with increased heart rate of 90. Patient stayed at the practice until 14:35 pm and left it afterwards in a relatively recovered state. On the next day, patient still had late allergic symptoms like feeling of heat in thigh and upper arms, malaise, and feeling of fevers, but no skin reactions or urticaria.

When re-exposure to Nebido was assessed in a blinded manner in study IP157-003, the patient had no reaction to skin prick testing with either diluted or undiluted Nebido. Intramuscular injections of placebo (saline) or Nebido administered in a double-blind fashion were next given. The subject had no reaction however, upon unblinding, he had received placebo. Subsequently, after the first injection of 0.4 ml (1/10th dose) of Nebido, the patient reacted within 15 minutes with erythema most pronounced at face, breast, and arms as well as a general feeling of warmth. In addition, blood pressure rose from 150/100 mmHg 30 min post injection to 205/130 mm Hg 30 min post injection and the patient had the feeling that there was a kind of external blockade in the thorax so that he could not breathe freely. The reaction was attributed to the high blood pressure and the skin sensations. It was not felt that this was a life-threatening reaction. Per the study protocol, the patient was treated with corticosteroids and antihistamines. The patient's blood pressure and erythema started to resolve within 2 minutes after injection and the reaction resolved completely within twenty minutes. He was dismissed according to the protocol on the following morning. No further symptoms occurred during the observation period or during a follow up call after 3 weeks.

An allergist involved in the re-exposure study witnessed the immediate post-injection reaction and did not feel it was either an anaphylactic reaction or consistent with POME. He noted that the subject stated that the reaction he had experienced upon re-exposure was essentially identical to that he had experienced in the past. Further questioning revealed that the subject has had hypersensitivity reactions to NSAIDS, including aspirin, in the past. The allergist therefore felt that both reactions the subject experienced, while due to Nebido, were most likely "nonallergic hypersensitivity reactions" rather than an IgE-mediated anaphylactic event and concluded that "an anaphylactic reaction can be ruled out; the reaction can be classified as a non-life-threatening, non-allergic, hypersensitivity-reaction , similar to those which can be observed with acetyl salicylic acid.

DPARP notes the conclusion of the allergist involved in the re-exposure study, including the statement that the patient did not have anaphylaxis and that he felt the reaction was linked to the subjects apparent sensitivity to NSAIDS. From DPARPs perspective, it is possible that the immediate systemic reaction the subject had when 1/10th dose (0.4 mL) of Nebido was related to his NSAID/aspirin intolerance as castor oil, the major excipient/testosterone diluent in Nebido, apparently contains natural plant-derived salicylates. However, while an immediate severe hypersensitivity reaction as a result of salicylate hypersensitivity may not be a classic IgE mediated reaction, as we have stated above, based on the clinical definition of anaphylaxis which the FDA uses, it is not necessary to determine that the immediate severe reactions are IgE mediated to classify them as anaphylactic reactions. The determination of the event being IgE mediated or mediated through some other non-IgE pathway is more of a scientific (rather than clinical) discussion.

Question #3: Is the "Patient Management Algorithm", as proposed by Sponsor, capable of guiding HCP's in the proper and safe recognition and management of anaphylactic reactions and other types of post-injection reactions, such as pulmonary oil embolism reactions?

DPARP Response: The Sponsor, as part of a Communication Plan for the proposed REMS for Aveed, plans to develop a patient management algorithm for the physician or health care provider. The algorithm is not included in the meeting package; rather the Sponsor included certain "bullet points" outlining what would be included in the algorithm such as including information regarding the approved indication, proper drug administration technique, a reminder that immediate post-injection reactions may occur, and suggested responses to new signs and symptoms (tachypnea, wheezing, cough, etc.) that may occur post-injection. DPARPs feeling is that with regard to any potential Communication Plan, health care providers who would potentially be administering Aveed should be made aware that potentially severe immediate post-injection reactions, including POME and anaphylaxis, have been observed with Aveed and that Aveed should be administered in a setting where emergency medical resuscitation equipment and physicians experienced in emergency resuscitation techniques are available. DPARP believes that including a formal patient management algorithm which includes specific treatments appropriate for post-injection reactions whether they are presumed to be POME, anaphylaxis, or any other event, is inappropriate as each case/patient response is likely to be different and best managed by a physician experienced in the recognition and treatment of a potentially life-threatening reaction, including anaphylaxis.

Question #4: Do you have any other comments, from the DPARP perspective, related to the February 16, 2011 meeting package?

DPARP Response: See Summary statement below.

SUMMARY

DPARP believes the Aveed product formulation is problematic in that it contains excipients (castor oil and benzyl benzoate) which, irrespective of the drug substance, testosterone undecanoate) appear to cause significant immediate adverse reactions in and of themselves. The castor oil has been associated with immediate POME reactions which can be severe. By the Applicant's admission, they may be observed more in the Aveed product due to the relatively greater injection volume of Aveed compared to similar products. Further, the effects of repeated pulmonary oil microembolism on future cardiopulmonary function are unknown. In addition, the case report described in DPARPs response the Question #2 suggest natural salicylates present in castor oil may have played a role in one NSAID-sensitive subject's hypersensitivity reactions to Aveed/Nebido. With regard to benzyl alcohol and benzyl benzoate, they frequently used as preservatives in medications and cosmetics. As a class (benzyl alcohol, benzoic acid, benzyl benzoate) benzoates are recognized to produce "non-immunologic" contact urticaria or "non-immunologic" immediate reactions, with non-immunologic signifying the reactions are not IgE-mediated. In the past these types of reactions would be considered "anaphylactoid" reactions rather than "anaphylactic" to differentiate the difference in pathogenesis (non-IgE mediated vs IgE mediated, respectively). As we have stated previously, our current definition of anaphylaxis for the purpose of classifying adverse reactions in clinical trials is based on clinical signs and symptoms and not pathogenesis. As such, we would not differentiate and a treating health care provider could not at the time of the reaction be able to differentiate an "anaphylactoid" from an "anaphylactic" reaction and the treatment would be the same.

As we have stated in previous consults DPARP believes that any immediate severe adverse reaction following injection of Aveed that requires treatment, whether or not it meets the classical or clinical definition of anaphylaxis, should be considered a safety risk and that the decision on whether to approve the product should be a risk benefit decision taking into consideration the seriousness of the indication, the availability of alternative products for that indication, and the extent of the safety data.

REFERENCES

1. Final Report on the Safety Assessment of Benzyl Alcohol, Benzoic Acid, and Sodium Benzoate International Journal of Toxicology 2001 20: 23
2. Sampson HA, et. al. J Allergy Clin Immunol. 115 (3):584-591, 2005.
3. Sampson HA, et. al. J Allergy Clin Immunol. 117 (2):391-397, 2006.

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/s/

ANTHONY G DURMOWICZ
06/10/2011

BADRUL A CHOWDHURY
06/13/2011
I concur

Division Director Summary Review for Regulatory Action

Date	December 2, 2009
From	Scott Monroe, MD Division of Reproductive and Urologic Products
Subject	Division Director Summary Review
NDA	NDA 22-219 (Complete Response)
Applicant Name	Endo Pharmaceuticals Solutions Inc.
Date of Submission	March 2, 2009
PDUFA Goal Date	December 2, 2009 (including 3-month extension)
Proprietary Name / Established (USAN) Name	AVEED™ Testosterone undecanoate
Dosage Forms/Strength	Injectable (intramuscular)/250 mg/mL
Proposed Indication	Replacement therapy in adult males with a deficiency or absence of endogenous testosterone
Action	***Complete response (see Section 13.1)***

Material Reviewed/Consulted OND Action Package, including	**Names of Reviewers**
Medical Officer Review	Harry Handelsman, DO
Statistical Review	Mahboob Sobhan, PhD
Pharmacology Toxicology Review	Eric Andreasen, PhD/Lynnda Reid, PhD
CMC Review/ONDQA	Yichun Sun, PhD/Moo Jhong Rhee, PhD
Microbiology Review	Vinayak Pawar, PhD
Clinical Pharmacology Review	Doanh Tran RPh, PhD/Myong-Jin Kim, PharmD
DDMAC	Janice Maniwang, PharmD, MBA
DSI	Not required
CDTL Review	Mark Hirsch, MD (also Clinical Team Leader)
OSE/DMEPA	Walter Fava, RPh/C. Mena-Grillasca, RPh/Denise Toyer, PharmD
OSE/DRISK	Sharon Mills, RN, CCRP/Jodi Duckhorn, MA
OSE/DRISK/REMS	Carolyn Yancey MD/Marcia Britt, PhD/Claudia Karwoski PharmD

OND	Office of New Drugs
DDMAC	Division of Drug Marketing, Advertising, and Communication
DSI	Division of Scientific Investigations
CDTL	Cross-Discipline Team Leader
OSE	Office of Surveillance and Epidemiology
DMEPA	Division of Medication Errors Prevention and Analysis
DRISK	Division of Risk Management
REMS	Risk Evaluation and Mitigation Strategy

1. INTRODUCTION

The purpose of NDA 22-219 is to obtain marketing approval for testosterone undecanoate administered by intramuscular (IM) injection for the indication of testosterone replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous testosterone. Testosterone undecanoate is an ester of testosterone that is metabolized to active testosterone by cleavage of the undecanoic acid side chain via serum esterases. The drug product consists of testosterone undecanoate (a long-acting depot formulation of testosterone) dissolved in castor oil and benzyl benzoate. Testosterone undecanoate (with the proprietary name of Nebido in most markets) was first approved for marketing in Finland in 2003. It has subsequently been approved for marketing in most western European countries and in almost 90 countries worldwide.

1.1 Original Review Cycle – Major Review Issues and Deficiencies

NDA 22-219 was original submitted by Indevus Pharmaceuticals in August 2007, but it was not approved because of (1) a chemistry, manufacturing and control (CMC) deficiency and (2) concerns about the safety of the product and its overall benefit/risk profile. The safety concern related to safety reports (almost entirely postmarketing reports) of serious, immediate post-injection respiratory and allergic adverse reactions in men who had received IM injections of testosterone undecanoate. In some of the cases, laryngeal tightness, respiratory distress, circulatory collapse, cyanosis, and loss of consciousness were also reported as part of the event. For most of these cases, pulmonary oil microembolism (POME), based upon the castor oil in the depot injection, was thought to be causative. In at least 4 of the cases, however, signs and symptoms of a clinically serious systemic allergic reaction were noted, including 2 cases meeting generally accepted criteria for anaphylaxis. Because of the CMC deficiency and the risks associated with the immediate post-injection adverse reactions, an Approvable Letter was issued by the Division of Reproductive and Urologic Drugs (DRUP) on June 27, 2008.

In the Approvable Letter, it was stated that the Applicant would need to provide, or address, the following clinical deficiencies:

1. Provide additional safety data concerning the occurrence of post-injection POME and allergic adverse reactions from completed and/or ongoing clinical studies sponsored by Bayer Healthcare (formerly Schering AG) outside of the US to better define the incidence of these adverse reactions.
2. Provide information from clinical investigations intended to characterize the nature and etiology of the anaphylaxis-like events reported immediately following injection of testosterone undecanoate.
3. Provide a plan to minimize the risks associated with the clinical use of testosterone undecanoate, namely, to reduce incidence and/or severity of the serious POME and anaphylaxis-like adverse events.

The Applicant also was informed that the CMC deficiency identified in the Drug Master File (DMF # (b) (4)) for testosterone undecanoate also would need to be satisfactorily resolved and submitted to the DMF to support of approval of NDA 22-219.

1.2 Complete Response

1.2.1 Information Provided to Address the Clinical Deficiencies

On March 2, 2009, the Applicant submitted a Complete Response. The Complete Response included the following components:

- A Summary Report entitled "Incidence of Injection-Based Pulmonary Oil Reactions and Allergic Reactions from Clinical Studies of Testosterone Undecanoate" (dated February 12, 2009)
- Complete or abbreviated study reports for 11 Phase 4 studies not included in the original NDA submission
  - The additional clinical trial data increased the total clinical trial safety database for testosterone undecanoate to 2,834 subjects, who had received a total of 16,191 documented injections.
- The most current Bayer/Schering Periodic Safety Update Report (PSUR) covering the interval of November 25, 2007 - November 24, 2008
  - In addition to the types of information generally included in a PSUR, the PSUR contained an Appendix entitled "Nebido and Anaphylaxis." (Nebido is the proprietary name for testosterone undecanoate injection in most markets throughout the world).
- A proposed Risk Evaluation and Mitigation Strategy (REMS)

Late in the current review cycle, DRUP requested that the Applicant provide an update on all postmarketing reports of serious immediate post-injection pulmonary and allergic reactions reported since the data-lock (November 24, 2008) of the last PSUR. This safety update covered the period from November 25, 2008 – August 29, 2009. Based on the additional cases of serious adverse reactions contained in the update and the need to thoroughly review them, the PDUFA goal date was extended to December 2, 2009.

The Complete Response did not include additional information to characterize the nature and etiology of the anaphylaxis-like events reported in the original submission of the NDA (Item # 2 in Section 1.1) because DRUP had agreed in September 2008, that such information could be submitted post approval.

1.2.2 Information to Address the CMC Deficiency

Separate from the Applicant's Complete Response, the holder of DMF # (b) (4) updated the DMF. The updated information satisfactorily addressed the CMC issues regarding the sterility of the final drug product.

1.2.3 Outstanding Approvability Issues

The only significant review/approvability issue that needed to be resolved during the current review cycle was the acceptability of the benefit/risk profile for IM testosterone undecanoate for the proposed indication of testosterone replacement therapy in adult men. The efficacy of testosterone undecanoate, based on pharmacokinetic data from Study IP157-001 Part C, was determined during the original review cycle to be acceptable. The overall safety profile for testosterone undecanoate, based on clinical trial data and postmarketing safety reports appeared to be comparable, with one significant exception, to that for other testosterone products indicated for replacement therapy. The exception was the occurrence of serious, immediate post-injection

respiratory and allergic adverse reactions. Based on the number and severity of these reports, both the primary Clinical Reviewer (Dr. Handelsman) and the Cross Discipline Team Leader (Dr. Hirsch), who also was the Clinical Team Leader, have recommended that testosterone undecanoate (Aveed) injection not be approved at this time because they do not find the overall benefit/risk profile to be favorable or acceptable. I concur with their recommendations.

2. BACKGROUND

2.1 Description of the Product

Testosterone undecanoate is an ester of testosterone that is metabolized to active testosterone by cleavage of the undecanoic acid side chain via serum esterases. The drug product (Aveed) consists of testosterone undecanoate (a long-acting depot formulation of testosterone) dissolved in castor oil and benzyl benzoate. It is to be supplied in sterile, single-use vials, containing 750 mg testosterone undecanoate in a 3 mL solution. The 3 mL solution also contains 885 mg of refined castor oil and 1,500 mg benzyl benzoate. Each mL of solution, which contains 250 mg/mL of testosterone undecanoate in solution, contains the equivalent of 157.9 mg of testosterone.

2.2 Testosterone Products for Hormone Replacement Therapy

There are many testosterone drug products approved in the US for the indication of testosterone replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous testosterone secondary to (1) primary hypogonadism (congenital or acquired) or (2) hypogonadotropic hypogonadism (congenital or acquired). These products include

- Injectable testosterone preparations, such as testosterone enanthate (Delatestryl)
- Transdermal testosterone preparations, such as the Androderm transdermal testosterone system, AndroGel (testosterone gel), and Testim (testosterone gel)
- Buccal testosterone preparations, such as the Striant testosterone buccal system
- Oral testosterone preparations, such methyltestosterone capsules (Testred)

Each of these preparations has their own individual advantages and disadvantages. The major advantage of testosterone undecanoate IM injections, compared to that for other injectable testosterone preparations would be (1) fewer injections per year and (2) possibly fewer testosterone values outside the generally accepted normal range.

2.3 Regulatory History and Major Review/Approvability Issues

An overview of the regularly history of NDA 22-219 and the major review/approvability issues for testosterone undecanoate injection has been provided in Section 1 (Introduction) of this Memorandum. Dr. Hirsch provided a detailed review of the regulatory history for NDA 22-219 in Section 2.2 of his Cross Discipline Team Leader (CDTL) Memo, signed on November 30, 2009.

2.4 Primary Medical Reviewer's and Cross Discipline Team Leader's Recommendations regarding Approvability

In his primary Clinical Review, signed on November 10, 2009, Dr. Handelsman made the following overall assessment and recommendation regarding approval of this Application:

> *"In the opinion of this reviewer, the evidence presented in the submission derived from adequate and well-controlled clinical trials, was adequate to support the effectiveness of this product. However, the safety concerns related to the risks, risk/benefit, and management of serious post-injection reactions which led to the original "Approvable action" have not been adequately addressed in Sponsor's "Summary Report of the Incidence of Injection-Based Pulmonary Oil Reaction and Allergic Reaction from Clinical Studies of Testosterone Undecanoate" nor in the rest of their "Complete Response to Approvable Letter". The application should not be approved at this time*."
>
> "*It is recommended that this product (Aveed), due to unresolved safety concerns, not be approved for the indication testosterone replacement in males for conditions associated with a deficiency or absence of endogenous testosterone (hypogonadism), including primary hypogonadism (congenital or acquired) and hypogonadotropic hypogonadism (congenital or acquired).*"

In his CDTL Memo, signed on November 30, 2009, Dr. Hirsch made the following overall assessment and recommendation regarding approval of this Application:

> "*I find the risk benefit profile for this product to be currently unacceptable. The product conveys a serious risk: the occurrence of severe, immediate, post-injection reactions. These reactions were reported in clinical trials and spontaneously in the postmarketing period. … Many of the cases that I have reviewed were treated as for anaphylactic reactions, with the use of oxygen, epinephrine, steroid and antihistamine. In some of the cases, the event was clearly life-threatening. Some required hospitalization or emergency resuscitation. The etiology for these events appears to be both allergic and respiratory…"*
>
> *"I recommend that the product not be approved at this time. Like the medical officer, I am deeply concerned by the risk of severe, immediate post-injection reactions, which include cases of anaphylaxis and angioedema. I do not believe that the demonstrated benefits of the product are sufficient to outweigh this demonstrated risk. I recommend that the application should receive a "Complete Response" action. The Sponsor should be asked to provide information to demonstrate an improved risk benefit profile, although I am unable to provide specific advice in this regard.*"

Division Director's Comment

- *I concur with the overall assessments of Drs. Handelsman and Hirsch and their recommendations that this Application not be approved at this time.*

3. CMC

In the Approvable Letter, issued on June 27, 2008, the Applicant was informed that there was a CMC deficiency that involved the Drug Master File (DMF # (b) (4)) for the drug product. This deficiency concerned a lack of sufficient detail in the DMF regarding the processes to ensure sterility of the final drug product. The deficiency was communicated to the holder of the DMF

and the DMF was subsequently updated to address this issue (also see Section 6, Clinical Microbiology).

In the primary CMC review of this Complete Response, signed on July 7, 2009, Dr. Sun stated that:

> *'The applicant has provided sufficient information on raw material controls, manufacturing processes and process controls, and adequate specifications for assuring consistent product quality of the drug substance and drug product. The NDA also has provided sufficient stability information on the drug product to assure strength, purity, and quality of the drug product during the expiration dating period. All facilities have acceptable site recommendations. However, labeling review is not completed as of the date of this review. Therefore, from the CMC perspective, this NDA is not recommended for approval until the labeling review is completed.*"

In an addendum to the primary CMC review, signed on August 14, 2009, Dr. Sun stated:

> *"At the time the CMC review was written, labeling review has not been completed. Therefore, from the CMC perspective, this NDA is not recommended for approval until the labeling review is completed. On August 14, 2009, the review on labeling, and mock-up labels for container and carton was completed. The labeling, and mock-up labels for container and carton are acceptable. Thus, this application is now recommended for approval from the perspective of Chemistry, Manufacturing and Controls."*

Division Director's Comment

- *I concur with the assessment/final recommendation of Dr. Sun that from a CMC perspective there are no unresolved issues.*

4. NONCLINICAL PHARMACOLOGY/TOXICOLOGY

Testosterone undecanoate is an ester of testosterone. Pharmacological activity is dependent upon *in vivo* esterase activity which releases the active moiety, testosterone, from the undecanoic acid side chain. There were no unresolved nonclinical toxicology issues, other than labeling, at the conclusion of the first review cycle. Recommendations regarding revisions to labeling were provided, and these were incorporated by the Applicant into proposed labeling. In her Memo, signed on August 20, 2009, Dr. Reid (supervisory pharmacologist) stated the following:

- *I concur with the primary nonclinical reviewer, Dr. Eric Andreasen, that the nonclinical data support approval of testosterone undecanoate (dose) for the treatment of men with a testosterone deficiency as proposed in this NDA.*
- *The final label for AVEED submitted by the Sponsor on August 14, 2009 is acceptable.*

Division Director Comment

- *I concur with the assessment and recommendation of Drs. Andreasen and Reid. There are no unresolved nonclinical pharmacology/toxicology issues.*

5. CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS

DRUP has accepted PK data (i.e., serum concentrations of testosterone) from a single adequate clinical trial as sufficient to support the efficacy of drug products for testosterone replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous testosterone. In support of the efficacy of testosterone undecanoate (750 mg by IM injection),

the Applicant submitted data from two Phase 3 clinical trials, Study IP157-001 Part A and Study IP157-001 Part C. Both studies were conducted in men with low serum testosterone concentrations (morning serum testosterone < 300 ng/dL). In Study IP157-001 Part A, subjects received IM injections of either 750 mg or 1000 mg testosterone undecanoate every 12 weeks. Based on the submitted PK data, the primary Clinical Pharmacology Reviewer (Dr. Tran) concluded that steady state levels of testosterone were not achieved. In the absence of achieving steady state concentrations of serum testosterone, it would not be possible to determine with sufficient accuracy the serum concentrations of testosterone that would be achieved with chronic dosing. In the absence of steady state serum concentration data, the PK data were not sufficient to support approval of the Applicant's proposed dosing regimen.

Based on discussions with DRUP (b) (4) the Applicant (b) (4) requested that the Division consider for approval an alternative dosing regimen (hereafter referred to as the 750 mg TU LOADING regimen in this Section and Section 7 of this Memorandum). The 750 mg TU LOADING regimen was investigated in Study IP157-001 Part C and consisted of IM injections of 750 mg testosterone undecanoate (administered in 3 mL at a single site) at initiation of treatment, Week 4 of treatment (28 days after the initial dose), and every 10 weeks thereafter. Because of this request to change the dosing regimen for which approval was being sought, PK data from Study IP157-001 Part C were used as the primary source of data to support the efficacy of testosterone undecanoate. PK findings for the 750 mg TU LOADING regimen are summarized in Section 7 (Clinical/Statistical Efficacy) of this Memorandum.

In his primary Clinical Pharmacology Review of the original NDA submission (first cycle review, signed on May 1, 2008), Dr. Tran made the following state:

> *"The Office of Clinical Pharmacology/ Division of Clinical Pharmacology 3 has reviewed NDA 22-219. We find this NDA acceptable from a Clinical Pharmacology perspective, pending labeling discussion."*

No new clinical pharmacology data were included in the Applicant's Complete Response. Dr. Tran made the following statement in his final review, signed on August 17, 2009, of the Complete Response"

> *"The Clinical Pharmacology review of NDA 22-219 resubmission (DFS, date 7/10/2009) recommended that NDA 22-219 was acceptable, provided that labeling recommendations are adequately addressed. This review amendment is to document that the sponsor has adequately addressed our labeling recommendations."*

Division Director's Comment

- *I concur with Dr. Tran that there are no outstanding clinical pharmacology issues.*

6. CLINICAL MICROBIOLOGY

During the original review cycle, the Microbiology Reviewer (Dr. Pawar) identified deficiencies in the Drug Master File (DMF # (b) (4)) for the drug product. These deficiencies concerned a lack of sufficient detail in the DMF regarding the processes to ensure sterility of the final drug product. These deficiencies were conveyed to the holder of the DMF and were subsequently corrected.

In her review of the Complete Response, signed on April 23, 2009, Dr. Pawar stated:

> *"The application is recommended for approval from microbiology product quality standpoint."*

Division Director Comment

- *The previous microbiology (CMC) deficiency has been resolved; there are no remaining microbiology deficiencies.*

7. CLINICAL/STATISTICAL-EFFICACY

DRUP has accepted PK data (i.e., serum concentrations of testosterone) from a single adequate clinical trial as sufficient to support the efficacy of drug products for testosterone replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous testosterone. The primary efficacy endpoint for a testosterone replacement study is the average total serum testosterone concentration (Cave) over the dosing interval. A successful outcome for a study subject is a Cave value for total testosterone that is within the range of 300-1000 ng/dL. To meet the overall efficacy criteria for a successful clinical trial, at least 75% of subjects must have a total testosterone Cave within the range of 300-1000 ng/dL, and the lower bound of the two-sided 95% confidence interval about the point estimate of the mean must not be lower than 65%.

Additionally, there are several key secondary endpoints. One of the most important of these is based on the maximal serum testosterone concentration (Cmax) value for each subject. For a clinical trial to be considered successful, the following also should be observed:

(1) $\geq$ 85% of subjects should have a Cmax value of $\leq$ 1500 ng/dL

(2) $\leq$ 5% subjects should have a Cmax value between 1800 ng/dL to < 2500 ng/dL

(3) No subjects should have a Cmax value $\geq$ 2500 ng/dL

The primary Clinical Reviewer described in detail in the original Clinical Review, signed June 16, 2008, the efficacy findings for Study IP157-001A (dosing regimens of 750 mg testosterone undecanoate and 1000 mg testosterone undecanoate once every 12 weeks) and Study IP157-001C (750 mg TU LOADING regimen). Because the Applicant is seeking approval only for the 750 mg TU LOADING regimen, the following discussion describes only the findings from Study IP157-001C.

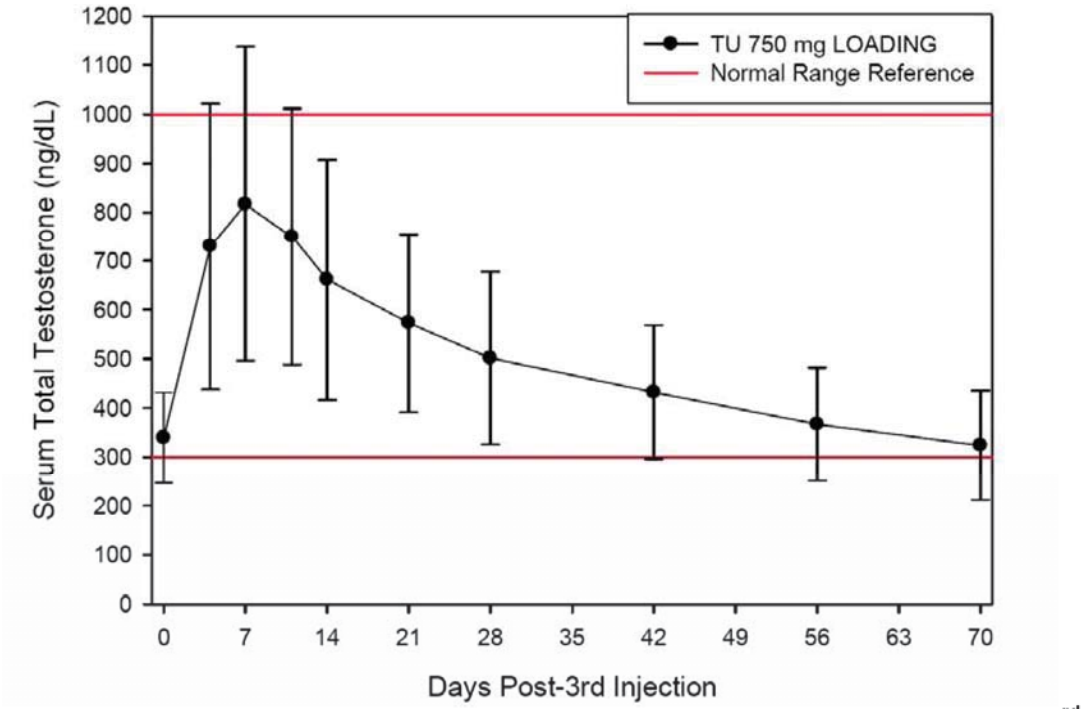
7.1 Overview of Study IP157-001C and Disposition of Subjects

The efficacy of testosterone undecanoate is supported primarily by the findings from Study IP157-001C. The main criteria for inclusion in Study IP157-001C were men at least 18 years of age with a morning screening serum testosterone concentration < 300 ng/dL. A total of 130 patients were enrolled at 31 US clinical sites. Subjects were to receive 750 mg (3 mL) of testosterone undecanoate by IM injection at initiation of treatment, at Week 4 of treatment (i.e., 28 days after the initial injection), and every 10 weeks thereafter for the duration of treatment. Of the 130 patients enrolled, 116 (89%) completed Stage 1 of Part C (i.e., they completed through the 4th injection visit [Week 24]). Of the 14 subjects who prematurely discontinued, the primary reason for premature discontinuation was an adverse event in 3.8% (5/130) of subjects.

7.2 Efficacy Findings from Study IP157-001C

The primary and secondary endpoints for Study IP157-001C were based on pharmacokinetic data obtained during the 3rd injection interval of 750 mg testosterone undecanoate. Figure 1 shows the mean serum concentrations for total testosterone following the 3rd injection of 750 mg of testosterone undecanoate. Mean serum testosterone concentrations at all sampling times fell within the target range of 300-1000 ng/dL.

Figure 1 Mean (±SD) Serum Testosterone Concentrations following the 3rd Injection Interval of 750 mg Testosterone Undecanoate (Study IP157-001 Part C)



Source: Clinical Pharmacology Review, Figure 4, pg. 9, signed May 1, 2008.

7.2.1 Primary Efficacy Endpoint (Cave)

The primary efficacy endpoint was defined as the percentage of subjects that had an average serum concentration of total testosterone within the normal range (300–1000 ng/dL). Ninety four percent (94%) of subjects (110 of 117) had serum total testosterone Cave values within the 300-1000 ng/dL range. The 95% confidence interval around this point estimate was 89.6%-98.5%. Of the 7 patients who did not meet this criterion, 6 failed due to a Cave below 300 ng/dL, and one failed due to a Cave above 1000 ng/dL.

Division Director's Comment

- *The above findings indicate that the primary efficacy objective (i.e., Cave) for Study IP157-001 Part C was achieved.*

7.2.2 Assessment of Cmax (Important Secondary Endpoint)

The percentages of Cmax values for serum testosterone that fell into predefined ranges are listed in Table 1.

Table 1 Distribution of Cmax Values for Serum Total Testosterone Concentrations during the 3rd Injection Interval (Study IP157-001 Part C)

	Number of Patients Exceeding/Number of Patients Assessed (Percent of Patients Exceeding)
C_{max} Outcome	**TU 750 mg LOADING (N=117)**
> 1500 ng/dL[1]	9 of 117 (7.7%)
≥ 1800 ng/dL and < 2500 ng/dL	0 of 117 (0%)
≥ 2500 ng/dL	0 of 117 (0%)
Did Dose Meet Threshold Limits?	**Yes**

Source: Clinical Pharmacology Review, Table 25, pg. 42, signed May 1, 2008.

Division Director's Comments

- *The Applicant excluded from the PK analysis subjects who weighed less than 65 kg. One subject (Patient 031-7021) fell into this category. This subject (not represented in Table 1) had a testosterone concentration above 2,500 ng/dL during the 3rd injection interval. Otherwise, only nine of the 117 patients (7.7%) had Cmax > 1500 ng/dL and no patient had Cmax ≥ 1800 ng/dL.*
- (b) (4)
- *In summary, the data show that the Cmax efficacy objective was achieved in men weighing more than 65 kg.*

7.3 FDA Statistical Reviewer's Assessment

In his final review, dated June 24, 2008, Dr. Sobhan (FDA statistician) concluded:

> *"The results support the efficacy of TU 750 mg LOADING in the treatment of hypogonadism in adult male as indicated by the attainment of steady state by the 3rd injection. The intensive sampling for PK outcomes (Cave and Cmax) also met FDA threshold for approvability and, therefore, can be extrapolated to represent PK outcomes under extended dosing beyond 3 injections."*

Overall Assessment of Efficacy

Pharmacokinetic data provided in the original submission for NDA 22-219 demonstrated that testosterone undecanoate (750 mg/injection) administered by IM injection at initiation of treatment, at Week 4 of treatment (i.e., 28 days after the initial injection), and every 10 weeks thereafter for the duration of treatment fully met DRUP's criteria for efficacy for a testosterone drug product for replacement therapy in adult men. In Study IP157-001C, 94% of subjects (110 of 117) had serum Cave values for total testosterone within the 300 - 1000 ng/dL range. The 95% confidence interval around this point estimate was 89.6% - 98.5%. Among subjects weighing > 65 kg (the intended population for the drug product), 93.3% had serum testosterone Cmax values ≤ 1,500 ng/dL and no subjects had a Cmax value ≥ 1,800 ng/dL.

8. SAFETY

The primary Clinical Reviewer and the Clinical Team Leader/CDTL have thoroughly reviewed the safety data submitted in support of the use of IM testosterone undecanoate for the indication of testosterone replacement therapy in adult males with a deficiency or absence of endogenous testosterone (see primary Clinical Reviews [signed June 16, 2008, and November 10, 2009] and the Clinical Team Leader/Cross-Discipline Team Leader Memos [signed June 27, 2008, and

November 30, 2009]). My review of the safety findings for NDA 22-219 in this Memorandum focuses primarily upon the safety issue of concern, namely, serious immediate post-injection adverse reactions.

8.1 Safety Data Submitted in Support of the Original Application

8.1.1 Safety Data from Clinical Trials

In the original Application, safety from (1) a single 3-part Phase 3 clinical trial conducted in the US and sponsored by the Applicant (formerly Indevus Pharmaceuticals and currently Endo Pharmaceuticals Solutions Inc and (2) 5 older European studies sponsored by the European Market Application Holder (MAH) Bayer/Schering for testosterone undecanoate (marketed as Nebido in most countries).

The single Phase 3 clinical trial was Study IP157-001, which consisted of 3 parts:

- Part A included of a total of 237 subjects in 2 dose arms (750 mg testosterone undecanoate every 12 weeks [n=120] and 1000 mg testosterone undecanoate every 12 weeks [n=117]).
- Part B included a total of 134 subjects, the majority of whom received 1000 mg testosterone undecanoate every 8 to 12 weeks.
- Part C initially enrolled a total of 117 subjects who were to receive 750 mg testosterone undecanoate at treatment onset, at Week 4, and every 10 weeks thereafter. An additional 36 subjects were subsequently treated with testosterone undecanoate (in what was referred to as Part C2 of the Study).

Among the 3 parts of Study IP157-001, a total of 524 subjects were treated with either 750 mg or 1,000 mg of testosterone undecanoate.

Among the 5 European studies, a total of 185 subjects were treated with 1,000 mg testosterone undecanoate.

In summary, a total of 709 adult male subjects were treated in studies submitted in the original application (Table 2, pg. 28 of the Application's Summary Report, dated February 12, 2009).

8.1.2 Data Based on Postmarketing Safety Reports

According to the CDTL Memo, the original NDA also contained 6 Bayer/Schering PSURs from several years of worldwide use of testosterone undecanoate (specifically from the period November 25, 2003 through June 30, 2007). The 120-Day Safety Update contained another Bayer/Schering PSUR (for the time period June 30, 2007 to October 12, 2007). The Sponsor also submitted, at the request of DRUP, a Summary Report entitled, "Immediate Post-Injection Reactions Suspect of Pulmonary Oil Microembolism" (dated February 12, 2008).

Division Director's Comments

- *The overall safety profile for testosterone undecanoate 750 mg, with one exception, was consistent with that for other testosterone products approved for replacement therapy in adult males with a deficiency or absence of endogenous testosterone. The safety concern related to reports (almost entirely postmarketing reports) of serious, immediate post-injection respiratory and/or allergic adverse reactions. These reports are discussed in detail in Section 8.4 of this Memorandum.*

- *As discussed earlier in Section 1 of this Memorandum, an Approvable Letter was issued by DRUP on June 27, 2008, because of (1) concern regarding the risks associated with the immediate post-injection adverse reactions and (2) a single CMC deficiency.*

8.2 Additional Safety Data Submitted in Applicant's Complete Response

8.2.1 Additional Safety Data from Clinical Trials

The Approvable Letter issued on June 27, 2008, requested that the Applicant "*provide additional safety data concerning the occurrence of post-injection POME and allergic adverse reactions from completed and/or ongoing clinical studies sponsored by Bayer Healthcare (formerly Schering AG) outside of the U.S. to better define the incidence of these adverse reactions*."

In the Complete Response, the Applicant provided safety data from an additional 11 studies: 7 completed and 4 ongoing studies. Final or interim study reports were provided for each of the 11 new studies. The applicant also submitted a Summary Report, entitled "*Incidence of Injection-Based Pulmonary Oil Reactions and Allergic Reactions from Clinical Studies of testosterone undecanoate*" (dated February 12, 2009). These 11 new studies comprised 2,125 additional subjects. Therefore, the overall clinical safety database (based on the original application and the Applicant's Complete Response) included a total 2,834 subjects from 17 clinical trials.

8.2.2 Additional Data Based on Postmarketing Safety Reports

The Applicant also submitted 2 additional postmarketing safety updates in the Complete Response:

- A Bayer/Schering PSUR for the time period November 25, 2007, through November 24, 2008.
- A Final Safety Update for the time period November 25, 2008 through August 29, 2009.

Division Director's Comment

- *In addition to the types of information generally included in a PSUR, the PSUR contained an Appendix entitled "Nebido and Anaphylaxis Reactions."*

8.3 General Safety Findings from Pivotal Phase 3 Study IP157-001 Part C

Overviews of the safety findings from all of the clinical trials, as well as a detailed review of the safety findings from Study IP 157-001 (Part A and Part C), are provided in Section 7 of the primary Clinical Review (signed on November 10, 2009). The following discussion is based on the general safety findings from Study IP 157-001 Part C because (1) this was the only clinical trial that employed the dosing regimen for which the Applicant is seeking approval and (2) general safety findings from this study are representative of those found in the other clinical trials with testosterone undecanoate.

8.3.1 Deaths and Serious Adverse Events

There were no deaths in Study IP157-001 Part C. Eight (6.2%) subjects experienced at least one serious adverse event (SAE) during the treatment period. No single SAE was reported in more than 1 subject. The reported SAEs included ischemic colitis, deep vein thrombosis (DVT), intervertebral disc protrusion, myocardial infarction, prostatitis, worsening of spinal column

stenosis, urinary tract infection, and wrist fracture. Only the DVT was judged by the investigator to be at least possibly related to treatment.

8.3.2 Adverse Events Associated with Discontinuation of Treatment

Treatment with testosterone undecanoate was permanently discontinued because of an adverse event in 5 of 130 (3.8 %) subjects. There adverse events associated with discontinuation of treatment were a single event each of acne, mood swings, myocardial infarction, increased estradiol, and DVT. Of these adverse events, all but the myocardial infarction were judged by the investigator to be at least possibly related to treatment with testosterone undecanoate.

8.3.3 Commonly Reported Adverse Events

During the 24-week study, 70 of 130 (53.8%) subjects reported at least one adverse event, regardless of relationship to study medication. Thirty-one (23.8%) of the 130 subjects experienced at least one adverse events judged by the investigators to be at least possibly related to treatment with study medication. Table 2 lists the adverse events judged by the investigator to be at least possibly related to study medication.

Table 2 Adverse Events Considered to be at least Possibly Related to Treatment and Reported in at ≥ 1% of Subjects (Study IP 157-001 Part C).

MedDRA Preferred term	Number (%) of Subjects
Acne	6 (4.6)
Fatigue	4 (3.1)
Injection site pain	4 (3.1)
Irritability	2 (1.5)
Hyperhidrosis	2 (1.5)
Hemoglobin increased	2 (1.5)
Estradiol increased	2 (1.5)
Insomnia	2 (1.5)
Mood swings	2 (1.5)
Aggression	2 (1.5)
Prostatic specific antigen increased *	2 (1.5)
Disturbance in attention	2 (1.5)

* Defined as a serum PSA concentration > 4 ng/mL

Source: Table 1 from proposed Package Insert, submitted on August 27, 2009.

Acne, fatigue, cough, injection site pain, nasopharyngitis, and pharyngolarangeal pain were the adverse events reported with the highest incidence regardless of the investigator's assessment of relationship to study medication.

8.4 Immediate Post-injection Adverse Reactions: Pulmonary Oil Microembolism (POME) and Serious Allergic Reactions

During the review of the original Application, the clinical review team identified a total of 68 cases that involved immediate post-injection adverse reactions. Of these, 2 cases were reported from clinical trials and the remaining 66 cases were identified from postmarketing safety reports. In the Complete Response, the Applicant identified no additional cases in the expanded clinical trial database. In the postmarketing safety data provided either with the initial

Complete Response or during the review of the submission, the clinical review team identified an additional 52 cases that involved immediate post-injection adverse reactions. Both the primary Clinical Reviewer and the CDTL have each conducted a very detailed and comprehensive analysis of these cases in their respective reviews. In the following sections, I provide an overview of the findings.

8.4.1 Immediate Post-injection Adverse Reactions in Clinical Trials

The original submission included data from approximately 700 subjects who had received one or more doses of testosterone undecanoate by IM injection. During review of the original submission, the clinical review team concurred with the Applicant that there were 2 cases in which subjects had experienced immediate post-injections adverse reactions. Both cases were associated with an urge to cough and both were attributed to POME. One of the 2 cases was classified as serious, perhaps because the subject also experienced "respiratory distress." Both subjects recovered without intervention within approximately 15 minutes of having receiving their injection of testosterone undecanoate.

In the Complete Response, the Applicant reported that there were no additional cases of POME and no systemic allergic reactions in clinical trial data from approximately 2,100 additional subjects who had not been included in the original submission. The Applicant therefore concluded that there was one serious case of POME and no systemic allergic reactions among the total of 2,834 clinical trial subjects (combining the data from the original submission and Complete Response). Based on these findings, the Applicant proposed an incidence of one serious case of POME in 2,834 subjects or 3.53 serious events per 10,000 subjects (0.035%). For systemic allergic reactions, the Applicant proposed an incidence of 0% (no cases) in the clinical trials.

The clinical review team, however, identified 6 additional cases of interest among the clinical trials. These cases consisted of one case each of convulsions, collapse, pre-syncope, and syncope, and 2 cases of circulatory collapse.

The Clinical Team Leader states in his memo that:

> "*information from these cases is too sparse to ascribe a specific etiology to the event, but they were all immediate post-injection reactions. The Clinical review team believes that the former 3 events have a greater chance of being serious POME or systemic allergic reactions compared to the latter 3, but all 6 are notable.*"
>
> *"If just these 3 cases were added to the numerator, this would markedly change the incidence of immediate post-injection reactions in clinical trials: 4 events /2834 subjects (0.14%)."*
>
> *"In our opinion, whether the number of cases of severe post-injection reactions in clinical trials is 1, 2, 5 or 8 is not as critical as the information gleaned from the spontaneously reported postmarketing adverse events provide in the PSURs and Safety Updates*."

Division Director's Comment

- *I agree that the information from these latter 6 cases is too sparse to ascribe a specific etiology to the event. I also agree with the Clinical Team Leader that these cases cannot be entirely ignored.*

8.4.2 Postmarketing Safety Reports of Immediate Post-injections Adverse Reactions

Original Submission

While the original submission was under review, the Applicant summarized, at the request of DRUP, the totality of the immediate post-injection adverse reactions, covering the period from first approval of testosterone undecanoate injectable in 2004 through the cut-off date of January 18, 2007. The Applicant's Safety Update, dated February 12, 2008, identified a total of 66 cases (64 from postmarketing safety reports). According to the CDTL Review, 28 of the 66 cases (42%) were reported as serious adverse events. Although there were no deaths reported among these 66 cases, emergency medical care was provided and/or the patient was hospitalized in 18% of the cases (12/66). Further discussion of these adverse events and the likelihood that some of these represented systemic allergic reactions, rather than POME, is provided in Section 8.4.3.1.

Complete Response

Among the postmarketing safety data submitted as part of the Complete Response, the clinical review team identified an additional 52 cases that involved immediate post-injection adverse reactions. The Clinical Team Leader states in his review that "*Of these, almost all are severe, and we believe that approximately 20 reflect anaphylactic reactions. We note that throat-related symptoms are prominent in these 2 Safety Updates (throat closing, throat tightness, throat tickling, throat fullness) and we believe that these symptoms reflect post-injection angioedema, not POME.*"

Included in the Applicant's Complete Response was the PSUR for testosterone undecanoate for the period November 25, 2007 - November 24, 2008, prepared by Bayer/Schering. Appendix 8 of the PSUR consisted of a document entitled "Nebido and Anaphylaxis Reactions." In this report, Bayer/Schering described 5 postmarketing cases in which they acknowledged that the clinical events of the immediate post-injection adverse reaction met generally-accepted criteria for anaphylaxis.

Further review and discussion of the 52 cases reported in the Complete Response is provided in Section 8.4.3.1.

8.4.3 Allergy Consultations

To more fully evaluate the nature and potential clinical significance of the immediate post-injection adverse events, the FDA's Division of Pulmonary and Allergy Products (DPAP) was consulted both during the review of the Applicant's original submission and during the review of the Applicant's Complete Response. In addition, DRUP consulted with 2 expert allergists outside of the FDA (see Section 8.4.3.2).

8.4.3.1 Consultation by the Division of Pulmonary and Allergy Products

Original Application

The 66 cases identified by DRUP and the Applicant as having experienced an immediate post-injections adverse reaction were reviewed further by Charles Lee, MD of the Division of Pulmonary and Allergy Products. Dr. Lee concluded in his consultation (signed April 14, 2008) that 2 cases (GB 2007-023826 and ZA-3007-035469) met currently accepted diagnostic criteria for anaphylaxis. In addition to these 2 cases, Dr. Lee identified 2 other cases for which anaphylaxis could not be excluded. Of the remaining 62 cases, Dr. Lee stated that "51 clearly did not meet the clinical criteria for the diagnosis of anaphylaxis. The majority of these 51 cases

were consistent with POME." Dr. Lee's consultation also included the following comments and recommendations:

> "*Ultimately, the decision to approve the product will be a risk versus benefit decision, and should be made in light of the degree of efficacy, the seriousness of the indication, the availability of alternative products for that indication, and the extent of the safety data."*
>
> *"The following are recommendations for your consideration if the product is to be approved.*
>
> 1. *It would be appropriate to note in the product label that it should be administered only in a practitioner's office.*
> 2. *Most of these adverse events occurred immediately after injection. It would also be appropriate to consider a labeling recommendation that there be a waiting period after injection.*"

Complete Response

The Division of Pulmonary and Allergy Products (DPAP) was asked to review the additional 52 postmarketing cases, which described the occurrence of immediate, post-injection adverse reactions, that were contained in the Complete Response. In their final consultation (signed November 25, 2009), Lynne Wu, MD and Anthony Durmowicz, MD of DPAP categorized the 52 cases as follows:

Anaphylaxis	11 cases
Possible anaphylaxis	9 cases
Allergic reactions	4 cases
Possible POME	8 cases
Injection site problem	1 case
Cases with too little information	13 cases
Cases with non-specific symptoms	6 cases

Drs. Wu and Durmowicz also provided the criteria that they had used to categorize the cases. They stated that DPAP used the clinical criteria for the diagnosis of anaphylaxis determined by the 2004 and 2005 Multinational Symposia convened by the National Institute of Allergy and Infectious Disease (NIAID) and the Food Allergy and Anaphylaxis Network (FAAN). They also stated that the Symposia defined anaphylaxis as a clinical syndrome characterized by acute onset of an illness with involvement of skin, mucosal tissue, and respiratory and/or cardiovascular systems. The criteria that they followed to categorize the cases were those described in (1) Sampson HA et al, J Allergy Clin Immunol 115 (3):584-591, 2005 and (2) Sampson HA et al, J Allergy Clin Immunol 117 (2):391-397, 2006.

Other comments/insight provided in the Consultation included the following:

- "*Post-marketing adverse events frequently contain incomplete information. DPAP has taken the position that an adverse event report submitted under the terms "anaphylaxis, anaphylactic shock, or anaphylactoid reaction" which was treated for anaphylaxis would be included as an anaphylaxis case.*"
- "*DPAP believes that whether the immediate adverse events following injection of Aveed can be classified as meeting the clinical definition of anaphylaxis is not the main concern*

but that any immediate severe adverse event following injection of Aveed requiring treatment should be considered a safety risk."

Division Director's Comments

- *I agree with the statement by Drs. Wu and Durmowicz that any immediate severe adverse event following injection of testosterone undecanoate requiring treatment should be considered a safety risk.*
- *It is of interest that Dr. Lee in his Consult of 2008 identified only 2 cases of anaphylaxis and 2 cases of possible anaphylaxis among 66 total cases. In contrast, Drs. Wu and Durmowicz identified 11 cases of anaphylaxis and 9 cases of possible anaphylaxis among 52 total cases. The basis for this difference in the incidence of cases classified as anaphylaxis between these consultants from DPAP is unclear.*

8.4.3.2 Opinions of Non-FDA Allergists

Additional insight as to the likely etiology and significance of the immediate post-injection adverse reactions was obtained from 2 non-FDA allergists. These experts in the field of allergy were Dr. James Li, the Chair of the Division of Allergic Disease in the Department of Internal Medicine at the Mayo Clinic in Rochester, Minnesota and Dr. Thomas Platts-Mills, Division Head, Division of Allergy and Clinical Immunology at the University of Virginia Health Center in Charlottesville, Virginia. Both experts were asked to review the 118 postmarketing cases that involved an immediate post-injections adverse reaction from both the original submission and the Complete Response. These were the same cases that had been reviewed by DPAP in their consultations of 2008 (66 cases) and 2009 (52 cases).

Consultation by Dr. Li

Among the 118 cases reviewed by Dr. Li, he stated that he had identified at least 4 cases that he considered as "probable anaphylaxis" and 22 cases that he called "possible anaphylaxis." He further stated that "For the cases of 'probable' and 'possible' anaphylaxis noted above, as well as for some additional cases, I would not be comfortable attributing the adverse events to POME." He further stated that … "there seems to be some risk of allergic-type reactions to this product distinct from POME."

Dr. Li also provided his views concerning the possible roles of castor oil and benzyl benzoate in causing these allergic reactions as reflected in the following statements:

- "*I have no information on benzyl benzoate as an agent that can cause anaphylaxis. It is possible that benzyl benzoate could be a cause of contact dermatitis.*"
- "*Plant oils per se are not common causes of anaphylaxis. However, as a plant-derived product, castor bean oil could theoretically contain toxins, allergenic proteins or contaminants. Castor bean protein and pollen can be highly allergenic*."

Consultation by Dr. Platts-Mills

Dr. Platts-Mills reviewed the same set of cases as had Dr Li. Dr. Platts-Mills identified 3 cases that he stated he "would regard as anaphylaxis." He also stated the following in his consultation:

> *"Please don't take my opinion that these cases are not anaphylactic as arguing that they are not severe. There are multiple descriptions here that are very severe including collapse, with apnea, severe chest pain, coughing sufficient to put patients in the intensive care unit, etc*."

Division Director's Comments

- *The total number of cases of anaphylaxis and/or possible anaphylaxis identified by Dr. Li (n = 26) is very similar to the total number of cases identified in the 2 reviews by DPAP (n = 24).*
- *Dr. Platts-Mills appeared to be using more demanding criteria for diagnosing anaphylaxis than either Dr. Li or Drs. Lee, Wu, and Durmowicz of DPAP. Dr. Platts-Mills appeared to be using a categorization that required rapid onset of at least two of the following: (a) skin itching and hives, (b) airway obstruction, or (c) fall in pressure. Without a clear description of cutaneous changes (e.g., hives or urticaria), Dr. Platts-Mills did not appear to categorize a case as anaphylaxis. In his consult, he stated "The rarity of 'hives' or 'urticaria' or equivalent words in these reports is striking. … Again, I stress that the very low prevalence of urticaria in these cases argues, strongly against histamine release as a significant mechanism."*
- *Dr. Platts-Mills did not provide the number of cases that he considered as "possible anaphylaxis." Had he done so, his overall assessment of the number of systemic allergic events might have been closer to those of Dr. Li and Drs. Lee, Wu and Durmowicz of DPAP.*

8.4.4 Summary of Immediate Post-injections Adverse Reactions

Based on a review of clinical trial data and postmarketing safety reports since approval of testosterone undecanoate injection in Europe through August 2009, approximately 120 cases were identified (2 from clinical trials and 118 from postmarketing reports) that involved immediate post-injection adverse reactions. For the most part, these reactions were attributed either to (1) vascularization of the oily drug product, leading to pulmonary microembolism (POME) or (2) an allergic reaction. Among the clinical trial data, there were 2 cases of POME (one classified as serious), and both resolved without intervention. Among the 118 postmarketing cases, many were classified as POME. Although it is generally believed that POME (which might occur following a 3 mL injection of testosterone undecanoate) will likely be a self-limited event, its initial presentation often cannot be differentiated from a severe anaphylactic reaction. As such, a healthcare provider may treat the event as if it were an anaphylactic reaction, and patients may be subjected to unnecessary medical interventions as well as considerable stress and discomfort. The occurrence of these reactions, although likely to be self-limited, must be considered in the overall assessment of the benefit/risk profile for testosterone undecanoate injection.

There were no well-documented cases of systemic allergic reactions in the clinical trial database. Among the postmarketing cases, FDA medical reviewers in DPAP (Drs. Lee, Wu, and Durmowicz), as well as both non-FDA consultants (Drs. Li and Platts-Mills), identified cases that they classified as anaphylaxis. The DPAP reviewers classified 13 of the 118 cases as anaphylaxis and 11 of the cases as possible anaphylaxis (total = 24). Dr. Li classified 4 of the cases as probable anaphylaxis and 22 of the cases as possible anaphylaxis (total = 26). Dr. Platts-Mills, who appeared to use more restrictive criteria, classified 3 of the cases as anaphylaxis, but did not provide an estimate of the number of possible cases of anaphylaxis. Bayer/Schering (the MAH for testosterone undecanoate outside of the US) acknowledged the occurrence of 5 likely cases of anaphylaxis in their last PSUR. Of note, none of patients who were assessed as having had an anaphylactic reaction was reported to have died.

The number of cases of anaphylaxis/possible anaphylaxis, based on non-US postmarketing reports, should be considered in conjunction with the estimated use of testosterone undecanoate injection. The Applicant stated in their submission dated November 20, 2009, that (b) (4) doses of testosterone undecanoate injection have been sold since approval of the drug product. The Applicant also stated that based on 4 injections per year, total sales would reflect 400,000 patient-years of use.

Division Director's Comments

- *The Applicant's estimate of patient-years of use may be too high because it is likely that the number of units sold reflects sales to pharmacies and not prescriptions filled.*
- *Although no deaths have been reported, to date, in association with the reported anaphylactic reactions, it must be remembered that anaphylaxis is a potentially fatal reaction.*
- *Because of the occurrence of these serious, immediate post-injection adverse reactions (both anaphylaxis and POME), I concur with Drs. Handelsman and Hirsch that the demonstrated benefits of the drug do not outweigh the additional potential risks associated with the use of testosterone undecanoate injection in the target population.*

8.5 Overall Assessment of Safety

Reported adverse events and changes in laboratory values from subjects treated with testosterone undecanoate intramuscular injection in the primary efficacy and safety clinical trial (Study IP157-001 Parts A and C) were similar to those reported in clinical trials for other approved testosterone drug products. Local tolerance to the testosterone undecanoate IM injections was acceptable. Postmarketing cases of immediate, serious post-injection adverse reactions, however, raise safety concerns regarding the overall benefit/risk profile for the use of testosterone undecanoate intramuscular injection for the Applicant's proposed indication. Although the exact etiology of these adverse reactions has yet to be determined, some of the reactions included clinical features more consistent with anaphylaxis or angioedema. Others appear to be more consistent with pulmonary oil microembolism (POME) reactions. These post-injection adverse reactions have included one or more of the following findings: respiratory distress, throat tightening or closing, wheezing, urge to cough, flushing, and/or rash. Some patients have lost consciousness during the event. Some were resuscitated with oxygen, fluids, epinephrine, steroids, and/or antihistamines, and some were hospitalized. Based on the reports of these serious, immediate, potentially life-threatening post-injection adverse reactions, the clinical review team (Drs. Handelsman and Hirsch) believe that the additional potential risks associated with the use of testosterone undecanoate injection outweigh the demonstrated benefits of the drug for the Applicant's proposed indication. I concur with their recommendation based on presently available information.

9. ADVISORY COMMITTEE MEETING

An Advisory Committee meeting was not held for this NDA during either review cycle. DRUP, however, requested outside consultations from two members of the Pulmonary and Allergy Products Advisory Committee. These were Dr. James Li of the Mayo Clinic and Dr. Thomas Platts-Mills of the University of Virginia Health System (see Section 8.4.3.2 for a summary of their findings).

In the Complete Response letter that will be issued for the current NDA submission, the Applicant will be informed that DRUP is amenable to future discussion of this application at a meeting of the Reproductive Health Drugs Advisory Committee to include discussion of whether the demonstrated benefits of treatment with testosterone undecanoate injection outweigh the risks associated with its use in the target population.

10. PEDIATRICS

The Applicant requested a full waiver of the requirement to conduct assessments of testosterone undecanoate injection in pediatric patients. On July 2, 2009, George Greely of the Pediatric and Maternal Health Staff stated the following in an e-mail communication to DRUP: "*The Aveed (testosterone undecanoate) full waiver was reviewed by the PeRC PREA Subcommittee on April 29, 2009. The Division recommended a full waiver because of too few children with the disease/condition to study. The PeRC agreed with the Division to grant a full waiver for this product*."

11. OTHER RELEVANT REGULATORY ISSUES

11.1 DSI Audits

No site inspections were requested by either the Clinical or Clinical Pharmacology reviewers because their reviews of the analytical methods, study conduct procedures, study findings, and/or financial disclosure information did not raise any concerns about the integrity or reliability of the submitted data. In addition, testosterone undecanoate is not a new molecular entity and the primary endpoint (serum testosterone concentrations) is a laboratory assessment that is not liable to subjective bias.

11.2 Financial Disclosure

According to the CDTL Review, all of the clinical investigators in pivotal Phase 3 Study IP157 001 responded to a request for financial disclosure, and none had any relevant financial disclosure information to declare. There were no investigators with a proprietary interest in the product and none with significant equity in the Applicant.

12. LABELING

See the CDTL Memo for an overview of the labeling negotiations that were conducted. After it was determined that the overall benefit/risk profile for testosterone undecanoate injection, based on presently available information, was not favorable and would not support approval, labeling negotiations were discontinued.

13. DECISION/ACTION/BENEFIT RISK ASSESSMENT

13.1 Regulatory Action

Testosterone undecanoate injection (Aveed) will not be approved at this time. Based on the reports of serious, immediate, potentially life-threatening post-injection adverse reactions, I do not believe that the demonstrated benefits of the drug outweigh the additional potential risks associated with the use of testosterone undecanoate injection for the indication of replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous

testosterone. Both the primary Clinical Reviewer and the Cross Discipline Team Leader have recommended that testosterone undecanoate injection not be approved at this time.

13.2 Benefit/Risk Assessment

Pharmacokinetic data provided in the original submission for NDA 22-219 demonstrated that testosterone undecanoate (750 mg) administered by IM injection at initiation of treatment, at Week 4 of treatment, and every 10 weeks thereafter for the duration of treatment met DRUP's criteria for efficacy for a testosterone drug product for replacement therapy in adult men. In Study IP157-001-Part C, 94% of subjects had average steady state serum testosterone concentrations within the normal adult male range of 300 - 1000 ng/dL.

Reported adverse events and changes in laboratory values from subjects treated with testosterone undecanoate intramuscular injection in the primary efficacy and safety clinical trial (Study IP157-001 Parts A and C) were similar to those reported in clinical trials for other approved testosterone drug products. Postmarketing reports of immediate, serious post injection adverse reactions, however, raise safety concerns regarding the benefit/risk profile for the use of testosterone undecanoate intramuscular injection for the Applicant's proposed indication. Although the exact etiology of these adverse reactions has yet to be determined, some of the reactions have included clinical features consistent with anaphylaxis or angioedema. Others appear to be more consistent with pulmonary oil microembolism (POME) reactions. These immediate post-injection adverse reactions have included one or more of the following findings: respiratory distress, throat tightening or closing, wheezing, cough, flushing, and/or rash. Some patients have lost consciousness during the event. Some were resuscitated with oxygen, fluids, epinephrine, steroids, and/or antihistamines, and some were hospitalized.

Based on the reports of these serious, immediate, potentially life-threatening post-injection adverse reactions, the clinical review team believes that the additional potential risks associated with the use of testosterone undecanoate injection outweigh the demonstrated benefits of the drug for the Applicant's proposed indication. I concur with their assessment based on the information provided in the Applicant's Complete Response.

Eventual approval of testosterone undecanoate intramuscular injection would be contingent upon the Applicant's demonstrating that (1) the benefits of treatment with testosterone undecanoate injection outweigh the potential risks associated with its use or (2) treatment with testosterone undecanoate injection offers a clinically significant benefit above that of currently available products that would justify the potential increased risk. Approaches that the Applicant might consider include the following:

1. Identify which components of the drug product may be contributing to the serious, immediate post-injection adverse reactions, reformulate the product, and demonstrate that the serious immediate post-injection adverse reactions have been reduced or mitigated; or
2. Identify a population of adult males who require testosterone replacement therapy and in whom the additional potential risks associated with the use of testosterone undecanoate injection as currently formulated would be acceptable.

The Complete Response Letter also will inform the Applicant that DRUP is amenable to future discussion of this application at a meeting of the Reproductive Health Drugs Advisory Committee to include discussion of whether the demonstrated benefits of treatment with

testosterone undecanoate injection outweigh the risks associated with its use in the target population.

13.3 Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies

The Applicant proposed a Postmarketing Risk Evaluation and Mitigation Strategies (REMS) in their Complete Response. The REMS, which included Patient Labeling (which was subsequently converted to a Medication Guide) and a Communication Plan directed to healthcare providers, is not considered by the clinical review team to be sufficient to ensure that the benefits of testosterone undecanoate injection (Aveed) outweigh the risks associated with use of the drug product for the proposed indication. A specific recommendation(s) for an adequate REMS cannot be made at this time. Such a recommendation(s) will be made if it is subsequently determined that the demonstrated benefits of testosterone undecanoate injection will outweigh the potential risks associated with use of the drug product.

13.4 Recommendation for Other Postmarketing Requirements and Commitments

The Applicant proposed 2 postmarketing studies in their Complete Response. (b) (4) DRUP cannot make any recommendations for postmarketing requirements or postmarketing commitments at this time. Such recommendations may be made if it is subsequently determined that the demonstrated benefits of testosterone undecanoate injection will outweigh the potential risks associated with use of the drug product.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22219	ORIG-1	ENDO PHARMACEUTICALS INC	NEBIDO

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SCOTT E MONROE
12/02/2009

Cross-Discipline Team Leader Memo

Date	November 30, 2009
From	Mark S. Hirsch, M.D.
Subject	Cross-Discipline Team Leader Memo
NDA/BLA #	22-219
Applicant	Endo Pharmaceuticals
Date of Submission	March 2, 2009
PDUFA Goal Date	September 2, 2009
Proprietary Name / Established (USAN) names	AVEED™ testosterone undecanoate injection
Dosage forms / Strength	750 mg in 3 mL solution for deep intramuscular injection
Proposed Indication(s)	Replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous testosterone
Recommended:	***Complete Response***

1. Executive Summary

1.1 Brief Overall Summary and Recommendation

AVEED (testosterone undecanoate) injection is intended for testosterone replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous testosterone. The active ingredient in AVEED is testosterone undecanoate, an ester of testosterone. AVEED also contains refined castor oil and benzyl benzoate. AVEED is administered as a deep intramuscular (IM) injection into the gluteus medius muscle. The dosage strength and the frequency of dosing is 750 mg in 3 mL (250 mg per mL) at start of therapy, then 4 weeks later, then every 10 weeks thereafter. In this memo, this regimen is referred to as the "750 mg LOADING regimen".

Multiple preparations of testosterone have been approved by the Agency for the same indication. These include:

- Injectable testosterone preparations, including testosterone enanthate (Delatestryl) and testosterone cypionate (Depo Testosterone).
- Transdermal testosterone preparations, including the Androderm transdermal testosterone system, AndroGel (testosterone gel) 1%, and Testim (testosterone gel) 1%.
- A buccal testosterone preparation, the Striant buccal testosterone system.
- Oral testosterone preparations, such methyltestosterone capsules (Testred).
- A subcutaneous testosterone implant, Testopel.

Each of these preparations has their own advantages and disadvantages. AVEED would be an option for testosterone replacement; its benefit over the available injectable products is fewer injections per year (approximately 6 injections per year compared to approximately 12 injections per years).

The efficacy of AVEED is supported by a single, open-label, pivotal study using the 750mg Loading regimen (Study IP157-001, Part C). Different dosage strengths and different dose regimens were tested during the development program for AVEED, and the results from these additional Phase 2 and Phase 3 studies were submitted for our review. In addition, a number of studies have been conducted outside the United States both prior to and since the time of initial approval of testosterone undecanoate injection outside the U.S. (in 2004), and these were also submitted for our review. AVEED 750 mg Loading regimen provides acceptable replacement of testosterone. The Sponsor has met the current requirement for demonstration of efficacy for this indication.

In regard to safety, the adverse reactions associated with AVEED are consistent with those of an injectable testosterone replacement therapy, except for the occurrence of serious post-injection reactions. These are sudden and often severe events that have been reported mainly in the postmarketing period outside the U.S. They have been reported to occur either during, or within a few minutes of testosterone undecanoate (TU) intramuscular injection. We reviewed a total of approximately 116 post-injection reactions reported during the postmarketing period, and between 5 and 8 such events from controlled trials. The events consisted of respiratory, skin-related, cardiovascular and upper airway signs and symptoms. The manifestations of the immediate post-injection reactions have included: cough, urge to cough, difficulty breathing, shortness of breath, flushing, sensation of warmth, urticaria, rash, throat tightness, throat closing, tickling in the throat, fullness in the throat, dizziness, palpitations, lowering (or raising) of the blood pressure, syncope, loss of consciousness, and cardiovascular collapse. The exact mechanism for these drug-related adverse events has not been elucidated, but two etiologies are believed to be underlying:

1) Pulmonary oil microembolism (POME) – as a consequence of the castor oil in AVEED, and
2) Anaphylaxis – likely due to a reaction to the castor oil, the benzyl benzoate and/or the testosterone undecanoate in AVEED.

In regard to the POME events, these are highlighted by a sudden urge to cough during or soon after injection, and usually accompanied by dyspnea. In some cases of POME, severe shortness of breath and severe cough were reported, and in a few cases, respiratory distress, cardiovascular symptoms, and loss of consciousness were also reported. Some of these patients required supportive therapy, including hospitalization.

In regard to the post-injection anaphylactic reactions, the signs and symptoms have included: shortness of breath, difficulty breathing, flushing, sensation of warmth, rash, urticaria, tightening of the throat, closing up of the throat, tickling and fullness in the throat, cardiovascular collapse, and loss of consciousness. The throat-related symptoms were prominent in many of the cases we reviewed. Most of these patients received standard treatment for an anaphylactic reaction, including epinephrine, steroid, antihistamine, and oxygen. Some required hospitalization. We believe that there are approximately 20 well-documented cases of anaphylactic reaction and approximately 35 cases total, if the less well-

documented cases are included. It can be difficult, and perhaps not always possible, to differentiate serious POME from anaphylaxis.

The Sponsor purports that safety data collected in 12 completed and 5 ongoing clinical trials, involving 2834 subjects receiving 16,191 injections, indicate just 1 serious POME (pulmonary oil microembolism) reaction and no systemic allergic reaction events. While on its face, this would appear to be a low incidence of these serious events in clinical trials, there were a significant number of cases of serious POME and anaphylactic reactions spontaneously reported in the postmarketing period, as well as a few additional clinical trial adverse events reported that could reflect serious POME or systemic allergic reaction.

In regard to the additional clinical trial cases, we have concerns in regard to 3 clinical trial reports of immediate post-injection adverse reactions that contained insufficient information to definitively ascribe the event to serious POME or to systemic allergy. These patients had post-injection convulsions, syncope and circulatory collapse, respectively. However, these 3 clinical trial cases should not be discounted due simply to insufficient information. The case numbers are: Patient # 001-0011 from Study 97173 (convulsions after 3rd injection), Patient #001-0017 from Study 97173 (collapse after 1st injection), and Patient #001-0004 from Study JPH04995 (circulatory collapse after 1st injection). If these 3 additional cases were to be counted as incident events, then the numerator would be 4 times higher, leading to an incidence not of 1 in 2,834 subjects (0.035%), but rather, 4 in 2,834 subjects (0.14%). In addition, there are three other cases in the clinical trial database for which the information is sparse, but these too might reflect "incident" post-injection reactions. These are: Patient #025-4187 in Study IP157-001 Part A Stage 1 (pre-syncope), and Patients #26 (syncope) and #35 (circulatory collapse) in Study 97029. While we have not counted these cases in the numerator, they are notable.

In addition, and more importantly, our review of the post-marketing experience has further raised our level of our concern over the nature and number of post-injection reactions that were reported as severe or life-threatening, many requiring urgent treatment and/or hospitalization. These events included POME reactions and anaphylactic reactions. The post-injection reactions reported in the Complete Response raise even greater concern about anaphylaxis compared to information in the original NDA, in terms of the quantity of anaphylactic cases reported, as well as the types of allergic reactions reported (angioedema reflected as throat closing, skin reactions, dyspnea, etc). We are particularly impressed by the number of postmarketing cases reporting throat tightness/swelling and trouble breathing in the Complete Response.

The spectrum of signs and symptoms of these post-injection reactions frequently overlap (between anaphylaxis and POME), making a precise diagnosis difficult. In any event, these reactions have led the Clinical review team to conclude that the risk-benefit profile for this drug is unfavorable, especially when compared to the currently approved products for testosterone replacement.

Although the Sponsor continues to believe that virtually all, if not all, of these post-injection reactions are POME, our consultants from the Division of Pulmonary and Allergy Products (DPAP) believe otherwise. They have confirmed the Clinical review team's suspicion that a large number were allergic in nature, including anaphylactic reactions. Regardless of the specific mechanism for these post-injection events, many have been reported as severe and

some life-threatening. Serious POME and anaphylactic reactions following intramuscular TU injection cannot easily be differentiated. In most cases, attending health care personnel have reported and treated the incident as an anaphylactic reaction. The mechanisms for allergic reactions to Aveed have not been elucidated. Two of the excipients in this product, benzyl benzoate, and castor oil are well known allergens and may possibly play some role in these post-injection adverse events, and in one case there was skin test documentation of an allergy to the product, and in another case, documentation of a positive skin test to benzyl benzoate. In addition, a product approved for the treatment of advanced breast cancer, (Faslodex®), and a product approved for estrogen replacement therapy (Delestrogen®) which contain the same excipients as Aveed were associated with post-injection reactions virtually identical to those associated with Aveed (FDA Adverse Events Reporting System; accessed September 25, 2009), and these events are reported in both the Faslodex and Delestrogen labeling as "anaphylactic or anaphylactoid reactions".

Taken together, the totality of the evidence leads the Clinical review team to conclude that the risk/benefit profile for Aveed is not acceptable for product approval. I concur with the primary medical officer, Dr. Harry Handelsman, in this decision.

1.2 Brief Overview of the Complete Response

In the Complete Response, the Sponsor provided the following items:

1. A Summary Report: "*Incidence of Injection-Based Pulmonary Oil Reactions and Allergic Reactions from Clinical Studies of TU.*" (dated February 12, 2009).
2. Complete or Abbreviated Study Reports for 11 Additional Phase 4 Studies:
    - AWB0105, Germany, 4 doses, n=870
    - NE0601 (IPASS), 18 countries, 4 doses, n=763
    - TG09, Germany (obesity), 4 doses, n=29
    - NB02, Germany (paraplegia), 2 doses, n=19
    - Czech NEO, Czechoslovakia, 4 doses, n=23
    - 303934, Finland (andropause), 1 dose, n=15
    - 97028, Germany, 4 doses, n=28
    - 97173, Italy, 1 dose, n=24
    - 99015, Germany, 4 doses, n=42
    - 98016, Germany, 4 doses, n=14
    - 42306, 6 countries, 4 doses, n=298
3. Another Bayer/Schering PSUR: November 25, 2007 – November 24, 2008
4. A Final Safety Update from Endo: November 25, 2008 – August 29, 2009
5. A Proposed REMS, including:
    - A Patient Package Insert
    - A Dear HCP Letter
    - A Video for HCPs re: IM injection
    - A Timetable for Assessments

6. Two (2) Phase IV Protocols

(b) (4)

For purposes of this Brief Overview section, I will provide the key findings and conclusions from each of these parts. Additional detail is provided in the medical officer's review and in other parts of this memo.

In regard to the incidence of post-injection reactions, the Original NDA contained 2 such cases from clinical trials and 66 such cases from the postmarketing period. The two Original NDA clinical trial cases were:

1. Patient #184 in Study 306605. A 54 year old male received his 10th injection of testosterone undecanoate on 3 April 2006 and shortly (1 minute) after the injection, he "experienced urge to cough associated with respiratory distress". Both symptoms lasted approximately 14-15 minutes. The event resolved without intervention and the subject continued in the study. The investigator and Sponsor both attributed the event to "pulmonary lipid (oil) microembolism" and cited the following possible reason: either too fast administration of the study drug or accidental intravascular placement of the study drug.

2. Patient #050-7006 in Study IP157-001 Part C). A 53 year old white male received his 3rd injection on 12 July 2007 and experienced a "mild and not serious coughing fit lasting 10 minutes following the injection." The narrative describes the patient's cough as not productive, without wheezing and without difficulty breathing. No intervention was given and the patient continued on-treatment without subsequent coughing event.

In the Complete Response, the Sponsor reported no additional cases in a total of another approximate 2100 subjects. The Sponsor therefore counted 1 serious POME case and no systemic allergic reactions in the numerator. The denominator was totaled as 2834 subjects (combining the Original NDA and Complete Response). The Sponsor thereby proposes an incidence of 1 serious POME in 2834 subjects, or 3.53 serious events per 10,000 subjects, or 0.035%. For systemic allergic reactions, the Sponsor proposes an incidence of 0% in clinical trials.

The Clinical review team detected 6 additional cases of interest from clinical trials. However, information from these cases is too sparse to ascribe a specific etiology to the event, but they were all immediate post-injection reactions. The Clinical review team believes that the former 3 events have a greater chance of being serious POME or systemic allergic reactions compared to the latter 3, but all 6 are notable. The former 3 cases are:

- Patient #11 in Study 97173 (convulsions)
- Patient #17 in Study 97173 (collapse),
- Patient #4 in Study JPH04995 (circulatory collapse)

If just these 3 cases were added to the numerator, this would markedly change the incidence of immediate post-injection reactions in clinical trials: 4 events /2834 subjects (0.14%). The latter three cases are:

- Patient #025-4187 in Study IP157-001 Part A (pre-syncope)
- Patient #26 in Study 97029 (syncope)
- Patient #35 in Study 97029 (circulatory collapse).

The Clinical review team believes that the Postmarketing Experience related to post-injection reactions is crucial to understanding the risk of Aveed. In this situation, we find the post-marketing experience to be even more important than the incidence of these events in clinical trials. From our review of the post-marketing safety updates, we have detected a total of 116 post-injection reactions in the post-marketing period outside the U.S., most of which are severe reactions, reflecting either anaphylaxis or serious POME. We find the Complete Response to be even more concerning that the Original NDA in this regard. This issue is discussed in more detail a bit later in this section, and in even more detail in the MO's review and in subsequent sections of this memo.

In regard to a risk management proposal, the Sponsor provided such a plan, in the form of a Risk Evaluation and Mitigation Strategy (REMS). The REMS proposal included a Patient Package Insert (PPI), a Dear Health Care Professional (HCP) letter, and a Video for HCPs in regard to proper intramuscular injection technique. The Sponsor also submitted a proposal for two Phase 4 studies.

After the Complete Response was submitted, the proposed REMS underwent review. The Agency advised that the PPI be converted to a Medication Guide. The intent of the Medication Guide was to inform patients of the risk of immediate post-injection reactions with Aveed and encourage them to remain in the healthcare professional's office for 30 minutes after each injection in case of a serious post-injection reaction. The Agency also advised that the Video be removed from the proposed REMS, as it was believed that intramuscular injection technique should be generally well known by the medical community. The intent of the Dear HCP letter was to introduce prescribers to the risks of the product, especially the immediate post-injection reactions. (b) (4)

The Clinical review team has considered the proposed REMS, and in light of the severe nature of the immediate post-injection reactions, we question the adequacy and appropriateness of this REMS to remedy the underlying serious risk of Aveed and what we believe to be an unfavorable risk/benefit profile.

In regard to the Safety Updates submitted in the Complete Response, the Clinical review team finds these items to provide crucial information in defining the risk profile for Aveed, with special regard for the immediate post-injection reactions. The Sponsor (Endo) has stated that

there were "*no new findings*" in the Bayer/Shering November 25, 2007 to November 24, 2008 PSUR and the Final Safety Update provide on August 31, 2009 and containing postmarketing data from November 25, 2008 to August 29, 2009. The Clinical review detected 52 new cases of immediate post-injection reactions in these 2 Safety Updates. Of these, almost all are severe, and we believe that approximately 20 reflect anaphylactic reactions. We note that throat-related symptoms are prominent in these 2 Safety Updates (throat closing, throat tightness, throat tickling, throat fullness) and we believe that these symptoms reflect post-injection angioedema. Representative case narratives are provided in the medical officer's review and later in this memo. We are deeply concerned by the severity of the post-injection reactions in these two Safety Updates. Finally, on September 21, 2009, we received a case of full-blown post-injection anaphylaxis in a 16 year old male. The Sponsor finds this to be "*the first instance of true anaphylaxis*". We requested another consult from the Division of Pulmonary and Allergy Products (DPAP) and in their draft consult dated November 16, 2009 (and final consult of November 25, 2009), they stated that 20 cases of these new 52 cases were either anaphylaxis (n=11) or possible (n=9) anaphylaxis. Another 4 cases were "allergic reactions". DPAP also stated that POME generally lacks cutaneous and mucosal symptoms, such as generalized flushing and swollen throat, as reflected in many of the post-injection reaction cases. In light of the findings in the Complete Response and the DPAP consult, the Clinical review team re-assessed the original 66 postmarketing post-injection reactions, and we find these even more concerning now, especially in regard to throat-related symptoms and the potential that they are allergic reactions. If we take just those cases from the Complete Response that we believe reflect anaphylactic reactions and we use sales data to calculate a rough incidence of postmarketing anaphylactic reactions, this is the assessment:

- Approximately 20 cases of anaphylaxis (definite cases and possible cases combined)
- Approximately (b) (4) vials sold
- (b) (4) per patient-year = approximately 100,000 patient-years
- Reported Incidence = 20 cases/100,000 patient-years = approximately 1 in 5,000 patients per year
- If corrected for underreporting (10-fold) = approximately 1 in 500 patients per year

Of note, this rough calculation excludes many postmarketing cases reported only a "allergic reaction" or those cases with information too sparse to ascribe an etiology.

Therefore, while the Sponsor has provided the information requested for the Complete Response, and has made an effort at a risk management proposal, we are uncomfortable with the occurrence of severe post-injection reactions, of both respiratory and allergic etiology. We are deeply concerned by the occurrence of anaphylactic reactions, with severe signs and symptoms and not rarely reported. Based on the totality of the evidence, and taking into consideration the Sponsor's contentions and consultant's opinion, we find the risk/benefit profile to be unacceptable for marketing at this time.

It should be noted that the Chemistry deficiency in the original NDA has also been satisfactorily resolved. The deficiency was related to drug sterility as described in Drug

Master File # (b) (4) The DMF holder provided appropriate information to resolve the deficiency. There are no other outstanding or unresolved issues from any other discipline.

The remainder of this memo describes in detail the efficacy and safety findings from the AVEED new drug application (NDA), including data from controlled clinical studies and the postmarketing period in Europe, as derived from the original NDA and the Complete Response. The memo also summarizes the perspectives of each discipline and each consultant team involved in this review.

2. Background

2.1 DESCRIPTION OF PRODUCT

Aveed contains testosterone undecanoate, an ester of testosterone. Although the esterified testosterone, T undecanoate is detected in the blood, the androgen testosterone is formed by cleavage of the ester side chain. Aveed is formulated as a clear, yellowish, sterile, oily solution for intramuscular injection. It is supplied in single use vials, as 750mg testosterone undecanoate in 3mL solution. The mixture also contains refined castor oil (885mg) and benzyl benzoate (1500mg) .

Aveed is intended for replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous testosterone.

2.2 REGULATORY HISTORY

On August 28, 2007, the original NDA was submitted.

On June 27, 2008, the application received an **Approvable** action based upon ***Clinical*** and ***Chemistry*** deficiencies.

The original ***Clinical*** deficiency centered on severe immediate post-injection reactions. The etiology of these was believed to be pulmonary oil microembolism (POME) and/or anaphylactic reactions. While immediate post-injection reactions were reported in just 2 patients in the clinical trials of AVEED (one serious), such events were reported in 66 patients in the postmarketing period in Europe. The postmarketing cases were described as coughing, difficulty breathing, flushing, throat-related symptoms (throat tightening/closing, throat tickling, throat fullness, lump in throat), allergic phenomenon (rash, swelling around eyes, itching, wheezing), paresthesias (burning in mouth, chest, hands and feet), and constitutional symptoms (headache, malaise, sweating, shivering, weakness, nausea, etc) in the immediate post-injection period. Of the 66 cases, 28 cases were serious adverse events, including 4 with respiratory distress and 4 with loss of consciousness. While none of the patients died, and all resolved without permanent sequalae, 12 patients required emergency treatment or hospitalization. In four of these postmarketing cases, signs and symptoms of a systemic allergic reaction were reported, including two (2) cases definitely meeting clinical criteria for

anaphylaxis, and 2 possibly meeting anaphylaxis criteria, as per DPAP. There were no cases with sufficient information to diagnose systemic allergic reactions in the AVEED clinical trials.

In the Approvable letter, the Sponsor was asked to submit additional information to further assess and mitigate the risk of these immediate post-injection adverse reactions. In this regard, the letter spelled out 3 specific Clinical deficiencies and 3 specific requests for Clinical information.

The 3 specific Clinical deficiencies were:

1. The likely incidence of serious POME and allergic reactions in men who would be treated with the product was not known. A precise estimate of the likely incidence of these serious adverse events was needed to make a meaningful risk/benefit assessment for the use of the product for the proposed indication.

2. The application did not include sufficient information to characterize the underlying etiology of the anaphylaxis-like reactions.

3. The application did not include an adequate plan to minimize or manage the risk of these potentially life-threatening events (both POME and anaphylaxis-like events).

The following information was requested in order to resolve the Clinical deficiencies:

1. *Detailed safety information from clinical studies to determine the incidence of serious post-injection POME and allergic reactions (in clinical studies).* The Division requested, at a minimum, the safety database should include information from the following completed or ongoing clinical studies of intramuscular testosterone undecanoate: (1) all subjects treated in Stage 2 of all parts of Study IP157-001, (2) all subjects in (a) Study NE0601 (IPASS), (b) Study AWB015 (the Non-Interventional Study [NIS]), and (c) Study 42306, and (3) all additional foreign data of which Sponsor was aware.

2. *Information from clinical investigations intended to characterize the nature and etiology of the anaphylaxis-like events with testosterone undecanoate injection.* The Division noted that this information could be obtained from (1) skin testing procedures to the product and its excipients, and (2) in vitro testing for the presence of specific IgG and IgE antibodies to both active and excipient components of the drug product.

3. *A plan to minimize the risks associated with the clinical use of the product, namely, to reduce incidence and/or severity of the serious POME and anaphylaxis-like adverse events.*

The specific **Chemistry** deficiency came from Drug Master File (DMF) # (b) (4) where deficiencies were identified. These deficiencies were related to the assessment of sterility of the drug product and were conveyed to the DMF holder in a regulatory letter dated June 25,

2008. The Approvable letter stated that these deficiencies must be satisfactorily resolved prior to approval. The reader is referred to Section 3 of the review for details of the Chemistry deficiency and the means by which it was ultimately resolved.

On September 24, 2008, the Division met with Sponsor in a Type A (End of Review) Meeting. The meeting focused on the information that would be submitted in the Complete Response to Approvable. Each of the 3 Clinical deficiencies was discussed:

- In regard to the safety database that would be submitted to determine a precise incidence of serious POME and anaphylaxis-like events, the Sponsor anticipated submitting data on approximately 2620 patients from 14 clinical trials.

  The Division stated that if the quality of the study reports was acceptable, then the safety database proposed appeared to be of sufficient size.

- In regard to characterizing the nature of the anaphylactic-like reactions, the Sponsor proposed conducting skin prick testing/re-challenge (b) (4)

  (b) (4)

  The Sponsor then asked about not conducting this study at all. They stated that if DPAP was firmly convinced that these events were anaphylactic reactions, then what was the Agency's rationale for the study at all.

  At this meeting, the Division stated that the proposed skin testing/re-challenge study would no longer be treated as a requirement.

  The Sponsor then asked specifically whether the Complete Response would be acceptable without results from the skin prick study.

  *The Division responded that while we would continue to encourage the Sponsor to conduct the skin prick testing/re-challenge study, we would **not** require it as part of the Complete Response (the reader is referred to the Meeting Minutes).*

- In regard to the risk minimization strategy, the Sponsor proposed to submit a Risk Evaluation and Mitigation Strategy (REMS) with the Complete Response. The REMS proposal would include a proposal for a Patient Package Insert, a Dear Health Care Professional letter, a Video and Brochure about intramuscular injection technique (intended for HCPs), and a Phase 4 study.

  The Division stated that the risk of anaphylaxis needed to be addressed in the plan.

On March 2, 2009, the Sponsor submitted the Complete Response.

On August 29, 2009, a Major Clinical Amendment was submitted. This amendment contained a Safety Update for the postmarketing period November 25, 2008 through August 29, 2009.

On September 2, 2009, the application received a 3-Month PDUFA goal date extension.

2.3 PRIMARY MEDICAL REVIEWER'S RECOMMENDATION FOR APPROVABILITY

The primary reviewer, Harry Handelsman, stated in his final review, dated November 10, 2009:

> *"Recommendation on Regulatory Action: It is recommended that this product (Aveed), due to unresolved safety concerns, not be approved for the indication testosterone replacement in males for conditions associated with a deficiency or absence of endogenous testosterone (hypogonadism), including primary hypogonadism (congenital or acquired) and hypogonadotropic hypogonadism (congenital or acquired)."*
>
> *In regard to the risk/benefit profile, the medical officer concluded:*
>
> *"Taken together, the totality of the evidence leads this reviewer to conclude that the risk/benefit profile for Aveed is not acceptable for product approval."*
>
> Also:
>
> *"Concerns regarding post-injection POME and anaphylactic reactions have not been not been allayed. Updated post-marketing data demonstrating numerous reported life-threatening post-injection reactions, many of which required on-site emergency treatment and/or hospitalization. Our consultants in allergy inform us that at least 22 cases of possible or definite anaphylaxis have been reported. Many more cases of angioedema have been reported. It appears that the incidence of the problem projected by Sponsor from clinical trials may be too low, based upon censoring of several cases possibly reflecting post-injection reaction. Taken together, the reviewer believes that the risks of the product do not outweigh its benefit."*

In regard to the individual components of the Complete Response, the medical officer made relevant statements. The following are taken directly from the final MO review and are representative of the MO's position on these issues:

In regard to the incidence of immediate post-injection reactions from Clinical trials:

- "*My review of the pivotal trial data (study IP 157-001) and the other clinical study reports submitted in this NDA indicated 5 additional cases, not included by Sponsor, that may be "incident cases": 2 cases with syncope, 1 case with presyncope (near fainting, but responsive), and 2 cases with circulatory collapse. The Sponsor has noted a single case with a "coughing fit" lasting approximately 10 minutes. I also detected 2*

cases with allergic skin reactions. The 5 additional cases, if coded as incident cases, would serve to change the numerator for the Sponsor's incidence data markedly."

- "*In regard to the additional clinical trial cases that might reflect "incident cases" (post-injection convulsions, syncope and circulatory collapse, respectively), these 3 reports contained insufficient information to definitively ascribe the event to serious POME or to systemic allergy. However, these 3 clinical trial cases should not be discounted due simply to insufficient information."*
- *"In addition, there are several other cases in the clinical trial database (n=3; pre-syncope, syncope and circulatory collapse) for which the information is sparse, but these too might reflect post-injection reactions."*

In regard to additional postmarketing experience from Safety Updates:

- "*In addition, and more importantly, our review of the post-marketing experience has further raised our level of our concern over the nature and number of post-injection reactions that were reported as life-threatening, many requiring urgent treatment and/or hospitalization. These events included POME reactions and anaphylactic reactions. The post-injection reaction events reported in the Complete Response raise even greater concern about anaphylaxis compared to information in the original NDA, in terms of the quantity of anaphylactic cases reported, as well as the types of allergic reactions reported (angioedema reflected as throat closing, skin reactions, dyspnea, etc).*"
- *"This reviewer carefully assessed all cases in the Nov 2007-Nov 2008 PSUR and in the Appendix 8 summary of the anaphylactic reaction issue. From these documents, 43 incident cases were extracted. In the opinion of this reviewer, the cases are very concerning and even more so compared to the cases in the original NDA. The cases in this document reveal clinical evidence for anaphylaxis as the etiology for a fairly significant percentage of the immediate post-injection reactions, including symptoms of throat tightening and throat fullness (a sign suspicious of angioedema), skin erythema, and dyspnea. The percentage of cases with transient cough and shortness of breath, more consistent with a diagnosis of POME, are fewer than previous. In Appendix 8, the European marketer, Bayer Schering acknowledged that 5 cases overall meet some criteria for anaphylaxis, with one case meeting strict criteria for anaphylaxis. Bayer acknowledged in Appendix 8 that it may be impossible to differentiate serious POME from anaphylaxis."*
- *"The cases submitted in the Nov 2007-Nov 2008 Safety Update (including Appendix 8) and the August 29, 2009 Safety Update have led the reviewer to conclude that the severity of the events and risks posed by post-injection immediate reactions are great. Further, the reviewer sees the cases as likely reflecting more than just transient pulmonary oil embolism, as they have been reported as devastating and serious events, consistent with serious POME and perhaps more importantly, with anaphylactic reactions."*
- *"The reader should be aware that DPAP has been re-consulted. At an internal meeting on November 3, 2009, DPAP stated that their review of the 52 new*

postmarketing cases reveals 9 cases of definite anaphylaxis, 7 cases of "possible" anaphylaxis, 2 cases of "borderline possible" anaphylaxis, 4 cases of allergy, and 8 cases of POME. These counts exclude 15 cases where information was scant, but in most of these 15 excluded cases, the event was reported as "anaphylactic reaction". DPAP cautioned that these excluded cases should not be summarily discounted by DRUP, but instead, it is the usual DPAP practice to include such cases, where postmarketing incidence are being assessed by FDA. The DPAP team leader remarked that if the case reporter stated "anaphylactic reaction" that such a case cannot be dismissed."

In regard to the proposed REMS:

- *"At this time, this reviewer does not recommend any specific post-marketing risk mitigation strategy because the current risk/benefit profile is not acceptable for marketing. The Clinical team has become aware that the issue of post-injection reactions is more complicated than we had previously believed, in that there are a significant number of cases of post-injection anaphylaxis and other allergic phenomenon despite the Sponsor's assertions of no such reactions. Our previous reviews had recommended a risk mitigation strategy that was focused on informing patients and providers about the risk of post-injection, pulmonary oil microembolism events, this before we had reviewed in detail the entire post-marketing experience, realized that many of the post-injection reactions were allergic in nature, and re-considered the risk/benefit profile."*
- *"Currently, we believe that anaphylaxis plays prominently in these post-injection reactions. We further understand that it may be impossible to differentiate serious POME from an anaphylactic reaction after an Aveed injection. In fact, most reported serious cases were diagnosed and treated as anaphylactic reactions. We also note that these post-injection reactions can be serious and life-threatening irrespective of the etiology. Taken together, we no longer find the previous MedGuide and REMS to be acceptable in this situation. These documents do not remedy the underlying problem, which is the occurrence of life-threatening post-injection reactions and the unacceptability of the risk/benefit profile for this product."*
- *"This reviewer has considered the proposed Medication Guide and the elements of the proposed REMS. Given the seriousness of the nature of the post-injection reactions, the role of allergy and oil embolism in their causation, and the availability of other testosterone replacement therapies which does not have life-threatening risks, this reviewer does not find the REMS to be appropriate nor an acceptable remedy for an underlying unacceptable risk/benefit ratio for this product."*
- *"The overall REMS is not considered sufficient to remedy the underlying risk/benefit problem with the product. It must be noted that the REMS for this product, which basically entails telling patients and providers about some of the risks of Aveed and advising them to wait in the office for 30 minutes after injection is essentially an untested hypothesis – that informing patients and providers may allow them to opt out, or if they opt in, would allow providers to effectively rescue patients who experience post-injection reaction. This hypothesis has a weak evidence base and is not satisfactory in the face of the risks we have identified."*

- *In summary, the reviewer no longer agrees that the Medication Guide and product labeling serve as sufficient risk mitigation strategies. The reviewer believes that the product has too much risk due to the occurrence of serious post-injection reactions to state that its benefits outweigh its risks.*

In regard to defining the etiology of the immediate post-injection reactions:

- *"This reviewer continues to advise investigations to determine the etiology of the reported immediate post-injection reactions, including anaphylactic and anaphylactic-like reactions to Aveed. Castor oil and benzyl benzoate are both known allergens. Are these excipients, both found in large amounts in the drug product, causative in the reported allergic reactions to Aveed? Can benzyl benzoate play some role in the post-injection reactions, through a non-allergic mechanism? The reviewer continues to encourage additional investigations to characterize the etiology of the immediate post-injection reactions, including the Phase 4 skin testing protocol."*

3. CMC/Device

The Chemistry Review team, Yichun Sun and Moo Jhong Rhee, made the following recommendation in their final CMC reviews dated July 7, 2009 and August 14, 2009:

On July 7, 2009:

> *"This NDA has provided sufficient information to assure identity, strength, purity, and quality of the drug product. An "Acceptable" site recommendation from the Office of Compliance has been made. However, labeling review is not complete yet as of the date of this review. Therefore, from the CMC perspective, this NDA is not recommended for approval until the labeling review is completed."*

On August 14, 2009"

> *"On August 14, 2009, the review on labeling and mock-up labels for container and carton was completed. The labeling and mock-up labels for the container and carton are acceptable. Thus, this application is now recommended for* ***approval*** *from the perspective of Chemistry, Manufacturing and Controls."*

At the time of the action on the original application, the Chemistry review team had unresolved concerns about the purity (sterility) of the drug product. Information for DMF # (b) (4) had been found lacking in support of the sterility of the product. The Chemistry review dated June 26, 2008 noted that the NDA had provided sufficient CMC information to assure the identity, strength, and quality of the drug product, but not its purity (sterility). Therefore, from a CMC perspective, the NDA was recommended for "*Approvable*" pending resolution of the microbiology deficiencies cited for DMF # (b) (4) in the regulatory letter dated June 25, 2008.

The original review by the microbiology team of Drs Pawar and Hussong (dated June 20, 2008) noted that the active ingredient testosterone undecanoate is [redacted] (b) (4)

The following deficiencies in DMF # [redacted] (b) (4) were related to the [redacted] (b) (4) for the drug product and were conveyed to the DMF holder on June 25, 2008:

[redacted] (b) (4)

The final review of the original application by the Microbiology review team stated:

> "*The application is recommended for approvable pending resolution of items listed as deficiencies in the DMF* (b) (4)

In the Complete Response, the Sponsor stated that the DMF had been updated on August 14, 2008 with all the information requested in the June 25, 2008 deficiency letter (in the 7th amendment to DMF # (b) (4)

In their final review of the Complete Response, dated April 23, 2009, the microbiology review team of Vinayak Pawar and David Hussong, made the following recommendation:

> *"The application is recommended for **approval** based on the data provided on DMF* (b) (4)
>
> From Dr. Pawar:
> *"Recommended for approval from the microbiology product quality standpoint.*
>
> From Dr. Hussong:
> *"I concur with the reviewer's assessment that the DMF holder has resolved remaining questions about the manufacturing controls for this product, and the microbiology aspects for this application are acceptable for approval."*

Finally, the overall CMC review by Drs. Sun and Rhee acknowledge that detailed CMC information had been referred to DMF # (b) (4) which was reviewed and found adequate for supporting the use of testosterone undecanoate oily solution in NDA 22-219.

4. Nonclinical Pharmacology/Toxicology

The Pharmacology/Toxicology review team, Eric Andreason and Lynnda Reid, made the following recommendations in their final reviews dated July 9, 2009 and August 20, 2009:

On July 9, 2009:

"*Recommendations on approvability: Nonclinical data support **approval**.*

Recommendation for nonclinical studies: None at this time. The nonclinical program was previously reviewed on April 18, 2008. Other than the new recommendations for labeling, changes to the nonclinical review are not necessary since new data was not submitted.

Recommendations on labeling: The major recommendations include addition of sections for the use in women (5.11), affects on spermatogenesis (5.12), drug interactions with anticoagulants (7.5), use in pregnant or nursing women (8.1, 8.3), use in pediatrics (8.4), and use in patients with impaired renal or hepatic function (8.6). The Sponsor's comments regarding hepatocellular carcinoma and prostatic hypertrophy and prostatic carcinoma in humans (b) (4) *were moved to section 5.5."*

On August 20, 2009:

"*From a pharmacology/toxicology perspective, the labeling for AVEED submitted by the Sponsor on August 14, 2009 is acceptable."*

In her August 20, 2009 final memo, the supervisory pharmacologist, Lynnda Reid made the following final recommendations:

"I concur with the primary nonclinical reviewer, Dr. Eric Andreason, that the nonclinical data support approval of testosterone undecanoate (dose) for the treatment of men with a testosterone deficiency as proposed in this NDA.

The final label for AVEED submitted by the Sponsor on August 14, 2009 is acceptable."

In regard to the original PharmTox review, I would point to one issue of potential clinical relevance: the potential for benzyl benzoate to act as a toxin.

In their original Pharmacology/Toxicology review, Drs. Andreason and Reid provided results from a local tolerance study of Nebido (containing intramuscular testosterone undecanoate, refined castor oil, and benzyl benzoate) in pigs. This study is reviewed on page 47 of the final PharmTox review, dated April 18, 2008. It is stated that this study was reviewed by Dr. McKinney. The results of this study, wherein pigs were injected intramuscularly with low and high volumes of the drug product, or with vehicle alone, showed areas of gross hemorrhage and necrosis at the injection sites, with necrotic tissue, inflammation and multinucleated giant cells on histopathology. All groups showed similar effects, including the vehicle alone group. The reviewer concluded that these observations are likely due to non-specific tissue injury, and that there is no direct evidence that either of the excipients, or testosterone undecanoate itself,

are directly toxic to human tissue. However, Dr. McKinney noted that benzyl benzoate is itself a toxin, as shown by its use in the treatment of scabies to kill the house mite that causes scabies. The review states: "*Whether it (benzyl benzoate) could directly activate macrophages, which would explain the presence of giant cells at the injection site, has not been established, but has been observed for other benzoates in vitro (Choi et al., Arch Pharm Res: 28[1]:49-54 [2005])*".

The reader should also be aware that AVEED contains 1500mg of benzyl benzoate per vial, a fairly large amount. I have discussed this with the PharmTox reviewer, Dr. Andreason, who has indicated that he could find no approved product containing more than 750mg of benzyl benzoate. Benzyl benzoate is the condensation product of benzyl alcohol and benzoic acid. In a final report on the safety of benzoates (benzyl alcohol, benzoic acid, and sodium benzoate) in cosmetics, the U.S. Cosmetic Ingredient Expert Panel noted that benzyl alcohol and benzoic acid can produce nonimmunologic contact urticaria and non-immunologic immediate contact reactions (Int J. Toxicology 2001; 20 Suppl 3:23-50). The Panel stated that such reactions were not a concern at concentrations up to 5% topically; that is, when bodily exposure is limited. Nonetheless, the panel stated that the clinical risks of these reactions should be considered by manufacturers when assessing topical use of products containing benzyl benzoate in infants and children; and that an inhalational route for these products could not yet be considered safe. It is not known what role benzyl benzoate has played, if any, in the immediate post-injection reactions. A nonimmunologic immediate "reaction" to benzyl benzoate might play some role in the allergic events have been reported in the postmarketing period.

In addition, the reader should also be aware that there have been reports of "benzyl alcohol poisoning" in neonates following repeated intravenous injections of benzyl alcohol in intravenous saline flushes (MMWR Weekly 1982: 31 [22]: 290-291). These were pre-term neonates weighing 2500 grams, with premature hepatic metabolism, in whom intravenous central catheters were flushed periodically each day with saline solutions containing 9mg/mL of benzyl alcohol. The events in these infants included the following: "gasping respirations", respiratory distress, convulsions, metabolic acidosis, intracranial hemorrhage, hypotension, cardiovascular collapse, and death. The MMRW citation states "On the basis of the animal studies, it has been estimated that rapid intravenous infusion of adult humans with as much as 30mL of 0.9% benzyl alcohol (approximately 4.5mg/kg) in saline should be safe (Kimura et al., Toxicol Appl Pharmacol 1971; 18: 60). It is not known whether this same data applies to benzyl benzoate, but this information is provided to the reader nonetheless, because: 1) there is a large amount of benzyl benzoate in each injection of Aveed (1500mg), and 2) serious POME reactions reported for Aveed have included signs and symptoms similar to these reported in the premature neonates who experienced benzyl alcohol poisoning.

5. Clinical Pharmacology/Biopharmaceutics

The Clinical Pharmacology Review team, Doanh Tran and Myong-Jin Kim, made the following recommendation in their final review dated July 10, 2009:

"The Division of Clinical Pharmacology 3/Office of Clinical Pharmacology finds NDA 22-219 for testosterone undecanoate acceptable, provided the labeling recommendations are adequately addressed."

A final memo, dated August 17, 2009, from the same Clinical Pharmacology review team, stated:

"This review amendment is to document that the sponsor has adequately addressed our labeling recommendations. The agreed labeling was submitted on 8/14/2009, (and is attached). Recommendation: The Division of Clinical Pharmacology 3/Office of Clinical Pharmacology finds NDA 22-219 for testosterone undecanoate acceptable

In their final review of the Complete Response, Drs. Tran and Kim further stated:

"In this resubmission, the sponsor provided responses to the Clinical and CMC deficiencies. No new pharmacokinetic (PK) information was provided. This review primarily involved labeling recommendations."

The principle Clinical Pharmacology concern during the review of the Complete Response was the effect of body weight on exposure; specifically, the increased exposure demonstrated in patients with lower body weight/lower body mass index, and especially the excessive exposure noted in a single patient who weighed <65 kg. (b) (4)

In addition, Section 12.3 (Pharmacokinetics) describes in detail the effect of body weight on exposure, including specific data in patients weighing 60-100kg and those ≥ 100kg (b) (4)

The following additional Clinical Pharmacology comments are derived from the original review and may be useful to the reader:

1. The TU 750mg Loading regimen successfully achieved the C_{avg} and C_{max} pre-set criteria at steady-state (in the Phase 3 pivotal trial).
2. (b) (4)
3. The assays of T and DHT for the primary analysis were valid.
4. While TU is generally converted to T, serum TU was shown to increase with all regimens tested. The concentration-time profile showed that T_{max} was approximately 4 days for TU and serum concentrations were generally short-lived.
5. Serum DHTU was also observed in blood sampling, but most attempts to measure this analyte showed concentrations below the limit of quantification.

The reader should also be aware that while TU may be found in the blood, nonclinical studies have shown that TU itself has little potential for clinical androgenic activity. The ability of TU to bind to the human androgen receptor was assessed and the results suggest that TU does not have significant androgenic activity since its relative binding affinity was only 1.3% of testosterone.

6. Clinical Microbiology

For detailed discussion of Microbiology issues for this application, the reader is referred to section 3 (CMC/Device).

In brief, in their final review of the Complete Response, dated April 23, 2009, the microbiology review team of Vinayak Pawar and David Hussong, made the following recommendation:

> *"The application is recommended for **approval** based on the data provided on DMF* (b) (4)

7. Clinical/Statistical - Efficacy

7.1 OVERVIEW OF CLINICAL PROGRAM

For efficacy, the NDA is supported by a single, two-part, phase 3 safety and efficacy study, referred to as Study IP157-001 - Parts C and A. Part C evaluated the 750 mg Loading regimen (n = 117) while Part A evaluated 750 mg (n=102) or 1000 mg (n=97) given every 12 weeks. The primary endpoints in this study were average and maximum serum testosterone concentrations.

Results from five (5) other Phase 1, Phase 2, and Phase 3 European studies and their extensions (including Study JPH01495, Study JPH04995, Study ME98096, Study ME97029, and Study 306605) were provided in the original NDA but were not reviewed in depth for efficacy because they employed dose regimens that were not sought. In addition, these older studies employed assay methods (radioimmunoassay or electrochemoluminescence immunoassay) that were regarded by Clinical Pharmacology as being not as accurate as the method used in Study IP157-001.

(b) (4)

in a teleconference dated January 15, 2008, the Sponsor requested that the Division consider for approval just the TU 750 mg Loading regimen, as studied in Study IP157-001 Part C. Due to this change, data from Study IP157-001 Part C were used as the source of steady state PK. Data from Study IP157-001 Part A was used as the source of first dose PK data because Part C did not evaluate first dose PK. Part A also served as the primary

source of data on serum TU and serum dihydrotestosterone undecanoate (DHTU) concentrations because these analytes were not measured in Study IP157-001 Part C.

7.2 DEMOGRAPHICS

The main diagnostic criteria for inclusion in Study IP157-001 were men at least 18 years of age with morning screening serum testosterone concentration < 300 ng/dL. Critical exclusion criteria included: 1) American Urological Association Symptoms Score ≥ 15 points, 2) Prostate symptoms, or induration of the prostate (or breast) suspicious for cancer, 3) Serum prostate specific antigen level ≥ 4 ng/mL, 4) Hyperplasia of the prostate, defined as prostate size ≥ 25 cm3 on transrectal ultrasononography, 5) Past or present history or liver tumors, acute or chronic liver disease, or serum liver function tests exceeding 1.5 times upper limit of normal, 6) History of deep vein thrombosis in the last 5 years, 7) Any history of cerebrovascular accident, 8) Severe acne, 9) Serious psychiatric disease or other uncontrolled medical illness, 10) Significant baseline hypertension (systolic BP > 160 mmHg and diastolic > 95 mm Hg), 11) Coronary artery disease not stabilized by therapy, and 12) Insulin dependent diabetes mellitus, or uncontrolled non-insulin dependent diabetes mellitus.

In brief, the demographics of the study population in Part C (n=130) were as follows:

In terms of race, the majority of subjects were White (76%), 12.3% were Black, 10.8 % were Hispanic, and 2.3% were "Other". The mean age was 54 years ± 0.9 years. The median age was 55 years. The minimum and maximum ages of subjects in the trial were 24 years and 75 years, respectively. Of the total, 23% (30/130) were between ages 40 - 50 years, 38% (50/130) were between ages 50 - 60 years, and 25% (33/130) were 60 - 70 years. The mean weight of subjects was 71 kg ± 14 kg. The median weight was 101 kg. The mean body mass index was 32 kg/m^2. Almost 60% of subjects had a body mass index over 30 kg/m^2. The average total testosterone concentration was 214 ng/dL.

7.3 DISPOSITION OF SUBJECTS

For Part C, a total of 130 patients were enrolled at a total of 31 U.S. clinical sites. Of the 130 patients enrolled, 116 (89%) completed Stage 1 of Part C; that is, they completed through the 4th injection visit. Of the 14 subjects who prematurely discontinued, the primary reason for premature discontinuation was adverse event (3.8%, or 5/130). Of the 5 who discontinued due to an adverse event, the adverse event was judged by the investigator to be related to treatment in 4 patients. The events in these 4 patients included: mood swings, acne, deep vein thrombosis, and estradiol increased. The fifth patients suffered a myocardial infarction, judged by the investigator as not related to study medication. Other reasons for premature discontinuation included patient non-compliance (3 subjects), withdrawal of patient consent (1 subject), loss to follow-up (2 subjects), and "other" reasons (3 subjects). The Sponsor notes that despite the requirement for frequent blood sampling in this study, persistence on drug therapy was very high.

Of note, two subjects were discontinued from the study for weighing less than 65 kg, but only after they were enrolled.

There were 4 pre-defined criteria in the protocol for subject discontinuation. These were: hemoglobin >21 gm/dL, PSA > 10 ng/mL, PSA > 4ng/mL but ≤ 10 ng/mL unless prostate

cancer was ruled out by new biopsy, or uncontrolled hypertension, defined as systolic blood pressure ≥ 160 and diastolic BP ≥ 95 mm Hg. There were no patients who terminated from the study due to any of these 4 criteria.

7.4 EFFICACY FINDINGS

7.4.1 Assessment of Efficacy

The primary efficacy variable was the percentage of patients with average T concentration at steady state within the normal range (above 300 ng/dL but below 1000 ng/dL). Testosterone undecanoate 750mg was given at baseline, week 4, and every 10 weeks thereafter. Steady state pharmacokinetic sampling occurred during the 3rd injection interval. This is an acceptable primary efficacy endpoint for the proposed indication of testosterone replacement.

A total of 117 patients were included in the PK population. The majority of patients in the PK population had complete data for most efficacy outcomes. The analysis presented descriptive statistics (mean, standard errors, etc) for all patients with non-missing values. A point estimate was provided for the number (%) of subjects meeting the C_{avg} threshold, as were the 95% confidence intervals about the point estimate. The protocol stated that in order to reject the null hypothesis (TU 750mg Loading regimen does not provide adequate T replacement) in favor of the alternate hypothesis (TU 750mg Loading regimen does provide adequate T replacement), the percentage of responders, defined as Cavg within the normal range (300-1000ng/dl), must be at least 75%, with the lower bound of the two-sided confidence interval not lower than 65%.

The protocol also stipulated that testosterone concentrations should not be excessively high outside the normal range; specifically, ≤ 1500 ng/dL in ≥ 85% of patients, 1800 – 2500 ng/dL in ≤ 5% of patients, and > 2500 ng/dL in no patients. All 3 criteria must be met to reject the null hypothesis (TU 750mg Loading regimen does result in excessively high serum T) in favor of the alternative hypothesis (TU 750mg Loading regimen does not result in excessively high serum T).

In addition, the following secondary endpoints were evaluated:

1. Other pharmacokinetic assessments of testosterone, including concentrations below the normal range (<300 ng/dL).
2. Other hormone concentrations, including free T, dihydrotestosterone (DHT), sex hormone binding globulin, estradiol (E_2) and the ratios of these hormones over time.
3. Clinical markers of testosterone replacement, including the Male Patient Global Assessment (M-PGA).
4. Body weight and BMI.
5. Correlations of T concentrations with clinical outcomes.
6. The impact of T concentrations on erythropoiesis and lipid markers.

7.4.1.1 Primary Efficacy Analysis

The mean data indicated that the serum testosterone C_{trough} values were similar at end of 2nd, 3rd, and 4th injection interval, as shown in *Figure 1*. A comparison of serum total T concentration at several time points post injection during the 3rd and 4th injection intervals demonstrates similar concentration-time profiles (*Figure 2*). Taken together, these data indicate that steady state was achieved during the 3rd injection interval in Part C, and that this was an appropriate timepoint for assessment of the primary endpoint.

Figure 1: Mean (±SD) trough serum total T concentrations at each injection visit from pre-treatment through 5th injection – Steady state PK population, Study IP157-001 Part C

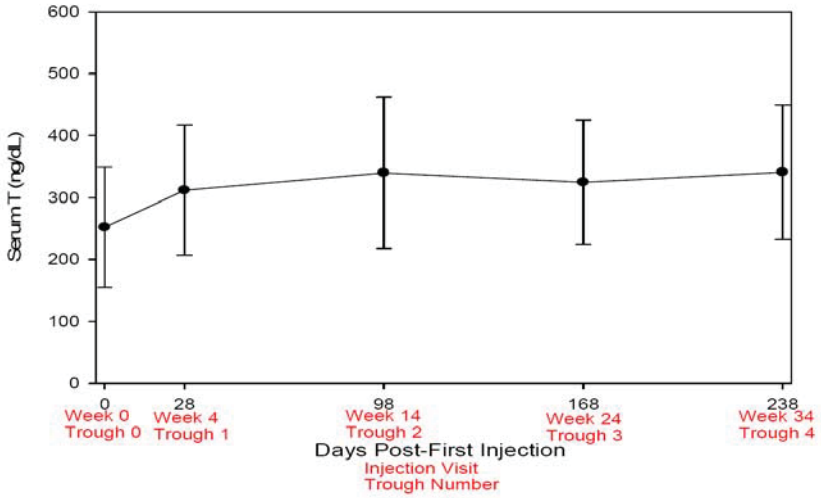
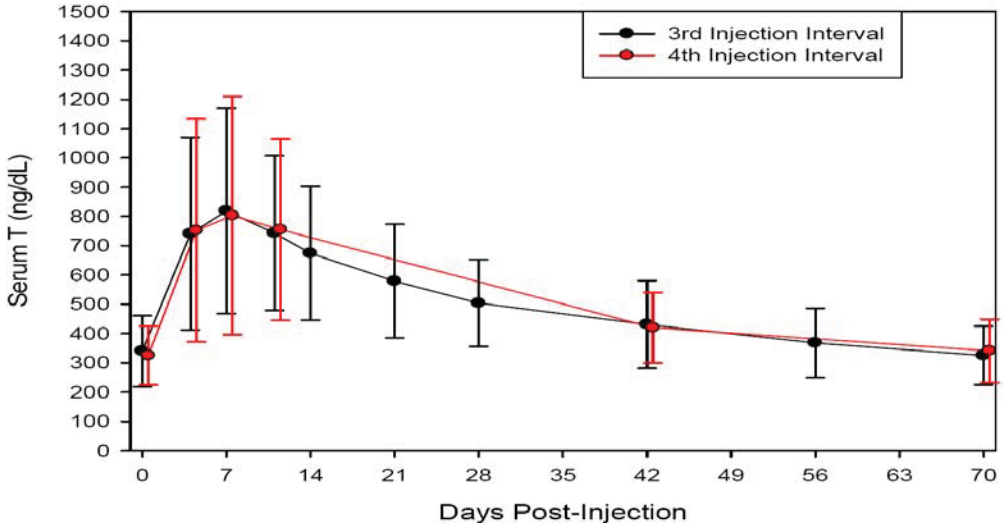


Figure 2: Comparison of serum total T concentrations between the 3rd and 4th injection intervals – Steady state PK population, Study IP157-001 Part C



Tables 1, 2 and 3 summarize the pharmacokinetic parameters of serum total T from the 3rd injection interval. The primary endpoint was $C_{average}$.

Table 1. Serum total T pharmacokinetic parameters from the 3rd injection interval, TU 750mg LOADING regimen, from Study IP157-001 Part C

PK parameter	Mean (n=117)	Standard deviation
C_{avg} (ng/dL)	495	141
C_{max} (ng/dL)	891	345
T_{max} (days)	7 (median)	4 – 42 (range)

Table 2: PK parameters of serum total T (ng/dL) following the 3rd injection interval of TU 750 mg LOADING regimen - PK population, Study IP157-001 Part C

TU Dose	Pharmacokinetic Parameter	Number Patients	Mean	Standard Deviation	Minimum	Median	Maximum	CV (%)	Geometric Mean
TU 750 mg LOADING	$AUC_{(0-70)}$ (days*ng/dl)	117	34645.6	9902.45	13755.1	33342.2	70016.9	28.6	33263.6
	C_{Trough} (Day 70)	117	323.5	99.11	138.2	316.9	611.1	30.6	309.0
	C_{max} (ng/dL)	117	890.6	345.11	311.0	813.6	1758.5	38.8	826.8
	Dose-normalized C_{max}(ng/dL)[1]	117	1.2	0.46	0.4	1.1	2.3	38.8	1.1
	T_{Last} (days)	117	70.0	0.00	70.0	70.0	70.0	0.0	70.0
	T_{max} (days)	117	10.0	7.11	4.0	7.0	42.0	71.1	8.4
	Dose-normalized $AUC_{(0-70)}$ (days*ng/dl)[1]	117	46.2	13.20	18.3	44.5	93.4	28.6	44.4
	$C_{avg, 0-70}$ (ng/dL)[2]	117	494.9	141.46	196.5	476.3	1000.2	28.6	475.2

Reference: Section 14.2 Table 9.2.1.1.1
CV = Coefficient of Variation
[1] Statistics for the dose normalized AUC were derived by dividing the mean of the original parameter ($AUC_{(0-70)}$) by the dose amount (750 mg). Thus, no measures of variability, geometric mean, or CV are presented for the dose normalized AUC.
[2] C_{avg} derived as $AUC_{(0-70)}$/70 days

Table 3: Serum total T concentrations (ng/dL) over 70 days (10 weeks) following the 3rd injection of TU 750 mg LOADING regimen - PK population, Study IP157-001 Part C

Treatment Group	Days Post-Injection	Number Patients	Mean	Standard Deviation	Minimum	Median	Maximum	CV%	Geometric Mean
TU 750 mg LOADING	0 (Pre-Injection)	117	339.5	122.69	141.4	303.0	754.1	36.1	319.8
	4	111	730.1	325.36	304.6	656.4	1715.0	44.6	662.9
	7	111	816.9	352.15	276.4	737.6	1758.5	43.1	747.5
	11	107	750.1	280.64	245.6	740.9	1757.0	37.4	697.9
	14	114	661.6	237.55	230.9	610.8	1352.3	35.9	619.2
	21	115	573.5	197.15	182.7	558.6	1350.4	34.4	541.3
	28	111	501.6	149.92	190.9	481.4	947.0	29.9	479.5
	42	109	432.3	152.16	171.3	399.8	1161.2	35.2	409.5
	56	115	367.0	120.67	144.5	349.8	780.8	32.9	348.7
	70[1]	116	323.8	99.51	138.2	317.2	611.1	30.7	309.2

Reference: Section 14.2 Table 9.2.1.2.1
[1] Note: As per the statistical analysis plan, for derivation of the PK parameters, if the concentration at the end (Day 70) of the 70-day dosing interval is missing, then the AUC was derived using λz as derived by curve-stripping. There was 1 patient who was missing a Day 70 concentration value; this table presents the data prior to the data imputation of Day 70 for this patient. However, the analysis for Table 25 was performed using the imputed data for the last value for that patient, and thus the C_{trough} value from that table will not match the Day 70 value from this table.

One patient was excluded from the PK analysis due to protocol violation. This was Patient 002-7022, who was taking concomitant DHEA, an androgenic steroid hormone prohibited in this study.

Figures 3 and 4 show the mean and individual concentration-time profiles for serum testosterone, respectively, following the 3rd injection interval.

Figure 3: Mean (±SD) serum total T concentrations following the 3rd injection interval of TU 750 mg LOADING regimen, from Study IP157-001 Part C

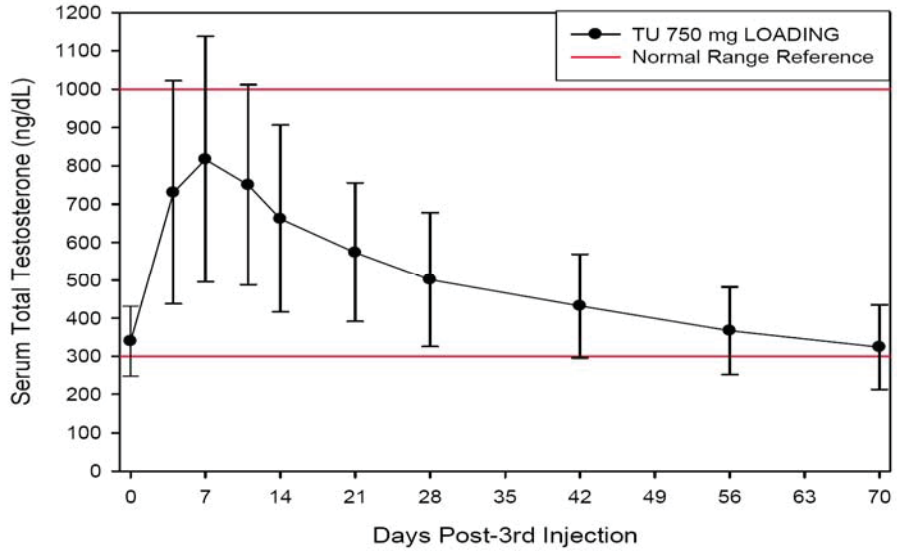
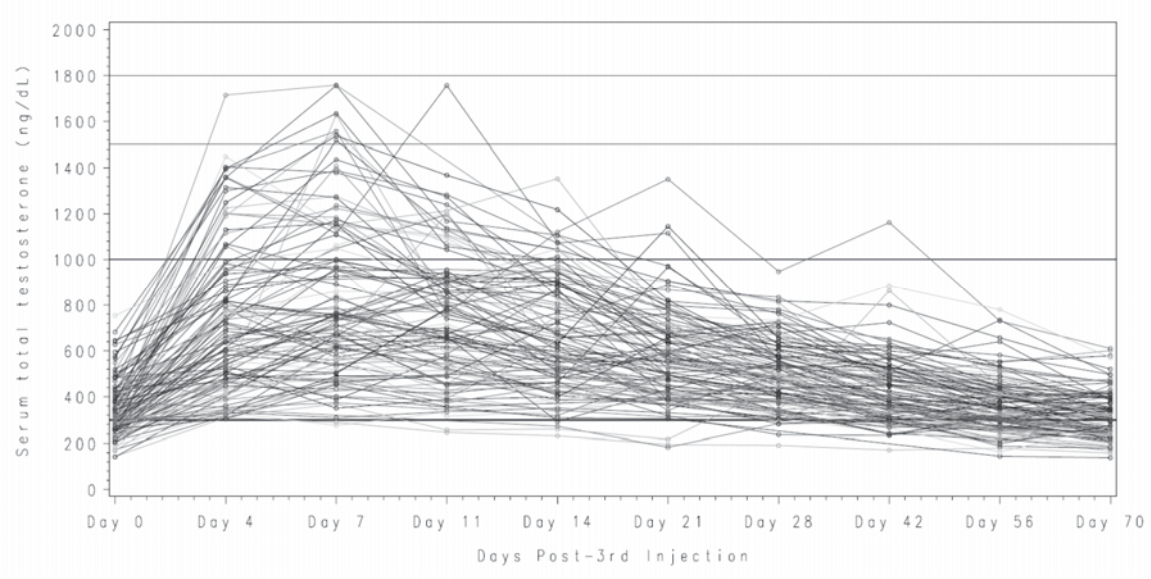


Figure 4: Composite of individual serum total T concentration following the 3rd injection of the TU 750 mg LOADING regimen – PK population, Study IP157-001 Part C



The primary efficacy endpoint in this study was the percentage of responders defined as C_{avg} within the normal range (300 – 1000 ng/dL). To meet the primary efficacy criterion, the point

estimate for the pre-determined primary endpoint was set as at least 75% and the lower bound of the two-sided 95% confidence interval was set as not lower than 65%.

Ninety four percent of patients (110 of 117) had serum total T C_{avg} within the 300 – 1000 ng/dL range. The 95% confidence interval around this point estimate was 89.6 - 98.5. Of the 7 patients who did not meet this criterion, 6 failed due to $C_{average}$ below 300ng/dL and one failed due to a $C_{average}$ above 1000ng/dL.

Therefore, the data from Part C show that the primary efficacy objective was achieved.

7.4.1.2 Secondary Efficacy Analysis

C_{max} was an important secondary efficacy endpoint in Part C. To meet the C_{max} efficacy criterion, the criteria shown in *Table 4* were pre-defined:

Table 4: Decision criteria for Cmax

Criteria for Serum Total Testosterone Maximum Concentration Observed	Criteria for Success	Not Meeting the Criteria for Success
≤ 1500 ng/dL	≥ 85% of Patients	< 85% of Patients
1800 - < 2500 ng/dL	≤ 5% of Patients	> 5% of Patients
≥ 2500 ng/dL	No Patients	At least 1 patient
All 3 criteria must be met in order to reject the null hypothesis in favor of the alternative hypothesis. If at least one of the 3 criteria is not met, the null hypothesis cannot be rejected. The time point for assessment of this secondary outcome is the post-3rd injection period (Weeks 14 - 24).		

The Sponsor excluded from the PK analysis those patients who weighed less than 65kg. One patient fell into this category in Part C (Patient 031-7021). This patient did experience a serum testosterone concentration above 2500 ng/dL during the 3rd injection interval. Otherwise, only nine of the 117 patients (7.7%) had C_{max} > 1500 ng/dL and no patient had $C_{max} \geq 1800$ ng/dL.

In summary, the data show that the C_{max} efficacy objective was achieved in Part C in men weighing more than 65 kg.

In addition to the increase in serum total T concentration, the serum concentrations of free T and known downstream metabolites of T, dihydrotestosterone and estradiol, were also increased. The increases in serum DHT and E_2 were expected. Average DHT concentrations tended to remain within the lower end of the normal range, while average E_2 concentrations tended to remain in the middle of the normal range. TU administration did not affect concentrations of sex hormone binding globulin (SHBG). With SHBG and albumin concentrations unchanged, the increase in free T concentration was also expected. The concentration versus time profiles for free T, DHT and E_2 generally paralleled the T concentration-time profile. DHT:T and E_2:T ratios were unchanged. The reader is referred to the medical officer's primary review and to the Clinical Pharmacology review for additional detail, tables and figures for these variables.

In regard to other secondary endpoints:

- Average values of hemoglobin and hematocrit increased slightly from pre-treatment, as average T concentrations increased. The average increases in these markers of erythropoiesis were small and average values remained within the normal range.
- The improvement seen in "treatment satisfaction" appeared to correlate with higher T concentrations in some patients. Overall, 92% of patients expressed satisfaction with treatment.
- At Day 21 of the 3rd injection interval, > 80% of patients demonstrated improvements in each item of the M-PGA questionnaire.
- Changes in T concentrations were weakly inversely correlated with changes from baseline in body mass index and weight. However, there were no notable changes in other body composition measures.

Statistician's Conclusion

In his final review of the original submission dated June 24, 2008, the Biometrics Team Leader Mahboob Sobhan had the following conclusion:

> "*The results support the efficacy of Nebido TU 750 mg LOADING in the treatment of hypogonadism in adult male as indicated by the attainment of steady state by the 3rd injection. The intensive sampling for PK outcomes (Cavg and Cmax) also met FDA threshold for approvability and, therefore, can be extrapolated to represent PK outcomes under extended dosing beyond 3 injections."*

In his final memo for this Complete Response re-submission, dated July 21, 2009, Dr. Sobhan had the following comment:

> "*In our earlier statistical review, we concluded that testosterone undecanoate (TU) was efficacious in treating hypogonadism in adult males. There were no new efficacy data submitted for our review to further substantiate or change the efficacy data in the label. We have reviewed the new label and from a statistical perspective, our conclusions remain unchanged.*"

7.4.2 Overall Assessment of Efficacy

The TU 750mg Loading regimen was found to provide adequate replacement of testosterone in hypogonadal men weighing >65kg (as measured by testosterone $C_{average}$), while not providing excessive testosterone (as measured by testosterone $C_{maximum}$). The dosing regimen demonstrated a C_{avg} within the normal range and a C_{max} profile that did not exceed the approvability thresholds provided. Thus, the primary efficacy objectives of the Phase 3 study were met.

8. Safety

8.1 SAFETY FINDINGS

Contents and Brief Safety Findings From the Original NDA
The original NDA submission contained safety data from the following 6 studies:

1) The single U.S. pivotal Phase 3 study IP157-001, including Parts A, B and C.
    a. Part A included a total of **237** adult male subjects, enrolled in two dose arms: 750mg every 12 weeks (*n=120 [102 evaluated for efficacy]*) and 1000mg every 12 weeks (*n=117 [97 evaluated for efficacy]*)

    b. Part B included a total of **134** new adult male subjects in two treatment groups: *112 patients* received an initial injection of TU 1000 mg, followed 8 weeks later with a loading injection of 1000 mg and then 1000 mg every 12 weeks thereafter, while *22 patients* received an initial injection of 1000 mg, followed 8 weeks later with a loading injection of 750 mg and then 750 mg every 10 weeks thereafter.

    c. Part C included a total of **117** adult male subjects enrolled in the 750mg Loading regimen. The Sponsor also submitted safety data on another **36** adult male subjects taking the 750 Loading regimen (referred to as Part C2)

2) Five, older, European, dose-finding trials comprising a total of **185** adult males subjects [176 evaluated for efficacy]. (Studies JPH01495, JPH04995, ME98096, ME97029 and 306605)

Therefore, when combined, a total of **709 adult male subjects** contributed safety data from controlled studies to the original NDA.

The original NDA also contained six (6) Bayer/Schering Periodic Safety Update Reports (PSURs) from several years of worldwide postmarketing use (specifically November 25, 2003 through June 30, 2007). The 120-Day Safety Update contained another Bayer/ Schering PSUR (for the time period June 30, 2007 to October 12, 2007). The Sponsor also submitted a Summary Report entitled, "Immediate Post-Injection Reactions Suspect of Pulmonary Oil Microembolism" (dated February 12, 2008).

The clinical trial safety data was consistent with an injectable androgen, except for the occurrence of immediate post-injection reactions in 2 patients. These 2 events were described as sudden and severe urge to cough, cough, and dyspnea immediately following injection. The PSURs and Summary Report of February 12, 2008, raised serious concerns related to immediate post-injection respiratory and allergy adverse events. These had only been reported in 2 patients in clinical trials, but the PSURs and Summary Reports included 66 postmarketing cases. The 66 postmarketing cases were marked by cough, shortness of breath, throat-related symptoms (throat tickle, throat tightness, throat fullness, etc), flushing, allergic phenomenon (such as rash, pruritis, itching), tachycardia, palpitations, BP changes, and constitutional symptoms, such as headache, malaise, shivering, sweating, weakness and nausea. The etiology of these events was not clear, but was believed to be related either to pulmonary oil microembolism or anaphylaxis or both. In response to the Division's concerns about these spontaneously-reported, respiratory and allergic postmarketing adverse events, on June 13,

2008 (two weeks prior to the PDUFA goal date), the Sponsor submitted safety information on an additional 1,451 subjects in 3 additional postmarketing clinical trials. However, the safety data submitted for these additional subjects was summary in nature and was not detailed. It was not possible to determine whether the data was derived from adequate studies, or whether it was collected properly. Therefore, in the Approvable letter, the Division asked that these data from additional clinical trial subjects be submitted with the Complete Response with as much detail as possible.

Contents and Brief Safety Findings from the Complete Response

In the Complete Response, the Sponsor provided safety data from an additional 11 studies; 7 completed and 4 ongoing. The data was submitted as a Summary Report, entitled, "*Incidence of Injection-Based Pulmonary Oil Reactions and Allergic Reactions from Clinical Studies of TU*" (dated February 12, 2009). Final or interim study reports were also provided for each of the 11 new studies. These 11 new studies comprised **a total of 2,125 additional subjects**. These studies were:

- AWB0105, Germany, 4 doses, n=870
- NE0601 (IPASS), 18 countries, 4 doses, n=763
- TG09, Germany (obesity), 4 doses, n=29
- NB02, Germany (paraplegia), 2 doses, n=19
- Czech NEO, Czechoslovakia, 4 doses, n=23
- 303934, Finland (andropause), 1 dose, n=15
- 97028, Germany, 4 doses, n=28
- 97173, Italy, 1 dose, n=24
- 99015, Germany, 4 doses, n=42
- 98016, Germany, 4 doses, n=14
- 42306, 6 countries, 4 doses, n=298

Therefore, the overall clinical trial safety database was **2,834 subjects** in 17 trials.

The Sponsor also submitted two additional postmarketing safety updates in the Complete Response:

- A Bayer/Schering PSUR for the time period November 25, 2007 through November 24, 2008
- A Final Safety Update from Endo for the time period November 25, 2008 – August 29, 2009

To briefly summarize the Safety findings from these items in the Complete Response:

1) In regard to the incidence of post-injection reactions in clinical trials, the Original NDA contained 2 such cases. The two Original NDA clinical trial cases were:

- Patient #184 in Study 306605. A 54 year old male received his 10th injection of testosterone undecanoate on 3 April 2006 and shortly (1 minute) after the injection, he "experienced urge to cough associated with respiratory distress". Both symptoms lasted approximately 14-15 minutes. The event resolved without intervention and the subject continued in the study. The investigator and Sponsor both attributed the event to "pulmonary lipid (oil) microembolism" and cited the following possible reason:

either too fast administration of the study drug or accidental intravascular placement of the study drug.

- Patient #050-7006 in Study IP157-001 Part C). A 53 year old white male received his 3rd injection on 12 July 2007 and experienced a "mild and not serious coughing fit lasting 10 minutes following the injection." The narrative describes the patient's cough as not productive, without wheezing and without difficulty breathing. No intervention was given and the patient continued on-treatment without subsequent coughing event.

In the Complete Response, the Sponsor detected no additional cases in a total of another approximate 2100 subjects. The Sponsor therefore counted 1 serious POME case and no systemic allergic reactions in the numerator. The denominator was totaled as 2834 subjects. The Sponsor thereby proposed an incidence of 1 serious POME in 2834 subjects, or 3.53 serious events per 10,000 subjects, or 0.035%. For systemic allergic reactions, the Sponsor proposed an incidence of 0% in clinical trials.

The Clinical review team detected 6 additional cases of interest from clinical trials. However, information from these cases is too sparse to ascribe a specific etiology to the events, but they were all severe, immediate post-injection reactions. The Clinical review team believes that the former 3 events have a greater chance of being serious POME or systemic allergic reactions compared to the latter 3, but all 6 are notable. The former 3 cases are:

- Patient #11 in Study 97173 (convulsions)
- Patient #17 in Study 97173 (collapse),
- Patient #4 in Study JPH04995 (circulatory collapse)

If just these 3 cases were added to the numerator, this would markedly change the incidence of immediate post-injection reactions in clinical trials: 4 events /2834 subjects (0.14%). The latter three cases are:

- Patient #025-4187 in Study IP157-001 Part A (pre-syncope)
- Patient #26 in Study 97029 (syncope)
- Patient #35 in Study 97029 (circulatory collapse).

In our view, whether the clinical trials show 1, 2, 5 or 8 incident cases is not as critical as the findings from postmarketing reports, which show the occurrence of severe and life-threatening immediate post-injection reactions.

2) In regard to the postmarketing Safety Updates submitted in the Complete Response, the Sponsor (Endo) has stated that there were "*no new findings*" in either the Bayer/Schering November 25, 2007 to November 24, 2008 PSUR or the Final Safety Update provided by Endo on August 31, 2009 containing postmarketing data from November 25, 2008 to August 29, 2009. However, our Clinical review detected 52 new cases of immediate post-injection reactions in these 2 Safety Updates. Of these 52 cases, almost all are severe, and we believe that approximately 20 are definite or possible anaphylactic reactions. We note that throat-related symptoms are prominent in these 2 Safety Updates (throat closing, throat tightness, throat tickling, throat fullness) and we believe that these symptoms reflect post-injection angioedema, not POME. Representative case narratives are provided in the medical officer's review and later in this memo. We are deeply concerned by the severity of the post-injection

reactions in these two Safety Updates. Finally, on September 21, 2009, we received a case of full-blown, post-injection anaphylaxis in a 16 year old male. The Sponsor finds this to be "the first instance of true anaphylaxis". We requested another consult from the Division of Pulmonary and Allergy Products (DPAP) and in their draft consult dated November 16, 2009, they stated that 20 cases of these new 52 cases were either definite (n=11) or possible (n=9) anaphylaxis. Another 4 cases were "allergic reactions". DPAP also stated that POME generally lacks cutaneous and mucosal symptoms, such as generalized flushing and swollen throat, as reflected in many of the post-injection reaction cases. In light of the findings in the Complete Response and the DPAP consult, the Clinical review team re-assessed the original 66 postmarketing post-injection reactions, and we find these even more concerning now, especially in regard to throat-related symptoms and the potential that they are allergic reactions. We can calculate a very rough incidence of postmarketing anaphylactic reactions by taking those cases from the Complete Response that we believe reflect anaphylactic reactions, and using sales data from that same time period:

- Approximately 20 cases of anaphylaxis (definite cases and possible cases combined)
- Approximately (b) (4) vials sold
- (b) (4) per patient-year = approximately 100,000 patient-years
- Reported Incidence = 20 cases/100,000 patient-years = approximately 1 in 5,000 patients per year
- If corrected for underreporting (10-fold) = approximately 1 in 500 patients per year

Of note, this rough calculation excludes some postmarketing cases reported only as "allergic reaction" or "anaphylactic reaction" without any other information (n= approximately 15), as well as those cases with information too sparse to ascribe an etiology.

Therefore, we remain very uncomfortable with the occurrence of severe immediate post-injection reactions to Aveed, of both respiratory and allergic etiology. We are deeply concerned by the occurrence of anaphylactic reactions to Aveed. The findings in the postmarketing safety updates show a serious risk.

> *The safety data presented in the next two sections (8.1.1 [Deaths and Serious Adverse Events] and 8.1.2 [Overall Adverse Events]) come from the pivotal U.S. trial IP157-001 (Parts A and C). The postmarketing safety data from the 11 additional postmarketing clinical studies, as well as data from spontaneously reported adverse events from periodic safety update reports, is presented in Section 8.1.3 (Postmarketing Safety Findings). The two sets of data are considered together in the final safety section of this memo (Section 8.1.4).*

8.1.1 Deaths and Serious Adverse Events

Deaths, Serious Adverse Events, and Discontinuations due to AEs in Study IP157-001 Part C

No subject died during the Part C study. Eight (6.2%) subjects experienced at least one SAE during the treatment period in Part C. No single SAE was reported in more than 1 subject. The SAE terms reported were: ischemic colitis, faecaloma, intervertebral disc protusion, wrist

fracture, worsening spinal column stenosis, myocardial infarction, deep vein thrombosis (DVT), and urinary tract infection/prostatitis. Only one of these was judged by the investigator to be at least possibly related to treatment (Patient 018-7078, DVT, possibly related).

One additional patient who participated in Part C had an SAE of prostate cancer reported on Day 196 of treatment (during Stage 2, the "long-term safety extension" of Part C). The investigator's judged this adverse event as "probably related" to treatment.

Study medication was permanently discontinued due to adverse events in five (3.8 %) patients in Part C for the following reasons: acne, mood swings, myocardial infarction, increased estradiol and DVT. There was no single event resulting in discontinuation that was reported in more than one subject during this study. Of these adverse events leading to discontinuation, all but myocardial infarction were judged by the investigator to be at least possibly related to study drug.

There was one patient in Part C who experienced an immediate post-injection reaction. Patient 050-7006, a 53 year old white male experienced a mild and non-serious "coughing fit" lasting approximately 10 minutes after his 3rd injection. The investigator reported that the patient's cough was non-productive, without wheezing and without difficulty breathing. No intervention was given and the patient recovered completely prior to leaving the office. That patient continued on-treatment without further cough events.

Deaths, Serious Adverse Events and Discontinuations due to AEs in Study IP157-001 Part A

There was 1 death reported in the Part A study. The cause of this patient's death was a homicide (by stabbing).

Eight (6.7%) subjects in the 750 mg group and ten (8.5%) subjects in the 1000 group experienced at least one SAE during the treatment period. Only two types of SAE were observed in more than 1 subject: atrial fibrillation in 2 subjects in the 750 mg group, and knee arthroplasty in 2 subjects in the 1000 mg group. No serious adverse events (SAEs) were judged by the investigator as being at least possibly related to study drug.

The SAE terms reported for the 750mg group were: atrial fibrillation [n=2], injury (stabbing), spinal stenosis, benign parathyroid tumor, congestive heart failure, tinnitus, acute pancreatitis, and sepsis. The SAE terms for the 1000mg group were: knee arthroplasty [n=2], spinal stenosis, arthritis, coronary artery disease, enterococcal bacteremia, malignant hepatic neoplasm, renal artery stenosis, viral gastroenteritis, prostatitis, cerebrovascular accident, and tendon rupture.

Study medication was permanently discontinued due to adverse events in 6 (5.0 %) patients in the 750 mg group and 4 (3.4 %) patients in the 1000 mg group. AEs judged by the investigator to be at least possibly related to study drug and leading to discontinuation were:

- Subject 027-4101 (TU 750 mg arm) - increased serum PSA.
- Subject 056-4077 (TU 1000 mg arm) - increased serum estradiol.

- Subject 040-4116 (TU 1000 mg arm) - increased red blood cell count.

The complete list of AE terms for the discontinuations reported for the 750mg group were: heat exhaustion, back pain, pain in extremity, PSA increased, prostatic intraepithelial neoplasia (PIN), and injury. The AE terms for the discontinuations for the 1000mg group were: estradiol increased, red blood cell count increased, hepatic neoplasm malignant, nasal congestion, and skin ulcer.

The reader is referred to the next section (8.1.2 Other Adverse Events) for discussion of "adverse events of interest", including tolerability of the injection, lipid profiles, erythropoiesis, aggression or depression, urinary symptoms, prostate health, and skin-related adverse reactions.

An Additional Clinical Trial Case of Injection-based POME

There was 1 patient in whom a serious "immediate post-injection reaction" was reported. This case occurred in a European supporting study (Patient #184 in Study 306605). This 54 year old male received his 10th injection of testosterone undecanoate on April 3, 2006 and shortly (1 minute) after the injection, the patient "experienced urge to cough associated with respiratory distress". Both symptoms lasted approximately 14-15 minutes. The event resolved without intervention and the subject continued in the study. The investigator and Sponsor both attributed the event to "pulmonary lipid (oil) microembolism" (POME) and cited the following possible reason: "either too fast administration of the study drug or accidental intravascular placement of the study drug."

8.1.2 Other Adverse Events

Overall Adverse Events

Overall Adverse Events in Adverse Events in Study IP157-001 Part C

In Part C, the most commonly reported adverse events, regardless of the investigator's judgment on relationship to treatment, were: acne, fatigue, cough, injection site pain, nasopharyngitis, pharyngolaryngeal pain, arthralgia, insomnia, prostatitis and sinusitis. The incidence rates are provided in Table 5 below.

The majority of reported adverse events were mild or moderate in severity; only 7 (5.4%) patients experienced at least one severe adverse event. No event was reported as severe by more than 1 patient. The complete list of severe AE terms were: DVT, aortic aneurysm, faecaloma, urinary tract infection/prostatitis, intervertebral disc protrusion, spinal stenosis, aortic aneurysm repair, and surgery.

Table 5. Incidence of All Adverse Events Regardless of Relationship to Study Medication, Reported in at Least 2.0% of Patients in Decreasing Frequency in study IP157-001 Part C

MedDRA Preferred term	Number of patients (%) TU 750 mg LOADING (N=130)
Total patients with at least 1 TEAE	70 (53.8)
Acne	6 (4.6)
Fatigue	6 (4.6)
Cough	4 (3.1)
Injection Site Pain	4 (3.1)
Nasopharyngitis	4 (3.1)
Pharyngolaryngeal Pain	4 (3.1)
Arthralgia	3 (2.3)
Insomnia	3 (2.3)
Prostatitis	3 (2.3)
Sinusitis	3 (2.3)

In Part C, approximately 24% of patient experienced at least 1 adverse event *judged by the investigator to be at least possibly related to treatment*. These events were generally consistent with the known adverse reactions to testosterone replacement therapy and events commonly reported in a testosterone replacement therapy population. These events included: acne (4.6%), fatigue (3.1%), injection site pain (3.1%), irritability (1.5%), hyperhidrosis (1.5%), hemoglobin increased (1.5%), estradiol increased (1.5%), insomnia (1.5%), mood swings (1.5%), aggression (1.5%), PSA increased (1.5%) and disturbance in attention (1.5%).

Overall Adverse Events in Adverse Events in Study IP157-001 Part A

In Part A, for the 750mg dose, the most commonly reported adverse events (≥ 2%), regardless of the investigator's judgment on relationship to treatment, were: fatigue, bronchitis, upper respiratory tract infection, nasopharyngitis, back pain, PSA increased, urinary tract infection, weight increased, hypertension, sinusitis, insomnia, nausea, and hypercholesterolemia.

In Part A, for the 1000mg dose, the most commonly reported adverse events (≥ 2%), regardless of the investigator's judgment on relationship to treatment, were: upper respiratory tract infection, diarrhea, pain in extremity, nasopharyngitis, hypertension, sinusitis, insomnia, headache, depression, weight increased, procedural pain, arthralgia, musculoskeletal pain, urinary tract infection, rash, pain, foot fracture, muscle strain, anxiety, nasal congestion, abdominal pain, constipation, vomiting, gout, benign prostatic hyperplasia, and cough.

The incidence rates for these AEs are provided in Table 6 below.

The majority of adverse events were judged by the investigator as mild or moderate in severity. Severe AEs were reported in 8.3% of 750 mg subjects and in 7.0% of 1000 mg patients. Atrial fibrillation was reported as a severe AE in 2 subjects in the TU 750 mg group; no other single event was reported as severe in more than 1 subject per treatment group. The other severe adverse events (regardless of investigator-attributed causality) were: cardiac

failure, coronary artery disease, chest discomfort, irritability, sudden hearing loss, and PSA increased.

In Part C, approximately 20% of patients in each treatment group experienced at least 1 adverse event *judged by the investigator to be at least possibly related to treatment*. These drug-related adverse events included:

> For the 750mg group: PSA increased (3.3%), insomnia (2.5%), fatigue (2.5%), injection site pain (1.7%), libido decreased (1.7%), hypercholesterolemia (1.7%), and benign prostatic hyperplasia (0.8%).
>
> For the 1000mg group: injection site pain (1.7%), benign prostatic hyperplasia (1.7%), blood cholesterol increases (1.7%), estradiol increased (1.7%), fatigue (0.9%), and insomnia (0.9%).

Table 6. Incidence of All Adverse Events Regardless of Relationship to Study Medication, Reported in at Least 2.0% of Patients in Either Treatment Group, by Preferred Term, in Decreasing Frequency in TU 1000 mg arm, from study IP157-001 Part A

MedDRA Preferred term	Number of patients (%)	
	TU 750 (N=120)	TU 1000 (N=117)
Total patients with at least 1 TEAE	70 (58.3)	73 (62.4)
Upper respiratory tract infection	5 (4.2)	5 (4.3)
Diarrhoea	2 (1.7)	5 (4.3)
Pain in extremity	2 (1.7)	4 (3.4)
Nasopharyngitis	5 (4.2)	4 (3.4)
Hypertension	3 (2.5)	4 (3.4)
Sinusitis	3 (2.5)	4 (3.4)
Insomnia	3 (2.5)	4 (3.4)
Headache	2 (1.7)	4 (3.4)
Depression	2 (1.7)	4 (3.4)
Weight increased	3 (2.5)	4 (3.4)
Procedural pain	0 (0.0)	3 (2.6)
Arthralgia	2 (1.7)	3 (2.6)
Musculoskeletal pain	1 (0.8)	3 (2.6)
Urinary tract infection	3 (2.5)	3 (2.6)
Rash	1 (0.8)	3 (2.6)
Pain	0 (0.0)	3 (2.6)
Foot fracture	0 (0.0)	3 (2.6)
Muscle strain	0 (0.0)	3 (2.6)
Anxiety	0 (0.0)	3 (2.6)
Nasal congestion	0 (0.0)	3 (2.6)
Abdominal pain	0 (0.0)	3 (2.6)
Constipation	0 (0.0)	3 (2.6)
Vomiting	1 (0.8)	3 (2.6)
Gout	0 (0.0)	3 (2.6)
Benign prostatic hyperplasia	2 (1.7)	3 (2.6)
Cough	1 (0.8)	3 (2.6)
Fatigue	7 (5.8)	2 (1.7)
Bronchitis	5 (4.2)	2 (1.7)
Back pain	4 (3.3)	2 (1.7)
Nausea	3 (2.5)	2 (1.7)
Prostatic specific antigen increased	4 (3.3)	1 (0.9)
Hypercholesterolaemia	3 (2.5)	1 (0.9)

Laboratory and vital signs data are discussed in the medical officer's review, and did not provide any signal of concern.

Adverse Events of Interest

"Adverse events of interest" in Part C included events related to endocrine disorders, injection site reactions, adverse lipid profiles, erythropoiesis, aggression or depression, urinary symptoms, prostate health, liver abnormalities, sleep apnea syndrome, cerebrovascular events and skin events. Such adverse events were reported in 28 subjects in Part C (21.5%) as shown in *Table 7* below.

Table 7. Adverse Events of Interest in Study IP157-001 Part C

Event Class	MedDRA System Organ Class	MedDRA Preferred term	Number of patients (%)
			TU 750 mg LOADING (N=130)
Total Patients With At Least One TEAE of Interest			28 (21.5)
Tolerability of Injection	General disorders and administration site conditions	Injection site irritation	2 (1.5)
		Injection site pain	4 (3.1)
		Injection site rash	2 (1.5)
Adverse Lipid Profiles	Investigations	Blood triglycerides increased	1 (0.8)
	Metabolism and Nutritional disorders	Hyperlipidemia	1 (0.8)
Erythropoiesis	Investigations	Haematocrit increased	1 (0.8)
		Haemoglobin increased	2 (1.5)
		Estradiol increased	2 (1.5)
Aggression or depression	Psychiatric disorders	Mood swings	2 (1.5)
		Aggression	2 (1.5)
Urinary Symptoms	Renal and urinary disorders	Urine flow decreased	1 (0.8)
		Nocturia	1 (0.8)
Prostate health	Investigations	Prostatic specific antigen increased	2 (1.5)
		Prostate examination abnormal	1 (0.8)
	Reproductive system and breast disorders	Prostatic intraepithelial neoplasia	1 (0.8)
		Prostatitis	3 (2.3)
		Paraesthesia of genital male	1 (0.8)
Skin	Skin and subcutaneous tissue disorders	Acne	6 (4.6)

"Adverse events of interest" in Part A were reported in 24 subjects treated with 750 mg (20%) and 30 subjects treated with 1000 mg (26%), as shown in *Table 8* below.

Table 8. Adverse Events of Interest in Study IP157-001 Part A

Event Class	MedDRA System Organ Class	MedDRA Preferred term	Number of patients (%)	
			TU 750 (N=120)	TU 1000 (N=117)
Total Patients With At Least One TEAE of Interest			**24 (20.0)**	**30 (25.6)**
Endocrine Disorder	Investigations	Oestradiol increased	0 (0.0)	2 (1.7)
		Glycosylated haemoglobin increased	0 (0.0)	1 (0.9)
	Metabolism and nutrition disorders	Diabetes mellitus	1 (0.8)	1 (0.9)
Tolerability of Injection	General disorders and administration site conditions	Injection site erythema	0 (0.0)	1 (0.9)
		Injection site irritation	0 (0.0)	1 (0.9)
		Injection site pruritus	1 (0.8)	1 (0.9)
		Injection site pain	2 (1.7)	2 (1.7)
		Injection site reaction	0 (0.0)	1 (0.9)
Adverse Lipid Profiles	Investigations	Blood triglycerides increased	1 (0.8)	2 (1.7)
		Blood triglycerides abnormal	0 (0.0)	1 (0.9)
		Blood cholesterol increased	0 (0.0)	2 (1.7)
		High density lipoprotein decreased	1 (0.8)	0 (0.0)
	Metabolism and Nutritional disorders	Hypercholesterolaemia	3 (2.5)	1 (0.9)
		Hyperlipidemia	1 (0.8)	1 (0.9)
Erythropoiesis	Investigations	Haematocrit increased	0 (0.0)	1 (0.9)
		Haemoglobin increased	0 (0.0)	1 (0.9)
		Red blood cell count increased	0 (0.0)	1 (0.9)
	Blood and lymphatic system disorders	Polycythaemia	1 (0.8)	1 (0.9)
Aggression or depression	Psychiatric disorders	Depression	2 (1.7)	4 (3.4)
Urinary Symptoms	Renal and urinary disorders	Pollakiuria	0 (0.0)	2 (1.7)
		Urinary hesitation	0 (0.0)	1 (0.9)
		Urinary retention	1 (0.8)	2 (1.7)
		Urine flow decreased	1 (0.8)	2 (1.7)
		Nocturia	0 (0.0)	1 (0.9)
		Dysuria	1 (0.8)	2 (1.7)
	Infections and infestations	Urinary tract infection	3 (2.5)	3 (2.6)
Prostate health	Investigations	Prostatic specific antigen increased	4 (3.3)	1 (0.9)
		Prostate examination abnormal	2 (1.7)	1 (0.9)
	Reproductive system and breast disorders	Benign prostatic hyperplasia	2 (1.7)	3 (2.6)
		Prostatic intraepithelial neoplasia	1 (0.8)	2 (1.7)
		Prostatitis	0 (0.0)	2 (1.7)
		Prostatic disorder	1 (0.8)	0 (0.0)
Liver Abnormalities	Neoplasms benign, malignant and unspecified	Hepatic neoplasm malignant	0 (0.0)	1 (0.9)
	Investigations	Aspartate aminotransferase increased	1 (0.8)	0 (0.0)
Cerebrovascular events	Nervous system disorders	Cerebrovascular accident	0 (0.0)	1 (0.9)

8.1.3 Postmarketing Safety Findings

As demonstrated in Section 8.1.1 and 8.1.2 of this memo, in the clinical trials from the Original NDA, including the U.S. Phase 3 study IP157-001, intramuscular testosterone undecanoate was associated with the expected adverse events and laboratory changes for an injectable testosterone replacement agent except for 2 reports of immediate, post-injection reactions. One of these was a serious adverse event (SAE), described as 14-15 minutes of respiratory distress, and one was not serious. Additional information on post-injection reactions was available from the worldwide postmarketing experience and we believe that this information is crucial to understanding the safety of intramuscular testosterone.

Immediate Post-Injection Reactions

Immediate Post-Injection Reactions in the Original NDA

As of the 120-Safety Update to the Original NDA submission, we were aware of a total of 10 spontaneously reported "immediate post-injection reaction" cases in the prior 11 months of worldwide postmarketing experience. These cases were documented in the Clinical Summary of Safety in the Original NDA and in the 120-Day Safety Update. Based upon concerns related to these 10 cases, the Division requested a summary document for all such cases from the entire postmarketing experience (form 2003 onward).

In response, the Sponsor summarized the totality of these events for the entire postmarketing experience in a Summary Report entitled, "*Immediate Post-Injection Reactions Suspect of Pulmonary Oil Microembolism*". The report detailed a total of 66 postmarketing cases of "immediate post-injection reaction" from the time of European approval in April 2004. The Sponsor noted that sales of the product in Europe occurred most heavily in the years 2006 and 2007.

Testosterone undecanoate has been approved in other parts of the world since 2004, using a dose of 1000mg, and a tradename of "Nebido". The dose proposed for U.S. approval is lower: 750mg, and the proposed tradename is "Aveed".

Of the total of 66 postmarketing reports of "post-injection reactions" for Nebido, 28 cases (42%) were reported as serious adverse events. Of those, the Division of Pulmonary and Allergy Products (DPAP) felt that four reflected systemic allergic phenomenon, including two which definitely met clinical criteria for anaphylactic reactions, and 2 which possibly met such criteria. For individual case narratives of those cases, the reader is referred to Section 11 of this memo, under the subheading, "*Division of Pulmonary and Allergy Products (DPAP)*"

Although there were no deaths reported amongst these 28 serious events (of 66 events in total), emergency medical care was provided or the patient was hospitalized in 18% of these cases (12/66).

The Clinical review team analyzed the 28 serious postmarketing adverse events in great detail. Of these cases, the following number of patients reported each of the following symptoms:

- Cough - 14 patients
- Dyspnea – 11 patients
- Symptoms related to the throat – 14 patients
    - *gagging, n=1*
    - *itching/tickle in throat, n=3*
    - *lump in throat, n=1*
    - *swollen throat, n=1*
    - *tightness in throat, n=2*
    - *swelling of neck, n=2*
    - *edema of the throat, larynx, or glottis, n=3*
    - *angioedema, n=1*
    - *laryngospasm, n=1*

- Cardiovascular symptoms -14 patients
    - *tachycardia/palpitations – 5 patients*
    - *dizziness/vertigo – 3 patients*
    - *flushing – 2 patients*
    - *increased blood pressure – 1 patient*
    - *hypotension – 1 patient*
    - *chest pain – 1 patient*
    - *"potential heart failure" – 1 patient*
- Paresthesias – 6 patients
    - *burning sensation in mouth, n=3*
    - *burning sensation in chest, n=2*
    - *tingling sensation in abdomen/hands/feet, n=1*
- Other allergic-type phenomenon – 5 patients
    - *rash, n=1*
    - *swelling around eyes, n=1*
    - *itching, n=1*
    - *bronchospasm, n=1*
    - *wheezing, n=1*
- Other constitutional symptoms – 10 patients
    - *headache, n=2*
    - *malaise, n=2*
    - *sweating, n=2*
    - *shivering/trembling, n=2*
    - *weakness, n=1*
    - *nausea, n=1*

In addition, there were 4 cases in which the patient was reported to have lost consciousness (fainting [n=1] or collapsing [n=3]). The patient who fainted lost consciousness for several minutes prior to recovering. All 3 patients who collapsed subsequently recovered, with one requiring hospitalization, and one requiring on-site, emergency treatment with epinephrine and oxygen.

Finally, there were 4 cases in which the patient was reported to have had respiratory distress: described as "respiratory distress" (n=1), "near respiratory arrest" (n=1), apnea "lasting 1-2 minutes" (n=1) and "20 minutes of" cyanosis (n=1).

These events were noted after the first injection of testosterone undecanoate (n=3), and also after subsequent injections:

- After 2nd injection, n=7
- After 3rd injection, n=3
- After 4th injection, n=1
- After 6th injection, n=1
- After 7th injection, n=1
- Dose number not listed, n=9.

Most of the events were reported to occur during the actual injection, or immediately thereafter, as follows:

- During injection , n=8
- Immediately after injection, n=4
- 15 - 30 seconds after injection, n=2
- 1 - 2 minutes after injection, n=1
- 3 minutes after injection, n=2
- Within minutes after injection, n=1
- Time not specified, n=6.

Finally, in most cases, patients' symptoms resolved within minutes of occurring, but not in all cases. Some patients reported coughing and having difficulty breathing for several hours, and a few reported their symptoms lasted for a few days.

The Clinical review team drafted narratives for 25 of the 28 serious cases and these narratives may be found in my Cross Discipline Team Leader's memo for the original NDA, and also in the Medical Officer's review of the Complete Response.

At the time of the Original NDA, the Sponsor had the following comments about these cases:

- They were all cases of pulmonary oil microembolism and none were allergic reactions
- They were all transient and resolved quickly
- Only 2 such cases had been reported in clinical trials, out of approximately 700 subjects.
- These cases had virtually all occurred at the 4mL dose, and lowering of the dose to 3mL was expected to reduce their already rare occurrence.
- Slow and careful injection would help avoid the occurrence of these events even further.
- The postmarketing incidence rate was low. According to the Sponsor, based solely on the number of Nebido units sold worldwide, the reporting of these "post-injection reactions" was 1 in 2,500 pt-years in 2006, and 1 in 3,300 pt-yrs in 2007.

Despite these arguments, the Division remained concerned by these events and took an Approvable action on the NDA, requesting additional information be submitted to resolve the concern.

Immediate Post-Injection Reactions in the Complete Response

Immediate Post-Injection Reactions in Controlled Trials

As previously noted, the Sponsor submitted results from 11 additional Phase IV clinical trials conducted outside the U.S. (n=2125 subjects). The Sponsor also submitted a Summary Report of these 11 trials, plus the original 6 trials. This totaled 17 clinical trials in 2834 subjects. The Clinical review team conducted a review of the Summary Report and of the 11 newly submitted studies, first to be assured that the studies had pre-defined protocols, procedures for capturing adverse events, and valid safety results, then to determine if any immediate post-injection reactions had been reported. The reader is referred to the Medical

Officer's review for brief summary reviews of each of these 11 studies. Some of these studies were conducted as postmarketing European surveillance studies in hypogonadal men, whereas others were conducted for different indications, including male contraception, treatment of obesity, treatment of paraplegia, and treatment of "andropause". All 17 studies are delineated in Table 9 below. The three largest of these studies are:

1) Study AWB 0105 Androgen Deficiency – Postmarketing Surveillance, n=870
2) Study 39732 (NE0601 IPASS) Hypogonadism – Postmarketing Surveillance, n=763
3) Study 42306 Male Contraception, n=298

The Medical Officer's individual reviews of the 11 submitted studies reveal that they were of generally acceptable quality for our purpose. The studies showed the expected adverse reactions for an androgen replacement product (e.g., increased serum PSA, worsening BPH, weight gain, edema, change in lipid profiles, acne, breast pain, sweating, depression, etc) and expected adverse reactions for an injection (e.g., injection site reactions). According to Sponsor, there were no new cases of immediate post-injection reaction. Thus, the Sponsor concluded that the incidence of serious POME reactions is 1 in 2,834 patients or 0.035%, and the incidence of anaphylactic reactions in 0%.

Table 9. Tabular Overview of Clinical Studies of Testosterone Undecanoate, Number of Patients Treated and Number of Injections (Total Patient Sample).

Patient Type	Study Number and Indication	Number Patients Treated		Number of Injections		Study Status	Contained in Original NDA (or Subsequent Amendments) or New in This Current Amendment
		750 mg	1000 mg	750 mg	1000 mg		
Patients	JPH01495 Hypogonadism	0	14	0	14	Completed	NDA
	JPH04995 Hypogonadism	0	14	0	152	Completed	NDA
	ME98096 Hypogonadism	0	26	0	300	Completed	NDA
	ME97029 Hypogonadism	0	36	0	640	Completed	NDA
	306605 Hypogonadism	0	95	0	1126	Completed	NDA
	IP157-001 Hypogonadism (US Study)	295	229	2409	1820	On-going	NDA
	AWB 0105 Androgen Deficiency - Post-marketing Surveillance	0	870	0	4990	Completed	New
	39732 (NE0601 IPASS) Hypogonadism - Post-marketing Surveillance	0	763	0	2815	On-going	New
	TG09 - Visceral Obesity - Post-marketing Surveillance	0	29	0	118	On-going	New
	303934 Male Andropause	0	15	0	15	Completed	New
	NB02 - Paraplegia - Post-marketing Surveillance	0	19	0	39	On-going	New
	Czech NEO Hypogonadism - Post-marketing Surveillance	0	23	0	92	On-going	New
	Total Hypogonadal Studies	**295**	**2133**	**2409**	**12121**		
Healthy Subjects	97028 Male contraception	0	28	0	112	Completed	New
	97173 Male contraception	0	24	0	139	Completed	New
	98016 Male contraception	0	14	0	56	Completed	New
	99015 Male contraception	0	42	0	166	Completed	New
	42306 Male contraception	198	100	816	372	Completed	New
	Total Eugonadal Studies	**198**	**208**	**816**	**845**		
TOTAL BY DOSE		**493**	**2341**	**3225**	**12966**		
TOTAL POOLED		**2834**		**16191**			

Reference: Section 7, Table 2.0.0 and 2.0.1

Data for on-going studies are locked through November 15, 2008; however, in some cases, data beyond November 15th have been included, where available.

On-going studies include those studies in which patients are undergoing continued treatment with Nebido or in which the data processing has not yet been completed. Data for on-going studies were cleaned and locked for purposes of this NDA amendment.

However, the Clinical review team does not agree with the Sponsor's conclusion about the results from these 17 clinical studies in regard to post-injection reactions. We detected 6 additional cases of interest from clinical trials. However, information from these cases is too sparse to ascribe a specific etiology to the event, but they were all immediate post-injection

reactions. The Clinical review team believes that the former 3 events have a greater chance of being serious POME or systemic allergic reactions compared to the latter 3, but all 6 are notable. The former 3 cases are:

- Patient #11 in Study 97173 (convulsions)
- Patient #17 in Study 97173 (collapse),
- Patient #4 in Study JPH04995 (circulatory collapse)

If just these 3 cases were added to the numerator, this would markedly change the incidence of immediate post-injection reactions in clinical trials: 4 events /2834 subjects (0.14%). The latter three cases are:

- Patient #025-4187 in Study IP157-001 Part A (pre-syncope)
- Patient #26 in Study 97029 (syncope)
- Patient #35 in Study 97029 (circulatory collapse).

In our opinion, whether the number of cases of severe post-injection reactions in clinical trials is 1, 2, 5 or 8 is not as critical as the information gleaned from the spontaneously reported postmarketing adverse events provide in the PSURs and Safety Updates. In this situation, we find the post-marketing experience to be more important than the incidence of these events in clinical trials because the cases offer greater information for risk assessment. From our review of the post-marketing safety updates, we have detected a total of 116 cases, with a total of 52 new cases in the Complete Response. These are described in the next section.

Immediate Post-Injection Reactions in Safety Updates

In regard to the Safety Updates submitted in the Complete Response, the Sponsor (Endo) has stated that there were "*no new findings*" in the two new Safety Updates; these are:

- The Bayer/Schering PSUR for the time period November 25, 2007 to November 24, 2008 PSUR, and
- The Final Safety Update provided by Endo on August 31, 2009 and containing postmarketing data from November 25, 2008 to August 29, 2009.

In fact, the Clinical review detected 52 new cases of immediate post-injection reactions in these 2 Safety Updates. Of these, almost all are severe, and we believe that approximately 20 reflect anaphylactic reactions. We note that throat-related symptoms are prominent in these 2 Safety Updates (throat closing, throat tightness, throat tickling, throat fullness) and we believe that these symptoms reflect post-injection angioedema, not POME. Case narratives are provided for all 52 cases:

From the November 25, 2007 - November 24, 2008 Bayer PSUR. As derived from listings in Attachment A to Appendix 8 (n=31)

1. 2008 15625 LA- 60 y/o, reported as "anaphylactic reaction" immediately after injection (cough, throat itching, glottis spasm, glottis edema).

2. 2008 18230 LA- 58 y/o, reported as "anaphylactic reaction" within 24 hours of dose. No further information.

3. 200828604 GPV- 41 y/o with Klinefelter's, reported as "anaphylactic reaction" during injection (feeling of tightness in region of thorax, burning eyes, flushing, tingling sensation in lungs ascending to nose, dry cough). Allergy testing planned.

4. 2008 12947 GPV- 38 y/o with acute lymphoblastic leukemia, status post radiotherapy, with two episodes. 1st episode reported as "mild allergic reaction" after first dose. 2nd episode 6 months later reported as "severe allergic reaction/potential heart failure" (severe throat swelling)

5. DE 2005008181- 67 y/o obese patient, "deep IM injection may have been diffcult", reported as "allergic reaction" (circulatory collapse, hypotension, nausea, retching, "fever attacks").

6. DE 2004037302- 38 y/o, reported as "allergic reaction" 2 minutes after injection (hyperventilation during injection, red face, shivers, tachycardia, hypertension, feeling heat in thighs and upper arms, "indisposition").

7. DE 2005008140- 56 y/o, reported as "allergic reaction" immediately after removal of needle (immediate ticking of throat, allergic reaction).

8. DE 2005 008146- 57 y/o, reported as "allergic reaction" (headache, temporary visual field defect, injection site hemorrhage).

9. DE 2005008154- 65 y/o, reported as "allergic reaction" ("pressing complaints after injection", "allergic reaction", injection site discomfort).

10. DE 2005008161- 70 y/o, reported as "allergic reaction" ("sensitive skin reaction", "allergic reaction").

11. DE 2005 008193- 69 y/o, reported as "allergic reaction" (headaches, hot head, pain at injection site, "allergic reaction").

12. DE 2005008199- 68 y/o, reported as "allergic reaction" ("short term cough with allergic sound"). Pt of opinion that it is more likely due to alcohol of disinfection than the injection.

13. NO 2007 008557- age not specified, reported as "hypersensitivity" (dry cough, itching, tingling sensation). No further information.

14. NO 2007 008581- age not specified, reported as "hypersensitivity" (itching all over).

15. DE 2005014372- age not specified, reported as "edema attributed to allergic reaction". No further information.

16. DE 2007 004748- age not specified, reported as "suspicion of allergic event" (urge to cough, dyspnea).

17. DE 2006 009799- age not specified, reported as "suspected allergic reaction, no local symptoms" shortly after injection (dyspnea, cold sweat).

18. 200821776 GPV- 33 y/o with nonseminoma testicular cancer, status-post unilateral orchiectomy, radiotherapy to remaining testicle reported as "allergic reaction" directly after injection (breathing problems, cough, felt bad, BP increased to 147/89).

19. 2008 13805 LA- 53 y/o with three episodes, including injection site pain, injection site mass, injection site warmth, injection site pruritis after first 2 injections. After 3rd injection, injection site, pain, warmth and pruritis, dry throat, sinusitis, nocturnal dyspnea, breathlessness at night, and increased blood pressure.

20. BR 2006019257- age not specified, reported as "allergic reaction". No further information.

21. 2007 11462 BNE- 44 y/o with cough, shortness of breath and flushing immediately after injection.

22. AT 2006 001317- 64 y/o with severe hot flush, dyspnea, anxiety, tachycardia(>109 bpm), fatigue, depression and sleep disorder after 2nd injection.

23. SE 2007 002541- age not specified, with cough, redness of face, feeling warm over chest and head. No further information provided.

24. SE 2006 039053- age not specified, with palpitations, rash, whole body itching, trembling, erection failure, intensive migraine for 1st week, and weight gain.

25. SE 2007002515- age not specified, with urticaria over whole body, itching. Other suspected drug: Plavix (clopidrogel sulfate).

26. CH 2005002386- 33 y/o, with patchy reddening of the whole integument and mild pruritis after 1st injection. Rash abated immediately with cortisone injection.

27. FR 2007035024- age not specified, with redness on face and chest, and pruritis on face and chest after 1st injection. No further information.

28. 2008 16799 GPV age not specified, with nervousness, hot flushes, sweats, rash around neck, unusual head hair, excessive hair growth, headache, difficulty sleeping, rosacea, slight depression and no sex drive 1 week after 1st dose.

29. 2008 15181 GPV- 52 y/o, reported as "assumed microfat embolization" (severe dyspnea, heat sensation in neck, muscle twitching, ticking in throat, loss of consciousness). CT scan: no pathological findings, no infarction, no bleeding.

30. 2008 19576 LA- age not specified, with sweating, cough, face redness, and dizziness during injection. No further information.

31. 2008 12881 BNE- 27 y/o with Noonan syndrome, primary testicular failure, asthma, with cough, flushing, wheezing and bronchopasm immediately after 2nd injection. Recovered after salbutamol nebulizer.

From the November 25, 2007 - November 24, 2008 Bayer PSUR. As derived from the body and line listings of the PSUR (n=12)

1. 2008 11461 BNE- 55 y/o history of hypopituitarism, with sharp increase in BP ('soared to 275/175"), heavy sweating, metallic taste in mouth, "burning up" sensation immediately after 3rd injection.

2. 2008 20307 GPV- 72 y/o with cyanosis, coughing continuously, dizziness, numbness of face, immediately after 4th injection.

3. 2008 21519 GPV- 21 y/o with sudden chest pain radiating towards neck and throat, light cough, and cold sweating.

4. 2008 26527 GPV- 72 y/o with severe coughing, temporary palsy of mouth and face, facial dysesthesia, and choking fit during injection.

5. 2008 26556 GPV- 76 y/o reported as POME (severe coughing, dyspnea, choking fit) during injection. Stated similar reaction previously.

6. 2008 11355 GPV- 30 y/o with dry cough episode, severe burning in throat, scratching in throat, moderate dyspnea, and sensation of heat.

7. 2008 l2136 GPV- 40 y/o with cough, sweating, dizziness and prickly feeling in fingers and toes after each of 2 injection.

8. 200825110 GPV- 21 y/o with chest pain, cold sweat, pain in throat and chest treated with adrenaline and betamethasone.

9. 200821057 GPV- 50 y/o with rash on whole body 3 days after injection. Treated with antihistamine and recovered.

10. 2008 22564 GPV- 30 y/o with urticaria at an unknown time after injection. Treated with antihistamine and not recovered. Also using Testogel.

11.2008 12867 LA- 22 y/o with red eyes, cough, malaise, and diarrhea 24 hours after injection. Previously using Durateston.

12. 2008 19842 GPV- age not specified, with pituitary hypogonadism, with sweating, light fall in BP, and "severe reaction" at unown time after injection.

From the Final Safety Update from Endo submitted on August 29, 2009, for the time period covering November 25, 2008 - August 29, 2009 (n=9)

1. 2009 10048 BNE - 39 y/o with Klinefelter's, reported as "anaphylactic shock" 16 months after starting treatment.

2. 2009 10221 BNE - 44 y/o with high prolactin, reported chest tightness, throat tightness, cough and sweatiness on same day as 1st dose.

3. 2009 12293 BNE - 53 y/o with 2 episodes. First episode reported as "mild anaphylactic shock" (couldn't breath very well, burning in throat, flushing). Second episode reported as "anaphylactic shock" (tight burning throat, shortness of breath, sweaty, red face, pulse rate thready and irregular).

4. 2009 12294 BNE - 32 y/o, reported as "anaphylactic shock" (felt odd, tightening of throat, shortness of breath, bronchospasm, flushing, panic attack). Additional injections without subsequent reaction

5. 2009 16799 LA - age not specified, reported as "possible anaphylactic reaction" (skin rash, breathing difficulty) immediately after injection.

6. 2009 19013 LA - 75 y/o reported burning sensation on skin, body formication, hot feeling on body, bad taste in mouth, malaise few minutes after injection.

7. 2009 19765 LA - 33 y/o with benign pituitary tumor, reported as "allergic reaction" (difficulty breathing, cyanosis, crying, cough, vomiting) acutely after 1st injection. Fever later that day.

8. 200924735 GPV - 22 y/o with Klinefelter's, with dyspnea, feeling scared, swollen mouth and throat, shivering in whole body during injection. Received injection from sister-in-law, a nurse, in apartment.

9. 2009 12132 GPV - 62 y/o from Australia, with burning, acid taste in mouth ("like cloves"), hacking cough, "fur ball in throat", burning in mouth, and seating 60 seconds into injection.

Dr. Handelsman and I reviewed each of these new 52 cases. We find that approximately 20 of these cases either possibly or definitely reflect anaphylaxis. This is consistent with the opinion of our consultants from the Division of Pulmonary and Allergy Products (see Section 11 below). We find that throat-related symptoms are prominent in this cohort (throat closing, throat tightening, throat fullness, throat tickling) and that these throat-related symptoms probably reflect angioedema, a serious concern. We note that Bayer/ Schering also believes that some of these cases (n=6) meet some published criteria for anaphylactic reactions, as

Bayer stated in their November 25, 2007 - November 24, 2008 PSUR, in an Appendix document ("Appendix 8") requested by a European regulatory authority and entitled "*Nebido & Anaphylaxis Reactions*". We find that the most recent Safety Update includes 9 serious immediate post-injection reactions, and we believe that most of these, perhaps all, reflect anaphylactic reactions. In contrast, the reader should be aware that the Sponsor has previously stated that none of these 52 cases meet clinical criteria for anaphylaxis and that all of the cases in the Final Safety Update are due to POME, rather than anaphylaxis. The Sponsor has subsequently acknowledged Bayer's contention that 6 of the cases in the Appendix 8 document may have some clinical criteria for anaphylaxis.

Finally, on September 21, 2009, the Sponsor submitted a spontaneously reported adverse event report of a 16 year old male (2009 32012 GPV) with testicular agenesis who experienced an "anaphylactic reaction", described as itching of the palms, groins, and feet, widespread urticaria, tightening of the throat, angioedema of the lips and face, shortness of breath, constriction of the chest, cough, dizziness, and hypotension less than 3 minutes after the 3rd dose. He received adrenaline, antihistamines, oxygen, steroid, and IV fluids and recovered. He was referred to an allergist who conducted skin testing showing "a very positive reaction to the product."

The reader should note that the Sponsor's position on this case was that it was the first instance of true anaphylaxis, the only case to be "*ruled in*". The Sponsor's position was that the 6 cases noted by Bayer to possibly be anaphylactic reactions "*had significant limitations in ascribing the signs and symptoms as anaphylaxis.*"

The reader should further be aware that a draft consult from Drs. Wu and Durmowicz of the Division of Pulmonary and Allergy Products found that 20 of these 52 cases were possibly (n=9) or definitely (n=11) anaphylactic reactions, while another 4 were allergic reactions. DPAP noted the following cases as either qualifying as anaphylaxis, or as "possibly" qualifying:

- Case 2009 32012 GPV – qualifies as anaphylaxis
- Case 2009 12293 BNE – qualifies as definite anaphylaxis
- Case 2009 12294 BNE – qualifies as anaphylaxis
- Case 2009 16799 LA – qualifies as anaphylaxis
- Case 2009 24735 GPV – qualifies as anaphylaxis
- Case 2008 12881 BNE – qualifies as anaphylaxis
- Case DE 2004 037302 – a case of anaphylaxis
- Case 2008 15625 LA – qualifies as possible anaphylaxis
- Case 2009 10048 BNE – submitted as life-threatening anaphylactic shock
- Case 2008 18230 LA – physician felt it to be an anaphylactic reaction
- Case 2008 15151 GPV – a case of possible anaphylaxis
- Case 2009 19765 LA – a case of possible anaphylaxis
- Case 2008 28604 GPV – qualifies as possible anaphylaxis
- Case 2009 10221 BNE – a possible case of anaphylaxis
- Case 2009 12132 GPV – a case of possible anaphylaxis

- Case 2008 12947 GPV – a possible case of anaphylaxis
- Case DE 2005 008181 – suggestive of some type of systemic allergic reaction
- Case 2008 19576 LA – a case of possible anaphylaxis
- Case 2008 11355 GPV – qualifies as possible anaphylaxis

DPAP found the following cases to be "allergic reactions":

- Case 2009 19103 LA – likely allergic in nature
- Case DE 2005 008140 – likely allergic in nature
- Case 2007 002541 – symptoms appear to be allergic in nature
- Case 2008 11461 BNE – (symptoms) point to an allergic etiology

The reader should also be aware that outside allergy consults were obtained from Drs. James T.C. Li, the Chair of the Division of Allergic Disease in the Department of Internal Medicine at the Mayo Clinic in Rochester, Minnesota and Dr. Thomas Platts-Mills, Division Head, Division of Allergy and Clinical Immunology at the University of Virginia Health Center in Charlottesville, Virginia.

Dr. Li found many of these cases to be either "probably" anaphylaxis or "possibly" anaphylaxis, as follows:

- Case 2009 32012 GPV – probable anaphylaxis
- Case 2008 15625 LA – probable anaphylaxis
- Case 2008 15181 GPV – probable anaphylaxis
- Case 2009 10048 BNE – possible anaphylaxis
- Case 2009 12293 BNE – possible anaphylaxis
- Case 2009 12294 BNE – possible anaphylaxis
- Case 2009 16799 LA – possible anaphylaxis
- Case 2009 19013 LA – possible anaphylaxis
- Case 2009 19765 LA – possible anaphylaxis
- Case 2009 2475 GPV – possible anaphylaxis
- Case 2008 18230 LA – possible anaphylaxis
- Case 2008 28604 GPV – possible anaphylaxis
- Case 2008 21776 GPV – possible anaphylaxis
- Case 2008 15181 GPV – possible anaphylaxis

Dr. Li further noted that shin flushing, throat tickling, or throat tightness can be symptoms of a systemic allergic reaction. He noted that pruritis, flushing, rash or urticaria, hypotension, wheezing, angiodema, are more characteristic of anaphylaxis. He noted that throat symptoms would seem to suggest an allergic reaction rather than POME. He stated:

> "*For the cases of probable or possible anaphylaxis (noted above), as well as for some additional case, I would not be comfortable attributing the adverse events to POME.*"

Dr. Platts-Mills felt that fewer cases were anaphylaxis (n=3), but he was using a categorization that required rapid onset and two of the following: a) skin itching and hives b) airway obstruction or c) fall in pressure. Most patient did not have skin itching and hives,

although many had throat-related symptoms believed to reflect angioedema. Without clear description of hives, Dr. Platts-Mills did not a categorize a case as anaphylaxis. Nonetheless, Dr. Platts-Mills did remind the reader that these cases were quite severe, including collapse, with apnea, severe chest pain, coughing sufficient to put patients in the intensive care unit, etc.

8.1.4 Overall Assessment of Safety Findings

My overall assessment of these safety findings is that intramuscular testosterone is associated with severe immediate post-injection reactions, which appear to be both anaphylactic reactions and pulmonary oil microembolism reactions. I am concerned largely by the immediacy and severity of these reactions, and particularly concerned about the anaphylactic reactions and by the throat-related symptomatology which I believe reflects angioedema. This is not to state that serious POME reactions aren't concerning or severe, but rather to point out my particular concerns relative to systemic allergic reaction. While only a handful of post-injection reactions were reported in clinical trials (as few as 2, or as many as 8 cases), the number of cases in the postmarketing period (n=116), their severity, and the number of cases of anaphylaxis is concerning. The characteristics of these post-injection reactions, with sudden difficulty breathing, throat tightening/fullness, cough, flushing, and cardiovascular, allergic and constitutional symptoms are quite impressive. Respiratory distress and cardiovascular collapse with loss of consciousness have been reported. Many patients have been resuscitated as for a catastrophic event, and as for anaphylaxis.

Aside from the severe post-injection reaction, the remainder of the safety results from clinical trials of testosterone undecanoate injection revealed the expected adverse reactions associated with the pharmacological action of testosterone (e.g., increased serum PSA, worsening BPH, weight gain, edema, change in lipid profiles, acne, breast pain, sweating, depression, etc) and expected adverse reactions for an injection (e.g., injection site reactions)

Overall, the safety data I have reviewed is not consistent with a safe product for testosterone replacement therapy.

9. Advisory Committee Meeting

An Advisory Committee was not held for this application.

However, the Division did request outside consultations from two members of the Pulmonary and Allergy Products Advisory Committee. These were Drs. James T.C. Li., Chair of the Division of Allergic Diseases in the Department of Internal Medicine at the Mayo Clinic, and Dr. Thomas Platts-Mills, Division Head, Division of Allergy and Clinical Immunology at the University of Virginia Health System. Both of these senior allergists provided consultative reports concerning the 116 post-injection reactions reported in the postmarketing period.

Dr. Li's Report

In Dr. Li's report of November 19, 2009, he suspected at least 4 of the cases to be probable anaphylaxis and another 22 cases to be possible anaphylaxis. Of the 26 cases of possible or probable anaphylaxis, Dr. Li categorized 14 of them as coming from the Complete Response bundle (n=52 total) and 12 of them coming from the Original NDA (n=66 total). He classified

almost all the cases in the Final Safety Update as possible anaphylaxis. His comments are considered critical to understanding the risks of the product, and they include:

- Skin flushing, throat tickling or tightness (*as noted in these cases*) can be symptoms of a systemic allergic reaction. These symptoms are fairly common in patients experiencing systemic reactions ("anaphylaxis") to allergen immunotherapy injections and food.

- Allergic reactions and POME may have some elements in common, such as development of symptoms immediately after exposure, cough and shortness of breath. (However) Isolated cough may be more suggestive of POME. Pruritus, flushing, rash or urticaria, hypotension, wheezing, angioedema, are more characteristic of anaphylaxis. Throat symptoms would seem to suggest an allergic reaction rather than POME.

- I have no information on benzyl benzoate as an agent that can cause anaphylaxis. It is possible that benzyl benzoate could be a cause of contact dermatitis.

- Plant oils per se are not common causes of anaphylaxis. However, as a plant-derived product, castor bean oil could theoretically contain toxins, allergenic proteins or contaminants. Castor bean protein and pollen can be highly allergenic.

- Several of the cases resulted in epinephrine administration, emergency department visits or brief hospitalizations, or were characterized as life-threatening.

- For the cases of "probable" and "possible" anaphylaxis noted above, as well as for some additional cases, I would not be comfortable attributing the adverse events to POME.

- A handful of cases seem consistent with anaphylaxis (immediate development of symptoms, shortness of breath, flushing or urticaria, upper airway obstruction and/or hypotension) treated with epinephrine. Other cases are suggestive, but are milder or self-limited. Known systemic reactions ("anaphylaxis") to insect stings, food and allergen immunotherapy injections do vary in severity. Some are life-threatening, but others can resolve without treatment. There seems to be some risk of allergic-type reactions to this product distinct from POME.

Overall, I find that Dr. Li's report confirms my concerns regarding the risks of intramuscular testosterone undecanoate. Many of the cases are possible or probable anaphylaxis. The events are severe. Both excipients, but perhaps more likely castor oil, can be causative in allergic reactions. Allergic reactions appear to be associated with the product, distinct from POME.

Dr. Platts-Mills Report

Dr. Platts-Mills report of November 16, 2009 states that he found only 3 cases that he would regard as anaphylaxis. It is notable that Dr. Platts-Mills used a fairly rigid criterion: rapid onset of at least two of the following:

- Skin itching and hives
- Airway obstruction
- Fall in blood pressure.

The cases he notes to be anaphylaxis are: 2009 32012 GPV and SE 2007 002515 (from the Complete Response) and Case GB-2007-023826 (from the Original NDA).

It is clear that the occurrence of "hives" is crucial to Dr. Platts-Mills definition of anaphylaxis. He does note, however, that cases where itching and cough, or throat tightening and cough, were reported cannot be strictly "ruled out".

Dr. Platts-Mills notes that the "*…consistency of the reports is remarkable, with tickling of the throat, urge to cough, and dyspnea in a large majority of the cases. Furthermore these responses are rapid. Indeed, the speed of these responses is reminiscent of the reactions to intramuscular immunoglobulin and also those to IV contrast media.*" Dr. Platts-Mills notes that, "*Classical IgE mediated anaphylaxis to venom, penicillin, food, or allergy shots is slower than this*."

Although Dr. Platts-Mills categorizes just a few cases as anaphylaxis, he does note the following:

> *"Please don't take my opinion that these cases are not anaphylactic as arguing that they are not severe. There are multiple descriptions here that are very severe including collapse, with apnea, severe chest pain, coughing sufficient to put patients in the intensive care unit, etc. I am assuming that no patient is known to have died during or rapidly following one of these injections."*

Dr. Platts-Mills makes a few other comments and provides some insights:

- There is no doubt that skin flushing and throat tightening can occur in anaphylaxis, but skin flushing in particular is not diagnostic.
- Throat tightening is a highly subjective symptom and Dr. Platts-Mills did not identify any reports where objective evidence for "throat tightening" was provided.
- In these cases, there seems to be a random distribution of first case reactions, and reactions occurring after several previous injections. There is not a consistent pattern that this drug needs repeated exposure for sensitization or that the reactions reflect pre-sensitization.
- The speed of these reactions is remarkable and could be taken as an argument against an anaphylactic reaction.
- Judging severity by either need for urgent treatment or by the decision to stop treatment with testosterone undeconate it is clear that these reactions were almost all severe.

I take from Dr. Platts-Mills report that the cases were severe and that he believes that few can be assuredly stated to be anaphylactic reactions. He notes that they are rapid in occurrence. His request for "objective evidence" for throat tightening seems curious to me, and indeed many practitioners would be reluctant to conduct an endoscopic exam of the larynx during or shortly after one of these events. I find the throat-related symptoms to be very concerning and I am somewhat at a loss to explain Dr. Platts-Mills need for "objective evidence" in a patient who is complaining of throat closing and throat tightening. It also seems clear that Dr. Platts-Mills definition of anphylaxis requires the presence of hives. Based on the recent literature and following discussions between DPAP and DRUP, it is my understanding that that skin or mucosal findings (coupled with either significant airway or cardiovascular compromise) can and do reflect anaphylaxis. It appears to me that Dr. Platts-Mills reluctance to accept generalized flushing or throat tightening/throat closing as the skin or mucosal signs of anaphylaxis precluded his categorizing more cases as anaphylaxis.

10. Pediatrics

The Applicant requested a full waiver of the requirement to conduct assessments in pediatric patients. The Sponsor stated that it is not likely to be used in a substantial number of pediatric patients. On April 29, 2009, the Division recommended to the Pediatric Review Committee (PeRC) that the Sponsor's request be granted. The PeRC agreed with the request but asked that the Sponsor confirm that it does not intend to apply for pediatric exclusivity in future submissions. On June 15, 2009, the Sponsor submitted a formal letter confirming that they had no intent to seek pediatric exclusivity. On July 2, 2009, George Greely of the Pediatric and Maternal Health Staff provided an eMAIL to DRUP stating:

> "*The Aveed (testosterone undecanoate) full waiver was reviewed by the PeRC PREA Subcommittee on April 29, 2009. The Division recommended a full waiver because too few children with the disease/condition to study. The PeRC agreed with the Division to grant a full waiver for this product.*"

11. Other Relevant Regulatory Issues

Division of Drug Advertising, Marketing and Communication (DDMAC)

A consultation regarding labeling for the new indication was requested and completed by DDMAC. In her final consult report dated July 15, 2009, Janice Maniwang provided comments on various sections of the label, including Warnings and Precautions (Section 5), Adverse Reactions (Section 6), Labor and Delivery (Section 8), Clinical Pharmacology (Section 12), and Information for Patients (Section 14). Comments were also provided on the original Patient Package Insert, although the Patient Package Insert was subsequently withdrawn and replaced with a Medication Guide.

Although I do not recommend approval at this time, nor do I recommend continued labeling discussions, it should be noted that each of the DDMAC comments was considered. During this review, the team did engage in discussions with Sponsor relevant to labeling and whatever DDMAC comments appeared appropriate and useful were conveyed to Sponsor. Only several

were not instituted, and these would require changes to the drug class. I advise that labeling discussions only be taken up again if the risk/benefit profile becomes acceptable for approval.

Division of Scientific Investigation (DSI)

Site inspections by the Division of Scientific Investigation were not requested. Clinical site inspections were not required as this was not a new molecular entity and the primary endpoint was a strict laboratory value (testosterone concentrations), not liable to subjective bias. Further, the Office of Clinical Pharmacology found that the assay methodology for measurement of testosterone was valid. In addition, no sites appeared unusual in terms of efficacy or adverse event reporting.

Financial Disclosure

All of the clinical investigators in the United States pivotal Phase 3 Study IP157-001 (42 out of 42 investigators at the U.S. clinical sites [only 31 sites actually enrolled subjects]) responded to request for financial disclosure and none had any relevant financial disclosure information to declare. There were no investigators with a proprietary interest in the product and none with significant equity in the Sponsor as defined in 21 CFR 54.2 (b). No investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(b).

Office of Surveillance and Epidemiology: Division of Risk Management (DRISK)

DRISK provided input during the review process relative to a Medication Guide and a REMS. While I currently do not agree that any prescriber or patient labeling or REMS is adequate to remedy the underlying risk/benefit problem, the reader should be aware that both items were reviewed during this second cycle.

In this regard, the reader should be aware that all DRISK comments concerning the Medication Guide were incorporated into a final document. I recommend that discussions of this Medication Guide only resume when the risk/benefit profile is deemed clinically acceptable.

In regard to the Risk Evaluation and Mitigation Strategy (REMS), DRISK was involved in its review. The REMS consisted simply of the Medication Guide, a Dear HCP communication to prescribers, and a timetable for assessments. A video education piece and prescriber brochure had been proposed by Sponsor, but these were later removed at the recommendation of DRISK. The video and brochure dealt with intramuscular injection technique and DRISK believed that this was adequately described in the prescriber labeling and generally well known to clinical practitioners.

It is notable that on August 28, 2009, Carolyn Yancey and Claudia Karwoski of DRISK conveyed a final review of the Aveed REMS. They stated:

> "*The AVEED REMS (received August 24, 2009) contains the agreed upon REMS components which include a Medication Guide, Communication Plan, and a Timetable for Submission of Assessments. The REMS Supporting Document outlines the*

information that the applicant will employ with HCP and patients to assess the effectiveness in achieving the specific goals.

The applicant incorporated the OSE/DRISK recommendations and revisions communicated in our Interim Comments (dated August 4, 2009). The AVEED REMS (received August 24, 2009) is acceptable to OSE/DRISK and would appropriately mitigate, to the extent possible, the risks of an injection-based pulmonary oil reaction (POME) event and assure appropriate recognition and treatment of a potentially serious anaphylactic reaction."

The reader should understand that this recommendation was made prior to the submission of the Final Safety Update on August 29, 2009, which showed 9 severe post-injection reactions, all suspicious for anaphylactic reaction. This recommendation also precedes the Division's and DPAP's more detailed review of all postmarketing cases, which showed a significant number of anaphylactic reactions, which confirmed suspicions of angioedema, and which highlighted the severe risk of the post-injection reactions.

Therefore, I continue to believe that the Medication Guide and REMS (consisting of the Medication Guide itself, a Dear HCP letter, and a timetable for assessments) do not remedy nor mitigate the underlying problem of excessive risk of the product relative to benefit. I advise that any additional discussions of a REMS for this product be postponed until the risk /benefit profile is clinically favorable.

Office of Surveillance and Epidemiology: Division of Medication Error Prevention and Analysis (DMEPA)

During both review cycles, DMEPA provided input on 1) the tradename, and 2) the container/carton and the Full Prescribing Information (FPI) and Medication Guide labeling, with regard to potential medication errors.

In regard to the tradename, DDMAC objected to the tradename (b) (4) In this regard, on January 7, 2008, Amy Toscano of DDMAC wrote:

(b) (4)

In response to this concern raised by DDAMC, on May 5, 2009, DRUP conveyed a regulatory letter to Sponsor concluding that the tradename (b) (4) was unacceptable. The letter noted that the re-submission included a "back-up" tradename, Aveed, and if the Sponsor would like to seek approval of the tradename "Aveed", then they would need to submit a new request for proprietary tradename review. On May 12, 2009, Sponsor submitted a new request for review of the tradename, Aveed.

On July 29, 2009, in their final consult report, Carlos Mena-Grillasca, Denise Toyer and Carol Holquist, provided the following final recommendation on the tradename Aveed:

> "*…DMEPA find the proposed proprietary name Aveed conditionally acceptable for this product. DMEPA considers this a final review; however, if approval of the NDA is delayed beyond 90 days from the date of this review, the proposed proprietary name, Aveed, must be re-evaluated.*"

In regard to the carton/container (as well as FPI and Medication Guide) labeling, Carlos Mena-Grillasca and Denise Toyer, provided several recommendations for revisions and these were all instituted. Perhaps the most relevant of these recommendations was that presentation of the Medication Guide statement on the container was quite small and could be overlooked by the reader. DMEPA advised that this be made more prominent and in response, the Sponsor enlarged and emboldened the font for the Medication Guide statement. Subsequently, DMEPA requested and Sponsor agreed to delete certain other carton information to make the Medication Guide statement even more conspicuous

Office of Compliance

The July 7, 2009 final Chemistry review states:

> *"The Office of Compliance has given an overall acceptable recommendation for the manufacturing facilities."*

The Establishment Evaluation Report is attached to the Chemistry review (pages 27 and 28 of 28) showing the overall acceptable recommendations (on June 26, 2008 and again on March 26, 2009).

Controlled Substances Staff (CSS)

DRUP requested a consult from CSS to verify the scheduling status of Aveed and to assess the labeling as it applies to Abuse and Dependence.

In their final consult report, dated August 19, 2009, James Tolliver, Silvia Calderon, and Michael Klein, stated that testosterone undecanoate (and thus Aveed) is in Schedule III of the Controlled Substances Act. They also provided recommendations for revisions to Section 9 (Drug Abuse and Dependence) of the label. Although labeling discussions have ceased based upon safety concerns, the CSS labeling recommendations had been wholly incorporated into the proposed Aveed labeling.

Division of Pulmonary and Allergy Products (DPAP)

DRUP requested a consultation from DPAP at the time of review of the original submission and again at the time of review of the Complete Response.

In their original consult to the Division (Dr. Charles Lee, final consult dated April 14, 2008), DPAP concluded that there had been 4 reports of anaphylaxis in the postmarketing period for intramuscular testosterone undecanoate, with two these meeting the currently accepted diagnostic criteria for anaphylaxis. Brief summaries of these two cases are provided:

1. (GB-2007-023826) A 46 year old male experienced "anaphylactic shock" including respiratory distress, "coughing fit", T wave inversions, tightening of the throat, respiratory wheeze, rash on abdomen, itchy scalp, and raised blotches across the chest. Symptoms began during his 2nd injection of testosterone undecanoate 1000mg. He was treated with adrenaline, chlorpheniramine, and oxygen, and his symptoms cleared upon arrival at the emergency room.

2. (ZA-2007-035469) A 29 year old male experienced "life-threatening bronchospasm" and tachycardia, became hypotensive and collapsed within minutes after receiving testosterone undecanoate 1000mg. He received emergency medical care with nebulized epinephrine and recovered completely.

The reader should be aware that Sponsor had disagreed (and continues to disagree) that either of these cases reflect anaphylaxis.

The 2 additional cases where anaphylaxis was possible, although these cases did not have sufficient information to confirm them, according to Dr. Lee, were:

1. (GB-2006-006197) A 67 year old male experienced "acute anaphylactic reaction" including tightness in throat and coughing fit "minutes" after his 2nd injection of testosterone undecanoate 1000mg. He was treated with epinephrine and chlorpheniramine. The event was considered life-threatening and involved hospitalization.

2. (SE-2006-02230) A 38 year old male experienced "angioedema", pruritis, malaise, "swelling around the eyes", and itching in the throat after his 1st injection of testosterone undecanoate 1000mg. Solu-Cortef and antihistamine were administered , the symptoms resolved, and the patient was discharged home after a few hours observation.

In concluding their April 14, 2008 consult, DPAP made the following comments:

- DPAP noted that IgE-mediated sensitivity to castor bean allergen in castor bean extract and castor wax extract had been reported in patients with occupational hypersensitivity to castor beans. Anaphylaxis had also been reported with use of polyethoxylated castor oil (Cremophor EL) when used as a solubilizing vehicle for various drugs.

- After considering the post-injection POME reactions and allergic reactions, DPAP noted that the decision to approve the product would be a risk versus benefit decision, and should be made in light of the degree of efficacy, the seriousness of the indication, the availability of alternative products for that indication, and the extent of the safety data.

- DPAP expressed the opinion that it would be appropriate to characterize the frequency of the POME and POME-like events prior to, not after, approval.

- DPAP stated that given the unclear mechanism of the allergic reactions, they would also recommend that Sponsor characterize the nature of the anaphylaxis events. In this regard, DPAP proposed several avenues for additional research:
    - Ask the Sponsor to develop an in vitro test for specific IgE and IgG antibody to the drug, including the active ingredient and the inactive excipients, and to evaluate the presence of antibodies in patients who have had anaphylaxis events

associated with the drug, those who have been exposed to the drug but who have not had anaphylaxis, and unexposed controls.

- Ask the Sponsor to develop a skin testing procedure to the product and its excipients to evaluate the same populations as recommended for the in vitro testing above.

Following the Approvable action on the Original NDA, DPAP continued to assist in the review of this application. The Sponsor proposed a (b) (4) study protocol (b) (4) DPAP felt that the study protocol was insufficient and proposed several modifications. Of importance, DPAP emphasized the limitations of the proposed study (b) (4)

On September 24, 2008, the Division met with Sponsor in a Type A (End of Review) Meeting. At this meeting, DRUP stated that while we would continue to encourage the Sponsor to conduct the skin prick testing/re-challenge study, we would not require it as part of the Complete Response.

Nonetheless, the Sponsor submitted a revised study protocol and DRUP again consulted DPAP. DPAP again voiced that the study was largely insufficient and that the modifications that they had advised were not made. More importantly, they reiterated the following:

> *Overall, DPAP maintains its previous position that the clinical criteria of anaphylaxis has been met after injection of the Aveed product and that if the product is to be approved, the risk of anaphylaxis should be stated in the labeling and that an appropriate risk management plan be developed for the product. The likelihood of the proposed re-challenge study to yield useful information regarding the mechanism through which the reactions occur is low. However, if the sponsor decides to conduct the study, we continue to recommend the study design changes previously conveyed to the sponsor which were outlined in the previous DPAP consult dated September 18, 2008.*"

Therefore, DPAP remained concerned about the potential for Aveed to cause anaphylactic reactions.

In the later part of the second cycle review, DPAP was re-consulted to review 52 cases from the two final Safety Updates (Bayer Schering November 25, 2007 – November 24, 2008 and Endo November 25, 2008 – August 29, 2009). The Clinical review team in DRUP was concerned that many of these cases appeared allergic in nature, including what appeared to be anaphylactic reactions and angioedema. DRUP met with the DPAP consultants on two occasions and DRUP received a final draft DPAP consult on November 16, 2009. In it, DPAP confirmed the Clinical review team's suspicions, specifically categorizing the cases as follows:

- Anaphylaxis 11 cases
- Possible anaphylaxis 9 cases
- Allergic reactions 4 cases

- Possible POME 8 cases
- Injection site problem 1 case
- Cases with too little information 13 cases
- Cases with non-specific symptoms 6 cases

DPAP provided the following additional insights and comments:

- For categorization of the cases, DPAP used the same criteria that FDA has generally used; specifically, the criteria determined by the National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network Symposium in 2005 (Sampson, HA, Second Symposium on the Definition and Management of Anaphylaxis: Summary Report – Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network Symposium; Annals of Emergency Medicine, Volume 47, Number 4, pages 373-380).
- Skin flushing and throat tightening can reflect anaphylaxis. Cutaneous and mucosal signs and symptoms such as generalized flushing, pruritis, hives, swollen lips, tongue and throat are commonly seen in anaphylaxis.
- POME generally lacks cutaneous/mucosal symptoms.
- Benzyl benzoate is known to cause Type XX (cell-mediated) hypersensitivity reactions when applied topically. It is known to be a possible source of contact dermatitis. It is also a component of several products with reported cases of anaphylaxis. Benzyl benzoate can cause hypersensitivity reactions, but not necessarily IGE mediated reactions. When delivered parenterally, is allergic profile could be different. Note, however, that any component of Aveed can be a possible allergen.
- DPAP believes that whether the immediate adverse events following injection can be classified as meeting the clinical definition of anaphylaxis is not the main concern, but any immediate severe adverse event following injection of Aveed requiring treatment should be considered a safety concern.
- The long-term cardiopulmonary consequence of repeated POME events, even if mild, are unknown.
- As previously conveyed, the decision on whether to approve the product will be a risk benefit decision that should take into consideration the seriousness of the indication, the availability of alternative products for that indication, and the extent of the safety data.

12. Labeling

Labeling was proposed by Sponsor as part of the Complete Response. (b) (4)

It recommended that patients wait for 30 minutes in a medical facility

after being injected with the product, in the event of a severe, immediate post-injection reaction. The proposed labeling included a Patient Package Insert, which was subsequently converted to a Medication Guide. Container/carton labeling was also subsequently revised to emphasize the existence of the Medication Guide.

Based upon my impression that there is excessive risk to the demonstrated benefit, I would not advise continuing labeling discussions at this time, either for the Full Prescribing Information or for the Medication Guide. I find the proposed labeling, including the labeling that was discussed with Sponsor during the Complete Response review, to be insufficient to address the underlying risk/benefit problem. Additional labeling discussions could re-commence once a clinically acceptable risk/benefit profile is demonstrated for the product.

13. Recommendations/Risk Benefit Assessment

13.1 Recommended Regulatory Action

I recommend that the product not be approved at this time. Like the medical officer, I am deeply concerned by the risk of severe, immediate post-injection reactions, which include cases of anaphylaxis and angioedema. I do not believe that the demonstrated benefits of the product are sufficient to outweigh this demonstrated risk. I recommend that the application should receive a "Complete Response" action. The Sponsor should be asked to provide information to demonstrate an improved risk benefit profile, although I am unable to provide specific advice in this regard.

13.2 Risk Benefit Assessment

I find the risk benefit profile for this product to be currently unacceptable. The product conveys a serious risk: the occurrence of severe, immediate, post-injection reactions. These reactions were reported in clinical trials and spontaneously in the postmarketing period. They are characterized by difficulty breathing, throat tightening, throat closing, throat fullness, angioedema, laryngospasm, cough, flushing, paresthesias (burning in hands, feet, chest and mouth), other allergic phenomenon (rash, itching, bronchospasm, wheezing, flushing), and constitutional symptoms (sweating, weakness, headache). Many of the cases that I have reviewed were treated as for anaphylactic reactions, with the use of oxygen, epinephrine, steroid and antihistamine. In some of the cases, the event was clearly life-threatening. Some required hospitalization or emergency resuscitation. The etiology for these events appears to be both allergic and respiratory. Some of the 116 postmarketing cases have been determined to be anaphylactic reactions by expert consultants in allergic diseases, both within and outside the FDA. The Clinical review team and the internal allergy consultant in DPAP concluded that approximately 24 cases are possible or probably anaphylaxis. One of our external consultants, Dr. James Li, Chair of the Division of Allergic Diseases at the Mayo Clinic finds at least 22 cases to be possible anaphylaxis and indeed Dr. Li notes that there appear to be allergic-type reactions to this product. Allergic reactions may be related to any of the three components: testosterone undecanoate, refined castor oil or benzyl benzoate. Castor oil may contain toxins, allergic components or contaminants that may be responsible for at least some

of these events. Benzyl benzoate is known to be associated with contact dermatitis, although the allergenic potential when injected intravenously is unknown. Regardless of the etiology, though, these events are severe and life-threatening. There is currently no known way to predict or to prevent them from occurring.

While the product does confer the expected benefit for a testosterone replacement therapy (TRT), with the need for fewer injections per year compared to other injectable TRT products, I do not find this benefit sufficient to outweigh the life-threatening risk of severe, immediate, post-injection reactions to this product. Like the primary MO, I do not find the Sponsor's proposed Medication Guide and Dear Doctor Letter to remedy the underlying risk/benefit problem.

The reader is referred to previous sections of this memo, including the Executive Summary and Safety Summary sections for additional discussion and detail. In short, I believe that the benefits of this product do not outweigh its risks and it should not be approved at this time.

13.3 Recommendation for Postmarketing Risk Management Activities

At this time, I believe that the underlying risk benefit profile must be improved prior to approval and that the product should not be approved. Like the primary MO, I believe that the Sponsor's proposed Medication Guide, Dear Doctor letter and timetable for assessments (essentially, the proposed REMS) are neither sufficient nor appropriate to remedy the underlying excessive risk to benefit problem. Discussions of postmarketing risk management can re-commence once the risk benefit profile is deemed clinically acceptable for marketing.

13.4 Recommendation for other Postmarketing Study Commitments

At this time, I believe that the underlying risk benefit profile must be improved prior to approval. Therefore, there are no recommendations for postmarketing studies. This issue could be re-visited at such time as the risk benefit profile is deemed acceptable for marketing.

13.5 Recommended Comments to Applicant

I recommend that the Complete Response letter emphasize that the Clinical review team believes that the risk/benefit profile is not clinically acceptable at this time, based upon the occurrence of severe and life-threatening, immediate post-injection reactions, including anaphylactic reactions, in light of the demonstrated benefits. The Sponsor should be asked to provide additional information in support of an improved risk/benefit profile.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22219	ORIG-1	ENDO PHARMACEUTICALS INC	NEBIDO

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MARK S HIRSCH
11/30/2009

SCOTT E MONROE
11/30/2009
I concur with the recommendation of Dr. Hirsch that this Application not be approved at this time.

DIVISION OF PULMONARY AND ALLERGY PRODUCTS (DPAP)
MEDICAL OFFICER CONSULTATION

DRAFT

Date:	November 24, 2009
To:	Jeannie Roule, Project Manager Division of Reproductive and Urologic Products
From:	Lynne H. Wu, MD, Medical Reviewer, DPAP
Through:	Anthony Durmowicz, MD, Team Leader, DPAP
Through:	Badrul A. Chowdhury, MD, PhD, Director, DPAP
Subject:	Aveed (testosterone undecanoate) for intramuscular injection

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General Information

NDA/IND#:	NDA# 22-219
Sponsor:	Indevus Pharmaceuticals, Inc.
Drug Product:	Aveed (testosterone undecanoate) for intramuscular injection
Request From:	Jeannie Roule, Project Manager, Division of Reproductive and Urologic Products
Date of Request:	October 15, 2009
Date Received:	October 15, 2009
Materials Reviewed:	52 new cases of post marketing adverse events reports

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Background

Aveed contains testosterone undecanoate in castor oil and benzyl benozate and is administered as IM injection for testosterone replacement in hypogonadal men with testosterone deficiency. It has been approved in Europe since 2004. The injection contains 250 mg/ml and is to be given at 750 mg per dose, repeated at 1 month, then at every 10 weeks. Post injection respiratory and anaphylactic reactions have been noted in post-marketing reports. The original NDA was submitted in August 2, 2007 and an approvable letter was issued in July 27, 2008 expressing safety concerns about serious post injection respiratory (pulmonary oil microembolism or POME) and allergic adverse reactions. DPAP initially consulted to the Division of Reproductive and Urologic Products (DRUP) for Aveed (Nebido in Europe) for evaluation of post injection anaphylaxis and pulmonary oil microembolism (POME) events in April 2008. Follow-up consultations were performed in September 2008 and in June 2009, during which we evaluated the sponsor's proposed protocol (b) (4) For this current consult, we are asked to review 52 additional cases of post-marketing adverse events reports to determine if the cases meet the criteria of anaphylaxis. Following is the clinical definition of anaphylaxis adopted by the

National Institute of Allergy and Infectious Disease (NIAID) and the Food Allergy and Anaphylaxis Network (FAAN) which the Division utilizes followed by a summary of our findings from the review of the cases submitted, our responses to questions raised by DRUP, and discussion of specific safety reports.

DPAP's working definition of anaphylaxis:

DPAP has used the clinical criteria for the diagnosis of anaphylaxis determined by the 2004 and 2005 multinational symposia convened by the National Institute of Allergy and Infectious Disease (NIAID) and the Food Allergy and Anaphylaxis Network (FAAN). The symposia involved over 18 physician, patient advocate, regulatory, and scientific organizations including the American Academy of Allergy, Asthma and Immunology, the American College of Allergy, Asthma and Immunology; the Centers for Disease Control and Prevention; the Food Allergy Initiative, the US Food and Drug Administration, the European Academy of Allergy and Clinical Immunology, the Australasian Society of Clinical Immunology and Allergy.

The symposia defined anaphylaxis as a clinical syndrome characterized by acute onset of an illness with involvement of skin, mucosal tissue, and respiratory and/or cardiovascular systems.

Clinical criteria for the diagnosis of anaphylaxis are outlined below: [1, 2]

Anaphylaxis is highly likely when **any one** of the following 3 criteria is fulfilled:

1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (e.g., generalized hives, pruritus or flushing, swollen lips-tongue- uvula), and at least one of the following:
    a) Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
    b) Reduced BP or associated symptoms of end-organ dysfunction (e.g., hypotonia (collapse), syncope, incontinence)

2. Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):
    a) Involvement of the skin-mucosal tissue (e.g., generalized hives, itch-flush, swollen lips-tongue-uvula)
    b) Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
    c) Reduced BP or associated symptoms (e.g., hypotonia (collapse), syncope, incontinence)
    d) Persistent gastrointestinal symptoms (e.g., crampy abdominal pain, vomiting)

3. Reduced BP after exposure to known allergen for that patient (minutes to several hours):
    a) Infants and children: low systolic BP (age specific) or greater than 30% decrease in systolic BP

b) Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that person's baseline

Post-marketing adverse events frequently contain incomplete information. DPAP has taken the position that an adverse event report submitted under the terms "anaphylaxis, anaphylactic shock, or anaphylactoid reaction" which was treated for anaphylaxis would be included as an anaphylaxis case.

Of note, the applicant has used a different definition of anaphylaxis. (Rüggeberg, et al., Vaccine, 2007; 25:5675–5684). It is one developed by Brighton Collaboration Anaphylaxis Working Group, which was formed in 2003 to assess anaphylaxis associated specifically with vaccine administration. The Rüggeberg definition follows similar principles as the NIAID/FAAN one but is in general is more strict in its interpretation. For example, throat tightness is categorized as a respiratory event instead of cutaneous/ mucosal event and flushing is thought of as a minor criteria. Thus, depending on the description, fewer events might be characterized as anaphylaxis than when the NIAID definition is used.

RESPONSE TO DRUP'S QUESTIONS

For this current consult, DRUP has asked DPAP to evaluate 53 additional cases of post marketing adverse event reports dating from November 2007 to September 2009 for possible anaphylaxis. One of the cases is a duplicate, so there are actually 52 additional cases. After analyzing the post marketing reports, these 52 cases can be broken down in the following categories:

Anaphylaxis	11 cases
Possible anaphylaxis	9 cases
Allergic reactions	4 cases
Possible POME	8 cases
Injection site problem	1 case
Cases with too little information	13 cases
Cases with non-specific symptoms	6 cases

The relevant cases will be discussed individually on page 4 – 14 of this consult.

Our responses to the questions raised in this consult are in italics below:

1. Of the 53 new cases submitted for your review, how many meet clinical criteria for anaphylaxis? In how many cases can anaphylaxis not be ruled out?

   Of the 53 cases submitted, one is a duplicate; therefore, there are actually 52 new cases. Of these 52 new cases, eleven cases met clinical criteria for anaphylaxis. In nine more cases of severe adverse reactions anaphylaxis cannot be ruled out (they are also called possible anaphylaxis cases). For evaluation of these cases, we have used

the same clinical criteria for diagnosis of anaphylaxis as we have used previously, which is the arrived at during the NIAID/FAAN symposia.

2. Many of the new cases (and some of the previously reviewed 66 cases) include skin flushing as well as throat pain/throat tightening/laryngeal edema, etc. DRUP is unable to find evidence that skin flushing and throat tightening reflect pulmonary oil microembolism. Can these symptoms reflect anaphylaxis?

   Yes, they can reflect anaphylaxis or other allergic reactions. Cutaneous/ mucosal signs and symptoms such as generalized flushing, pruritis, hives and swollen lips, tongue and throat are commonly seen in anaphylaxis. To meet the NIAID diagnostic criteria for anaphylaxis, signs and symptoms from at least two systems need to be observed. In additional to the cutaneous/ mucosal system, patients also often have signs and systems of respiratory compromise or reduced blood pressure. Gastrointestinal symptoms can also be part of the presentation of anaphylaxis.

3. Do you agree with Bayer Shering-Plough that it can be impossible to differentiate anaphylaxis from POME?

   While it may be difficult for the physician attending to the patient at the time of a severe post-injection reaction to differentiate between anaphylaxis and severe POME, DPAP believes that the safety issue at hand is the severity of the adverse events observed after administration of Aveed, not whether they can be definitively classified as anaphylaxis or POME. Stating that, we do not completely agree. Signs and symptoms associated with POME generally lack cutaneous/mucosal symptoms as described above in question two but instead appear to consist of cough, transient dyspnea, and, in more severe forms, syncope presumably from decreased cardiac output due to acute pulmonary hypertension from the oil emboli. POME also does not present with persistent gastrointestinal symptoms such as abdominal cramp, diarrhea and vomiting that can be seen with anaphylaxis.

4. Is benzyl benzoate an allergen and if so, can it be playing a role in the immediate post-injection reactions reported with the product?

   Benzyl benzoate has many uses. Applied topically, it is used to treat scabies and in that context is known to cause delayed cell-mediated hypersensitivity reactions. It is also used as a fixative in perfume and in that context is known to be a possible source for contact dermatitis with positive patch testing results. It is also a component in several approved products that have reported cases of anaphylaxis. As such, benzyl benzoate applied topically can be the cause of hypersensitivity reactions, although not necessarily immediate IgE mediated reactions. When delivered parenterally, its "allergic profile" may be different. However, note that any component of Aveed can be a possible allergen.

5. Do you have any general thoughts or comments on the pulmonary/allergy risks demonstrated for the product?

Additional Comments:

- The safety evaluation appears to focus on the number of cases that meet the clinical definition of anaphylaxis. DPAP believes that whether the immediate adverse events following injection of Aveed can be classified as meeting the clinical definition of anaphylaxis is not the main concern but that any immediate severe adverse event following injection of Aveed requiring treatment should be considered a safety risk.

- The long-term cardiopulmonary consequences of repeated POME events, even if mild, are unknown.

- As previously conveyed, the decision on whether to approve the product will be a risk benefit decision that should take into consideration the seriousness of the indication, the availability of alternative products for that indication, and the extent of the safety data.

Case description

Reviewer's comment: For the cases below, Aveed is sometimes called Nebido or Reandron. These are the approved brand names of testosterone undecanoate in the other countries.

A. Cases felt to be Anaphylaxis

Case 1)
Case 2009 32012 GPV
Country: Australia
Report received by manufacturer: September 21, 2009
Reason for use: testicular agenesis
Reporter: allergist

This 16 year old male has received two injections of testosterone undecanoate (Reandron) without problems previously. On unspecified date, IM Reandron was administered by general practitioner. Within 3 minutes, patient experience itching of palms, groin, feet, followed by widespread/ generalized urticaria, tightening in the throat, angioedema of the lips and face, shortness of breath, constriction of the chest, hypotension, cough and dizziness, constriction of chest, hypotension. Patient was given IV adrenaline, antihistamines and IV fluids. The patient recovered without sequelae. The case was described as life threatening.

Patient has a history of eczema, asthma, food allergies and other drug allergies. Prior to Reandron, the patient received Sustanon (testosterone esters). Patient was referred to the allergist who performed skin test with Reandron, which showed a very positive reaction (type I reaction).

Reviewer's comment: This case qualifies as anaphylaxis: it involved cutaneous system (generalized urticaria, diffuse itching, angioedema, throat tightness) and respiratory system (shortness of breath, cough). The rapid onset within 3 minutes is also classical for anaphylaxis.

Case 2)
Bayer case ID: 2009 12293 BNE
Country: acromegaly
Date of incidence: (b) (4)
Reason for use: high prolactin level
Reporter:

This 53 year old male had received more than 5 doses of Nebido previously. Patient received Nebido on June 4, 2009 and immediately noted onset of shortness of breath, flushing and bronchospasm which lasted for 30 minutes. The incident, which occurred on site, was witnessed by a staff nurse and a consultant. The patient was positioned and calmed and recovered 45 to 60 minutes later. It is unclear if patient was treated or not. At the initial report, it stated "the reporter thinks the event may have been treated with hydrocortisone," and at the follow-up report, it stated "the nurse reports the patient recovered unaided with supervision." Patient had a similar although significantly mild reaction to his previous Nebido injection.

Reviewer's comment: This qualifies as a definite anaphylaxis case. The patient's symptoms were immediate and involved cutaneous (flushing) and respiratory systems (shortness of breath).

Case 3)
Case 2009 12294 BNE
Country: UK
Date of incidence: (b) (6)
Reason for use: hypopituitarism
Reporter: health professional

This 32 years old man has received Nebido for 2 years. On (b) (6) patient's mother who is a nurse administered the injection to the patient. Having received the injection, the patient immediately felt odd, experienced a tightening of the throat, shortening of breath, and flushing. His mother reported that it was a bit like a panic attack. The patient was admitted to casualty that day. The symptoms lasted 1 hour. It is unclear what treatment the patient has received.

Reviewer's comment: This case qualifies as anaphylaxis. The symptoms were immediate and involved two systems: cutaneous (flushing, tightening of the throat) and respiratory (shortness of breath).

Case 4)
Case 2009 16799 LA
Country: Ecuador
Date of incidence: (b) (4)
Reason for use: unknown

Reporter: Pharmacist

This male patient of unknown age reported symptoms of skin rash and difficulty breathing immediately after administration of Nebido by a pharmacist. Patient was treated with intravenous hydrocortisone and recovered. Patient has received Nebido 3 months prior to this application. It is unknown whether any concomitant drugs have been given. No other information was given.

Reviewer's comment: This case qualifies as anaphylaxis. The symptoms were immediate and involved two systems- cutaneous (rash) and respiratory (difficulty breathing).

Case 5)
Bayer Case ID 2009 19765 LA
Country: Honduras
Date that report was received: July 23, 2009
Reason for use: hypogonadism
Reporter: Health care professional

This 33 years old male had his first application of Nebido in June 2009. Nebido was still being administered intramuscularly when the patient started complaining about difficulty breathing. This difficulty increased and patient became cyanotic so the treating physician stopped the administration and started administering intravenous hydrocortisone and chlorpheniramine. The condition improved within minutes and the patient started crying and he said he did not know why. Patient also experienced cough and vomiting. That night, at 8 pm, the patient called the physician to inform him that he was having fever (40 Celsius) which was treated with an unspecified NSAIDS. The fever disappeared by midnight. No concomitant drugs have been given.

Reviewer's comment: This case qualifies as anaphylaxis. The symptoms were immediate and involved two systems- respiratory (cough, difficulty breathing), and gastrointestinal (vomiting).

Case 6)
Case 2009 24735 GPV
Country: Sweden
Date that report was received:
Reason for use: Klinefelter's syndrome
Reporter: Physician

This 22 years old male started treatment with Nebido in February 2006. On (b) (6) patient received an injection from his sister-in-law in her apartment. During the injection, the patient suddenly developed dyspnea and his throat became swollen when approximately 1ml of the drug was left in the syringe. The patient became scared and he shivered with his whole body. Patient was admitted to the hospital and stayed there for 1 day for observation. He was treated with Solu-cortef, Ventolin, Travagil (clemastine) and adrenaline.

Reviewer's comment: This case qualifies as anaphylaxis. The symptoms were immediate and involved two systems- respiratory (dyspnea) and cutaneous (throat swollen which is angioedema).

Case 7)
Bayer Case ID: 2008 12881 BNE
Country: Great Britain
Date that report was received: October 21, 2008
Reason for use: Noonan Syndrome
Reporter: physician

This 27 years old male received Nebido on August 19, 2008 and October 1, 2008 at 1000mg intramuscularly. Immediate after the second injection on October 1, 2008, patient experienced bronchospasm, cough, wheezing and felt flushed. Patient was treated with salbutamol 2.5mg nebulizer. Patient recovered after 20 minutes

Reviewer's comment: This case qualifies as anaphylaxis. The symptoms were immediate and involved two systems- respiratory (cough, wheezing) and cutaneous (flushing).

Case 8)
Bayer Case ID: DE 2004 037302
Country: Germany
Date that report was received: December 22, 2004
Reason for use: transsexualism.
Reporter: health care professional
On December 21, 2004 12:56 pm the patient received the first dose of Nebido at 1000mg, 1 dose via intramuscular route of administration. During the injection, the patient experienced hyperventilation followed by pronounced redness in face (blood pressure was 132/ 102 and heart rate normal). No local complaints of urticaria were seen. Afterwards, patient experienced malaise and shivers. He was treated with Prednisolone IV at 250 mg and cetirizine hydrochloride at 10 mg (1 tablet). Repeated measurement of blood pressure showed moderate increase (172/109) with increased heart rate of 90. Patient stayed at the practice until 14:35 pm and left it afterwards in a relatively recovered state. On the next day, patient still had late allergic symptoms like feeling of heat in thigh and upper arms, malaise, and feeling of fevers, but no skin reactions or urticaria.

Reviewer's comment: This is a case of anaphylaxis. The reaction was immediate and involved respiratory (hyperventilation is likely dyspnea) and cutaneous (redness of face or flushing).

Case 9)
Bayer Case ID: 2008 15625 LA
Country: Brazil
Date that report was received: July 4, 2008
Reason for use: unknown
Reporter: physician

This 60 years old male started receiving Nebido at 4ml every 3 months in July 2007. On (b) (6) instantaneously after Nebido's injection, the consumer experienced "anaphylactic reaction" (throat itching followed cough, glottis spasm and glottis edema.) Event was treated with adrenalin and Solu-cortef intravenously and Talerc orally. He stayed in a hospital under observation and after 6 hours he recovered and was discharged.

Reviewer's comment: This case qualifies as anaphylaxis. The adverse event report was submitted as an "anaphylactic reaction and the symptoms were immediate and involved two systems- respiratory (cough) and cutaneous (glottis edema which is throat edema).

Case 10)
Case ID: 2009 10048 BNE
Country: UK
Report received by manufacturer: January 7, 2009
Reason for use: Klinefelter's syndrome
Reporter: health professional (regulatory authority of Great Britain)

On (b) (6) about 1 year and 4 months after starting treatment, this 39 years old male experienced anaphylactic shock considered serious due to life threatening nature and hospitalization. Patient was treated with adrenaline 0.5 µg administered twice in surgery and then patient was transferred to hospital. Other concomitant drugs include aspirin and bisoprolol. No other information was given.

Reviewer's comment: Despite a lack of specific information this event was submitted as life-threatening anaphylactic shock and treated as such with administration of adrenaline and hospitalization. We therefore consider it to be anaphylaxis.

Case 11)
Bayer Case ID: 2008 18230 LA
Country: Brazil
Date that report was received: September 17, 2008
Reason for use: hormone replacement therapy
Reporter: physician

This 58 years old male has been receiving Nebido for an unknown amount of time when he experienced anaphylactic reaction and was hospitalized. No other information was given.

Reviewer's comment: Again, while there is a lack of specific information for this event the physician felt it to be an anaphylactic reaction for which the patient was hospitalized. We therefore consider it to be anaphylaxis.

B. Cases that anaphylaxis cannot be ruled out (or possible anaphylaxis)

Reviewer's comment: Although the cases below did not fulfill the strict diagnostic criteria of anaphylaxis due to reasons such as a lack of description of more severe symptom in one of the two systems, unclear description of timing, few of the events were quite severe, involving syncope and hospitalization.

Case 1)
Bayer Case ID: 200815181GPV
Country: Germany
Date that report was received: April 24, 2008
Reason for use: TDS (testosterone deficiency syndrome)
Reporter: physician (urologist)
After the last administration of Nebido this 52 years old patient experienced heat sensation in the neck and tickling in the throat. He also had severe dyspnea and muscular twitching. Later the patient lost consciousness for about 20 seconds. Shock position and fluid substitution with 0.9% NaCl was done. The patient was admitted for clarification. A CT did not reveal any pathological findings. Twenty-eight hours later, the patient was discharged. A physician assumed micro fat embolism retrospectively. No other information was given.

Reviewer's comment: This is a case of anaphylaxis or severe life-threatening POME. It involved respiratory (dyspnea) and cardiovascular systems (loss consciousness). Heat sensation and tickling of throat are also suggestive of an allergic reaction.

Case 2)
Bayer Case ID: 2009 19765LA
Country: Honduras
Date that report was received: August 7, 2009
Reason for use: hypogonadism
Reporter: Health care professional

This 33 years old male received Nebido for the first time and while Nebido was still being administered (still 1 cc left in syringe), the patient started complaining about difficulty to breath. This difficulty intensified and the patient became cyanotic and the treating physician stopped the administration and started giving intravenous hydrocortisone and chlorpheniramine. The patient improved within minutes. Then the patient said he needed to cry without knowing why. Patient then left the office. During the episode, the patient experienced cough and vomiting. Later on that night, the patient called the physician stating he had fever (up to 40 Celsius) for which he took NSAIDS. The fever disappeared by midnight.

Reviewer's comment: This is a case of possible anaphylaxis. The primary symptoms were of respiratory system (shortness of breath and cough) which appeared to be severe in causing the patient cyanotic. However, since patient also had vomiting and responded within minutes to intravenous antihistamine (corticosteroid was also given- but effect unlikely to be so soon). This then points more to an allergic etiology. The cause of fever later in the day without

other accompanying symptoms is less clear. However, it can still be a presentation of delayed hypersensitivity.

Case 3)
Bayer Case ID: 2008 28604 GPV
Country: Germany
Date that report was received: October 17, 2008
Reason for use: Klinefelter's
Reporter: physician

This 41 years old male patient has received Nebido 1000 mg every 12 weeks for 6 years. In August 2008, during Nebido injection in the gluteal region, patient experienced a tingling sensation which started in the lungs and ascended to the nose. Patient also suffered from dry cough, burning eyes and flush symptoms. After 30 minutes, with treatment with prednisone, Fenistil (dimetindene maleate) and Zantac (ranitidine), the patient recovered.

On January 2009, prick testing of the single ingredients of Nebido was conducted. After 20 minutes, prick skin test of testosterone, castor oil, benzyl benzoate, saline negative control, and latex was negative. Histamine positive control was reported to be 4/10.

Reviewer's comment: This case qualifies as possible anaphylaxis. Although the symptoms were immediate and involved two systems- respiratory (cough), cutaneous (flush), severe POME could not be excluded.

Case 4)
Bayer case ID: 2009 10221 BNE
Country: UK
Report received by manufacturer: January 21, 2009
Reason for use: high prolactin level
Reporter: regulatory authority of Great Britain

This 44 year old Caucasian male received treatment on January 8, 2009 and on the same day of treatment, patient experienced "pulmonary microembolism" with symptoms of chest tightness, cough, sweaty, and throat tightness. Patient has also depression, cardiac syncope, and gastroesophageal reflux. No other information was given.

Reviewer's comment: This case was reported as POME but anaphylaxis cannot be ruled out. The symptoms do involve two systems: cutaneous (throat tightness which is angioedema) and respiratory (cough, chest tightness).

Case 5)
Bayer Case ID: 2009 12132 GPV
Country: Australia
Date that report was received: January 28, 2009
Reason for use: hypogonadism
Reporter: physician

This 62 years old male patient has used Reandron for 12 months. On January 28, 2009 about 60 seconds into the injection, patient complained of sudden burning acid taste in the mouth like cloves, followed by hacking cough ("felt like a fur ball in throat"), then burning in the mouth. The patient was given ice water and subsequently started sweating. The event lasted 20 minutes. The physician reassured the patient and kept him for observation.

Reviewer's comment: This is a case of possible anaphylaxis. The symptoms were immediate and involved two systems- respiratory (cough) and cutaneous (fur ball in throat which is suggestive of angioedema).

Case 6)
Bayer Case ID: 2008 12947 GPV
Country: Sweden
Date that report was received: February 7, 2008
Reason for use: s/p lymphoblastic leukemia
Reporter: nurse, via cell phone to Bayer, nurse heard about this case from the patient

This 38 years old male received Nebido twice. After his first injection, the patient experienced a mild allergic reaction. Six months later in (b) (6) another injection was given in hospital and he developed a "severe allergic reaction" (severe throat swelling) and "potential heart failure". Events were reported to be life-threatening. Information about treatment of these symptoms was not given.

Reviewer's comment: Not enough information is given to qualify this case as definite anaphylaxis, but this very likely could be anaphylaxis. Throat swelling can be a symptom of anaphylaxis. However, "potential heart failure" is vague and can suggest number of things from respiratory issues to blood pressure problems.

Case 7)
Bayer Case ID: DE 2005 008181
Country: Germany
Date that report was received: May 18, 2005
Reason for use: hypogonadal
Reporter: physician

A physician reported the occurrence of "allergic reaction" with circulatory collapse, nausea, retching and fever attacks in this 67 years old male who was prescribed Nebido. This may be patient's first dose of Nebido as it is unknown if Nebido was taken previously. After this episode, "patient felt insecure about hormone replacement and did not want to continue hormone replacement." No other detail was given.

Reviewer's comment: Limited information was given in this case- not much information was given about timing of the event, the duration of symptoms, the treatment given. However, it is suggestive of some type of systemic allergic reaction involving multiple systems:

cardiovascular (circulatory collapse), gastrointestinal (nausea, retching), cutaneous (fever attack is likely flushing), thus anaphylaxis is possible.

Case 8)
Bayer Case ID: 200819576LA
Country: Brazil
Date that report was received: September 26, 2008
Reason for use:
Reporter: Health professional

Age was not given. Patient was listed with symptoms of sweating, cough, face redness and dizziness during injection. No other information was given.

Reviewer's comment: This is a case of possible anaphylaxis. Limited information was given but it appears that the reaction was immediate and involved multiple systems including cutaneous (face redness), and respiratory (cough), and dizziness. If more information was given and more severe symptoms were described, this case would qualify as anaphylaxis.

Case 9)
Bayer Case ID: 2008 11355 GPV
Country: Germany
Date that report was received: January 27, 2008
Reason for use: anorchia
Reporter: physician-pediatrician

This is a 30 years old male who in October 2007, approximately 2 years and 4 months after starting treatment, patient experienced itchiness in throat. In January 2008, approximately one minute after the injection, the patient experienced dry cough, severe burning in throat, and sensation of heat. No other information was given.

Reviewer's comment: This case qualifies as possible anaphylaxis. The reaction started immediately and affected two systems: cutaneous (sensation of heat is probably flushing and severe burning in throat) and respiratory (dry cough). However, the respiratory symptom of dry cough did not appear severe.

C. Allergic Reaction Cases

Case 1)
Case 2009 19103 LA
Country: Brazil
Date that report was received: July 11, 2009
Reason for use: benign pituitary tumor
Reporter: patient

This 76 year old male has been receiving Nebido since 2007. On (b) (6) patient received Nebido in a pharmacy and few minutes later experienced bad taste in mouth, malaise

hot feeling in body, body formication and burning sensation on skin. Patient was taken to a hospital and received parenteral adrenaline and corticosteroids and recovered. No concomitant dugs were given. No other information was given.

Reviewer's comment: There is not enough information to qualify this case as anaphylaxis but this reaction occurred immediately and is likely allergic in nature. Patient experienced cutaneous symptoms (hot feeling and burning sensation on skin).

Case 2)
Case ID: DE 2005 008140
Country: Germany
Date that report was received: May 18, 2005
Reason for use: secondary hypogonadism
Reporter: Physician

On May 13, 2005 patient received the first dose of Nebido (1 ampule dose) via the intramuscular route. Immediately patient developed tickling of throat after removal of needle. Patient was treated with Travagil (which is clemastine). Patient recovered without problems.

Reviewer's comment: Patient's symptom of tickling of throat was mild and responded quickly with antihistamine. However, it occurred immediately with administration of Nebido and is likely allergic in nature.

Case 3)
Case 2007 002541
Country: Sweden
Date that report was received: Jan 24, 2007
Reason for use:
Reporter: physician

A physician reported in this 64 year old man the occurrence of feeling of warmth over the chest and head, coughing and redness of face in a male who was prescribed Nebido. The patient recovered from these symptoms. No other information was given.

Reviewer's comment: Patient's symptoms appear to be allergic in nature with flushing and cough. However, little information was given about timing of the complaints relative to administration of Nebido.

Case 4)
Case ID: 2008 11461 BNE
Country: Great Britain
Date that report was received: July 2, 2008
Reason for use: unknown
Reporter: nurse

This 55 years old man received a third injection of Nebido and as soon as the injection was completed, he immediately complained of a metallic taste in his mouth. He also began to sweat profusely and experienced a "burning up" sensation. The general practitioner took his blood pressure and it had soared to 275/175. Patient was not treated for the event and he recovered. Patient had a history of diabetes, hypertension, and hyperlipidemia. No other information was given.

Reviewer's comment: The description of this case is somewhat vague. However, the immediate nature of the symptoms after injection of Nebido, and the description of "burning up" (which is likely flushing) and metallic taste in his mouth point to an allergic etiology.

REFERENCES

1. Sampson HA, et. al. J Allergy Clin Immunol. 115 (3):584-591, 2005.
2. Sampson HA, et. al. J Allergy Clin Immunol. 117 (2):391-397, 2006.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22219	ORIG-1	ENDO PHARMACEUTICALS INC	NEBIDO

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ANTHONY G DURMOWICZ
11/25/2009
Dr. Durmowicz is also signing for Dr. Lynne Wu who is the primary medical officer for the consult.

BADRUL A CHOWDHURY
11/25/2009
I concur

Clinical Review (DRAFT)

NDA 22-219 Aveed (testosterone undecanoate)

Application Type	NDA
Application Number(s)	22219
Priority or Standard	Standard
Submit Date(s)	March 2, 2009
Received Date(s)	March 2, 2009
PDUFA Goal Date	December 2, 2009
Division / Office	CDER/DRUP
Reviewer Name(s)	Harry Handelsman, DO
Review Completion Date	
Established Name	Testosterone undecanoate
(Proposed) Trade Name	Aveed
Therapeutic Class	Androgen
Applicant	Endo Pharmaceutical Solutions Inc.
Formulation(s)	Injectable, oily solution
Dosing Regimen	750 mg loading regimen followed by 750 mg every 10 weeks
Indication(s)	Treatment of male hypogonadism
Intended Population(s)	Males ≥ 18 years old

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1. RECOMMENDATIONS/RISK BENEFIT ASSESSMENT

In the opinion of this of this reviewer, the evidence presented in the submission derived from adequate and well-controlled clinical trials, was adequate to support the effectiveness of this product. However, the safety concerns related to the risks, risk/benefit, and management of serious post-injection reactions which led to the original "Approvable action" have not been adequately addressed in Sponsor's "Summary Report of the Incidence of Injection-Based Pulmonary Oil Reaction and Allergic Reaction from Clinical Studies of Testosterone Undecanoate" nor in the rest of their "Complete Response to Approvable Letter". The application should not be approved at this time.

1.1 Recommendation on Regulatory Action

It is recommended that this product (Aveed), due to unresolved safety concerns, not be approved for the indication testosterone replacement in males for conditions associated with a deficiency or absence of endogenous testosterone (hypogonadism), including primary hypogonadism (congenital or acquired) and hypogonadotropic hypogonadism (congenital or acquired).

1.2 Risk Benefit Assessment

The Sponsor purports that safety data collected in 12 completed and 5 ongoing clinical trials, involving 2834 subjects receiving 16,191 injections, indicate just 1 serious POME (pulmonary oil microembolism) reaction and no systemic allergic reaction events. While on its face, this would appear to be an adequate sample

indicating a low incidence of these serious events in clinical trials, there were a significant number of cases of serious POME and anaphylactic reactions spontaneously reported in the postmarketing period, as well as a few additional clinical trial adverse events reported that could reflect serious POME or systemic allergic reaction.

In regard to the additional clinical trial cases (post-injection convulsions, syncope and circulatory collapse, respectively), these 3 reports contained insufficient information to definitively ascribe the event to serious POME or to systemic allergy. However, these 3 clinical trial cases should not be discounted due simply to insufficient information. The case numbers are: Patient # 001-0011 from Study 97173 (convulsions after 3rd injection), Patient #001-0017 from Study 97173 (collapse after 1st injection), and Patient #001-0004 from Study JPH04995 (circulatory collapse after 1st injection). If these 3 additional cases were to be counted as incident events, then the numerator would be 4 times higher, leading to an incidence not of 1 in 2,834 subjects (0.035%), but rather, 4 in 2,834 subjects (0.14%). In addition, there are several other cases in the clinical trial database (n=3; pre-syncope, syncope and circulatory collapse) for which the information is sparse, but these too might reflect post-injection reactions. These are: Patient #025-4187 in Study IP157-001 Part A Stage 1, and Patients #26 and #35 in Study 97029. While we have not counted these in the numerator, they are notable.

Reviewer's Comments: *My review of the pivotal trial data (study IP 157-001) and the other clinical study reports submitted in this NDA indicated 5 additional cases, not included by Sponsor, that may be "incident cases": 2 cases with syncope, 1 case with presyncope (near fainting, but responsive), and 2 cases with circulatory collapse. The Sponsor has noted a single case with a "coughing fit" lasting approximately 10 minutes. I also detected 2 cases with allergic skin reactions. The 5 additional cases, if coded as incident cases, would serve to change the numerator for the Sponsor's incidence data markedly.*

In addition, and more importantly, our review of the post-marketing experience has further raised our level of our concern over the nature and number of post-injection reactions that were reported as life-threatening, many requiring urgent treatment and/or hospitalization. These events included POME reactions and anaphylactic reactions. The post-injection reaction events reported in the Complete Response raise even greater concern about anaphylaxis compared to information in the original NDA, in terms of the quantity of anaphylactic cases reported, as well as

the types of allergic reactions reported (angioedema reflected as throat closing, skin reactions, dyspnea, etc).

The spectrum of signs and symptoms of these post-injection reactions frequently overlap, making a precise diagnosis difficult. In any event, these reactions have led this reviewer to conclude that the risk-benefit profile for this drug is unfavorable compared to the currently approved products for testosterone replacement.

Although the Sponsor continues to believe that virtually all, if not all, of these post-injection reactions are POME, our consultants from the Division of Pulmonary and Allergy Products (DPAP) confirm our Clinical review team belief that a large number were allergic in nature, including serious anaphylactic reactions. Regardless of the specific mechanism for these post-injection events, many have been reported as serious and potentially life-threatening. Serious POME and anaphylactic reactions following Aveed injection cannot easily be differentiated. In most cases, attending health care personnel have reported and treated the incident as an anaphylactic reaction. The mechanisms for allergic reactions to Aveed have not been elucidated. Two of the excipients in this product, benzyl benzoate, and castor oil are well known allergens and may possibly play some role in these post-injection reactions, and in one case there was documentation of an allergy to benzyl benzoate. In addition, a product approved for the treatment of advanced breast cancer, (Faslodex®), and a product used as estrogen replacement therapy (Delestrogen®) which contain the same excipients as Aveed were associated with post-injection reactions virtually identical to those associated with Aveed (FDA Adverse Events Reporting System; accessed September 25, 2009), and these events are included in Faslodex and Delestrogen labeling as anaphylactic or anaphylactoid reactions.

Taken together, the totality of the evidence leads this reviewer to conclude that the risk/benefit profile for Aveed is not acceptable for product approval.

1.3 Recommendations for Post-market Risk Evaluation and Mitigation Strategies

At this time, this reviewer does not recommend any specific post-marketing risk mitigation strategy because the current risk/benefit profile is not acceptable for

marketing. The Clinical team has become aware that the issue of post-injection reactions is more complicated than we had previously believed, in that there are a significant number of cases of post-injection anaphylaxis and other allergic phenomenon despite the Sponsor's assertions of no such reactions. Our previous reviews had recommended a risk mitigation strategy that was focused on informing patients and providers about the risk of post-injection, pulmonary oil microembolism events, this before we had reviewed in detail the entire post-marketing experience, realized that many of the post-injection reactions were allergic in nature, and re-considered the risk/benefit profile.

As background for this section of the review, DRUP had made a formal request for a REMS on June 5, 2009, including a request for a Medication Guide as a replacement for proposed Patient Package Insert (telephone conference with Sponsor on July 14, 2009).

At that time, the goals of the REMS were:

(b) (4)

Currently, we believe that anaphylaxis plays prominently in these post-injection reactions. We further understand that it may be impossible to differentiate serious POME from an anaphylactic reaction after an Aveed injection. In fact, most reported serious cases were diagnosed and treated as anaphylactic reactions. We also note that these post-injection reactions can be serious and life-threatening irrespective of the etiology. Taken together, we no longer find the previous MedGuide and REMS to be acceptable in this situation. These documents do not remedy the underlying problem, which is the occurrence of life-threatening post-injection reactions and the unacceptability of the risk/benefit profile for this product.

1.4 Recommendations for Post-market Requirements and Commitments

This reviewer recommends not approving the application, therefore, there are no recommendations for post-market studies, requirements, or other commitments.

Prior to and during this review, the Division had discussed with Sponsor the need for a post-marketing risk mitigation strategy. While DRUP did not initially request a REMS, the Sponsor submitted one nonetheless ("Proposed REMS Supporting Document" dated February 17, 2009). The Sponsor's proposal included:

1. A Health Care Practitioner (HCP) Introduction Letter
2. A Physician Guide to Safety Injection Brochure
3. A Physician Guide to Safety and Injection Video
4. A Patient Package Insert(PPI)
5. A Phase-4 Study (b) (4)

In addition, the Sponsor planned a Phase 4 clinical stud (b) (4) At the time of submission of these proposals, the Sponsor continued to disagree with the conclusion of the Division

of Pulmonary and Allergy Drug Products (DPAP) that at least 2 of the 4 reports of serious allergic reactions were anaphylactic reactions. Therefore, at the time of the Complete Response throughout its 6 month review, the Sponsor persisted in the belief that no anaphylactic reactions had been reported. Our detailed review of the Bayer Schering Post-Marketing Safety Updates for Nebido shows that Bayer had already acknowledged several anaphylactic reactions had occurred. We also have the opinion of our DPAP collegues that anaphylactic reactions have occurred, by generally accepted standards of categorization.

At the time of the Complete Response, the Sponsor had also proposed to implement a communication plan to HCPs directed to membership of the American Urological Association, the Endocrine Society, the Sexual Medicine Society of North America, and targeted primary care physicians and nurses who are likely to prescribe or administer Aveed. The Sponsor planned to provide the following educational materials to HCPs:

1) A Medication Guide stating that the Aveed injection be given in a health care facility by HCPs experienced in proper injection technique, and that the patient should wait for 30 minutes after each injection.

2) An Introductory Dear HCP letter to be distributed at the time of launch to likely prescribers of Aveed, describing its risks and benefits, and explaining the importance of dispensing the Medication Guide to patients prior to each injection.

In addition, the Sponsor planned to distribute the following materials outside the formal requirements of the REMS:

A video and an accompanying educational brochure demonstrating proper IM injection technique, used to instruct nurses and physicians on the proper technique for injecting an oil-based solution to reduce the risk of a POME reaction. The Sponsor believed and continues to believe that slow and cautious injection technique is the most important factor in preventing a post-injection reaction. These materials would also state that injections be administered in a health care facility by HCPs experienced in proper IM injection technique, and that patients be monitored for 30 minutes after each injection. The video and

educational brochure would inform the HCPs of the possibility of an anaphylactic reaction or serious POME event occurring after an Aveed injection.

The Sponsor proposed to conduct assessments of the REMS at (b) (4) at 3 and 7 years post-approval, and more frequently if needed. The results of these assessments would be submitted to the Agency and would include:

(b) (4)

Reviewer's Comments: *This reviewer has considered the proposed Medication Guide and the elements of the proposed REMS. Given the seriousness of the nature of the post-injection reactions, the role of allergy and oil embolism in their causation, and the availability of other testosterone replacement therapies which do not have life-threatening risks, this reviewer does not find the REMS to be appropriate nor an acceptable remedy for an underlying unacceptable risk/benefit ratio for this product.*

As background, the reviewer notes that the FDA Division of Risk Management (DRISK) had reviewed the sponsor's REMS submission, and based upon their understanding that the Division had originally accepted the Sponsor's interpretation of the post-injection reactions, as well as the Sponsor's assertions about risk/benefit, DRISK concluded that the REMS goals were acceptable, and

recommended removal of two specific items from the REMS Document (the video and the instructional brochure related to IM injection technique) in favor of such information in the Prescribing Information; as well as recommending a Medication Guide in place of the proposed Patient Package Insert.

DRISK rationale for their proposed modification to the Sponsor's proposal was that the IM injection technique was adequately explained in the Prescribing Information, and that IM technique is well known to healthcare providers, DRISK recommended that the proposed instructional video and educational brochure be deleted from Sponsor's Communication Plan materials and could be resubmitted to FDA as promotional material. This recommendation was conveyed to Sponsor during an August 10, 2009 teleconference, at which time Sponsor indicated that such material would be used as promotional material.

At the time of the original DRISK review of the proposed REMS, DRISK noted that a Medication Guide would be provided in accordance with 21 CFR 208, and it was expected that the Med Guide would be dispensed to patients at the time of each Aveed injection. The Med Guide that had been developed by Sponsor with input from DRUP and DRISK included the following sections:

- *What is the most important information I should know about Aveed?*
- *What is Aveed?*
- *Who should not* (b) (4) *Aveed?*
- *What should I tell my doctor before* (b) (4) *Aveed?*
- (b) (4)
- *What are the possible side effects of Aveed?*
- *General information about Aveed.*
- *What are the ingredients in Aveed?*

Reviewer's Comment: The reviewer no longer agrees that the Medication Guide and product labeling serve as sufficient risk mitigation strategies. The reviewer believes that the product has too much risk due to the occurrence of serious post-injection reactions to state that its benefits outweigh its risks.

The Sponsor had also proposed a Phase-4 post-marketing study (b) (4) that was to provide additional post-marketing safety

information, particularly related to the incidence of POME and anaphylactic reactions in U.S. post-marketing use. The Sponsor had proposed the submission of the final protocol for this study in October, 2009 and study completion in June, 2013 with final study report expected in October, 2013.

Reviewer's Comment: *The overall REMS is not considered sufficient to remedy the underlying risk/benefit problem with the product. It must be noted that the REMS for this product, which basically entails telling patients and providers about some of the risks of Aveed and advising them to wait in the office for 30 minutes after injection is essentially an untested hypothesis – that informing patients and providers may allow them to opt out, or if they opt in, would allow providers to effectively rescue patients who experience post-injection reaction. This hypothesis has a weak evidence base and is not satisfactory in the face of the risks we have identified.*

2. INTRODUCTION AND REGULATORY BACKGROUND

Testosterone undecanoate (TU) is a member of the endogenous androgens drug class, which includes both testosterone and dihydrotestosterone, responsible for normal growth and development of the male sex organs and the maintenance of secondary male sex characteristics, in addition to playing a role in numerous other normal physiologic and metabolic functions. Various administration routes are used in testosterone replacement therapy, including oral, transdermal, and buccal formulations, as well as parenteral (intramuscular) formulations, all of which have associated advantages and disadvantages. The inconvenience of frequent physician visits and fluctuations in T concentrations are among the disadvantages of currently approved intramuscular T products that the Sponsor purports as the rationale for preferential use of TU.

In an amendment to the NDA dated February 22, 2008, Sponsor (b) (4) in favor of the use of a 750 mg loading dose regimen (3mL on Day 1, on Day 28, then every 10 weeks thereafter), and submitted the tradename Aveed ((b) (4) which was unacceptable to DDMAC).

The original NDA for this product was submitted August 28, 2007 and an Approvable Letter was issued on June 27, 2008 expressing concerns about reports of serious post-injection respiratory and allergic adverse reactions.

Sponsor submitted a Complete Response to Approvable Letter on March 2, 2009.

On September 2, 2009, the Division extended the duration of this review for an additional 3 months, based upon the submission of a major Clinical amendment (a Safety Update) submitted on August 29, 2009 and received on August 31, 2009.

2.1 Product Information

TU for injection is a clear, yellowish, sterile, oily solution. Each (b) (4) amber glass vial contains 3 mL of 250mg/mL (750mg) TU in a solution of refined castor oil and benzyl benzoate. There is 885 ng per vial of refined castor oil (mL) and 1500 mg per vial of benzyl benzoate.

TU (17β-undecanoyloxy-4-androsten-3-one) is a testosterone ester which forms active testosterone by cleavage of the side chain.

2.2 Table of Currently Available Treatments for Proposed Indication

Current US marketed alternatives to the proposed product include:

1) Androderm (transdermal patch)
2) AndroGel (transdermal gel)
3) Striant (buccal patch)
4) Testim (transdermal gel)
5) Testopel (subcutaneous implant)
6) Testro AQ (intramuscular injection)
7) Delatestryl (intramuscular injection)
8) Generic versions of testosterone enanthate and testosterone cypionate (intramuscular injections).

2.3 Availability of the Proposed Active Ingredient in the United States

The active moiety, testosterone undecanoate, is not currently marketed

in the United States. However, the active moiety is rapidly and largely converted to testosterone. However some testosterone undecanoate is detectable systemically and its metabolite dihydrotestosterone undecanoate may also be found.

2.4 Important Issues With Consideration to Related Drugs

The single issue with consideration to other approved agents for this indication remains that of relative risk-benefit, and it would appear that the number of life-threatening post-injection reaction events associated with the use of Aveed compared to related drugs leads to an unacceptable risk-benefit ratio for Aveed.

2.5 Summary of Pre-Submission Regulatory Activity Related to Submission

A) 11/30/05: Pre-IND meeting, type B. Summary of key issues.

1) The NDA for this product would need to be supported by Phase-3 clinical efficacy and safety studies. The studies already conducted would not suffice.
2) No labeling claims would be allowed for testosterone replacement for (b) (4)

Sponsor agreed to:

1) Provide requested toxicology studies
2) Request waiver from study in all females, and males up to age 10.
3) Provide detailed injection site assessments in a Phase 3 study
4) Provide data in units requested for hormone concentrations
5) Conduct a U.S. Phase-3 study

B) 2/17/06: Amendment 001 letter. Sponsor agreed to perform:

1) A 3-month bridging study in rats using an active control
2) A mass balance study in humans.

C) 3/6/06: Teleconference. For the Phase 3 study, Sponsor agreed to:

1) Perform PK assessments of patients at steady-state
2) Perform all hormonal measurements at a central laboratory
3) Monitor for injection site reactions using a standardized assessment
4) Monitor subjects using the AUA symptom score

There was no End of Phase-2 meeting.

D) 8/24/07: Original NDA submitted.

E) 6/27/08: Approvable action taken for the Original NDA. The following summarizes the Deficiencies and the Information Needed to Resolve the Deficiency:

Clinical Deficiency

Reports of serious post-injection respiratory and allergic adverse events raise significnt safety concerns regarding the risk/benefit profile for the use of testosterone undecanoate intramuscular injection for the proposed indication. The drug-related respiratory events were reported in just 2 patients in the clinical trials and in approximately 60 patients in the postmarketing period in Europe. In some of the cases, laryngeal tightness, respiratory distress, circulatory collapse, cyanosis and loss of consciousness were reported as part of the event. In at least four of these post-marketing cases, signs and symptoms of a clinically serious systemic allergic reaction were reported, including two (2) cases meeting criteria for anaphylaxis.

In the Approvable letter, the Sponsor was asked to submit additional information to further assess and mitigate the risk of these post-injection adverse reactions. The letter outlined 3 requests for Clinical information:

- The likely incidence of serious POME and allergic reactions in men who would be treated with the product was not known. A precise estimate of the likely incidence of these serious adverse events was needed to make a

meaningful risk/benefit assessment for the use of the product for the proposed indication.
- The application did not include sufficient information to characterize the underlying etiology of the anaphylaxis-like reactions.
- The application did not include an adequate plan to minimize or manage the risk of these potentially life-threatening events (both POME and anaphylaxis-like events).

The specific Chemistry deficiency came from Drug Master File (DMF) # (b) (4) where deficiencies were identified. These deficiencies were related to the assessment of sterility of the drug product and were conveyed to the DMF holder in a regulatory letter dated June 25, 2008. The Approvable letter stated that these deficiencies must be satisfactorily resolved prior to approval.

F) 9/24/08: Type A (End of Review) Meeting.

G) 3/2/09: Submission of Complete Response.

H) 9/2/09: 3-month Extension of PDUFA date.

2.6 Other Relevant Background Information

TU intramuscular injection was initially developed by Bayer Schering Pharma in Germany and was first marketed in Finland in 2004, which was followed by marketing throughout Europe, and is now marketed in more than 80 countries.

3. Ethics and Good Clinical Practice

The clinical study protocol, protocol amendments, and informed consent documents were reviewed and approved for most sites by a central IRB. There were 3 sites that used local IRBs for study-related document approvals.

3.1 Submission Quality and Integrity

The quality of the overall submission was very good, with the information organized and readily located. Requests for further information regarding post-injection adverse events during the post-marketing period was complete and received in a timely manner.

3.2 Compliance with Good Clinical Practices

This study was conducted in accordance with Good Clinical Practice as required by the guidelines of the European Community and the International Committee on Harmonization guidelines. The Clinical and Clinical Pharmacology teams decided that DSI inspections were not needed

3.3 Financial Disclosures

In compliance with 21 CFR part 54 sponsor has adequately disclosed the absence of investigator proprietary interest in this product or participation in financial arrangements with sponsor.

4. Significant Efficacy or Safety Findings Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls (CMC)

The Chemistry review team for this NDA concluded that the submission provided sufficient information to assure identity, strength, purity, and quality of the drug product. In addition, an “Acceptable” site recommendation from the Office of Compliance has been made. The Chemistry Approvable issue was resolved. From the CMC perspective, this NDA submission was recommended for approval.

4.2 Clinical Microbiology

There were no microbiology deficiencies, and the application was recommended for approval based on the data provided in the Drug Master File (b) (4)

4.3 Preclinical Pharmacology/Toxicology

The Pharmacology/Toxicology review team for this NDA stated that the nonclinical data in this submission supported approval. There was no recommendation for additional nonclinical studies. Recommendations on labeling included adding sections for use in women, effects on spermatogenesis, drug interactions with anticoagulants, use in pregnant or nursing women, use in pediatrics, and use in patients with impaired renal or hepatic function.

4.4 Clinical Pharmacology

The Clinical Pharmacology review team found the application acceptable for approval. All labeling issues were adequately resolved through labeling negotiations.

It is notable that the Sponsor conducted a mass balance study to address the conversion of TU to testosterone in humans, as well as its elimination and excretion pathways. Despite rapid and extensive cleaving of the undecanoate ester, a very small amount of TU and DHT-U may be found in the blood.

4.4.1 Mechanism of Action

The active moiety is testosterone. The affinity of TU for binding to the human androgen receptor was tested and measured by in vitro competition experiments using radioactive metribolone as ligand and testosterone compounds as reference. TU had little affinity for the testosterone receptor, and is not expected to have any clinically meaningful androgenic effect on its own.

4.4.2 Pharmacodynamics

As with other androgens, TU promotes the maintenance of secondary sex characteristics. Drugs in this class also promote retention of nitrogen, sodium,

potassium, and phosphorus. Exogenous administration of androgens may inhibit endogenous release of testosterone through feedback inhibition of pituitary luteinizing hormone.

4.4.3 Pharmacokinetics

Absorption:
Following IM administration of TU, the compound is gradually released from the depot and cleaved by serum esterases into testosterone and undecanoic acid. The release rate is characterized by a half-life of 90±40 days.

Distribution:
Circulating testosterone is chiefly bound (approx. 40%) in the serum to SHBG (approx. 6% remains unbound) and the rest is bound to albumin and other proteins.

Metabolism:
The testosterone generated by cleavage from TU is metabolized and excreted the same way as endogenous testosterone with a reported half-life of 10-100 minutes. Testosterone is metabolized to various 17-keto steroids, and the major active metabolites are estradiol and DHT. The cleaved undecanoic acid is metabolized by β-oxidation in the same way as other aliphatic carboxylic acids.

Excretion:
About 90% of the IM dose is excreted in the urine as glucuronic and sulfuric acid conjugate; about 6% is excreted in the feces.

<u>Reviewer's Comment</u>: The Clinical Pharmacology review team noted excessive T concentrations in one patient who weighed <65 kg. Based upon this patient's data and concerns about excessive T concentrations in light weight hypogonadal men, [redacted] (b) (4) *the Office of Clinical Pharmacology found the NDA acceptable.*

5. Sources of Clinical Data

The Clinical data in this application come from European and U.S. pre- and post-marketing clinical studies, as well as spontaneously reported post-marketing adverse events and Periodic Safety Update reports (PSURs).

In the Original NDA, the sponsor submitted data from a single two-part pivotal Phase-3 trial, **IP157-001 Part A, Stage 1** involving 220 subjects at 54 U.S. study sites, and **IP157-001 Part C, Stage 1** involving 130 subjects at 31 U.S. study sites In addition, the original NDA also contained data from earlier PK studies, including data from 4 completed European studies (Studies JPH01495, JPH04995, ME98096 and 306605, totaling 185 subjects) and an ongoing study in Germany (**ME97029**) designed to assess the effects of TU1000 mg in 95 subjects over the course of 3 years.

In the Complete Response, the Sponsor submitted reports for another 11 clinical studies of TU intramuscular injection, all completed or ongoing in the worldwide postmarketing period. These studies were:

- AWB 0105/ Post-Marketing Surveillance (n=870)
- 39732 (NE0601 IPASS)/ Post-Marketing Surveillance (n=763)
- TG09/ Visceral Obesity & Post-Marketing Surveillance (n=29)
- 303934/ Andropause (n=15)
- NB02/ Paraplegia & Post-Marketing Surveillance (n=19)
- Czech NEO/Post-Marketing Surveillance (n=23)
- 97029/Male contraception (n=28)
- 97173/Male contraception (n=24)
- 98016/Male contraception (n=14)
- 99015/Male contraception (n=42)
- 42306/Male contraception (n=100)

IP571-001 Part A was a 2-arm, open-label, randomized, multi-center PK and long-term safety study of intramuscular (IM) injections of TU 750 mg and 1000 mg in hypogonadal men.

In the original NDA, the Part A submission reflected only data through the 5th injection visit. The Part C submission reflects data up to 9 injections (20 months).

Reviewer's Comment: The Sponsor subsequently submitted longer-term information on Part A (referred to as Part A "Stage 2").

The primary objective in Part A was to evaluate the PK of TU750 mg and 1000 mg given every 12 weeks, over the 12 week interval following the 4th injection, in approximately 110 subjects per treatment arm.

The primary objective in **Part C** was to evaluate the PK of the TU 750 mg loading regimen (the to-be-marketed dose regimen) in approximately 130 hypogonadal men.

The secondary objectives in **Part A** were 1) to evaluate the PK of the TU 750 mg and 1000 mg doses of TU over the 12 week intervals following the 1st, 2nd and 3rd injections in a subset of 20 subjects per treatment arm, and 2) to compare the simultaneous serum levels of total T to levels of DHT, E2, SHBG, TU, and DHTU.

The secondary objectives in **Part C** were 1), to evaluate the PK of the TU 750 mg loading regimen given at baseline, 4 weeks and every 10 weeks thereafter, over 10 week intervals following the 4th dose, 2) to compare the simultaneous serum levels of total T to .levels of DHT, E2, SHBG, TU, and DHTU, and 3) to evaluate safety at baseline, week 4, and every 10 weeks through 9 injections.

5.1 Tables of Studies

The following studies were analyzed during the review of the original NDA:

JPH01495 - a PK study (single injection, n=14)
JPH04995 - a PK study (multiple injections, n=14)
ME97029 - a PK comparator study versus T enanthate (n=36)
ME98096 - a PK study (multiple injections, n=26)

Study IP157-001 was a Phase 3, randomized, multi-center, open-label, studies of efficacy and safety of TU conducted in the US for terms of up to 48 weeks.

The largest supporting study (ME97029) was a single-center, open-label, controlled, 2-arm, parallel study in 40 hypogonadal men of the safety and efficacy of multiple injections of TU1000 mg given at 6-week intervals for 3 doses followed by a final injection after a 9-week interval, compared to T enanthate 250 mg injections for 10 doses given at 3-week intervals.

5.2 Review Strategy

In the original NDA, the reviewer chose to focus primarily on the study reports from Part A and Part C of the US Phase-3 trial and the ongoing German study ME970029. Safety data from all sources were reviewed in detail. The Sponsor submission of Feb 12, 2008, entitled "Immediate Post-Injection Reactions Suspect of Pulmonary Oil Microembolism", was reviewed in great detail.

In the Complete Response, the reviewer conducted individual reviews of each of the new 11 clinical study reports (see Section 5). The reviewer also conducted individual reviews of each Bayer Shering PSUR for Nebido from the first marketing of the drug in 2004 until November 2008. The reviewer also reviewed the Safety Update submitted by Endo on August 29, 2009 containing data from November 2008 to August 29, 2009. The reviewer focused on the Sponsor's summary report "Summary Report of the Incidence of Injection-Based Pulmonary Oil Reaction and Allergic Reaction from Clinical Studies of Testosterone Undecanoate". Another important document was Appendix 8 of the November 2007 to November 2008 Bayer Shering PSUR,entitled "Nebido and Anaphylactic Reactions".

5.3 Discussion of Individual Studies

In **Study IP157-001 Part A**, a total of 237 subjects were randomized to receive TU 750 mg (N=120) or to 1000 mg (N=117). In **Part C**, a total of 130 subjects were enrolled to receive the TU 750 mg Loading Regimen.

Descriptive methods were used to present the data, reflecting baseline characteristics and exposure in the pivotal studies. Pharmacokinetics were

presented via descriptive statistics and figures were used to demonstrate the concentration-time profiles. Incidence rates of meeting certain PK-based criteria, including assessment of Cmax success criteria, were presented in concordance with study objectives.

In Part A, of the 237 subjects enrolled at the 54 sites, 193 completed the study (81.4 %). The primary reasons for dropouts were AE's and withdrawal of consent, and the treatment groups (750mg and 100mg) were generally similar for the rates and reasons for discontinuation. The two treatment groups were well matched for demographic and baseline characteristics. The majority of subjects were White (87.4 %), mean age was 55.

The baseline characteristics of the treatment groups in the pivotal Part A study are shown in Table 1.

Table 1: Demographic and Baseline Characteristics – Total Patient Sample (Study IP157-001 Part A Stage 1)

Characteristic	TU 750 (N=120)	TU 1000 (N=117)
Age (in years)		
Mean ± SE	55.0 ± 0.97	55.9 ± 1.00
Median (range)	54 (30, 82)	56 (23, 83)
Age Categories, N (%)		
< 30	0 (0.0)	1 (0.9)
30 - <40	9 (7.5)	5 (4.3)
40 - <50	23 (19.2)	28 (23.9)
50 - <60	48 (40.0)	36 (30.8)
60 - <70	28 (23.3)	40 (34.2)
70 - <80	10 (8.3)	4 (3.4)
≥ 80	2 (1.7)	3 (2.6)
Gender, N (%)		
Male	120 (100.0)	117 (100.0)
Race, N (%)		
White	101 (84.2)	106 (90.6)
Black	11 (9.2)	8 (6.8)
Hispanic	3 (2.5)	3 (2.6)
Asian	2 (1.7)	0 (0.0)
Other	3 (2.5)	0 (0.0)
Height (in cm)		
Mean ± SE	178.5 ± 0.72	179.4 ± 0.70
Weight (in kg)		
Mean ± SE	101.4 ± 1.68	101.7 ± 1.89
BMI (kg/m^2)[1]		
Mean ± SE	31.8 ± 0.47	31.5 ± 0.51

SE = Standard Error
Note: A few patients did not have values reported for some parameters, and thus the number of patients contributing to some descriptive statistics may vary.
[1]BMI was derived from the reported weight and height.

The population was characterized by a majority of patients who had been diagnosed with primary or secondary hypogonadism 2 to 7 years prior to entry into this study; thus, most patients in this study were not newly-diagnosed. This characteristic was consistent with the finding that 80% of patients in each treatment group had received prior TRT before enrolling into the study; thus, few patients were naïve to the effects of testosterone

Reviewer's Comment: *The demographics for the population sample for Part C were essentially the same as those in Part A, excepting the category of race where the percentage of Whites were 74.6%; Blacks, 12.3%; and Hispanics 10.8%.*

Inclusion Criteria

1. Male with primary or secondary hypogonadism at least 18 years of age.
2. Morning screening serum testosterone concentration < 300 ng/dL.
3. If receiving other endocrine replacement hormones (e.g., thyroid), antihypertensives, lipid lowering agents, antidepressants or anxiolytic medications, the dose must be stable for least 28 days prior to entry OR the subject is not currently on such medications.
4. Able to consent to participate by signing an Informed Consent Form following an explanation of the nature and purpose of this study.

Exclusion Criteria

1. Participation in another clinical trial within the 30 days preceding the first of the study drug.
2. Simultaneous participation in another clinical trial.
3. AUA Symptom Score ≥ 15.
4. Blood donation (including plasmapheresis) or blood loss of ≥500 mL in the last 30 days before the beginning of the study or in the 30 days preceding a visit which includes a determination of serum hormone levels.
5. Prostatic symptoms, tumors or induration of the prostate or the male mammary gland including suspicion of cancer. In case of serum PSA levels ≥ 4 ng/mL or hyperplasia of prostate (size = 25 cm^3 as measured by transrectal ultrasonography), the investigator may include the respective patient if a carcinoma of the prostate has been ruled out (e.g., by biopsy).
6. Past or present liver tumors or acute or chronic hepatic disease with impairment of function; liver function tests (AST, ALT) exceeding 1.5 times upper limit of normal (normal range provided by central laboratory).
7. History of deep vein thrombosis in the past 5 years or any history of cerebrovascular accident.
8. Severe acne.
9. Serious psychiatric disease or uncontrolled medical illness, as suspected from medical history and/or the clinical examination.
10. Significant hypertension (systolic blood pressure >160 mmHg and diastolic >95 mmHg) or coronary heart disease not stabilized by therapy as assessed by the investigator.

11. Insulin-dependent diabetes mellitus or uncontrolled non-insulin-dependent diabetes mellitus.
12. Use of any sex hormones within 28 days (for injectable testosterone preparations) or 7 days (for oral, gel, or patch testosterone preparations) prior to Screening serum testosterone collection for PK assessment, and at any time throughout the study.
13. Biochemical and/or hematological laboratory values outside the normal ranges, unless the investigator confirms that the deviations are of no clinical relevance.
14. Any chronic use of drugs and/or alcohol abuse.
15. Use of steroidal anabolic drugs or supplements (e.g., DHEA) by any application method within the 28-days prior to the first administration of the study drug and throughout the study (exclusive of the administered study drug).
16. Medication with substances which might interfere with testosterone metabolism within 28 days before the first administration of the study drug and throughout the study.
17. Use of anticoagulants (with the exception of low-dose aspirin) within 28 days before the first administration of the study drug and throughout the study.
18. Use of antiandrogens, estrogens, p450 enzyme inducers, barbiturates or antidepressant concomitant medication therapy.
19. Clinical history suggestive of allergy to Testosterone Undecanoate or to the excipients and/or severe intolerances, allergies or idiosyncrasies to other drugs.
20. History of sleep apnea.

Subject Discontinuation

If a subject was discontinued from the study prematurely, the Investigator was to select a reason for discontinuation on the End of Study Phase Status eCRF. In addition, every effort was made to complete the assessments listed under the End of Study visit.

Subjects withdrawn from the study were generally considered evaluable for statistical assessments, but may have been excluded from some assessments (e.g., PK) if insufficient data was present to warrant inclusion in the analysis.

The study protocols and amendments listed the following reason for why a subject may have been removed from the study:

• Adverse Event: If a subject experienced an adverse event that the subject found unacceptable or that, in the judgment of the Principal Investigator, EndoPharmaceuticals, Inc., or the Medical Monitor presented an unacceptable or risk to the subject , the subject may have been discontinued from further study.

• Administrative Discontinuation: After consultation with the Sponsor or Monitor, a subject may have been discontinued from the study for failure to comply protocol requirements. All instances of noncompliance must be documented eCRF.

• Refusal of Treatment: If for any reason the subject refused treatment during the study, the subject was to be discontinued from the study and the reasons for refusal documented on the eCRF. Reasonable efforts were to be made to monitor the adverse events following such discontinuation. Such efforts shall be documented in the eCRF.

Early Discontinuation Criteria

In the event a subject experienced any of the following events, or a significant change in status was detected by the investigator, the evaluation should have been repeated and if confirmed, the subject should have been terminated from the study:

1. Hemoglobin > 21.0 gm/dL

2. Uncontrolled hypertension, defined as blood pressure with systolic blood pressure ≥180 and diastolic blood pressure ≥ 95 mmHg

3. PSA > 4 ng/mL and ≤ 10 ng/mL, unless prostate cancer is ruled out by new testing

4 PSA > 10 ng/mL.

Reviewer's Comment: The eligibility criteria and subject discontinuation criteria in Part C were the same as in Part A.

Reviewer's Comment: The design and procedures for each of the 11 new clinical studies with Complete Response is not described here. The reader is referred to

Section 8 of this review. Those 11 studies were not reviewed for efficacy. For safety, those 11 reports were reviewed for serious adverse events and for any evidence of post-injection reactions.

6. Review of Efficacy

The primary objective of **Study IP157-001 Part A** was to evaluate the pharmacokinetics of TU 750 mg and 1000 mg given every 12 weeks, over the 12-week interval following the 4th injection (the dosing interval that Sponsor had anticipated to reflect steady-state). Secondary objectives included the comparison of other serum hormone levels (including DHT, E2, and SHBG) to simultaneous levels of serum total T.

Reviewer's Comment: (b) (4)

(b) (4)

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Secondary objectives also included the comparison of other serum hormone levels to simultaneous levels of serum total T, which can be seen in Figures 2 (serum free T), 3 (serum DHT), 4 (estradiol), and 5 (sex hormone globulin binding globulin).

Figure 2. **Free Testosterone and Ratio of Free Testosterone to Total Testosterone Following the 1st and 4th Injections**

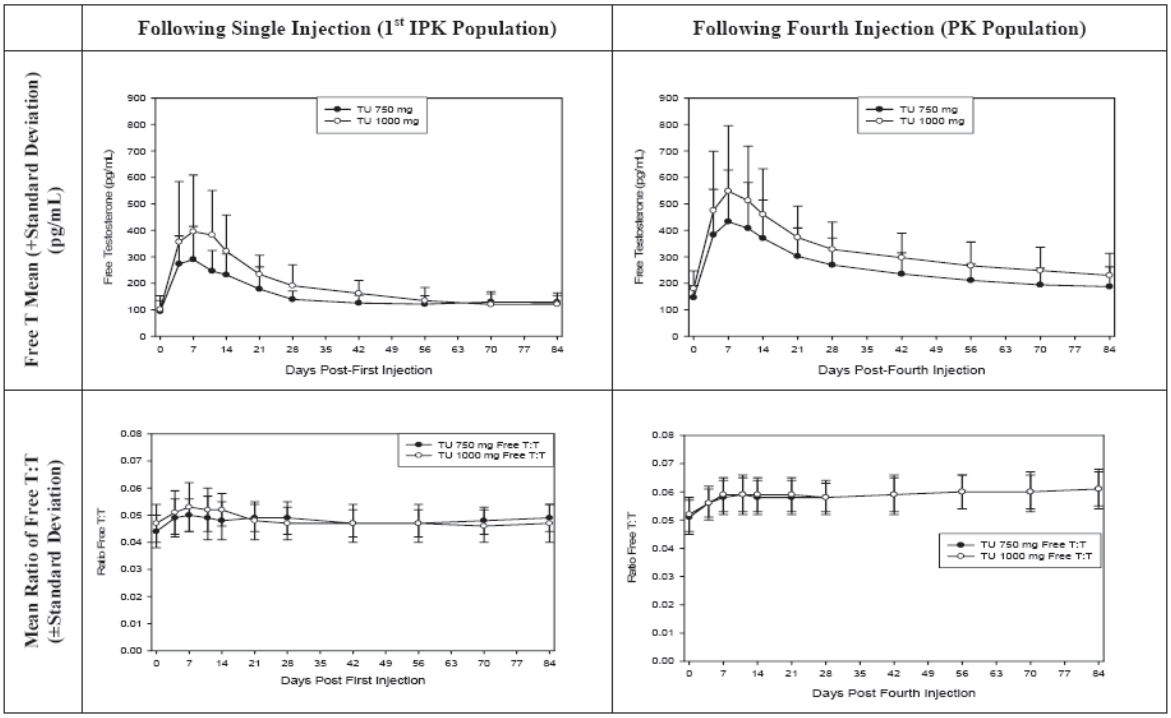


Figure 3. Dihydrotestosterone and Ratio of Dihydrotestosterone to Total Testosterone Following the 1st and 4th Injections

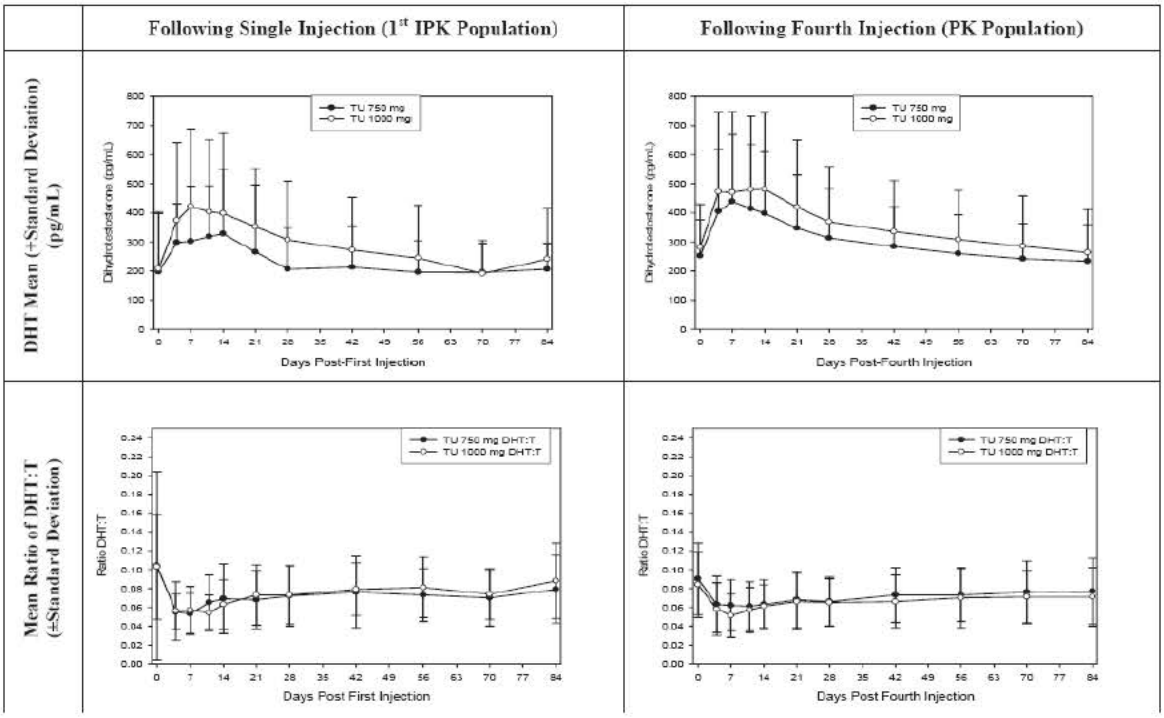


Figure 4. Estradiol and Ratio of Estradiol to Total Testosterone Following the 1st and 4th Injections of TU

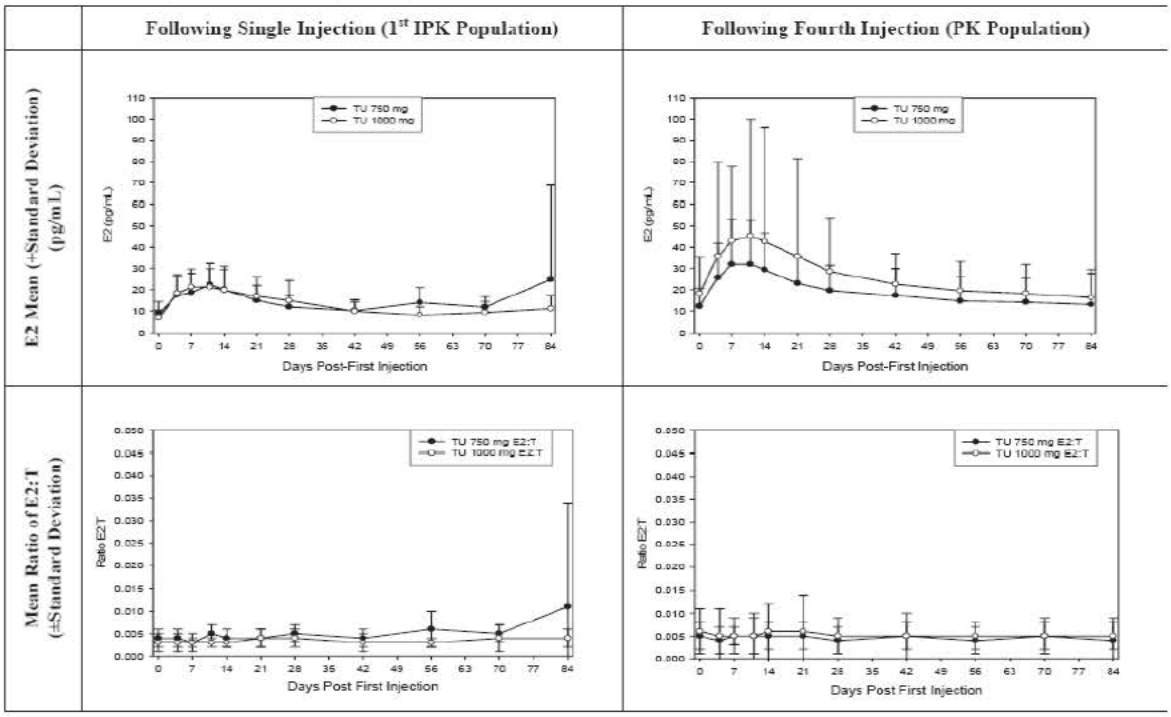
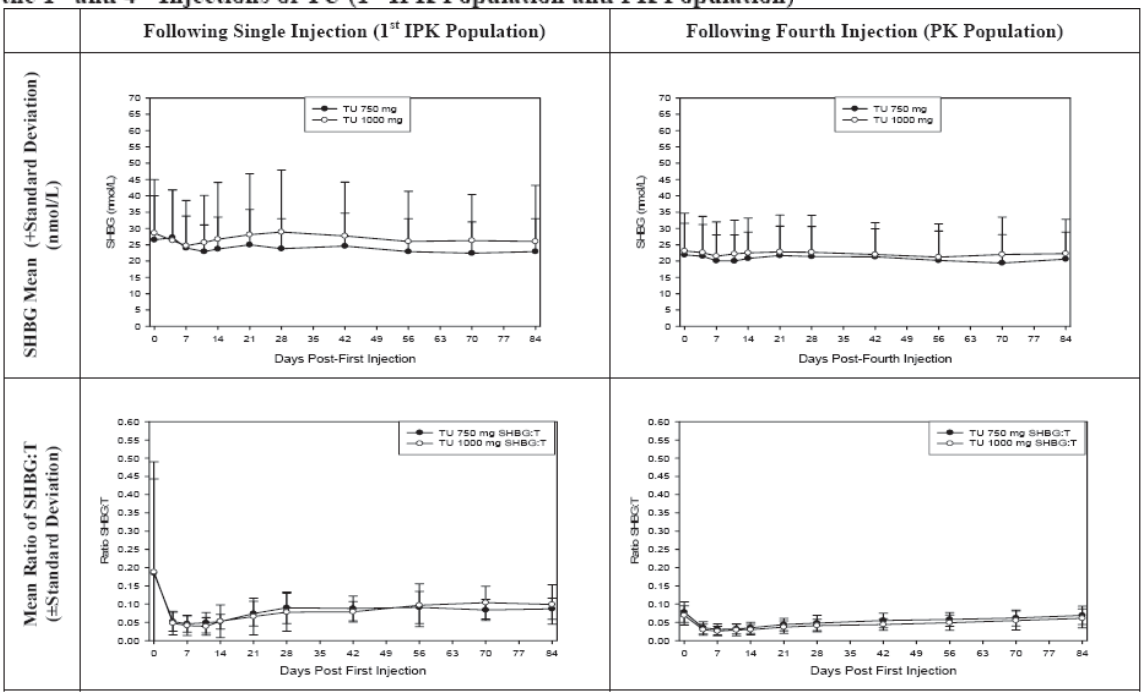


Figure 5. **Sex Hormone Binding Globulin and Ratio of Sex Hormone Binding Globulin to Total Testosterone Following the 1st and 4th Injections of TU (1st IPK Population and PK Population)**

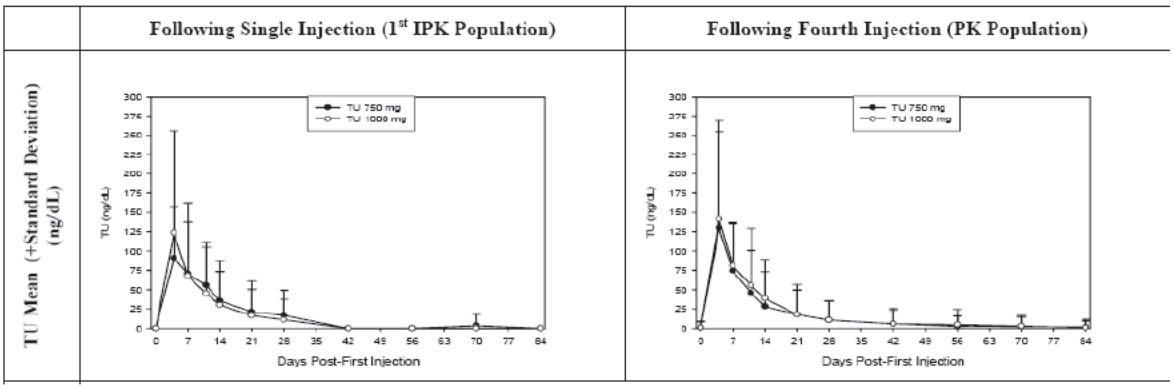


These figures demonstrate acceptable levels of serum free T, DHT, estradiol and SHBG, and acceptable ratios for DHT:T and estradiol:T for both dose regimens, with the caveat that these hormone levels were not assessed at steady-state.

TU and DHTU concentrations over time were also assessed. However, excepting for a few samples, levels of DHTU were below the limit of quantification of the assay, making detailed analysis of DHTU inappropriate. Figure 6 provides 2 plots summarizing the concentrations of TU during the 1st and 4th injection intervals.

Figure 6.

Testosterone Undecanoate Following the 1st and 4th Injections of TU (1st IPK Population and PK Population)



Reviewer's Comments: (b) (4)

(b) (4)

Efficacy Results for Pivotal Study Part C

The primary objective of **Study IP157-001 Part C** was to evaluate the pharmacokinetics of TU 750 mg given at baseline, at 4 weeks, and every 10 weeks, over the 10-week interval following the 3rd injection. This dose schedule is referred to as the 750 mg Loading Regimen,

Secondary objectives included the comparison of other serum hormone levels (including DHT, E2, and SHBG) to simultaneous levels of serum total T over the 3rd injection interval.

Figure 7 provides the steady-state group-mean concentration-time profile for T following the 3rd injection of TU 750 mg given with the loading injection.

Figure 7. Steady-state group-mean concentration-time profile for T following the 3rd injection of Aveed 750 mg Loading Regimen

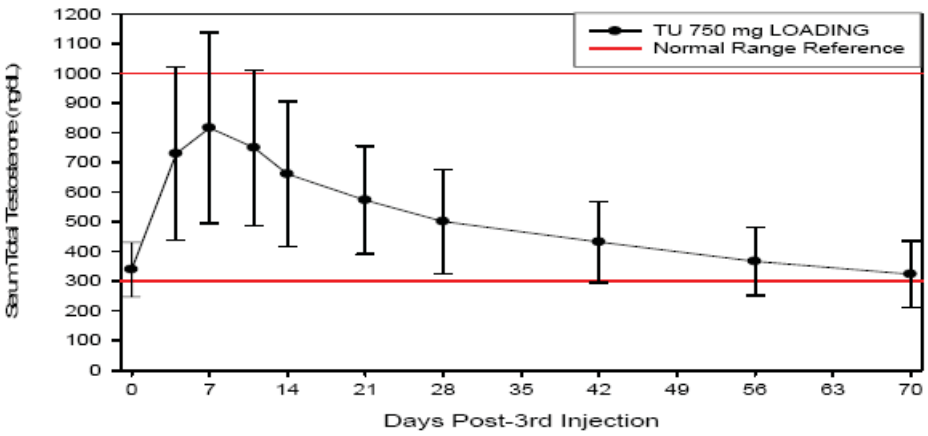


Table 7 presents a summary of PK parameters during the 3rd injection interval.

Table 7. Summary of PK parameters during the 3rd injection interval of the 750mg Loading Regimen.

TU Dose	Pharmacokinetic Parameter	Number Patients	Mean	Standard Deviation	Minimum	Median	Maximum	CV (%)	Geometric Mean
TU 750 mg LOADING	$AUC_{(0-70)}$ (days*ng/dl)	117	34645.6	9902.45	13755.1	33342.2	70016.9	28.6	33263.6
	C_{Trough} (Day 70)	117	323.5	99.11	138.2	316.9	611.1	30.6	309.0
	C_{max} (ng/dL)	117	890.6	345.11	311.0	813.6	1758.5	38.8	826.8
	Dose-normalized C_{max}(ng/dL)[1]	117	1.2	0.46	0.4	1.1	2.3	38.8	1.1
	T_{Last} (days)	117	70.0	0.00	70.0	70.0	70.0	0.0	70.0
	T_{max} (days)	117	10.0	7.11	4.0	7.0	42.0	71.1	8.4
	Dose-normalized $AUC_{(0-70)}$ (days*ng/dl)[1]	117	46.2	13.20	18.3	44.5	93.4	28.6	44.4
	$C_{avg, 0-70}$ (ng/dL)[2]	117	494.9	141.46	196.5	476.3	1000.2	28.6	475.2

Reviewer's Comment: *When compared with outcomes from Part A, treatment with the Aveed loading dose regimen provided C_{avg} and C_{max} estimates* (b) (4) *The levels achieved with the 750 mg Loading Regimen are acceptable. The Clinical Pharmacology review team has determined that the 3rd injection interval did represent steady-state for the 750 mg Loading Regimen.*

Table 8 provides a summary of selected secondary efficacy outcome results during the 3rd injection interval. This table includes the Division's pre-defined safety criteria for Cmax.

Table 8. Summary of selected secondary efficacy outcome results during the 3rd injection interval for the 750mg Loading Regimen

Secondary Outcome Parameter	TU 750 mg LOADING (N=117)
Number Patients with C_{avg} < 300, 300 - 1000, > 1000 ng/dL	
<300 ng/dL	6 (5.1)
300 to 1000 ng/dL	110 (94.0)
>1000 ng/dL	1 (0.9)
Number Patients with C_{avg} ≥ 300 ng/dL	
<300 ng/dL	6 (5.1)
≥300 ng/dL	111 (94.9)
Number Patients with at least one serum total testosterone below 300 ng/dL	
At least one concentration < 300 ng/dL	61 (52.1)
No concentration < 300 ng/dL	56 (47.9)
Number Patients with C_{max} ≤1500, > 1500 - < 1800, 1800 - <2500, ≥ 2500 ng/dL	
≤ 1500 ng/dL	108 (92.3)
> 1500 - < 1800 ng/dL	9 (7.7)
1800 - <2500 ng/dL	0 (0.0)
≥ 2500 ng/dL	0 (0.0)
Number Patients with at least one serum total testosterone > 1000 ng/dL	
At least one T concentration > 1000 ng/dL	35 (29.9)
No T concentration > 1000 ng/dL	82 (70.1)

Figure 8 provides a presentation of the mean T concentrations at each trough time point - demonstrating that steady state was achieved as early as Week 4 and definitely by the 3rd dosing interval for the 750mg Loading Regimen, which was the pre-determined time-point of interest for the primary endpoint.

Figure 8. Mean T concentrations at each trough time point in Part C – 750mg Loading Regimen

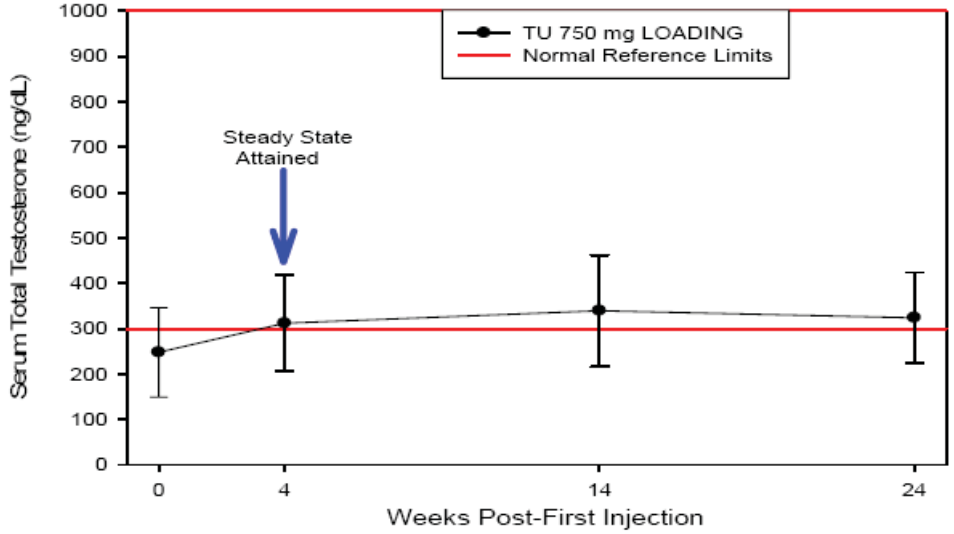


Table 9 presents a summary of Cmax assessments of T concentrations during the 3rd injection interval in Part C.

Table 9. Summary of Cmax assessments of T concentrations during the 3rd injection interval in Part C – 750mg Loading Regimen

	Number of Patients Exceeding/Number of Patients Assessed (Percent of Patients Exceeding)
C_{max} Outcome	**TU 750 mg LOADING (N=117)**
> 1500 ng/dL[1]	9 of 117 (7.7%)
≥ 1800 ng/dL and < 2500 ng/dL	0 of 117 (0%)
≥ 2500 ng/dL	0 of 117 (0%)
Did Dose Meet Threshold Limits?	**Yes**


(b) (4)

(b) (4) Part C TU 750 mg loading regimen was clearly demonstrated to have reached steady state by the 2nd injection. Thus, treatment with TU 750 mg loading regimen resulted in attainment of steady state (b) (4)

Reviewer's Comment: (b) (4)

(b) (4)

Sponsor requested that the Division consider only the 750 mg Loading Dose regimen (from Part C). Subsequent analysis of $C_{troughs}$ with the 750mg Loading Dose regimen indicated that steady-state conditions were achieved at the 3rd injection interval.

The Sponsor summarized the results of some secondary efficacy assessments (eythropoiesis, serum lipids and other serum hormones) as follows:

> Secondary efficacy objectives included the assessment of clinical markers related to changes in T concentrations, ie, changes in body weight and patient satisfaction with the treatment. Objectives also included the study of changes in clinical laboratory parameters as related to changes in T, specifically outcomes related to erythropoiesis, lipids, and hormones.
>
> Average changes from pre-treatment to on-treatment in both hematocrit and hemoglobin as they related to changes in T concentrations over time were as expected for a TRT. Erythropoiesis outcomes demonstrated that:
>
> - Average values of hemoglobin and hematocrit increased slightly from pre-treatment to Week 24 as average T concentrations increased; however, the average increases in these erythropoietic markers were small in magnitude and well within the normal range.
> - Slight changes from pre-treatment in hemoglobin or hematocrit were seen at the Week 24 time point.
>
> Hemoglobin and hematocrit demonstrated low variability across treatments and visits, and thus were relatively stable during the treatment period.
>
> Lipid changes were as expected, with minor changes in the parameters from pre-treatment to the Week 24 time point.
>
> Average changes from pre-treatment to on-treatment in hormones as they related to changes in T concentrations over time were as expected for a TRT. Hormone outcomes were marked by:
>
> - Average Free T concentrations closely paralleled T concentrations and tended to remain within or above the normal range. Mean ratios of Free T:T remained relatively constant throughout.
> - Average DHT concentrations closely paralleled T concentrations and tended to remain within the lower end of the normal range. Mean ratios of DHT:T remained relatively constant.
> - Average E2 concentrations closely paralleled T concentrations and tended to remain within the middle of the normal range. Mean ratios of E2:T remained relatively constant. The average on-treatment ratios remained similar to the average pre-treatment ratios.
> - Average SHBG concentrations remained constant and tended to remain within the middle of the normal range. Mean ratios of SHBG:T tended to drop immediately following the injection (at the Day 4 time point); this was due to changes in T concentrations (and not changes in SHBG concentrations).

<u>Reviewer's Comment:</u> This reviewer agrees with Sponsor's summary of these secondary efficacy results.

Efficacy Summary

In **Study IP157-001 Part C,** the 750 mg Loading Dose regimen provided satisfactory average and maximum T concentrations in hypogonadal men. C_{avg} was within the normal range and the C_{max} profile did not exceed the FDA thresholds. These assessments were made at steady-state.

6.1 Indication

The applicant's proposed indication is replacement therapy in adult males for conditions associated with deficiency or absence of endogenous testosterone. The product will be administered as the "750 mg loading regimen" with 750 mg given at initiation and at 4 weeks, followed by 750 mg every 10 weeks thereafter. The evidence from Study IP157-001 shows that adequate T replacement is achieved with the use of that regimen.

6.1.1 Methods

The reviewer's basic approach to the efficacy review involved:

- Review of the proposed indication, key protocols, and regulatory and scientific background.
- Identification and review of the well-controlled studies to support the indication.
- Conduct of a detailed review of each key study for efficacy.

- Generate conclusions regarding efficacy from the pivotal and supporting studies.

The following studies were reviewed for efficacy during the review process:

IP157-001 - the Pivotal Phase 3 studies - Parts A and C
JPH01495 - a PK study (single injection)
JPH04995 - a PK study (multiple injections)
ME97029 - a supporting PK study using TE intramuscular as a comparator
ME98096 - a PK study (multiple injections)

The pivotal efficacy trial (IP157-001 Parts A and C) was a two-part, Phase 3, randomized, multi-center, open-label, study of efficacy and safety of Aveed conducted in the US for terms of up to 48 weeks.

One supporting study (ME97029) was a single-center, open-label, controlled, 2-arm, parallel study in 40 hypogonadal men of the safety and efficacy of multiple injections of TU 1000 mg given at 6-week intervals for 3 doses followed by a final injection after a 9-week interval, compared to T enanthate 250 mg injections for 10 doses given at 3-week intervals.

6.1.2 Demographics

See ***Section*** **5.3 Discussion of Individual Studies**, pp.15-20

6.1.3 Subject Disposition

See ***Section*** **5.3 Discussion of Individual Studies**, pp.18-19

6.1.4 Analysis of Primary Endpoints

See ***Section*** **6. Efficacy Summary,** pp. 20-22

6.1.5 Analysis of Secondary Endpoints

See ***Section*** **6. Efficacy Summary,** pp. 24-28

6.1.6 Analysis of Clinical Information Relevant to Dosing Recommendations

The dosing regimens selected for Phase 3 were based on modeling and simulations using data from earlier clinical studies of 1000 mg to provide steady state C_{max} T values that would not exceed 2500 ng/dL in any subject, would not exceed 1800 mg/dL in more than 5% of subjects, and would not exceed 1500 ng/dL in more than 15 % of subjects. Dosing regimens selected were expected to provide steady state C_{avg} values within the range of 300-1000 ng/dL for at least 75 % of subjects (with a lower bound for the 95 % confidence interval about the proportion being no lower than 65 %).

(b) (4)

Data from Part C demonstrated that steady-state was more rapidly achieved using the 750 mg Loading Regimen, while not providing excessive Cmax (>1500 ng/dL, and no subject ≥ 1800 ng/dL).

7. Review of Safety

Safety Summary

Treatment with the TU 750 mg LOADING regimen in the Phase 3 Study IP157-001 resulted in safety outcomes consistent with those expected for a testosterone replacement therapy provided to men with primary or secondary hypogonadism. Treatment resulted in a low overall incidence rate of treatment-emergent adverse events (TEAEs) in all system organ classes, with some reports of expected TEAEs. Changes in routine clinical laboratory parameters were generally minor and not clinically meaningful, while changes in serum lipids, erythropoiesis (hemoglobin and hematocrit), and other hormone parameters were consistent with changes that have been reported for other testosterone replacement medications. Prostate health was carefully monitored, and no unexpected incidence rates of any untoward event were observed. PSA concentrations increased slightly. No clinically meaningful changes in vital signs were noted, and the injections were generally well-tolerated. In Study IP157-001, the average safety follow-up was over 160 days, with the vast majority of subjects completing all 4 injections.

In general, in Study IP157-001, treatment with TU intramuscular was associated with adverse events and laboratory changes expected for a testosterone replacement agent. **However**, there were reports of "coughing fits" immediately following injection in the clinical trials submitted with the original NDA (n=2) as well as in the PSURs describing the post-marketing safety experience in Europe (n=66). This reviewer conducted a detailed review in this Complete Response of all known post-injection reactions, from clinical trials, from postmarketing safety updates, and from all documents submitted by Sponsor to this NDA (Complete Response and Original NDA).

As background for the issue of post-injection reactions, the reader should be aware of the course of events in the Clinical review.

Prior to the Sponsor's submission of data for Study IP157-001 Part C, safety data had been submitted for Study IP157-001 Part A and for 4 small Phase 1 European PK studies, totaling 422 hypogonadal patients treated in the TU drug development program. Among these 422 patients, there was 1 patient in whom an "immediate post-injection reaction" was reported. This case occurred in a European supporting study (Patient #184 in Study 306605) and was reported in the Clinical Summary of Safety in the original NDA. This 54 year old male received his 10th injection of TU on 3 April 2006 and shortly (1 minute) after the injection, the patient "experienced urge to cough associated with **respiratory distress**". Both symptoms lasted approximately 14-15 minutes. The event resolved without intervention and the subject continued in the study. The investigator and Sponsor both attributed the event to "*pulmonary lipid microembolism*" and cited the following possible reason: either too fast administration of the study drug or accidental intravascular placement of the study drug.

Upon submission of an amendment to the original NDA containing data from another 117 patients who participated in Study IP1157-001Part C, the Division learned of one more patient who experienced an "immediate post-injection reaction". This 53 year old white male (Patient 050-7006) received his 3rd injection on 12 July 2007 and experienced a "mild and not serious **coughing fit** lasting 10 minutes following the injection." The narrative describes the cough as not productive and the patient had no wheezing and no difficulty breathing. No intervention was given and the patient continued TU therapy without subsequent coughing event.

In addition to these 2 "coughing fit" cases, the Clinical Summary of Safety in the original NDA contained six (6) cases of "***immediate post-injection reactions***" reported during the previous 7 months of post-marketing use of TU in Europe. The 120-Day Safety Update to the original NDA contained an additional four (4) cases of "immediate post-injection reaction" reported in the previous 4 month of post-marketing use in Europe. Based upon the 2 cases reported in clinical trials and the 11 known cases from the post-marketing experience recognized during the 1st cycle review, the Division made request to Sponsor to submit all known cases of "coughing fits" or "post-injection reactions" following injection of TU intramuscular. In response, the Sponsor provided a Summary Report on February 12, 2008 entitled "*Immediate Post-Injection Reactions Suspect of Pulmonary Oil Microembolism*". This summary report also contained individual case narratives for each of a total of **66 individual cases** of "immediate post-injection reaction" reported in the post-marketing period. The Clinical review team conducted a detailed analysis of these cases in conjunction with a consult team from the Division of Pulmonary and Allergy Products. The team determined that these post-injection reactions reflected mostly pulmonary oil embolism **and** several severe systemic allergic reactions. The DPAP team was convinced that 2 cases met criteria for anaphylaxis, but another 2 cases were probably anaphylaxis. Some of these post-injection reaction cases (POME and alklergy) were serious and required hospitalization. Serious post-injection reactions had not been reported for other T replacement products.

As a consequence of this safety concern the Division issued an Approvable Letter requesting that the Sponsor provide a precise estimate of the likely incidence of the serious post-injection reactions (pulmonary oil embolisms and systemic allergic reactions) so that a meaningful risk/benefit assessment for the proposed indication could be made. Additionally, in at least four cases identified by the Division, signs and symptoms of a clinically serious systemic allergic reaction had been reported, including two cases believed to meet clinical criteria of anaphylaxis. The Division also requested information from clinical investigations (for example skin testing) intended to characterize the nature and etiology of the anaphylaxis-like events in those 4 patients. Finally, the Approvable letter requested a plan to minimize or manage the risk of developing these potentially life-threatening events (both POME and anaphylaxis-like events).

The Division met with Sponsor on September 24, 2008 to discuss the contents and format of the Complete Response. There was extensive discussion of the clinical trials that would comprise the controlled clinical trial experience for estimating a

precise incidence of post-injection reactions. There was brief discussion of a post-marketing risk mitigation strategy. There was discussion of the need to submit skin testing data (b) (4) At that meeting, the Division decided that the skin testing information (b) (4) need not be a mandatory part of the Complete Response.

On March 2, 2009, the Sponsor submitted the Complete Response to Approvable, which provided the following safety information relevant to the post-injection reaction issue:

A. Incidence of POME and Allergic Reactions

The Sponsor provided a summary report of the incidence of the post-injection serious POME and allergic reactions from 17 completed and ongoing US and foreign clinical studies involving 2834 subjects treated with a total of 16,191 injections. Across these studies, the Sponsor believed that there was just 1 serious POME reaction reported and no allergic reaction events reported. The one case that was counted by Sponsor in this analysis was the same case as has been previously noted (Patient #184 in Study 306605). If just one case is counted, this translates to 3.53 events per 10,000 patients, and 0.62 events per 10,000 injections.

This would appear to reflect a reasonable sample and a relatively low incidence of these sorts of serious events; however, this reviewer continues to have concerns. First, there remains the issue of a a significant number of spontaneously reported post-marketing cases of serious POME and anaphylactic reactions. For this issue, the reader is referred to Item D of this section, as well as subsequent sections of this review (p81-97 and Section 8). Second, the reviewer points out that a few additional clinical trial adverse event reports have been noted that these too could reflect serious POME or systemic allergic reaction.

In regard to the additional clinical trial cases that might reflect “incident cases” (post-injection convulsions, syncope and circulatory collapse, respectively), these 3 reports contained insufficient information to definitively ascribe the event to serious POME or to systemic allergy. However, these 3 clinical trial cases should not be discounted due simply to insufficient information. The

case numbers are: Patient # 001-0011 from Study 97173 (convulsions after 3rd injection), Patient #001-0017 from Study 97173 (collapse after 1st injection), and Patient #001-0004 from Study JPH04995 (circulatory collapse after 1st injection). If these 3 additional cases were to be counted as incident events, then the numerator would be 4 times higher, leading to an incidence not of 1 in 2,834 subjects (0.035%), but rather, 4 in 2,834 subjects (0.14%), or 1 in approximately 700 patients. In addition, there are several other cases in the clinical trial database (n=3; pre-syncope, syncope and circulatory collapse) for which the information is sparse, but these too might reflect post-injection reactions. These are: Patient #025-4187 in Study IP157-001 Part A Stage 1, and Patients #26 and #35 in Study 97029. While we have not counted these in the numerator, they are notable.

Reviewer's Comments: *My review of the pivotal trial data (study IP 157-001) and the other 16 clinical study reports submitted in this NDA indicated 5 additional cases, not included by Sponsor, that may be "incident cases": 2 cases with syncope, 1 case with presyncope (near fainting, but responsive), and 2 cases with circulatory collapse. The Sponsor notes just a single case with a "coughing fit" lasting approximately 10 minutes. I further detected 2 cases with allergic skin reactions. The 5 additional cases, if coded as incident cases, would serve to change the numerator for the Sponsor's incidence data markedly.*

B. Characterization of Allergic Reactions

At the September 24, 2008 Type A meeting with Sponsor, the Division withdrew the original FDA request for the Complete Response to contain information characterizing the allergic reactions. Nonetheless, we continued to encourage such efforts. To our knowledge, the Sponsor has already initiated a Phase 4 clinical study (b) (4) This study is a skin prick/re-challenge study and is intended to provide information towards characterizing the etiology of observed allergic reactions.

In regard to skin testing, and the pursuit of a pathophysiologic etiology for the immediate post-injection reactions, this reviewer points out that skin testing has

already been conducted and reported in a few spontaneously reported adverse events. For example, a 16 year old male with history of testicular agenesis and asthma had a post-injection event reported as "anaphylactic reaction", described as itching of palms, groins, and feet, widespread urticaria, tightening of throat, angioedema of lips and face, shortness of breath, constriction of chest, cough, dizziness and hypotension less than 3 minutes after his 3rd dose. The report describes subsequent skin testing by an allergist, who reported a "very positive reaction" in this young man. The manufacturer's (Mfr) report number for this case is 200932012 GPV. Another case of interest is Mfr Report # 200910189GPV, a 71 year old "xx-man" in whom skin testing was done prior to TU intramuscular administration and the report states, "Epicutanic tests to Nebido revealed positive findings for a single substance benzyl benzoate". Finally, in the case of Mfr Report # DE-2005-011567, a 48 year old male-to-female transsexual, castor oil is suspected to be the cause of a hypersensitivity reaction to TU intramuscular. The event included the feeling of "lump in the throat" and dizziness, vertigo, headache and palpitations.

Reviewer's Comment: *This reviewer continues to advise investigations to determine the etiology of the reported immediate post-injection reactions, including anaphylactic and anaphylactic-like reactions to Aveed. Castor oil and benzyl benzoate are both known allergens. Are these excipients, both found in large amounts in the drug product, causative in the reported allergic reactions to Aveed? Can benzyl benzoate benzoate play some role in the post-injection reactions, through a non-allergic mechanism? The reviewer continues to encourage additional investigations to characterize the etiology of the immediate post-injection reactions, including the Phase 4 skin testing protocol.*

C. Sponsor's Proposed Risk Evaluation and Mitigation Strategy (REMS)

Prior to and during this review, the Division had discussed with Sponsor the need for a post-marketing risk mitigation strategy. Although the Division did not specifically request one, Sponsor submitted a "Proposed REMS Supporting Document" with their Complete Response which included;

1. A Dear Health Care Practitioner (HCP) Introduction Letter
2. A Physician Instructional Guide to Safety & Injection Brochure
3. A Physician Video Guide to Safety and Injection
4. A Patient Package Insert (PPI)

5. A protocol synopsis for [redacted] (b) (4) Phase 4 ,observational safety study to assess the incidence of serious POME reactions and anaphylactic reactions post-marketing.

Reviewer's Comment: This reviewer has considered the proposed Medication Guide and the elements of the proposed REMS. Given the seriousness of the nature of the post-injection reactions, the role of allergy and oil embolism in their causation, and the availability of other testosterone replacement therapies which do not have life-threatening risks, this reviewer does not find the REMS to be appropriate nor an acceptable remedy for an underlying unacceptable risk/benefit ratio for this product.

As background, the reviewer notes that the FDA Division of Risk Management (DRISK) had reviewed the sponsor's REMS submission, and based upon their understanding that the Division had originally accepted the Sponsor's interpretation of the post-injection reactions, as well as the Sponsor's assertions about risk/benefit, DRISK concluded that the REMS goals were acceptable, and recommended only removal of two specific items from the REMS Document (the video and the instructional brochure related to IM injection technique) in favor of such information in the Prescribing Information; as well as recommending a Medication Guide in place of the proposed Patient Package Insert. Currently, the DRISK review has been placed on hold, awaiting the review Division's final decision on risk/benefit and approvability.

In summary, the reviewer no longer agrees that the Medication Guide and product labeling serve as sufficient risk mitigation strategies. The reviewer believes that the product has too much risk due to the occurrence of serious post-injection reactions to state that its benefits outweigh its risks.

D. Additional Post-Marketing Safety Updates (PSUR)

In the March 2, 2009, Complete Response, the Sponsor submitted another Bayer PSUR for the time period November 2007 to November 2008. This document is a particularly important item for the review of the Complete Response, in that it contained a large number of additional post-marketing cases of immediate post-injection reactions. It also contained a document entitled "Nebido & Anaphylactic Reactions", **Appendix 8**. This Appendix 8 document was compiled by Bayer, the marketer of TU intramuscular worldwide, at the request of a European regulatory

authority. This reviewer carefully assessed all cases in the Nov 2007-Nov 2008 PSUR and in the Appendix 8 summary of the anaphylactic reaction issue. From these documents, 43 incident cases were extracted. In the opinion of this reviewer, the cases are very concerning and even more so compared to the cases in the original NDA. The cases in this document reveal clinical evidence for anaphylaxis as the etiology for a fairly significant percentage of the immediate post-injection reactions, including symptoms of throat tightening and throat fullness (a sign suspicious of angioedema), skin erythema, and dyspnea. The percentage of cases with transient cough and shortness of breath, more consistent with a diagnosis of POME, are fewer than previous. In Appendix 8, the European marketer, Bayer Schering acknowledged that 5 cases overall meet some criteria for anaphylaxis, with one case meeting strict criteria for anaphylaxis. Bayer acknowledged in Appendix 8 that it may be impossible to differentiate serious POME from anaphylaxis.

As part of the Division's routine review procedures, the Sponsor was asked to submit another Safety Update, from November 2008 to the present (August 29, 2009), and they did so on August 29, 2009. This most recent Safety Update included a total of 18 cases, of which 9 appeared to be serious post-injection reactions, and most appeared to be allergic in nature (anaphylactic or anaphylactic-like reactions).

The cases submitted in the Nov 2007-Nov 2008 Safety Update (including Appendix 8) and the August 29, 2009 Safety Update have led the reviewer to conclude that the severity of the events and risks posed by post-injection immediate reactions are great. Further, the reviewer sees the cases as likely reflecting more than just transient pulmonary oil embolism, as they have been reported as devastating and serious events, consistent with serious POME and perhaps more importantly, with anaphylactic reactions. The reader should be aware that DPAP has been re-consulted. At an internal meeting on November 3, 2009, DPAP stated that their review of the 52 new postmarketing cases reveals 9 cases of definite anaphylaxis, 7 cases of "possible" anaphylaxis, 2 cases of "borderline possible" anaphylaxis, 4 cases of allergy, and 8 cases of POME. These counts exclude 15 cases where information was scant, but in most of these 15 excluded cases, the event was reported as "anaphylactic reaction". DPAP cautioned that these excluded cases should not be summarily discounted by DRUP, but instead, it is the usual DPAP practice to include such cases, where post-marketing incidence are being assessed by FDA. The DPAP team leader remarked that if the case reporter stated "anaphylactic reaction" that such a case cannot be dismissed.

Each incident case from these two new Safety Updates is described in narrative form in a subsequent section of this review. Reviewer's comments are provided for the individual cases.

In addition, in light of the information gained from the more recent safety updates, the reviewer went back to the PSURs submitted in the original NDA and assessed those in detail for "incident" cases. Previously, 66 cases had been reported and analyzed and are detailed in the original MO and CDTL memos. This reviewer re-assessed each incident case from the original PSURs and these are described in brief narrative form in a subsequent section, along with reviewer's comments.

7.1 Methods

Method of Safety Review

1. Review of the proposed indication, the protocol for the pivotal Phase 3 study IP157-001, and the regulatory and scientific backgrounds.
2. Detailed review of the safety parameters from the pivotal Phase 3 study IP157-001 and summary review of the safety from 5 supporting Phase 1 studies from the original NDA.
3. Summary reviews of the 11 additional post-marketing clinical trials submitted in the Complete Response, focusing on the quality of those Phase 4 studies and the reported adverse events that may reflect post-injection reactions.
4. Review of the Sponsor's Summary Report for the entire 17 clinical trial experience, entitled "*Summary Report of the Incidence of Injection-Based Pulmonary Oil Reaction and Allergic Reaction from Clinical Studies of TU.*"
5. Review of the Nov 2007-Nov 2008 Bayer PSUR, including Appendix 8.
6. Review of the Nov 2008- August 31, 2009 Endo PSUR.
7. Re-review of all previously submitted Bayer PSURs from the original NDA.
8. Review of the consultations from the Division of Pulmonary and Allergy Drug Products (DPAP).
9. Meeting with the DPAP consultants.

The Phase-3 pivotal study IP157-001 was adequate and well-controlled. The data from the 5 Phase 1 studies contributes some additional safety information. The data from the additional eleven Phase 4 European studies also contributes

information about safety of TU intramuscular. The PSURs contribute a significant amount of safety information about the product. Overall, then, this NDA contains substantial evidence to assess safety.

The next sections of this review present the safety results from Study IP157-001 Part A and then from Part C. The reader should be aware that all safety results from Part A are presented first. The presentation of safety data for Part C begins on page 75.

Adequacy of Safety Assessments in Study IP157-001

In Part A, exposure to TU averaged approximately 375 days in both treatment groups; over 80% of patients in each group received 5 injections, and thus patients were exposed to treatment with TU in this study for over a year. However, consistent with the study design, safety outcomes in this study report reflect an actual median follow-up period of 334 days (47.7 weeks) for each treatment group.

The planned duration of exposure to study medication was calculated as number of days from first injection to the last injection, plus 84 days. For most patients, the last injection was the 5th injection (48 weeks following the first injection). Exposure to TU would have been derived as 60 weeks. Exposure as measured by the duration of safety follow-up was calculated as through the 5th injection visit, and is limited to approximately 48 weeks. Procedures employed in this study to evaluate safety included prostate health assessment via the measurement of PSA and performance of digital rectal examinations. Further, laboratory measurements and urological data (e.g., via the AUA scale) were collected every 6 months; lipid profiles were collected every 12 weeks; and monitoring of adverse events was performed in an ongoing manner throughout the course of the study.

7.2 Major Safety Results

Table 10 summarizes treatment-emergent-adverse-events (TEAEs) reported in at least 2 % of subjects in both groups irrespective of relationship to study medication, by preferred term in decreasing order based on incidence rates in the TU 1000 group in Study IP157-001 Part A.

Table 10.

Incidence of All TEAEs Regardless of Relationship Reported in at Least 2.0% of Patients in Either Treatment Group by Preferred Term in Decreasing Frequency in TU 1000 mg arm – Total Patient Sample (Study IP157-001 Part A Stage 1)

MedDRA Preferred term	Number of patients (%)	
	TU 750 (N=120)	TU 1000 (N=117)
Total patients with at least 1 TEAE	70 (58.3)	73 (62.4)
Upper respiratory tract infection	5 (4.2)	5 (4.3)
Diarrhoea	2 (1.7)	5 (4.3)
Pain in extremity	2 (1.7)	4 (3.4)
Nasopharyngitis	5 (4.2)	4 (3.4)
Hypertension	3 (2.5)	4 (3.4)
Sinusitis	3 (2.5)	4 (3.4)
Insomnia	3 (2.5)	4 (3.4)
Headache	2 (1.7)	4 (3.4)
Depression	2 (1.7)	4 (3.4)
Weight increased	3 (2.5)	4 (3.4)
Procedural pain	0 (0.0)	3 (2.6)
Arthralgia	2 (1.7)	3 (2.6)
Musculoskeletal pain	1 (0.8)	3 (2.6)
Urinary tract infection	3 (2.5)	3 (2.6)
Rash	1 (0.8)	3 (2.6)
Pain	0 (0.0)	3 (2.6)
Foot fracture	0 (0.0)	3 (2.6)
Muscle strain	0 (0.0)	3 (2.6)
Anxiety	0 (0.0)	3 (2.6)
Nasal congestion	0 (0.0)	3 (2.6)
Abdominal pain	0 (0.0)	3 (2.6)
Constipation	0 (0.0)	3 (2.6)
Vomiting	1 (0.8)	3 (2.6)
Gout	0 (0.0)	3 (2.6)
Benign prostatic hyperplasia	2 (1.7)	3 (2.6)
Cough	1 (0.8)	3 (2.6)
Fatigue	7 (5.8)	2 (1.7)
Bronchitis	5 (4.2)	2 (1.7)
Back pain	4 (3.3)	2 (1.7)
Nausea	3 (2.5)	2 (1.7)
Prostatic specific antigen increased	4 (3.3)	1 (0.9)
Hypercholesterolaemia	3 (2.5)	1 (0.9)

There were no clinically meaningful differences in the incidence of any TEAE noted across the age, BMI, prior T replacement, or Cmax subgroups.

The majority of TEAEs were judged as mild or moderate in severity; 10 (8.3%) TU 750 mg subjects and 7 (6.0%) TU 1000 mg patients experienced at least one severe TEAE. Atrial fibrillation was reported as severe in 2 (1.7%) subjects in the

TU 750 mg group; no other event was reported as severe in more than 1 patient per treatment group. Severe events (regardless of investigator-attributed causality) included cardiac failure, coronary artery disease, chest discomfort, irritability, sudden hearing loss, and PSA increased.

> *Reviewer's comment: In the reviewer's opinion, it is not possible to directly attribute any of these individual severe adverse events in Study IP157-001 Part A to Aveed, although there may be some relationship between androgen replacement in general and such adverse events as "PSA increased", "irritability", "cardiac failure", "coronary artery disease" and "chest discomfort".*

There was 1 patient who died during this study. A 54 year old Caucasian male who received 2 injections of TU 750 mg died of injuries sustained from being stabbed. The patient died 165 days following his first injection; the death was considered unrelated to study treatment.

Adverse events attributable to androgen replacement in general, and injection site AEs were designated TAES of interest. TEAEs of interest were experienced by 24 (20.0%) of subjects treated with TU 750 mg and 30 (25.6 %) of subjects treated with TU 1000 mg, as seen in Table 11.

Table 11. TEAEs of Interest in Part A

Event Class	MedDRA System Organ Class	MedDRA Preferred term	Number of patients (%)	
			TU 750 (N=120)	TU 1000 (N=117)
Total Patients With At Least One TEAE of Interest			**24 (20.0)**	**30 (25.6)**
Endocrine Disorder	Investigations	Oestradiol increased	0 (0.0)	2 (1.7)
		Glycosylated haemoglobin increased	0 (0.0)	1 (0.9)
	Metabolism and nutrition disorders	Diabetes mellitus	1 (0.8)	1 (0.9)
Tolerability of Injection	General disorders and administration site conditions	Injection site erythema	0 (0.0)	1 (0.9)
		Injection site irritation	0 (0.0)	1 (0.9)
		Injection site pruritus	1 (0.8)	1 (0.9)
		Injection site pain	2 (1.7)	2 (1.7)
		Injection site reaction	0 (0.0)	1 (0.9)
Adverse Lipid Profiles	Investigations	Blood triglycerides increased	1 (0.8)	2 (1.7)
		Blood triglycerides abnormal	0 (0.0)	1 (0.9)
		Blood cholesterol increased	0 (0.0)	2 (1.7)
		High density lipoprotein decreased	1 (0.8)	0 (0.0)
	Metabolism and Nutritional disorders	Hypercholesterolaemia	3 (2.5)	1 (0.9)
		Hyperlipidemia	1 (0.8)	1 (0.9)
Erythropoiesis	Investigations	Haematocrit increased	0 (0.0)	1 (0.9)
		Haemoglobin increased	0 (0.0)	1 (0.9)
		Red blood cell count increased	0 (0.0)	1 (0.9)
	Blood and lymphatic system disorders	Polycythaemia	1 (0.8)	1 (0.9)
Aggression or depression	Psychiatric disorders	Depression	2 (1.7)	4 (3.4)
Urinary Symptoms	Renal and urinary disorders	Pollakiuria	0 (0.0)	2 (1.7)
		Urinary hesitation	0 (0.0)	1 (0.9)
		Urinary retention	1 (0.8)	2 (1.7)
		Urine flow decreased	1 (0.8)	2 (1.7)
		Nocturia	0 (0.0)	1 (0.9)
		Dysuria	1 (0.8)	2 (1.7)
	Infections and infestations	Urinary tract infection	3 (2.5)	3 (2.6)
Prostate health	Investigations	Prostatic specific antigen increased	4 (3.3)	1 (0.9)
		Prostate examination abnormal	2 (1.7)	1 (0.9)
	Reproductive system and breast disorders	Benign prostatic hyperplasia	2 (1.7)	3 (2.6)
		Prostatic intraepithelial neoplasia	1 (0.8)	2 (1.7)
		Prostatitis	0 (0.0)	2 (1.7)
		Prostatic disorder	1 (0.8)	0 (0.0)
Liver Abnormalities	Neoplasms benign, malignant and unspecified	Hepatic neoplasm malignant	0 (0.0)	1 (0.9)
	Investigations	Aspartate aminotransferase increased	1 (0.8)	0 (0.0)
Cerebrovascular events	Nervous system disorders	Cerebrovascular accident	0 (0.0)	1 (0.9)

Based upon the potential effect of androgen replacement on the cardiovascular system, ECGs were obtained and results assessed. There were very few TEAEs of ECG abnormalities reported in this study, and none of these events included as ECG abnormalities were judged to be at least possibly related to study medication by the investigator.

7.3 Supportive Safety Results and Discussion

Serious AEs (SAEs) were defined as those events that led to death, were immediately life-threatening, resulted in a persistent or significant disability or incapacity, required or prolonged hospitalization, involved congenital anomaly, or required intervention to prevent one of the prior conditions from occurring. Eight (6.7%) subjects in the TU 750 group and 10 (8.5%) subjects in the TU 1000 group experienced at least one treatment-emergent SAE during the treatment period. Only 2 SAEs were observed in more than 1 subject: Atrial fibrillation was reported in 2 subjects in the TU 750 mg group, while knee arthroplasty was reported in 2 subjects in the TU 1000 mg group. No treatment-emergent SAEs judged by the investigator as at least possibly related to study medication were observed in either treatment group.

AEs were defined as “other significant events” if they met 1 or more of the following criteria: led to discontinuation of study medication, led to temporary interruption of study medication, or required dose reduction. Table 12 summarizes these events.

Table 12.

Incidence of Other Significant TEAEs by Criterion Regardless of Relationship – Total Patient Sample (Study IP157-001 Part A Stage 1)

Other significant TEAE criterion	Number of patients (%) TU 750 (N=120)	TU 1000 (N=117)
Led to discontinuation of study medication	6 (5.0)	4 (3.4)
Led to temporary interruption of study medication	2 (1.7)	1 (0.9)
Required dose reduction of study medication	0 (0.0)	0 (0.0)

AEs Leading to Discontinuation

Those AEs judged by the investigator to be at least possibly related to study drug and leading to discontinuation were:

• Subject 027-4101 (TU 750 mg arm) was discontinued from the study due to an increased PSA.

• Subject 056-4077 (TU 1000 mg arm) was discontinued from the study due to increased estradiol.

• Subject 040-4116 (TU 1000 mg arm) was discontinued from the study due to an increased red blood cell count.

Clinical laboratory data were collected at screening, baseline (1st injection visit), Week 12 (2nd injection visit) and Week 36 (4th injection visit). Lipids (total cholesterol, LDL, HDL, triglycerides) and PSA data were collected at screening, baseline, and at every injection visit (Weeks 12, 24, 36 and 48).

Laboratory data were reviewed for changes that occurred from baseline to each protocol-scheduled time point. In addition, laboratory data were analyzed using predefined criteria to identify potentially clinically significant abnormal laboratory values.

The Sponsor's analysis of average changes from pre-treatment to endpoint is summarized as follows:

• With the exception of changes in erythropoiesis, hormones, and a few other outcomes, the mean and median changes from baseline to endpoint were generally small in magnitude and similar between the treatment groups for most laboratory parameters.

• Liver function tests (e.g., alkaline phosphatase, ALT, and AST) demonstrated slight average decreases from pre-treatment to endpoint; these reductions in these enzymes were judged to be not clinically meaningful.

• Blood urea nitrogen (BUN) and calcium decreased from pre-treatment in both treatment groups; the average decreases were similar between the treatment groups.

• The Sponsor believes that decreases in calcium and phosphorus are to be expected, as E2 is known to regulate bone resorption; the Sponsor believes that higher levels of E2 following testosterone replacement would be expected to lead to less bone resorption (and thus lower serum calcium and phosphorus levels).

• The most notable changes from pre-treatment to endpoint were the decreases in average FSH and LH. Average FSH and LH each decreased approximately 60% from pre-treatment to the endpoint in both treatment arms. The TU 1000 mg arm had a slightly higher pre-treatment mean LH, and the Sponsor believes that the slightly larger decrease to the endpoint is possibly a result of the higher pre-treatment mean, as compared to the TU 750 mg arm.

Subjects with primary hypogonadism are marked by testicular failure, and thus these subjects may have higher average LH and FSH values than subjects with secondary hypogonadism (who are marked by a systemic failure of the pituitary-hypothalamic-gonadal axis, and thus by generally lower LH and FSH). In this study; there were slightly more subjects diagnosed with primary hypogonadism than with secondary hypogonadism. Therefore, the Sponsor believes that the changes in LH and FSH values observed in this study reflect the fact that the majority of subjects in this study were diagnosed with primary hypogonadism (per the medical history data). Pre-treatment concentrations of both LH and FSH were in the middle of their normal ranges for both treatment groups, but there were many subjects with elevated (above-normal) LH and FSH values pre-treatment. By Week 36 of treatment, average LH and FSH values had dropped to near the lower limits of normal for both hormones, and the majority of subjects had both LH and FSH values within the normal range.

7.3.1 Laboratory Findings

With the exception of changes in erythropoiesis, hormones, and a few other outcomes, the mean and median changes from baseline to endpoint for most laboratory parameters were generally small in magnitude and similar between the treatment groups.

Table 13 provides a summary of the average changes for most laboratory parameters in Study IP157-001 Part A.

Table 13. **Changes from Pre-Treatment to Endpoint in Clinical Laboratory Parameters (Hematology, Serum Chemistry, and Lipids) – Total Patient Sample (Study IP157-001 Part A Stage 1)**

Laboratory Parameter	TU 750 (N=120)			TU 1000 (N=117)		
	Pre-Treatment	Endpoint	Change	Pre-Treatment	Endpoint	Change
Hematology						
WBC (10^3/uL) N	119	119	119	114	114	114
Mean (SE)	6.7 (0.16)	6.8 (0.18)	0.01(0.14)	6.5 (0.15)	6.8 (0.18)	0.3 (0.15)
Median	6.4	6.5	-0.0	6.4	6.5	0.3
Range	2.3, 14.9	2.6, 15.7	-4.2, 7.6	2.9, 11.7	3.6, 15.4	-5.1, 8.6
Lymphocytes (%) N	119	119	119	114	114	114
Mean (SE)	30.2 (0.73)	29.5 (0.73)	-0.7 (0.56)	29.7 (0.66)	29.2 (0.66)	-0.5 (0.60)
Median	29.7	28.4	-1.2	28.6	28.8	-0.1
Range	12.5, 54.2	11.2, 53.8	-16.9, 19.4	9.8, 53.9	17.3, 50.4	-18.6, 19.0
Monocytes (%) N	119	119	119	114	114	114
Mean (SE)	6.0 (0.14)	6.2 (0.17)	0.2 (0.18)	6.2 (0.16)	6.3 (0.15)	0.0 (0.16)
Median	5.8	6.1	0.1	6.1	6.2	0.2
Range	1.0, 12.2	0.0, 15.0	-7.0, 8.5	2.7, 11.5	3.0, 10.9	-6.8, 4.0
Basophils (%) N	119	119	119	114	114	114
Mean (SE)	0.9 (0.04)	0.9 (0.04)	0.0 (0.05)	0.8 (0.04)	0.9 (0.06)	0.1 (0.07)
Median	0.8	0.8	0.0	0.8	0.8	0.0
Range	0.0, 2.5	0.0, 3.0	-1.3, 2.1	0.0, 2.6	0.0, 3.0	-1.9, 2.5
Eosinophils (%) N	119	119	119	114	114	114
Mean (SE)	2.6 (0.14)	3.0 (0.18)	0.4 (0.15)	2.6 (0.13)	2.9 (0.16)	0.2 (0.15)
Median	2.2	2.7	0.2	2.5	2.5	0.2
Range	0.3, 9.4	0.0, 13.2	-6.4, 9.9	0.4, 7.0	0.0, 8.5	-4.4, 5.1
Neutrophils (%) N	119	119	119	114	114	114
Mean (SE)	60.3 (0.74)	60.4 (0.78)	0.1 (0.65)	60.6 (0.73)	60.6 (0.72)	0.0 (0.71)
Median	60.2	61.4	0.7	60.8	60.6	-0.4
Range	37.4, 81.7	36.9, 77.4	-25.4, 16.4	39.5, 82.2	39.3, 76.4	-27.4, 20.6
RBC (10^6/uL) N	119	119	119	114	114	114
Mean (SE)	5.2 (0.04)	5.1 (0.04)	-0.1 (0.03)	5.2 (0.04)	5.2 (0.04)	-0.0 (0.04)
Median	5.2	5.2	-0.1	5.3	5.2	0.0
Range	4.0, 6.3	3.9, 5.9	-1.0, 0.8	4.1, 6.5	3.9, 6.6	-0.9, 1.0
Hematocrit (%) N	119	119	119	114	114	114

Mean (SE)	45.0 (0.36)	45.1 (0.36)	0.1 (0.32)	44.8 (0.34)	45.9 (0.36)	1.0 (0.34)
Median	45.0	45.0	0.0	45.0	46.0	1.0
Range	28.0, 56.0	30.0, 55.0	-15.0, 11.0	35.0, 52.0	34.0, 61.0	-7.0, 12.0
Hemoglobin (g/dL) N	119	119	119	114	114	114
Mean (SE)	15.0 (0.12)	15.3 (0.12)	0.3 (0.11)	14.9 (0.13)	15.5 (0.13)	0.6 (0.11)
Median	15.0	15.5	0.3	15.0	15.5	0.5
Range	9.9, 17.8	10.4, 18.3	-3.4, 4.0	11.2, 18.2	11.2, 18.9	-3.0, 4.0
Platelet Count (10^3/uL) N	117	117	117	114	114	114
Mean (SE)	240.8 (5.34)	240.2 (5.59)	-0.6 (3.43)	244.3 (5.33)	241.5 (5.59)	-2.9 (2.97)
Median	234.0	232.0	-1.0	239.5	232.0	-3.5
Range	122.0, 392.0	114.0, 384.0	-94.0, 164.0	120.0, 416.0	138.0, 463.0	-80.0, 89.0
PT Value (sec) N	115	115	115	112	112	112
Mean (SE)	12.0 (0.07)	12.4 (0.08)	0.4 (0.09)	12.1 (0.07)	12.3 (0.07)	0.2 (0.07)
Median	11.9	12.3	0.4	12.0	12.2	0.2
Range	10.6, 17.3	10.9, 16.6	-4.6, 5.5	10.7, 15.8	10.9, 14.6	-3.9, 1.6
PTT Value (sec) N	115	115	115	112	112	112
Mean (SE)	23.8 (0.29)	24.9 (0.27)	1.1 (0.27)	24.0 (0.37)	24.8 (0.34)	0.8 (0.39)
Median	23.1	24.6	1.1	23.4	24.4	1.0
Range	18.4, 42.7	20.0, 36.6	-16.2, 10.1	18.5, 54.5	17.8, 48.4	-31.1, 20.1
INR Value N	115	115	115	112	112	112
Mean (SE)	1.0 (0.01)	1.1 (0.01)	0.0 (0.02)	1.1 (0.01)	1.1 (0.01)	-0.0 (0.01)
Median	1.0	1.1	0.0	1.0	1.0	0.0
Range	0.8, 2.1	0.8, 1.9	-1.0, 1.0	0.8, 1.7	0.8, 1.6	-0.8, 0.3
Serum Chemistry						
Total Protein (g/dL) N	119	119	119	114	114	114
Mean (SE)	7.3 (0.04)	7.3 (0.04)	0.0 (0.03)	7.3 (0.04)	7.3 (0.04)	0.0 (0.03)
Median	7.2	7.3	0.0	7.3	7.3	0.0
Range	6.0, 8.3	6.2, 8.1	-0.8, 1.2	6.2, 8.5	6.4, 8.3	-1.0, 0.8
Albumin (g/dL) N	119	119	119	114	114	114
Mean (SE)	4.3 (0.03)	4.2 (0.03)	-0.1 (0.02)	4.3 (0.03)	4.2 (0.03)	-0.1 (0.02)
Median	4.2	4.1	-0.1	4.3	4.2	-0.1
Range	3.5, 5.5	3.6, 5.3	-0.9, 0.8	3.4, 4.8	3.5, 4.9	-0.6, 0.7

Laboratory Parameter	TU 750 (N=120)			TU 1000 (N=117)		
	Pre-Treatment	Endpoint	Change	Pre-Treatment	Endpoint	Change
Creatinine (mg/dL) N	119	119	119	114	114	114
Mean (SE)	1.0 (0.02)	1.1 (0.02)	0.1 (0.01)	1.0 (0.02)	1.1 (0.02)	0.1 (0.01)
Median	1.0	1.1	0.1	1.0	1.0	0.1
Range	0.6, 1.6	0.6, 1.7	-0.2, 0.8	0.7, 1.6	0.7, 1.9	-0.3, 0.5
Urea Nitrogen (BUN) (mg/dL) N	119	119	119	114	114	114
Mean (SE)	17.5 (0.42)	16.9 (0.42)	-0.6 (0.32)	19.4 (0.52)	17.5 (0.42)	-1.9 (0.35)
Median	17.0	16.0	-1.0	19.0	17.0	-2.0
Range	7.0, 31.0	7.0, 30.0	-8.0, 7.0	7.0, 43.0	9.0, 34.0	-13.0, 9.0
Uric Acid (mg/dL) N	119	119	119	114	114	114
Mean (SE)	6.5 (0.12)	6.3 (0.13)	-0.2 (0.10)	6.9 (0.14)	6.5 (0.15)	-0.4 (0.11)
Median	6.4	6.2	-0.2	6.7	6.2	-0.4
Range	3.3, 10.1	3.7, 10.7	-3.3, 4.6	3.9, 12.8	3.9, 16.4	-4.1, 3.6
Direct Bilirubin (mg/dL) N	119	119	119	114	114	114
Mean (SE)	0.1 (0.01)	0.1 (0.01)	0.0 (0.01)	0.1 (0.01)	0.2 (0.01)	0.0 (0.01)
Median	0.1	0.1	0.0	0.1	0.1	0.0
Range	0.1, 0.3	0.1, 0.4	-0.2, 0.1	0.1, 0.3	0.1, 0.4	-0.1, 0,2
Total Bilirubin (mg/dL) N	119	119	119	114	114	114
Mean (SE)	0.6 (0.05)	0.6 (0.05)	0.1 (0.02)	0.6 (0.02)	0.6 (0.02)	0.1 (0.02)
Median	0.5	0.5	0.0	0.5	0.6	0.1
Range	0.2, 5.5	0.2, 6.2	-0.5, 0.7	0.2, 1.3	0.2, 1.8	-0.6, 0.9
Alkaline Phosphatase (U/L) N	119	119	119	114	114	114
Mean (SE)	72.4 (1.92)	69.8 (1.77)	-2.6 (0.86)	73.9 (1.88)	71.1 (1.76)	-2.8(0.97)
Median	68.0	67.0	-2.0	73.0	68.5	-2.0
Range	27.0, 140.0	25.0, 124.0	-38.0, 19.0	25.0, 143.0	23.0, 126.0	-39.0, 33.0
SGPT (ALT) (U/L) N	119	119	119	114	114	114
Mean (SE)	32.0 (1.25)	31.1 (1.31)	-0.9 (0.98)	30.0 (1.13)	28.4 (1.00)	-1.6 (1.06)
Median	30.0	27.0	-1.0	27.0	26.0	0.5
Range	11.0, 87.0	13.0, 95.0	-48.0, 34.0	8.0, 84.0	11.0, 66.0	-56.0, 30.0
SGOT (AST) (U/L) N	119	119	119	114	114	114
Mean (SE)	26.8 (0.74)	25.6 (0.86)	-1.2 (0.68)	26.6 (1.17)	24.5 (0.88)	-2.2 (1.22)
Median	25.0	23.0	-1.0	24.5	23.0	-1.0
Range	15.0, 62.0	13.0, 81.0	-27.0, 39.0	16.0, 139.0	13.0, 103.0	-110.0, 56.0

Creatine Phosphokinase (U/L) N	119	119	119	114	114	114
Mean (SE)	172.8 (10.92)	184.8 (17.90)	12.0 (16.71)	191.5 (34.35)	170.3 (12.84)	-21.2 (33.86)
Median	136.0	139.0	0.0	123.0	139.0	-1.5
Range	44.0, 715.0	40.0, 1944.0	-374.0, 1633.0	28.0, 3922.0	26.0, 930.0	-3686.0, 566.0
Fasting Glucose (mg/dL) N	96	96	96	106	106	106
Mean (SE)	105.8 (3.00)	110.2 (3.39)	4.4 (2.20)	104.1 (2.16)	109.0 (2.82)	4.9 (2.20)
Median	97.5	102.0	4.0	100.0	101.0	3.0
Range	71.0, 260.0	48.0, 264.0	-92.0, 81.0	74.0, 212.0	79.0, 243.0	-58.0, 135.0
Calcium (mg/dL) N	119	119	119	114	114	114
Mean (SE)	9.8 (0.04)	9.7 (0.03)	-0.1 (0.04)	9.8 (0.03)	9.7 (0.03)	-0.1 (0.04)
Median	9.8	9.7	-0.1	9.8	9.7	-0.1
Range	8.9, 11.4	9.0, 10.6	-1.1, 1.2	9.1, 11.0	8.8, 10.4	-1.7, 0.9
Phosphorus (mg/dL) N	119	119	119	114	114	114
Mean (SE)	3.4 (0.05)	3.2 (0.06)	-0.2 (0.06)	3.5 (0.05)	3.3 (0.05)	-0.2 (0.06)
Median	3.4	3.2	-0.1	3.5	3.3	-0.1
Range	1.8, 5.6	1.6, 5.1	-2.2, 1.4	2.2, 5.6	2.3, 4.5	-2.0, 1.1
Sodium (mEq/L) N	119	119	119	114	114	114
Mean (SE)	140.6 (0.24)	140.4 (0.24)	-0.2 (0.24)	140.5 (0.24)	140.7 (0.21)	0.2 (0.23)
Median	140.0	140.0	0.0	140.0	140.0	0.0
Range	133.0, 151.0	133.0, 152.0	-8.0, 7.0	134.0, 153.0	136.0, 150.0	-7.0, 7.0
Potassium (mEq/L) N	119	119	119	114	114	114
Mean (SE)	4.3 (0.04)	4.3 (0.03)	0.0 (0.04)	4.3 (0.04)	4.3 (0.04)	0.1 (0.03)
Median	4.2	4.3	0.0	4.3	4.3	0.0
Range	3.0, 5.4	3.4, 5.6	-0.9, 1.3	3.3, 5.5	3.2, 5.7	-0.9, 1.2
Chloride (mEq/L) N	119	119	119	114	114	114
Mean (SE)	102.9 (0.23)	102.6 (0.22)	-0.3 (0.23)	102.3 (0.27)	102.2 (0.24)	-0.1 (0.27)
Median	103.0	102.0	0.0	103.0	102.0	0.0
Range	99.0, 112.0	96.0, 112.0	-11.0, 7.0	94.0, 110.0	93.0, 111.0	-7.0, 9.0
Bicarbonate (mEq/L) N	119	119	119	114	114	114
Mean (SE)	26.2 (0.23)	25.8 (0.24)	-0.3 (0.25)	26.3 (0.24)	26.1 (0.26)	-0.2 (0.23)
Median	26.2	26.3	-0.4	26.4	25.8	-0.4
Range	18.2, 34.1	18.8, 32.8	-7.6, 6.9	18.3, 32.0	19.6, 33.7	-6.4, 7.7

Laboratory Parameter	**TU 750 (N=120)**			**TU 1000 (N=117)**		
	Pre-Treatment	**Endpoint**	**Change**	**Pre-Treatment**	**Endpoint**	**Change**

Laboratory Parameter	TU 750 (N=120)			TU 1000 (N=117)		
	Pre-Treatment	Endpoint	Change	Pre-Treatment	Endpoint	Change
FSH (mIU/dL) N	119	119	119	114	114	114
Mean (SE)	9.4 (1.11)	3.6 (0.67)	-5.8 (0.78)	9.9 (1.27)	2.9 (0.85)	-7.0 (0.72)
Median	6.0	1.0	-3.0	6.0	1.0	-5.0
Range	1.0, 71.0	1.0, 66.0	-62.0, 3.0	1.0, 113.0	1.0, 92.0	-41.0, 2.0
LH (mIU/dL)	119	119	119	114	114	114
Mean (SE)	5.7 (0.57)	2.1 (0.41)	-3.5 (0.44)	6.4 (0.89)	1.6 (0.31)	-4.7 (0.66)
Median	4.0	1.0	-2.0	4.0	1.0	-2.5
Range	1.0, 34.0	1.0, 44.0	-29.0, 10.0	1.0, 82.0	1.0, 34.0	-48.0, 2.0
Lipids[1]						
Triglycerides (mg/dL) N	98	98	98	107	107	107
Mean (SE)	204.6 (13.17)	193.3 (16.64)	-11.4 (12.59)	192.9 (15.17)	169.6 (11.74)	-23.2 (15.67)
Median	170.0	155.5	-9.0	165.0	146.0	-12.0
Range	47.0, 776.0	50.0, 1391.0	-396.0, 615.0	49.0, 1333.0	47.0, 1044.0	-1158.0, 639.0
Total Cholesterol (mg/dL) N	98	98	98	107	107	107
Mean (SE)	190.5 (4.17)	187.1 (4.22)	-3.4 (3.32)	190.1 (3.62)	181.4 (3.78)	-8.7 (3.34)
Median	191.0	187.5	-2.5	193.0	180.0	-11.0
Range	100.0, 327.0	91.0, 345.0	-107.0, 94.0	106.0, 281.0	103.0, 328.0	-112.0, 101.0
HDL (mg/dL) N	98	98	98	107	107	107
Mean (SE)	44.3 (1.07)	41.4 (1.08)	-2.9 (0.85)	44.9 (0.94)	43.1 (0.95)	-1.7 (0.70)
Median	44.0	40.0	-2.0	43.0	42.0	-1.0
Range	25.0, 71.0	21.0, 86.0	-48.0, 15.0	30.0, 75.0	29.0, 77.0	-35.0, 34.0
LDL (mg/dL) N	89	89	89	106	106	106
Mean (SE)	105.9 (3.57)	108.5 (3.40)	2.6 (2.89)	109.1 (3.11)	105.9 (3.37)	-3.2 (2.81)
Median	104.0	110.0	3.0	109.5	104.0	-2.0
Range	40.0, 200.0	43.0, 206.0	-81.0, 90.0	27.0, 197.0	33.0, 228.0	-79.0, 85.0

Individual potentially clinically significant (PCS) abnormalities in hematology laboratory parameters in Study IP157-001 Part A are shown in Table 14:

Table 14.

Hematology: PCS Abnormal Values Reported in at least 2 Patients in Either Treatment Group at Endpoint – Total Patient Sample (Study IP157-001 Part A Stage 1)

Hematology PCS abnormal value	TU 750 (N=120)		TU 1000 (N=117)	
	n/N (%)	Normal at BL n/N (%)	n/N (%)	Normal at BL n/N (%)
Number of patients with at least 1 Hematology PCS abnormal value	7/119 (5.9)	4/119 (3.4)	4/114 (3.5)	2/114 (1.8)
Eosinophils – High (≥ 10%)	2/119 (1.7)	2/119 (1.7)	0/114 (0.0)	0/114 (0.0)
Hematocrit – Low (≤ 37%)	2/119 (1.7)	0/115 (0.0)	2/114 (1.8)	0/111 (0.0)
PT Value – High (≥ 16 seconds)	2/116 (1.7)	2/114 (1.8)	0/113 (0.0)	0/112 (0.0)

Table 15 summarizes serum chemistry individual PCS abnormalities in Part A.

Table 15.

Serum Chemistry, FSH, LH, and Lipids: PCS Abnormal Values Reported in at least 2 Patients in Either Treatment Group at Endpoint – Total Patient Sample (Study IP157-001 Part A Stage 1)

Chemistry PCS abnormal value	TU 750 (N=120)		TU 1000 (N=117)	
	n/N (%)	Normal at BL n/N (%)	n/N (%)	Normal at BL n/N (%)
Number of patients with at least 1 Chemistry PCS abnormal value	9/119 (7.6)	5/119 (4.2)	5/114 (4.4)	0/114 (0.0)
Urea Nitrogen (BUN) – High (≥ 30 mg/dL)	1/119 (0.8)	0/118 (0.0)	2/114 (1.8)	0/110 (0.0)
Phosphorus – Low (≤ 1.7 mg/dL)	2/119 (1.7)	2/119 (1.7)	0/114 (0.0)	0/114 (0.0)
Follicle Stimulating Hormone – High (> 20 mIU/mL)	2/119 (1.7)	0/107 (0.0)	2/114 (1.8)	0/103 (0.0)
Luteinizing Hormone – High (>18 mIU/mL)	2/119 (1.7)	0/112 (0.0)	1/114 (0.9)	0/107 (0.0)
Fasting Triglycerides – High (>600 mg/dL)	2/109 (1.8)	1/97 (1.0)	1/110 (0.9)	1/105 (1.0)
Fasting HDL – Low (≤ 30 mg/dL)	14/109 (12.8)	7/90 (7.8)	6/110 (5.5)	4/104 (3.8)
Fasting LDL – High (≥ 200 mg/dL)	2/105 (1.9)	2/88 (2.3)	1/109 (0.9)	1/106 (0.9)

PCS abnormalities in serum hormone levels were defined as follows:

- DHT > 1300 pg/mL
- E2 > 70 pg/mL
- Free T > 800 pg/mL
- SHBG > 70 nmol/L
- DHT:T Ratio > 0.25
- E2:T Ratio > 0.025

Using these definitions, abnormal hormone PCS values in Study IP157-001 Part A are summarized in Table 16.

Table 16.

Hormone PCS abnormal value	TU 750 (N=120)		TU 1000 (N=117)	
	n/N (%)	Normal at BL n/N (%)	n/N (%)	Normal at BL n/N (%)
Number of patients with at least 1 Hormone PCS abnormal value	3/118 (2.5)	3/118 (2.5)	1/113 (0.9)	1/113 (0.9)
E2 – High (> 70 pg/mL)	2/117 (1.7)	2/116 (1.7)	0/113 (0.0)	0/112 (0.0)
DHT – High (> 1300 pg/mL)	0/118 (0.0)	0/118 (0.0)	0/113 (0.0)	0/113 (0.0)
Free T – High (> 800 pg/mL)	0/118 (0.0)	0/118 (0.0)	1/113 (0.9)	1/113 (0.9)
SHBG – High (> 70 nmol/L)	0/118 (0.0)	0/116 (0.0)	0/113 (0.0)	0/110 (0.0)
DHT:T Ratio – High (> 0.25)	1/117 (0.9)	1/109 (0.9)	0/112 (0.0)	0/106 (0.0)
E2:T Ratio – High (> 0.025)	1/116 (0.9)	1/106 (0.9)	0/113 (0.0)	0/103 (0.0)
Free T:T Ratio – High (> 0.08)	0/117 (0.0)	0/114 (0.0)	0/113 (0.0)	0/110 (0.0)

7.3.2 Vital Signs, Physical Findings and Other Safety Related Observations in Part A

A summary of mean changes in vital signs in Study IP157-001 Part A is shown in Tables 17 and 18.

Table 17.

Changes from Pre-Treatment to Endpoint in Vital Sign Parameters – Total Patient Sample (Study IP157-001 Part A Stage 1)

Vital Sign Parameter	TU 750 (N=120)			TU 1000 (N=117)		
	Pre-Treatment	Endpoint	Change	Pre-Treatment	Endpoint	Change
Systolic BP (mm Hg) N	113	113	113	106	106	106
Mean (SE)	127.0 (1.11)	128.6 (1.28)	1.5 (1.22)	126.8 (1.16)	129.1 (1.37)	2.3 (1.30)
Median	127.0	126.0	2.0	126.0	130.0	2.0
Range	96.0 to 154.0	86.0 to 175.0	-46.0 to 36.0	94.0 to 163.0	90.0 to 185.0	-35.0 to 70.0
Diastolic BP (mm Hg) N	113	113	113	106	106	106
Mean (SE)	79.3 (0.69)	80.1 (0.75)	0.8 (0.79)	78.3 (0.73)	79.4 (0.90)	1.1 (0.91)
Median	80.0	80.0	0.0	79.5	80.0	0.0
Range	58.0 to 97.0	46.0 to 96.0	-20.0 to 28.0	60.0 to 99.0	58.0 to 114.0	-16.0 to 38.0
Pulse (bpm) N	113	113	113	106	106	106
Mean (SE)	72.1 (0.88)	71.4 (0.85)	-0.7 (0.96)	70.2 (0.80)	71.0 (0.95)	0.8 (0.91)
Median	72.0	70.0	0.0	70.0	72.0	0.0
Range	54.0 to 100.0	48.0 to 96.0	-42.0 to 20.0	52.0 to 88.0	52.0 to 97.0	-26.0 to 23.0

Table 18.

Vital Signs: PCS Abnormal Values Occurring at Endpoint in at least 2 Patients in Either Treatment Group – Total Patient Sample (Study IP157-001 Part A Stage 1)

Vital signs PCS abnormal value	TU 750 (N=120)		TU 1000 (N=117)	
	n/N (%)	Normal at BL n/N (%)	n/N (%)	Normal at BL n/N (%)
Systolic blood pressure:				
Low: < 90 or decrease ≥ 20 mmHg	7/113 (6.2)	7/113 (6.2)	4/106 (3.8)	4/106 (3.8)
High: >180 or increase ≥ 20 mm Hg	6/113 (5.3)	6/113 (5.3)	11/106 (10.4)	11/106 (10.4)
Diastolic blood pressure:				
Low: < 50 or decrease ≥ 15 mm Hg	3/113 (2.7)	3/113 (2.7)	6/106 (5.7)	6/106 (5.7)
High: >105 or increase ≥ 15 mm Hg	9/113 (8.0)	9/113 (8.0)	7/106 (6.6)	7/106 (6.6)
Pulse				
Low: Decrease ≥ 15 bpm	9/113 (8.0)	9/113 (8.0)	7/106 (6.6)	7/106 (6.6)
Low: <50, Decrease ≥15 bpm or both	10/113 (8.8)	10/113 (8.8)	7/106 (6.6)	7/106 (6.6)

There were no meaningful changes in any physical examination assessments of abnormalities from pre-treatment to the 4th injection visit; further, the treatment groups were similar in the incidence of abnormal findings at both pre-treatment and the 4th injection visit.

7.3.3 ECG's

Descriptive statistics for changes in ECG parameters in Study IP157-001 Part A are provided in Table 19.

Table 19.

Changes from Pre-Treatment to Endpoint in ECG Parameters – Total Patient Sample (Study IP157-001 Part A Stage 1)

Vital Sign Parameter	TU 750 (N=120)			TU 1000 (N=117)		
	Pre-Treatment	Endpoint	Change	Pre-Treatment	Endpoint	Change
PR Interval (msec) N	109	109	109	103	103	103
Mean (SE)	165.7 (2.30)	166.0 (2.22)	0.3 (1.10)	166.2 (2.85)	165.9 (2.69)	-0.3 (2.09)
Median	164.0	164.0	0.0	162.0	162.0	-1.0
Range	110.0 to 252.0	128.0 to 256.0	-50.0 to 50.0	82.0 to 284.0	118.0 to 256.0	-90.0 to 76.0
QRS Interval (msec) N	111	111	111	103	103	103
Mean (SE)	92.3 (2.10)	95.3 (1.31)	3.0 (1.77)	94.0 (1.86)	97.1 (1.60)	3.0 (1.56)
Median	94.0	96.0	0.0	96.0	94.0	0.0
Range	6.0 to 174.0	33.0 to 160.0	-75.0 to 95.0	21.0 to 166.0	60.0 to 164.0	-22.0 to 99.0
QTcF (msec) N	111	111	111	103	103	103
Mean (SE)	405.9 (2.03)	403.6 (1.94)	-2.3 (1.96)	408.4 (2.29)	403.1 (2.71)	-5.4 (2.39)
Median	406.2	402.1	-4.2	404.7	401.9	-5.5
Range	336.9 to 490.4	344.7 to 490.4	-48.1 to 91.1	338.8 to 477.3	242.1 to 485.6	-155.2 to 48.1
Heart Rate (bpm) N	111	111	111	103	103	103
Mean (SE)	67.5 (1.01)	68.2 (0.98)	0.7 (0.92)	65.6 (1.00)	67.7 (1.02)	2.1 (0.92)
Median	67.0	66.0	2.0	66.0	66.0	3.0
Range	47.0 to 108.0	45.0 to 95.0	-39.0 to 29.0	41.0 to 92.0	44.0 to 97.0	-23.0 to 31.0

Reviewer's Comment: There do not appear to be any significant changes from baseline in mean ECG parameters.

7.3.4 Special Safety Studies

Prostate-Related Assessments in Part A

Special attention was given to the prostate health of subject in Study IP157-001 Part A. Subjects were excluded from this study if they had a screening serum PSA level > 4 ng/mL or hyperplasia of the prostate (defined as prostate volume > 75 cm3 as measured by transrectal ultrasonography). During the study, PSA and digital rectal examinations (DRE) were performed at every injection visit, and prostate biopsies were to have been performed for any subject with a PSA > 4 ng/dL.

There were 9 subjects in the 750 mg arm and 4 in the 1000 mg arm with at least one post-baseline PSA value > 4 ng/mL during this study. There were elevated PSA values observed at each post-baseline injection visit during the study.

Table 20 provides the number (%) of patients who had PSA value > 4 ng/mL at each injection visit and at any time during this study.

Table 20.

Time (Visit)	Relation to normal range	Number (%) of Patients	
		TU 750 (N=120)	TU 1000 (N=117)
Screening	Within 0 to 4 ng/mL	120 (100.0)	116 (100.0)
	Above 4 ng/mL	0 (0.0)	0 (0.0)
Baseline (1st Injection Visit)	Within 0 to 4 ng/mL	116 (100.0)	116 (100.0)
	Above 4 ng/mL	0 (0.0)	0 (0.0)
Week 12 (2nd Injection Visit)	Within 0 to 4 ng/mL	109 (97.3)	114 (100.0)
	Above 4 ng/mL	3 (2.7)	0 (0.0)
Week 24 (3rd Injection Visit)	Within 0 to 4 ng/mL	99 (96.1)	104 (100.0)
	Above 4 ng/mL	4 (3.9)	0 (0.0)
Week 36 (4th Injection Visit)	Within 0 to 4 ng/mL	99 (97.1)	95 (99.0)
	Above 4 ng/mL	3 (2.9)	1 (1.0)
Endpoint - Week 48 (5th Injection Visit) or Early Discontinuation	Within 0 to 4 ng/mL	112 (94.1)	111 (97.4)
	Above 4 ng/mL	7 (5.9)	3 (2.6)
Any Time[1]	Within 0 to 4 ng/mL	110 (92.4)	110 (96.5)
	Above 4 ng/mL	9 (7.6)	4 (3.5)

Figure 9 provides a plot of the by-treatment mean PSA values over time in Part A, from the screening visit through the Injection 5 visit, and the corresponding mean (standard deviation) T concentrations at the same time points.

Figure 9. Mean (Standard Deviation) Serum Total Testosterone – PK Population Compared to Mean (Standard Deviation) PSA over Time by Treatment in Part A

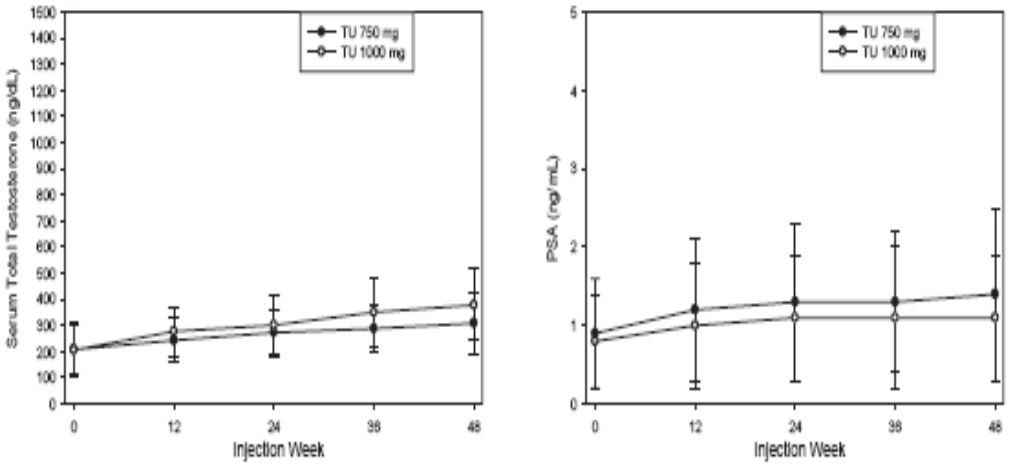


Table 21 presents a list of the incidence rates of prostate-related TEAEs in Part A.

Table 21. **Incidence of TEAEs related to Prostate Health by Preferred Term – Total Patient Sample (Study IP157-001 Part A Stage 1)**

MedDRA System Organ Class	MedDRA Preferred term	Number of patients (%)	
		TU 750 (N=120)	TU 1000 (N=117)
Investigations	Prostatic specific antigen increased	4 (3.3)	1 (0.9)
	Prostate examination abnormal	2 (1.7)	1 (0.9)
Reproductive system and breast disorders	Benign prostatic hyperplasia	2 (1.7)	3 (2.6)
	Prostatic intraepithelial neoplasia	1 (0.8)	2 (1.7)
	Prostatitis	0 (0.0)	2 (1.7)
	Prostatic disorder	1 (0.8)	0 (0.0)

The Sponsor provides the following summary of prostate health assessments in Part A:

• Approximately 5% of the 237 subjects treated in this study had at least one on-treatment PSA concentration >4 ng/mL.

• A higher percentage of subjects in the low-dose arm (TU 750 mg) had at least one elevated PSA (as compared to the TU 1000 mg arm).

• There were 6 subjects with a pre-treatment PSA between 3 ng/mL and 4 ng/mL; 3 (50%) of these subjects had at least one on-treatment PSA >4 ng/mL.

• Rigorous tracking of PSA was performed in this study, with an average of 4 on-treatment PSA assessments performed per subject in this study (a PSA sample was collected once every 12 weeks while the subjects were on-treatment). The Sponsor believes that the high level of rigor in the assessment of PSA may account for the incidence of elevated PSA concentrations in this study.

• PSA increased, as expected, with the TU 1000 mg pre-treatment median PSA 0.6 ng/mL and the endpoint median PSA 0.9 ng/mL (the median increase was 0.2 ng/mL during the 48-week treatment period).

• There were no prostate cancers reported in this 48 week study. However, there were a number of AEs related to the prostate reported in both treatment groups (PSA increased, prostate examination abnormal, benign prostatic hyperplasia, prostatic intraepithelial neoplasia, prostatitis, and prostate disorder).

• The incidence of on-treatment (visit-wise) DRE findings were similar to the incidence observed pre-treatment.

• A higher percentage of subjects in the low-dose arm (TU 750 mg) had at least one DRE finding as compared to the TU 1000 mg arm.

• The Sponsor believes that the prostate health outcomes in this study were clinically consistent with those expected in a population of hypogonadal men receiving testosterone replacement; there was no evidence that treatment with TU 750 mg or with TU 1000 mg resulted in unexpected prostate health outcomes.

Changes in Mood States (POMS) in Part A

Both study arms (750mg and 1000mg) demonstrated similar mood disturbance scores, using the Profile of Mood States questionnaire, as seen in Table 22.

Table 22.

Summary Statistics For Changes in POMS: Change from Pre-Treatment to 5th Injection Visit (or End of Study) – PK Population (Study IP157-001 Part A Stage 1)

POMS Parameter	TU 750 (N=102)			TU 1000 (N=97)		
	Pre-Treatment	5th Injection Visit	Change	Pre-Treatment	5th Injection Visit	Change
Total Mood Disturbance N	100	100	100	95	95	95
Mean (SE)	34.0 (3.37)	14.1 (2.60)	-19.8 (2.82)	28.2 (3.05)	14.6 (2.89)	-13.6 (2.98)
Median	27.0	10.0	-13.0	25.0	7.0	-13.0
Range	-20.0 to 115.0	-24.0 to 90.0	-106.0 to 49.0	-19.0 to 133.0	-24.0 to 100.0	-85.0 to 94.0
Subscales						
Tension-anxiety N	100	100	100	95	95	95
Mean (SE)	10.4 (0.57)	7.5 (0.44)	-2.9 (0.51)	9.8 (0.56)	7.8 (0.51)	-2.0 (0.50)
Median	8.5	7.0	-3.0	8.0	7.0	-2.0
Range	2.0 to 26.0	2.0 to 23.0	-17.0 to 15.0	2.0 to 24.0	0.0 to 25.0	-16.0 to 11.0
Depression-dejection N	100	100	100	95	95	95
Mean (SE)	10.2 (1.02)	5.8 (0.70)	-4.3 (0.83)	9.0 (0.92)	6.4 (0.88)	-2.5 (0.94)
Median	7.0	4.0	-2.0	6.0	3.0	-2.0
Range	0.0 to 39.0	0.0 to 28.0	-31.0 to 10.0	0.0 to 46.0	0.0 to 35.0	-33.0 to 25.0
Anger-hostility N	100	100	100	95	95	95
Mean (SE)	9.0 (0.87)	5.6 (0.66)	-3.4 (0.73)	7.8 (0.79)	5.9 (0.73)	-1.9 (0.90)
Median	6.0	3.5	-1.5	5.0	3.0	-1.0
Range	0.0 to 37.0	0.0 to 25.0	-32.0 to 11.0	0.0 to 33.0	0.0 to 31.0	-23.0 to 29.0
Vigor-activity N	100	100	100	95	95	95
Mean (SE)	14.8 (0.59)	17.5 (0.64)	2.6 (0.61)	16.2 (0.61)	18.7 (0.67)	2.5 (0.58)
Median	14.0	18.0	2.0	16.0	20.0	2.0
Range	0.0 to 32.0	1.0 to 32.0	-13.0 to 18.0	2.0 to 31.0	1.0 to 32.0	-10.0 to 16.0
Fatigue-inertia N	100	100	100	95	95	95
Mean (SE)	11.9 (0.70)	6.8 (0.56)	-5.1 (0.62)	10.8 (0.65)	7.1 (0.56)	-3.7 (0.63)
Median	12.0	6.0	-4.0	10.0	6.0	-3.0
Range	0.0 to 27.0	0.0 to 21.0	-19.0 to 14.0	0.0 to 26.0	0.0 to 21.0	-20.0 to 12.0
Confusion-bewilderment N	100	100	100	95	95	95
Mean (SE)	7.4 (0.39)	5.9 (0.32)	-1.5 (0.32)	7.0 (0.37)	6.1 (0.34)	-0.9 (0.39)
Median	6.0	5.0	-1.0	6.0	5.0	-1.0
Range	0.0 to 18.0	0.0 to 15.0	-11.0 to 6.0	2.0 to 16.0	1.0 to 17.0	-11.0 to 13.0

"Urological Health" Parameters in Part A

"Urological health" was assessed via measurement of changes in lower urinary tract symptoms via the AUA Symptoms Score, and via the review of AEs related to urological health. Table 23 presents summary statistics for the AUA symptoms scores.

Table 23.

Summary Statistics For AUA: Baseline, Post-4th Injection Day 21 and Change from Baseline to Post-4th Injection Day 21 - PK Population (Study IP157-001 Part A Stage 1)

AUA Parameter	TU 750 (N=102)			TU 1000 (N=97)		
	Baseline	Day 21 of 4th Injection Interval	Change	Baseline	Day 21 of 4th Injection Interval	Change
Overall Total N	98	98	98	93	93	93
Mean (SE)	6.1 (0.42)	6.2 (0.60)	0.1 (0.42)	6.2 (0.44)	6.7 (0.57)	0.6 (0.44)
Median	5.0	4.0	0.0	6.0	6.0	0.0
Range	0.0 to 17.0	0.0 to 28.0	-13.0 to 15.0	0.0 to 14.0	0.0 to 27.0	-8.0 to 16.0
Subscales						
Incomplete Emptying N	98	98	98	93	93	93
Mean (SE)	0.8 (0.10)	0.7 (0.10)	-0.1 (0.08)	0.9 (0.12)	0.9 (0.12)	-0.0 (0.13)
Median	0.5	0.0	0.0	1.0	0.0	0.0
Range	0.0 to 4.0	0.0 to 4.0	-2.0 to 2.0	0.0 to 5.0	0.0 to 4.0	-5.0 to 3.0
Frequency N	98	98	98	93	93	93
Mean (SE)	1.2 (0.10)	1.4 (0.14)	0.2 (0.10)	1.3 (0.11)	1.4 (0.11)	0.1 (0.10)
Median	1.0	1.0	0.0	1.0	1.0	0.0
Range	0.0 to 4.0	0.0 to 5.0	-3.0 to 3.0	0.0 to 4.0	0.0 to 4.0	-3.0 to 3.0
Intermittency N	98	98	98	93	93	93
Mean (SE)	0.5 (0.08)	0.6 (0.09)	0.0 (0.07)	0.6 (0.08)	0.7 (0.11)	0.1 (0.08)
Median	0.0	0.0	0.0	0.0	0.0	0.0
Range	0.0 to 3.0	0.0 to 5.0	-2.0 to 3.0	0.0 to 3.0	0.0 to 4.0	-2.0 to 3.0
Urgency N	98	98	98	93	93	93
Mean (SE)	0.7 (0.10)	0.9 (0.13)	0.2 (0.11)	0.8 (0.10)	0.8 (0.12)	0.1 (0.11)
Median	0.0	0.0	0.0	0.0	0.0	0.0
Range	0.0 to 4.0	0.0 to 5.0	-2.0 to 4.0	0.0 to 4.0	0.0 to 5.0	-3.0 to 3.0
Weak stream N	98	98	98	93	93	93
Mean (SE)	0.9 (0.12)	0.9 (0.12)	-0.0 (0.10)	0.8 (0.12)	1.0 (0.14)	0.1 (0.11)
Median	1.0	0.0	0.0	0.0	0.0	0.0
Range	0.0 to 5.0	0.0 to 5.0	-5.0 to 3.0	0.0 to 5.0	0.0 to 5.0	-3.0 to 3.0
Straining N	98	98	98	93	93	93
Mean (SE)	0.4 (0.08)	0.4 (0.09)	-0.1 (0.09)	0.4 (0.08)	0.6 (0.10)	0.2 (0.09)
Median	0.0	0.0	0.0	0.0	0.0	0.0
Range	0.0 to 5.0	0.0 to 5.0	-5.0 to 4.0	0.0 to 5.0	0.0 to 4.0	-2.0 to 4.0
Nocturia N	98	98	98	93	93	93
Mean (SE)	1.5 (0.10)	1.5 (0.12)	-0.0 (0.12)	1.4 (0.10)	1.3 (0.12)	-0.1 (0.11)
Median	1.0	1.0	0.0	1.0	1.0	0.0
Range	0.0 to 5.0	0.0 to 5.0	-3.0 to 4.0	0.0 to 5.0	0.0 to 5.0	-3.0 to 5.0
Urinary Condition	98	98	98	93	93	93
Mean (SE)	1.7 (0.14)	1.5 (0.14)	-0.2 (0.09)	1.6 (0.14)	1.5 (0.13)	-0.1 (0.10)
Median	1.0	1.0	0.0	1.0	1.0	0.0
Range	0.0 to 5.0	0.0 to 5.0	-2.0 to 3.0	0.0 to 5.0	0.0 to 4.0	-2.0 to 3.0

Local Tolerability Assessments in Part A

Local tolerability was assessed approximately 10 minutes following each injection. Table 24 presents a list of the incidence rates of local tolerability-related TEAEs.

Table 24

Incidence of TEAEs related to Local Tolerability by Preferred Term – Total Patient Sample (Study IP157-001 Part A Stage 1)

MedDRA System Organ Class	MedDRA Preferred term	Number of patients (%)	
		TU 750 (N=120)	TU 1000 (N=117)
Total patients with at least 1 TEAE Associated with Local Tolerability		2 (1.7)	5 (4.3)
General disorders and administration site conditions	Injection site erythema	0 (0.0)	1 (0.9)
	Injection site irritation	0 (0.0)	1 (0.9)
	Injection site pruritus	1 (0.8)	1 (0.9)
	Injection site pain	2 (1.7)	2 (1.7)
	Injection site reaction	0 (0.0)	1 (0.9)

Summarized Safety Results from Study IP157-001 Part C

Exposure to TU in Part C averaged approximately 226 days; over 94% of patients received 4 injections, and thus patients were exposed to treatment with TU for almost 6 months. However, consistent with the study design, safety outcomes in this study report reflect an actual median follow-up period of 168 days (24 weeks).

• The planned duration of exposure to study medication was calculated as number of days from first injection to the last injection, plus 70 days. For most patients, the last injection was the 4th injection (24 weeks following the first injection). Exposure to TU would have been derived as 34 weeks.

• Exposure as measured by the duration of safety follow-up was calculated as through the 4th injection visit, and is limited to approximately 24 weeks.

• Patients receiving their 4th injection continued into the Stage 2 of the Part C study.

Duration of exposure in Part C is seen in Table 25.

Table 25. Duration of exposure in Part C.

Duration[1] of Exposure (Weeks)	Number (%) of Patients
	TU 750 mg LOADING (N=130)
0 ≤ Duration ≤ 12 weeks	4 (3.1)
12 < Duration ≤ 24 weeks	112 (86.2)
24 < Duration ≤ 36 weeks	14 (10.8)
36 < Duration ≤ 48 weeks	0 (0.0)
> 48 weeks	0 (0.0)

Brief Summary of TEAE's in Part C:

Approximately 53.8% of patients experienced at least one AE during the Part C study, with acne and fatigue being the AEs reported with the highest incidence; each was reported in 6 (4.6%) patients. Cough, injection site pain, nasopharyngitis, and pharyngolaryngeal pain were each reported in 4 (3.1%) patients.

In the Part C study, there was one "**coughing fit**" that immediately followed an injection with TU. Patient 050-7006 is a 53-year old white male who was diagnosed with primary hypogonadism in August 2006. The patient had been briefly treated with a transdermal TRT (Androgel) but discontinued that treatment due to lack of efficacy. He received his 3rd TU intramuscular injection on Day 98, and immediately experienced a mild and non-serious "coughing fit lasting ~10 minutes following [the] injection". The investigator reported the cough was non-productive and that the patient experienced no wheezing or difficulty breathing; no intervention was given, and the patient recovered prior to leaving the office. The patient received his 1st, 2nd, and 4th injections with no associated cough event; further, the patient continued into Stage 2 with no further cough events having been reported. The Sponsor commented that this event was similar to the post-marketing "coughing fit" events that have been reported. The Sponsor believes that these events are suspected to be associated with pulmonary oil microembolism.

There were no other coughing fits associated with the IM injection of TU during any office visit in Part C.

No AE was reported with an incidence higher than 6 patients, and thus the overall incidence of individual AEs was relatively low in this 24 week study. Table 26 below summarizes TEAEs reported in at least 2.0% of patients, irrespective of relationship to study medication, by preferred term in decreasing order based on incidence rate.

The Sponsor's analysis of AE'S in Part C is provided herein:

• The events reported as at least possibly related were generally consistent with those expected for a population treated with a TRT. For instance, hemoglobin increased, mood swings, prostatic specific antigen increase, and irritability.

• There were only 3 types of at least possibly related TEAEs reported in more than 2 patients: acne, fatigue, and injection site pain. All other events were reported in 2 or fewer patients. Injection site pain was reported in 4 (3.1%) patients.

• The only hormone parameter with an associated TEAE was estradiol. Increased estradiol was reported in 2 (1.5%) patients.

There were no deaths in this study.

Table 26 presents a summary of the incidence of treatment-emergent SAE's in Part C.

Table 26. Incidence of treatment-emergent SAE's in Part C

MedDRA Preferred term	Number of patients (%) TU 750 mg LOADING (N=130)
Total patients with at least 1 TEAE	70 (53.8)
Total patients with at least 1 Treatment-emergent SAE	8 (6.2)
Colitis ischaemic	1 (0.8)
Deep vein thrombosis	1 (0.8)
Faecaloma	1 (0.8)
Intervertebral disc protrusion	1 (0.8)
Myocardial infarction	1 (0.8)
Prostatitis	1 (0.8)
Spinal column stenosis	1 (0.8)
Urinary tract infection	1 (0.8)
Wrist fracture	1 (0.8)

Table 27 presents the incidence of TEAE's leading to discontinuation.

Table 27. Incidence of TEAE's leading to discontinuation in Part C.

MedDRA Preferred term	Number of patients (%) TU 750 mg LOADING (N=130)
Total patients with at least 1 TEAE	70 (53.8)
Total patients with at least 1 TEAE Leading to Discontinuation of Study Medication	5 (3.8)
Acne	1 (0.8)
Mood swings	1 (0.8)
Myocardial infarction	1 (0.8)
Estradiol increased	1 (0.8)
Deep vein thrombosis	1 (0.8)

Summary of Laboratory Outcomes in Part C

The analysis of clinical laboratory data for Part C reveals changes in lipids, red cells, and other parameters over the treatment period that are consistent with testosterone replacement medications. The outcomes from the analysis of laboratory data reveal that treatment with TU 750 mg loading regimen resulted in expected changes in parameters known to be affected by testosterone replacement, and in no clinically relevant changes in parameters thought to be generally unaffected by testosterone replacement.

Safety Conclusions from Part C

Patient safety was monitored during this 24-week study. In addition to the assessment of measured serum free testosterone and other hormones, regular collection of data for PSA, DRE, clinical laboratory data (including serum chemistry, coagulation, lipids, hematology, and urinalysis), vital signs (including pulse, blood pressure, and temperature), and adverse event monitoring were performed. Further, tolerability at the injection site was assessed at every injection visit, following the injection.

Average safety follow-up was over 160 days (i.e., 23 weeks), with the majority of patients completing all 4 injections (and thus completing the 24-week treatment period).

The Sponsor's summary of the key safety conclusions follows:

Approximately 53.8% of patients experienced at least one AE during the study; acne and fatigue were the AEs reported with the highest incidence, each in 6 (4.6%) patients. Cough, injection site pain, nasopharyngitis, and pharyngolaryngeal pain were each reported in 4 (3.1%) patients. No AE was reported with an incidence higher than 6 patients, and thus the overall incidence of individual AEs was relatively low in this 24 week study. General disorders and administration site conditions, infections and infestations, and respiratory, thoracic and mediastinal disorders were the 3 system organ class reported with the highest incidence.

There was one coughing fit event that immediately followed an injection with TU. Patient 050-7006, a 53-year old white male who was diagnosed with primary hypogonadism in August 2006 and who had previously discontinued treatment with transdermal TRT (Androgel) due to lack of efficacy, received his 3rd injection on Day 98. The patient experienced a mild and non-serious “coughing fit lasting ~10 minutes following [the] injection”. The investigator reported the cough was non-productive, and that the patient experienced no wheezing or difficulty breathing. No intervention was given, and the patient recovered prior to leaving the office. The patient received his 1st, 2nd, and 4th injections with no associated cough event; further, the patient continued into Stage 2 and no further cough events were reported for this patient.

The proportion of patients experiencing at least one TEAE was similar across age, race, BMI, prior TRT, and Cmax subgroups, with no notable trends observed. Importantly no clinically meaningful difference in the incidence of any type of individual TEAE was noted across these subgroups.

Approximately 23.8% of patients experienced at least one TEAE that was judged to be at least possibly related to study medication. In summary:

• The events reported as at least possibly related were generally consistent with those expected for a population treated with a TRT. For instance, haemoglobin increased, mood swings, and irritability.

• There were only 3 types of at least possibly related TEAEs reported in more than 2 patients: fatigue, acne, and injection site pain. All other events were reported in 2 or fewer patients. Injection site pain was reported in 4 (3.1%) of patients.

• The only hormone parameter with an associated TEAE was estradiol; Increased estradiol was reported in 2 (1.5%) patients.

In general, this study was characterized by a low incidence of individual AEs, reasonable local tolerability, and not unexpected changes in clinical laboratory outcomes, physical examinations and the other safety markers. The Sponsor believes that safety is strongly supported by the data collected in this Part C study.

There were no deaths in this study.

Eight (6.2%) patients experienced at least one treatment-emergent SAE during the treatment period. No SAE was observed in more than 1 patient. There were 5 (3.8%) patients who experienced TEAEs that led to discontinuation from the study medication (and from the study). Four AEs that resulted in discontinuation from the study were judged by the investigator as at least possibly related to study medication: a deep vein thrombosis, estradiol increased, mood swings, and acne. There were no patients who had their study medication temporarily interrupted due to AEs.

Prostate health assessments in this study included measurement of serum PSA and performance of digital rectal examinations (DREs) at injection visits. Further, laboratory measurements, including lipid profiles were collected. Monitoring of adverse events was performed in an ongoing manner throughout the course of the study. There were very few serious events reported.

Changes in laboratory values over the treatment period in Part C were consistent with those changes that have been reported for other testosterone replacement medications. The outcomes from the analysis of laboratory data reveal that treatment with TU 750 mg loading regimen resulted in expected changes in parameters known to be affected by testosterone replacement. These data are generally consistent with those observed in Part A.

Included here is a summary of outcomes for vital signs, prostate health, mood states, and local tolerability in Part C.

There were no clinically meaningful changes in average blood pressure or pulse from pre-treatment to endpoint; average (median) systolic BP increased approximately 0.4 (0.0) mmHg, while average (median) diastolic BP increased approximately 0.8 (0.0) mmHg. No clinically relevant changes in pulse rate were noted.

A summary of prostate health in this Part C study is as follows:

• There were 5 (3.9%) patients with at least one post-baseline PSA value over 4 ng/mL during this study. However, 2 of these patients had a baseline (pre-1st injection) PSA of 4.2 ng/mL. Thus, there were 3 (3.2%) patients who had a new-onset PSA value over 4 ng/mL.

• Patients with a higher pre-treatment PSA were more likely to exceed the 4 ng/mL threshold during the study than those patients with a lower pre-treatment PSA. Notably, there were 7 patients with pre-treatment PSA concentrations between 3 and 4 ng/mL. Of these 7 patients, 2 (33.3%) exceeded the 4 ng/mL PSA threshold at some time in this study. In contrast, patients who had a pre-treatment PSA < 3 ng/mL rarely exceeded the 4 ng/mL threshold while under treatment with TU.

• Average PSA values did not increase by more than 0.3 ng/mL from pre-treatment to the end of the 24 week treatment period. According to the Sponsor, treatment with other TRT preparations has been reported to increase PSA by approximately 0.5 ng/mL per year, and this study demonstrated consistent PSA as that reported for other preparations.

• Average PSA velocity was = 0.3 ng/mL over the 24-week treatment period, and a few individual patients in this study had a PSA velocity that exceeded 2 ng/mL.

• A review of TEAEs was performed to identify any events related to prostate health. Events included prostatitis, benign prostatic hyperplasia, and PSA elevations. The most commonly reported AE associated with prostate health was prostatitis, reported for 3 (2.3%) patients. PSA increased was reported by 2 (1.5%) patients. Note that some of the prostate health-related events were judged by the investigator to be at least possibly related to study treatment.

• The incidence of abnormal prostate findings varied from visit to visit. The screening visit had the highest incidence of abnormal prostate findings, with 17 (13.1%) patients having an abnormal outcome on the screening DRE. Of these 17 patients with abnormal findings, 16 (94.1%) patients had an enlarged prostate at the screening visit. The incidence of on-treatment abnormal prostate exams was generally the same across the on-treatment weeks.

• There was a low incidence of any abnormal prostate findings on DRE during the treatment period. Only 11 (8.5%) of patients had, at any given time post-1st injection, an abnormal prostate finding based on their DRE; most of these 11 patients had an enlarged prostate as their abnormality. When compared to the incidence rate of abnormal prostate outcomes pre-treatment, the incidence on-treatment was unremarkable.

These data are generally consistent with those observed in Part A.

Mood States in Part C

In order to assess changes in mood states, a review of TEAEs was performed to identify any events related to changes in mood during the course of the study. TEAEs related to mood states included mood swings, aggression, anxiety, and irritability. There were no reports of anger or depression in the Part C study.

"Urological Health" in Part C

"Urological health" was assessed in Part C via the review of AEs related to urological health. A review of TEAEs was performed to identify any events related to urinary health, and specifically bothersome lower urinary tract symptoms. Events that the data were reviewed for included pollakiuria, urinary hesitation, urinary retention, urine flow decreased, and nocturia. Bothersome urinary symptoms were reported in a total of 2 (1.5%) patients; no individual event of this type was reported in more than 1 patient.

Local Tolerability in Part C

Approximately half of patients in this study reported mild pain following at least one of their injections; however, only 4 (3.1%) patients reported injection site pain as an adverse event during the study. Further, only 2 (1.5%) patients reported moderate pain, while no patient reported severe pain associated with the injection in this study.

Overall Safety Conclusion, Part C

In Study Part C, except for the single "coughing fit" case, treatment with TU 750 mg loading regimen resulted in safety outcomes consistent with those expected for a TRT provided to men with primary or secondary hypogonadism. Treatment resulted in a low overall incidence rate of TEAEs in all system organ classes, with some reports of expected TEAEs. Changes in laboratory parameters were generally minor and not clinically meaningful, while changes in lipids, erythropoiesis, and hormone parameters were consistent with those changes that have been reported for other testosterone replacement medications. Prostate health was monitored, and while there were expected changes in serum PSA and occurrence of urological adverse events, no unexpected incidence rates of any untoward event were observed. PSA concentrations increased slightly, as expected. No clinically meaningful changes in vital sign or other safety outcomes were noted, and the injections were generally well-tolerated. Average safety follow-up was over 160 days, with the majority of patients completing all 4 injections. One patient reported a "coughing fit" event in the Part C study. Overall, reasonable safety and tolerability of treatment with TU 750 mg loading regimen was demonstrated in Part C, excluding consideration of concerns related to reports of immediate post-injection reactions.

7.4 Additional Safety Explorations

7.4.1 Immediate Post-Injection Reactions in the Bayer Periodic Safety Update Reports (PSURs)

The key safety concern for this NDA has been the occurrence of immediate post-injection reactions in the post-marketing period. Therefore, a major element of this review was an analysis of all Bayer Periodic Safety Update Reports seeking post-injection reactions of interest. The reviewer defined these as events occurring immediately or soon after an TU intramuscular injection and suggestive of POME or hypersensitivity (allergy). A review of each Periodic Safety Update Report, beginning with the November, 2003 – November 2004 PSUR, focused on these reactions. Cases are shown for each PSUR.

Reviewer's Comment: The key PSURs for this cycle were Bayer's November 2007 – November 2008 PSUR which contains "Appendix 8" (Nebido & Anaphylactic Reactions) and Endo's August 29, 2009 PSUR, which served to extend the review clock.

PSUR: November 25, 2003 - May 24, 2004

There were no reported POME or allergic reactions.

PSUR: May 25, 2004 - November 24, 2004

There were no reported POME or allergic reactions.

PSUR: November 25, 2004- May 24, 2005

There were **11 reactions** suggestive of POME or allergy:

DE-2005-005199. A 30 y/o with Klinefelter's syndrome experienced chest pain (sternocardia), tickle of the throat, shortness of breath, and sweat following the first 2 doses of TU. Symptoms subsided after 30 minutes. Reported as a cardiac disorder. A positive rechallenge result was reported.

DE-2004-037302. A 38 y/o experienced hyperventilation 2 minutes after injection, and 11 hours later had "indisposition" (malaise), redness in face, chills, and feeling of heat in thigh and upper arm. Patient recovered after IV prednisone and oral antihistamine. Reported as an allergic reaction.

DE-2005-008181. A 67 y/o experienced circulatory collapse (measured hypotension is documented), nausea, retching, and fever attacks. Outcome not reported. Reported as an allergic reaction.

DE-2005-008140. A 56 y/o experienced tickling of throat immediately after 1st injection. Patient recovered after oral antihistamine. Reported as an allergic reaction.

DE-2005-008146. A 57 y/o experienced injection site hemorrhage, headache, and temporary visual field defect. Outcome not reported. Reported as an allergic reaction.

DE-2005-008154. A 65 y/o had "pressing complaints" after injection. Outcome not reported. Reported as an allergic reaction.

DE-2005-008161. A 70 y/o had a sensitive skin reaction after injection. Outcome not reported. Reported as an allergic reaction.

DE-2005-008193. A 69 y/o experienced hot flush, headache, and injection site pain. Outcome not reported. Reported as an allergic reaction.

DE-2005-008199. A 68 y/o experienced a short-term cough with an allergic sound after injection. Outcome not reported. Reported as an allergic reaction.

DE-2005-004016. Age not reported. Circulatory collapse occurred within several minutes of injection, unconsciousness, nausea, tickling cough, and defecation after injection. Recovered.

CH-2005-002386. A 33 y/o experienced patchy reddening of whole body skin with mild pruritis 2 days after injection. Recovered.

Reviewer's Comments: *In 5 of these cases from this PSUR (DE-2005-008146, DE-2005-008154, DE-2005-008161, DE-2005-009193, DE-2005-008199) there was insufficient information on which to base a definite assessment of the nature of the reaction. Two cases (DE-2005-004016, DE-2005-008181) were suggestive of anaphylaxis, 1 case (DE-2005-005199) was suggestive of angioedema, and 3 cases (DE-2005-008140, DE-2005-037320, CH-2005-002386) were suggestive of allergic reactions.*

PSUR: May 25, 2005 - November 24, 2005

There were **9 reactions** suggestive of POME or allergy.

DE-2005-009283. A 54 y/o experienced cough, flush, sweating attacks, unrest, trembling, dizziness, cold sweat, and hypotension immediately after 1st dose, and this event persisted longer than 20 minutes. Patient was treated with steroids, antihistamine and H_2 blockers and was hospitalized. Recovered that same evening.

DE-2005-001567. A 48 y/o experienced dizziness, headache and palpittions. Reported as hypersensitivity reaction by an internist and a panic attack by a psychiatrist. Patient recovered. Previously had a similar reaction to Testoviron (which contains the same excipients as Aveed).

DE-2005-015256. A 61 y/o experienced a "cough attack" which subsided after 10 minutes. Recovered.

DE-2005-016985. A 81 y/o experienced a "racking dry cough" lasing 5-15 minutes during the 1st 3 injections. Outcome not reported.

DE-2005-017955. Age not reported. Patient experienced dyspnea and tickling in throat during 1st injection, lasting 10 and 20 minutes respectively. Recovered.

DK-2005-018395. Age not reported. Patient experienced dyspnea, chest discomfort and shallow breathing after injection. Recovered.

DE-2005-018516. Age not reported. Cough and dyspnea lasting approximately 3 hours after injection. Recovered.

SE-2005-021116. Age not reported. Cough during injection. Recovered.

DK-2005-009832. Age not reported. Patient experienced intense cough, chest pain, burning sensation in body, and pruritis in the palate. Recovered.

Reviewer's Comments: *In 1 case among these cases from this PSUR (DK-2205-018395) there was insufficient information for a definite assessment of the nature of the reaction. Four cases were suggestive of POME (DE-2005-015256, DE-2005-016985, DE-2005-018516, SE-2005-021116), 2 cases were suggestive of allergic reactions (DE-2005-001567, DE-2005-017955), 1 case suggestive of angioedema (DK-2005-00982), and 1 case suggestive of anaphylaxis (DE-2005-009283).*

PSUR: November 25, 2005 - November 24, 2006

There were **21 reactions** suggestive of POME or allergy.

SE-2006-014505. A 44 y/o experienced burning pain radiating from sternum to chin, and dyspnea right after starting 3rd injection. Patient was hospitalized and recovered.

DE-2006-003298. A 42 y/o had hot flushes, paresthesias of mouth and head, increasing dyspnea, coughing and a short period of apnea (1-2 minutes), 3 minutes after his 4th injection. Recovered after 20 minutes.

SE-2006-017516. Age not reported. Patient experienced swelling of the neck and palpitations. Outcome not reported. A positive rechallenge was reported.

SE-2006-022116. A 47 y/o developed swelling of the neck, and difficulty in breathing after the 1st dose. Spontaneous recovery after 5 minutes. Six weeks later a similar reaction was seen after a half dose. Positive rechallenge.

SE-2006-022330. A 38 y/o had pruritis, swelling around eyes, nausea, malaise, and itching of throat during 1st injection. Treated with SoluCortef and antihistamines and discharged home after a few hours of observation. Recovered

DE-2006-022513. A 39 y/o had acute dyspnea, tingling of the whole body and a "strong taste" for 10 minutes, occurring 1 minute after injection. Recovered.

DE-2006-008415. A 54 y/o had 15 minutes of cough and dyspnea beginning 1 minute after 10th injection. Recovered.

AT-2006-020143. A 51 y/o developed a very severe "irritative" cough and dyspnea during 1st injection. Cough resolved in 5 minutes, and dyspnea resolved in 2 days. No treatment was given.

BR-2006-032646. A 46 y/o had cough and breathlessness during an injection. He was treated with hyperbaric oxygen for 20 minutes. The outcome was not reported.

DE-2006-002815. A 15 y/o experienced an extremely severe urge to cough, lasting 10-15 minutes, retrosternal pain, dyspnea, redness of eyes and

tachycardia, immediately after his 2nd injection. Recovered after prednisolone and antihistamines.

DE-2006-010466. A man in his late 30's had cough attack after injection. Not resolved.

DE-2006-021129. A 73 y/o had a coughing fit and mild dyspnea after 5th injection Recovered.

DK-2006-002013. Age not reported. Patient had a massive fit of coughing 1 minute after injection, lasting 1 hour, and followed by a persistent irritating, hacking cough.

DE-2006-021339. A 43 y/o experienced a cough after injection.

SE-2006-027304. A 60 y/o had a cough lasting 30 minutes after his 1st dose. Recovered.

GB-2006-006197. A 67 y/o was reported as having an acute anaphylactic reaction within minutes after his 2nd injection, with a coughing fit and tightness in the throat. Treated with adrenaline and an antihistamine and hospitalized.

GB-2006-000495. A 23 y/o has itchiness in his groin area (no rash) every time he has an injection.

SE-2006-017518. Age not reported. Pruritis after injection. No other information.

AR-2006-008403. A 58 y/o had cough and dyspnea after injection. Outcome not reported.

AT-2006-001317. A 64 y/o experienced dyspnea, hot flush, tachycardia, anxiety, fatigue and depression after injection. Outcome not reported.

BR-2006-019257. Age not reported. Reported as having an allergic reaction. No other information. Outcome not reported.

Reviewer's Comments: *In 5 of the cases in this PSUR, there was insufficient information with which to provide a definite assessment of the nature of the*

injection reactions; (SE-2006-014505, SE-2006-017516, GB-2006-000495, AT-2006-001317, BR-2006-019257). Ten of the cases were suggestive of POME; (DE-2006-008415, AT-2006-020143, BR-2006-032646, DE-2006-002815, DE-2006-010466, DE-2006-021129, DK-2006-002013, DE-2006-021339, SE-2006-027304, AR-2006-008403. Four cases were suggestive of angioedema;(SE-2006-017516, SE-2006-022116, SE-2006-022330, GB-2006-006197),and 2 cases were suggestive of allergic reactions; (DE-2006-002513 and DE-2006-003298).

PSUR: November 25, 2006- November 24, 2007

There were **28 reactions** suggestive of POME or allergy.

SE-2006-039053. A 60 y/o had palpitations, rash, whole body pruritis and trembling. Outcome not reported.

CH-2007-042227. A 60 y/o had cough and respiratory distress during an injection. Reported as medically relevant. Recovered after 30 minutes.

DE-2007-004747. A 74 y/o had dyspnea, cough and cyanosis, 3 minutes after injection. Reported as life-threatening.

DE-2007-030464. A 47 y/o had laryngospasm and dyspnea during an injection, followed by a cough after the injection. Reported as medically relevant.

AU-2007-031936. A 38 y/o experienced injection site redness and pruritis. Reported as an injection site allergic reaction. Recovered.

SE-2007-002541. Age not reported. Patient experienced cough, redness of face and a feeling of warmth over chest and head. Recovered.

NO-2007-008581. A 54 y/o developed generalized pruritis which was reported as a hypersensitivity reaction. Outcome unknown.

AU-2007-008333. Age not reported. Patient developed a tingling sensation and a hot flush 1 minute after injection. Outcome not reported.

DE-2007-004746. Age not reported. Patient had cough and dyspnea during injection. Recovered.

DE-2007-004750. A 51 y/o had cough and dyspnea approximately 2 minutes after 2nd injection. Recovered.

DK-2007-030285. A 66 y/o developed a cough "in connection with injection". Recovered.

DK-2007-031980. A 62 y/o had dyspnea and malaise. Recovered.

NO-2007-008557. A 35 y/o had a dry cough, pruritis and a tingling sensation. Recovered.

NO-2007-038349. A 34 y/o developed a cough. Recovered.

SE-2007-038495. Age not reported. Patient had cough and dyspnea immediately after injection. Recovered.

SE-2007-038496. Age not reported. Patient had cough and itching in the throat. Recovered.

FR-2007-035024. A 57 y/o developed redness and pruritis of his face and chest. Not resolved.

SE-2007-002515. Age not reported. Patient developed generalized urticaria and pruritis. Not resolved.

SE-2007-041917. A 63 y/o developed urticaria. Not resolved.

ZA-2007-035469. A 29 y/o developed bronchospasm, circulatory collapse, and hypotension. Reported as life-threatening. Recovered.

BR-2007-010933. Age not reported. Patient had syncope during injection. Recovered.

BR-2007-029503. A 40 y/o had injection site redness and pruritis. Not resolved.

NO-2006-038451. Age not reported. Patient experienced a feeling of heat on penis and legs, and a skin rash. Outcome not reported.

GB-2007-036451. Age not reported. Patient had tingling sensation in toes, fingers and tongue. Outcome not reported.

BR-2007-015689. Age not reported. Patient had nervousness, burning in chest, dizziness, sweating and palpitations. Not recovered.

BR-2006-037980. A 52 y/o had pruritis, headache, and irritability. Outcome not reported.

AU-2007-035848. A 67 y/o developed rash on neck, hot sweats, headache, and anxiety after 1st and 2nd injections. Recovered.

AU-2007-023898. A 67 y/o developed hot flushes, papular rash, urticaria, nausea and nervousness. Outcome not reported.

Reviewer's Comments: *In 8 of the cases in this PSUR there was insufficient information with which to make a definite assessment of the nature of the post-injection reactions; (AU-2007-008333, DK-2007-031980, NO-2007-038349, SE-2007-038496,BR-2007-010933, BR-2007-015689, GB-2007-036451, BR-2006-037980). However, three of these may involve allergic reaction (SE-2007-038496 with itching in throat, GB-2007-036451 with tingling in fingers, toes and tongue, and BR-2006-037980 with pruritis). In 12 cases the information was suggestive of allergy; (SE-2006-039053,AU-2007-031936, SE-2007-002541, NO-2007-008581, NO-2007-008557,FR-2007-035024, SE-2007-002515, SE-2007-041917, BR-2007-029503,NO-2006-038451, AU-2007-035848, AU-2007-023898). In 7 cases the information was suggestive of POME; (CH-2007-042227, DE-2007-004747,DE-2007-030464, DE-2007-004748, DE-2007-004750, DK-2007-030285, SE-2007-038495), and in 1 case the information was suggestive of anaphylaxis; (ZA-2007-035469).*

PSUR: November 25, 2007- November 24, 2008

There were **24 reactions** suggestive of POME or allergy. Narratives are provided for 21 of these 24 cases.

BR-2008-15625LA. A 60 y/o developed cough, throat itching, glottis spasm, and glottis edema, which was reported as an anaphylactic reaction and listed as being life-threatening. Patient was treated with adrenaline, oxygen, IV saline, SoluCortef, and antihistamine. Recovered.

BR-2008-18230LA. A 58 y/o was hospitalized after a reported anaphylactic reaction, and recovered. No additional information provided.

DE-2008-28604GPV. A 41 y/o experienced a feeling of tightness in the region of the thorax, dry cough, burning eyes, flush, and tingling sensation in lungs ascending to nose. Reported as a "possible anaphylactic reaction", and recovered after treatment with prednisone, Zantac, and an anti-histamine.

SE-2008-12947GPV. A 38 y/o experienced throat swelling. Reported as an allergic reaction and potential heart failure. Patient had a reported allergic reaction to the drug 6 months earlier.

DE-2005-014372. Age not stated. Patient exhibited "edema, attributed to an allergic reaction". No additional information provided.

DE-2007-004748. Age not stated. Patient had urge to cough and dyspnea. Reported as "suspicion of an allergic event".

DE-2006-009799. Age not provided. Patient had dyspnea and a cold sweat. No additional information provided.

DK-2008-1479. A 33 y/o had a cough, breathing problems, "felt bad", and had a blood pressure increased to 147/89. Reported as an allergic reaction. Treated with antihistamine and bronchodilator nebulizer. Recovered.

BR-2008-13805LA. A 53 y/o experienced injection site pain, mass, warmth and pruritis, in addition to dry throat and nocturnal dyspnea. Similar injection site reactions at time of previous injection. Treated with Phenergan and a diuretic. Recovered.

2007-11462BNE. A 44 y/o had a cough, shortness of breath, and a flush. Recovered in 24 hours. No other information provided.

2008-15181GPV. A 52 y/o experienced severe dyspnea, muscle twitching, heat sensation in neck and tickling in throat, in addition to loss of consciousness. Treated with "shock position", and saline IV. Reported as "assumed micro-fat embolism". Hospitalized and recovered.

BR-2008-19576LA. Age not stated. Patient experienced sweating during injection, cough, facial redness and dizziness. No other information provided.

2008-12881BNE. A 27 y/o had a cough, wheeze, bronchospasm, and felt flushed after his 2nd injection. Recovered after treatment with Salbutamol nebulizer.

DE-2008-21776. A 33 y/o experienced cough, breathing problems, a "bad feeling" and increased BP after injection. Reported as allergic reaction. Treated with Ventolin, salbutamol and antihistamine. Recovered in 1 hour.

GB-2008-11461. A 55 y/o experienced sharp increase in BP (275/175 mm Hg), sweating, metallic taste, and "burning up" sensation after injection. BP recovered in 30 minutes.

2008-207307GPV. A 72 y/o experienced cough, cyanosis, dizziness, and numbness of face after injection.

GB-2008-11268. A man of unknown age experienced coughing, breathlessness, and burning sensation in mouth and chest after injection, apparently by wife. Patient was hospitalized. Reported as "presumed embolus".

SE-2008-21519. A 21 y/o experienced cough, sweating and chest pain during injection. Treated with adrenaline and betamethosone.

DE-2007-18455. A 68 y/o experienced sensation of numbness and tingling around his mouth and lips after injection. Reported as "allergic reaction". Treated with antihistamine and H2 blocker.

DE-2008-26527. A 72 y/o experienced coughing, choking, facial, dysesthesia, and temporary palsy of face and mouth musculature after injection.

26556GPV – A 76 y/o experienced coughing, dyspnea and choking after injection. Reported as "pulmonary oil microembolism".

Reviewer's Comments: *In 5 of these cases from this PSUR, there was insufficient information to make a definite assessment of the nature of the post-injection reaction; (DE-2005-014372, BR-2008-18230LA, DE-2006-009799,* DE-2008-21776 *and GB-2008-11461). However, in one of these cases (BR-2008-18230LA), it is notable that the reporter referred to the event as an anaphylactic reaction and the patient was hospitalized. In another (DE-2008-21776), the event was reported as an allergic reaction and was considered life-threatening. Nine cases were suggestive of POME;(DE-2008-28640GPV, DE-2007-004748, DK-2008-1479, 2007-1462BNE,BR-2008-19576LA, 2008-12881BNE, SE-2008-21519, DE-2008-26527, 26556GPV). Two cases were suggestive of angioedema; (BR-2008-15625LA, SE-2008-12947GPV). Two cases were suggestive of allergy;(BR-2008-13805LA, DE-2008-18455) and 1 case was suggestive of anaphylaxis;(2008-15181GPV). In 2 cases, it was not possible to differentiate POME from allergy/anaphylaxis (2008-207307 and BG-2008-11268).*

In the November 25, 2007- November 24, 2008 PSUR, Bayer included an Appendix, entitled "Nebido and Anaphylactic Reactions" (Appendix 8). This Appendix was submitted at the request of a "Health Authority" and it included a compilation of all postmarketing cases suspicious for anaphylactic reactions following injection of TU intramuscular. Bayer reported a total of 49 cases derived from their search from marketing until November 24, 2008. Of these 49 cases, Bayer believed that just 5 cases met diagnostic criteria for anaphylactic reactions, including 1 case with Ruggeberg Level 1 evidence, and 4 cases with Ruggeberg Level 2 evidence (Ruggeberg et al, Vaccine 25[2007] 5675-5684). However, Bayer noted that differentiating between anaphylactic reactions, anaphylactoid reactions, POME and other entities may be difficult or even impossible in reactions occurring during or immediately after injection of Nebido. Bayer further acknowledged that symptoms of POME may mimic a hypersensitivity or anaphylactic reaction. Finally, Bayer acknowledged that POME may occur after injection of TU intramuscular after inadvertent IV injection or after appropriate IM injection.

Reviewer's Comment: It is important to note that the worldwide marketer of TU intramuscular has acknowledged anaphylactic reactions with this product and further acknowledges that differentiating POME from anaphylaxis is difficult.

Further, it is important to note that Bayer has used very strict criteria to categorize cases as anaphylaxis. Many of the cases in Appendix 8 could be considered to b anaphylactic reactions if less stringent criteria are applied (e.g., Sampson et al, Annals Emerg Med 2006, 47[4], 373-380). We have engaged consultants in allergy to review all the suspicious cases. To date, our consultant from the Division of Pulmonary Allergy Products have found that 2 Nebido cases are anaphylactic reactions, and two more could be anaphylactic reactions. DPAP believes that the Ruggeberg criteria are too stringent and they use the more widely accepted Sampson criteria, as supported by the United States National Institute of Allergy and Infectious Disease and the Food Allergy and Anaphylaxis Network. Our consult from DPAP provided preliminary findings from a second cycle review and they believe that additional Nebido post-marketing cases are anaphylactic reactions, including several cases from the November 2007-November 2008 PSUR/Appendix 8.

7.4.2 Immediate Post-Injection Reactions: Cases from Sources Other Than Bayer PSURs

The Original NDA contained a table of 6 clinically important postmarketing adverse events occurring between November 25, 2006 and June 30, 2007, and obtained from CIOMS reports submitted to Bayer, the worldwide marketer of TU intramuscular. This table is shown below as Table 28. Two of these cases (DE-2007-004747 and BR-2007-010933) were detected in the November 25, 2006-November 24, 2007 Bayer PSUR line listings, but the other 4 cases (GB-2007-000740, BR-2007-005496, AU-2007-014016 and GB-2007-023826) were not. These 4 cases all were reported as “anaphylactic reaction, anaphylactic shock, or suspected allergic type reaction

Table 28. Table from Original NDA showing 6 clinically important post-marketing adverse event reports occurring between November 25, 2006 and June 30, 2007.

Case Number	Event onset date	AE Term(s)	Time to onset (from injection)	Time to worse symptom level	Treatment given	Injection Number	Outcome	Comment
DE-2007-004747	8-Dec-06	Dyspnea, cough, cyanosis	3 minutes	Unk	None listed	Unk - first dose Jan 2005	Resolved	Dyspnea and cyanosis lasted 20 minutes
GB-2007-000740	(b) (6)	Anaphylactic reaction, laryngeal edema, respiratory arrest, dyspnoea, cough, throat irritation, hyperhidrosis	Halfway through injection	Progressively worse - transferred to hospital	Adrenaline and oxygen	2nd injection	Resolved	Physician stated that possible some Nebido may have gone IV and into circulation
BR-2007-005496	5-Feb-07	Anaphylactic shock, malaise, dyspnea	Immediately	30 minutes	Corticosteroids	First injection	Resolved	
BR-2007-010933	Unk-Jan-07	Syncope	After injecting 3 of 4ml TU	Immediately	None listed	3rd injection	Resolved	States that pt. Recovered and received the 1mL remainder.
AU-2007-014016	Unk[1]	Suspected allergic type reaction – Hypersensitivity, cough, chills	Shortly after injection of Reandron (TU)	Unk	Prednisolone and oxygen	2nd injection	Resolved	
GB-2007-023826	Unk[1]	Anaphylactic shock, respiratory distress, T-wave inversion, cough	Unk	Unk	Epinephrine and chlorphenamine maleate	2nd injection	Unk	

Unk=Unknown.
Case number based on CIOMS reporting system from Bayer Schering Pharma.
[1]Minimal information is available for these events, as they were only recently reported.

The 120-Safety Update to the Original NDA contained a table of 9 clinically important postmarketing adverse event reports occurring between June 30, 2007 and October 12, 2007 (DE-2007-023890, DE-2007-030464, AT-2007-035468 and ZA-2007-035469). This table contained 4 reports of post-injection reactions, suspicious for anaphylactic reactions. Three of these had been reported in the November 25, 2006 – November 24, 2007 Bayer PSUR, but one hd not previously been detected (DE-2007-023890). This table is provided below as Table 29.

Table 29. Table from 120-Day Safety Update showing 9 clinically important postmarketing adverse event reports occurring between June 30, 2007 and October 12, 2007.

Case Number	Event Term(s) Verbatim	Onset Date	Relatedness to Nebido	Initial Report	Follow-up Report(s)
DE-2007-023890	Anaphylactic reaction	(b) (6)	possible	4-Jul-2007	13-Jul-2007, 11-Sep-2007
CO-2007-025007	Cardiac failure	unk	possible/unlikely	13-Jul-2007	18-Jul-2007
BR-2007-028116	Retinal detachment	unk-Jun-2007	none	1-Aug-2007	7-Sep-2007
AU-2007-029476	Lymphoedema	8-Aug-2007	none	14-Aug-2007	
DE-2007-030464	Dyspnea, cough, laryngospasm	(b) (6)	possible	20-Aug-2007	
RU-2007-031850	PSA level increased	26-Jun-2007	unclassifiable	28-Aug-2007	3-Sep-2007
AT-2007-035468	Anaphylactic reaction, retching, throat irritation	13-Jun-2007	possible	25-Sep-2007	
ID-2007-032962	Tooth disorder	13-Aug-2007	none	7-Sep-2007	
ZA-2007-035469	Bronchospasm	(b) (6)	certain/unclassifiable	24-Sep-2007	

Finally, an abbreviated Safety Update was submitted by Sponsor on August 29, 2009 containing 18 cases of post-injection reactions occurring between November 25, 2008 and August 28, 2009. This Safety Update led to the extension of the review clock for this application and it is summarixed in detail later in this review.

7.5 Additional Submissions

7.5.1 Executive Summary Report of Post-Injections Reactions Submitted Original NDA

The tables of CIOMS reports in the Original NDA and in 120 Day-Safety Update, containing a total of 12 post-injection adverse event reports raised serious concerns regarding the risk/benefit ratio for the use of this product in the intended population.

The Sponsor was contacted on January 15, 2008 about the unresolved concerns related to POME and hypersensitivity reactions. A discussion was held with sponsor regarding the possible etiologies for the immediate post-injection reactions

and number of total cases known to Sponsor. The Sponsor was aware of additional cases reported to CIOMS during the post-marketing period in Europe and they agreed to forward all the case narratives to be reviewed by FDA.

On February 12, 2008, the Sponsor submitted a 28-page report titled *"Immediate Post- Injection Reactions Suspect of Pulmonary Oil Microembolism".*

The report identified a total of **66 cases suspect of these reactions** from April 2004 to January 18, 2007. Of these, 28 cases (42%) were reported as serious adverse events. Although there were no deaths in the combined post-marketing and clinical trial experience, review of the CIOMS forms submitted by Sponsor indicated emergency medical care and/or hospitalization in 12/66 (18 %).

Below are the CIOMS identifications and brief narratives for 24 of these 28 serious events. Selection was based upon the seriousness of the event, including need for emergency medical care and/or hospitalization. Many of these cases have already been shown above.

1. (AT-2006-020143) A 51 year old male experienced very severe irritative cough and dyspnea beginning during his first intramuscular injection of TU. Cough resolved in 5 minutes and dyspnea persisted for 2 days.

2. (DE-2005-011567) A 48 year old male experienced "hypersensitivity reaction certainly to castor oil" described as dizziness, headaches, palpitation, vertigo, lump in throat, tachycardia at an unspecified time after his second and third doses of TU. The reaction lasted 3 weeks. Tachycardia, palpitations and lump in throat resolved in 5 hours. Past history of atopy, and similar complaints related to previous treatment with Testoviron-Depot (castor oil).

3. (DE-2005-019516) A male (unknown age) experienced 3 hours of cough and dyspnea after the TU injection.

4. (DE-2006-002815) A 15 year old male experienced extremely severe urge to cough, retrosternal pain, mild dyspnea, eye redness, and tachycardia immediately (within less than a minute) after his second TU injection. Patient was treated with antihistamine, and a steroid (Solu-DecaCortin H).

5. (DK-2006-002013) A male (unknown age) experienced “massive coughing fit” 1 minute after TU injection lasting 1 hour – described as irritating hacking cough.

6. (20071127BNE) A male (unknown age) experienced immediate coughing, unable to catch breath, “collapse”, severe dyspnea, burning sensation in mouth and chest upon TU injection (given by wife). Patient was hospitalized for 2 days and recovered. No reaction to subsequent TU injection administered by a clinic nurse.

7. (200718455GPV) A 68 year old male experienced “allergic reaction” including sensation of numbness of mouth, tingling sensation mouth and lips (“paresthesias”) during his 6th TU injection. Patient treated with H1 and H2 blockers. The complaints resolved after 6 hours.

8. (AT-2007-035468) A 46 year old male experienced “anaphylactic reaction” including “gagging” and “tickle in throat” 30 seconds after administration of his 7th dose of TU. Patient was given an oral antihistamine and recovered within 15 minutes.

9. (AU-2007-014016) A male (unknown age) experienced “suspected allergic type reaction to the excipient (i.e. the oil)” including severe coughing, and shivering during the 3rd TU injection. Patient was treated with oxygen, antihistamine, and prednisone and symptoms subsided.

10. (BR-2007-005496) A 57 year old male experienced “anaphylactic shock” including “glottis edema”, “breathlessness” and “malaise” immediately after injection. Breathlessness became worse 30 minutes after injection. He was treated with corticosteroids and was “ventilated in the drug store”.

11. (BR-2007-010933) A male (unknown age) “fainted during injection” with “loss of consciousness for several minutes”. The reporter suspected possible intravenous injection. A similar injection 6 months earlier was well tolerated.

12. (DE-2005-004016) A male (unknown age) experienced “circulatory collapse, nausea, cough, several minutes unconsciousness, and encopresis”, approximately 15 seconds following his 2nd dose of TU. There was subsequent recovery.

13. (DE-2005-009-283) A 54 year old male with “suspected fat microembolism” described as “cough, red head, sweating attacks, trembling, dizziness, increased blood pressure, and dizziness” immediately after injection of 1st dose of TU. Patient had previously tolerated Testosterone-Depot.
Symptoms lasted longer than 20 minutes and patient was hospitalized. He was treated with cortisone and antihistamines and discharged home
the same evening.

14. (DE-2006-003298) A 42 year old male experienced “idiosyncratic drug reaction, possible oily microembolism” including 1-2 minutes of apnea, and hot flush, paresthesias in area of mouth and head, dyspnea and cough 3 minutes after his 4th TU injection. Patient recovered after 10 minutes.

15. (DE-2007-004747) A 74 year old male experienced “pronounced urge to cough”, “dyspnea” and “20 minutes of cyanosis” at 3 minutes after “slow injection” of TU. The event was described as “life-threatening”. Nebido had been previously well tolerated.

16. (DE-2007-023890) A 57 year old male experienced “suspected anaphylactoid reaction, possible oil microembolism” including dizziness, tingling sensation upper part of abdomen, hands and feet, weakness, pressure in head, headache, numbness sensation in fingers and toes
after first dose of TU. Injection site was hot, hard, red and sensitive to pressure. Patient was treated with antihistamines and prednisolone and taken to emergency unit where symptoms persisted..

17. (DE-2007-030464) A 47 year old male experienced “laryngospasm”, “severe dyspnea” and cough during 2nd TU injection. An emergency physician was called, however patient spontaneously recovered after a few minutes. Patient had cough reaction to previous injection.

18. (GB-2006-006197) A 67 year old male experienced “acute anaphylactic reaction” including tightness in throat and coughing fit “minutes” after his 2nd injection. He was treated with epinephrine and chlorpheniramine. The event was considered life-threatening and involved hospitalization.

19. (GB-2007-000740) A 54 year old male experienced “anaphylactic reaction, including acute laryngeal edema, and near respiratory arrest”, half-way through

his 2nd TU injection. Patient began coughing, had tickle in throat, and the reaction worsened. He became sweaty, had trouble breathing, was given adrenaline and oxygen and was hospitalized.

20. (GB-2007-023826) A 46 year old male experienced "anaphylactic shock" including respiratory distress, coughing fit, T wave inversions, tightening of the throat, respiratory wheeze, rash on abdomen, itchy scalp, raised blotches across the chest. Symptoms began during his 2nd injection. He was treated with adrenaline and chlopheniramine, and symptoms cleared upon arrival at emergency room.

21. (SE-2006-014505) A 44 year old male experienced "burning pain lower sternum going up to the chin" and dyspnea during the 3rd TU injection. The administration was discontinued, symptoms lasted 2-3 minutes, and the patient was hospitalized.

22. (SE-2006-07516) A 47 year old male experienced "angioedema" including swollen throat, palpitations, difficulty breathing, cough and swelling of the neck immediately after his 2nd TU injection. Fatigue and cough persisted for several hours. The report describes an event of "serious swollen throat" and "non-serous palpitations" after his 1st TU injection.

23. (SE-2006-022330) A 38 year old male experienced "angioedema", pruritis, malaise, swelling around the eyes, itching in the throat after the 1st TU injection. Solu-Cortef and antihistamine was administered and patient discharged after a few hours observation.

24. (ZA-2007-035469) A 29 year old male developed "life-threatening bronchospasm" and tachycardia, became hypotensive and collapsed within a minute after receiving TU. He received emergency medical care with nebulized epinephrine and recovered from the bronchospasm.

An additional case was reported 29 February 2008 (200812947GPV) in which a 38 year old male received TU twice. He experienced a mild allergic reaction following the 1st injection, and 6 months later a 2nd injection was administered in hospital and he developed a severe allergic reaction (severe throat swelling and "potential heart failure") Patient recovered "shortly after".

At the time of the original NDA, and up to the current moment, the Sponsor attributes all the post-injection reactions to pulmonary oil microembolism (POME), while it is the opinion of this reviewer and our collegues in DPAP (as well as Bayer, the worldwide marketer of TU intramuscular), that at least a subset of these events are severe allergic (or anaphylactic) reactions, which have similar clinical presentations to that of POME, making it difficult to discriminate between them. Both benzyl benzoate and castor oil (excipients in this product) are well-known allergens. Castor oil has been cited by FDA in several circumstances as being associated with vehicle-related allergic reactions, including anaphylaxis (e.g., cyclosporine injection, tacrolimus injection and taxane-based chemotherapy including Taxol). In one post-marketing report of a serious post-injection reaction, the patient exhibited a positive reaction to skin testing with benzyl benzoate.

Both serious and non-serious post-injection reactions had been noted in earlier PSURs. In the original NDA, the Sponsor focused on the most recent 2 year period which included more than 85% of all exposure to TU worldwide. According to the Sponsor, and based upon the number of TU units sold, the reporting of "post-injection cough reactions" was approximately 1/12,000 injections in 2006, and 1/15,000 injections in 2007.

Sponsor also referenced a case series (Mackey et al, 1995) of hypogonadal men treated with depot T preparations containing castor oil as the vehicle, in which similar pot-injection events were reported in 8/551 injections (1.5 %). The authors concluded that "An improved depot form of testosterone would be highly desirable for androgen replacement therapy and hormonal male contraception." This is the only reference and only cases of post-injection reaction that could be found for testosterone enanthate, an approved injectable testosterone formulation.

After the Clinical review of these 66 post-injection reaction cases that are "suspect of POME" 28/66, this reviewer had identified at least 14 cases which appear to have clinical manifestations suggesting allergic elements exclusively or in addition to POME symptomatology.

Even though there were no deaths in the clinical trials or in the post-marketing experience, many of the cases manifested life-threatening signs and symptoms, requiring emergency medical care and/or hospitalization.

The Sponsor believes that these events are all related to POME and may be reduced in incidence or severity by lowering the injection volume (to 3 mL) and by careful, slow intramuscular injection. However, the Sponsor acknowledged that data to support these hypotheses are not yet available. In addition, this reviewer continues to believe that some of the cases reported as POME showed signs and symptoms suggestive of allergic reaction, which would not be resolved by reduction in dose from 4 cc to 3cc, or by slower injection.

Therefore, at the time of the original NDA, the reviewer expressed some possible pathways for resolving the issue of post-injection reactions: such as change in vehicle, lowering the dose, and lowering the injection volume. We also obtained a consultation from the Division of Pulmonary and Allergy Products (DPAP) concluded that the above cases #20 and #24 met clinical criteria for anaphylaxis, and that given the unclear mechanism of these reactions, DPAP also recommend that consideration be given to advising Sponsor to characterize the nature of the anaphylaxis and anaphylaxis-like events, and to develop an *in vitro* test for specific IgE and IgG antibody to the drug, both active and excipient ingredients, and to evaluate the presence of antibodies in patients who have had anaphylaxis events associated with the drug, those who have been exposed to drug but have not had anaphylaxis, as well as unexposed controls. In addition, DPAP proposed that the sponsor might develop a skin testing procedure to the product and its excipients to evaluate the same populations to be studied with *in vitro* testing.

On March 2, 2009, the Sponsor submitted a Response to the Approvable action that was taken by DRUP. The Response contained data from controlled clinical trials, a Summary Report of those clinical trials, and an additional PSUR. The Response also includes a final Safety Update. The November 25, 2006 – November 24, 2007 PSUR has been reviewed above. The next section of the review describes: 1) the set of controlled clinical studies submitted with the intent of supporting an incidence rate for post-injection reactions, an 2) the August 29, 2009 Safety Update.

7.5.2 Summary Report of the Incidence of Injection-Based Pulmonary Oil Reaction and Allergic Reaction from Clinical Studies of Testosterone Undecanoate (submitted February 12, 2009)

This summary is based on a safety database derived from 17 pre-approval and post-marketing domestic and foreign trials, and reflect a total of 2834 patients treated with 16191 injections. The Sponsor believes that across these studies, there was just 1 mild and 1 serious POME reaction and no allergic reaction event reported. Using the numerator of 1 case, the Sponsor translates this experience to 7.06 events per 10,000 patients, and 1.24 events per 10,000 injections. Therefore, the Sponsor posits an underlying incidence rate for serious post-injection POME reactions of 3.53 events per 10,000 patients, and 0.62 events per 10,000 patients.

> ***Reviewer's Comments:*** *My review of the clinical trials indicates 3 additional patients in whom post-injection events occurred (post-injection convulsions, syncope and circulatory collapse, respectively). The information provided for these 3 reports is insufficient to definitively ascribe the event to serious POME or to systemic allergy. However, these 3 clinical trial cases should not be discounted simply due to insufficient information. The case numbers are: Patient # 001-0011 from Study 97173 (convulsions after 3rd injection), Patient #001-0017 from Study 97173 (collapse after 1st injection), and Patient #001-0004 from Study JPH04995 (circulatory collapse after 1st injection). If these 3 additional cases were to be counted as incident events, then the numerator would be 4 times higher, leading to an incidence of not 1 in 2,834 subjects (0.035%), but rather, 4 in 2,834 subjects (0.14%). In addition, there are several other cases in the clinical trial database (n=3; pre-syncope, syncope and circulatory collapse) for which the information is sparse, but these events might also reflect post-injection reactions. They are: Patient #025-4187 in Study IP157-001 Part A Stage 1, and Patients #26 and #35 in Study 97029, respectively. While we have not counted these in the numerator, they are notable. There are also 2 cases with allergic skin reactions.*

The Complete Response contained study reports for 11 post-marketing studies of TU intramuscular. This includes 6 studies where TU was used as a single agent to treat hypogonadism, visceral obesity, or paraplegia, and 5 studies where TU was combined with other hormones for male contraception. Of these 11 studies, 7 were complete and 4 were ongoing. In these 11 studies, there were a total of 1927 patients treated with 8914 injections.

A brief synopsis of each of the 7 completed and 4 ongoing post-marketing studies follows:

Study AWB 0105 (conducted entirely in Germany; a completed study-- 259 private practice physicians). This study involved 870 androgen deficiency patients who received a total of 4990 injections of TU 1000mg and were observed over 1 year.

Study Design

This was a prospective, non-interventional, post-marketing observational study to examine the efficacy and tolerability of TU and to quantitatively record AEs.

Safety: Assessed via Case Report Forms, and CIOMS forms were submitted for serious untoward events.

Safety Results

Reported AEs included; limb or joint pain, increased PSA, skin problems, injection site pain, change in liver/lipid values, weight gain, edema, dizziness, hair loss, GI complaints, and BPH.

There were 3 reported SAEs: prostate cancer; recurrence of prostate cancer; and recurrence of bladder cancer. There were no POME or hypersensitivity reactions reported.

Study NE0601 IPASS (conducted at approximately 300 sites in 18 countries worldwide; an ongoing study). This study involves 763 hypogonadism patients who have received 2815 injections of TU 1000mg at the time of the Complete Response.

Study Design

This study was planned to assess the safety profile and treatment outcomes in approximately 1500 patients in the post-marketing period. Treating physicians or nurses documented safety variables (AEs and Adverse Drug Reactions/ADR) and treatment outcomes in case report forms

Safety Results

As of December, 2008, there were 6 reported SAEs: suicide in a 56 year old after his second injection; pituitary adenoma; myocardial infarction; tooth problem; lymphedema; and polypectomy. There were a total of 44 adverse drug reactions (ADR) reported; most frequently, injection site reactions, hyperhydrosis and increased PSA.

The tabulated list of ADRs failed to note any reaction suggestive of POME or hypersensitivity reaction. There was one case in this study of interest: Patient #36010 experienced flushing, sweating, and oropharyngeal discomfort after his 1st injection of TU intramuscular.

Ten patients were excluded for failing to meet documentation criteria.

Study TG09 (conducted entirely in Germany; at 1 site; an ongoing study). This study involves 29 hypogonadal patients with abdominal obesity, who had received 118 injections of TU 1000mg at the time of the Complete Response.

Study Design

This is a 2-arm, non-randomized, open-label, post-marketing study comparing hypogonadal men treated with TU for up to 12 months (5 injections), with a group of men treated by a diet and exercise program.

Safety: Assessed every 3 months by patient questionnaire.

Safety Results

There were no AEs reported during this study. There were no reports of POME or allergic reactions reported in this study.

Study NB02 (conducted entirely in Germany; at 1 site, an ongoing study). This study involves 19 hypogonadal patients with osteoporosis secondary to

paraplegia, who had received 39 injections of TU 1000mg at the time of the Complete Response.

Study Design

This is a single-center, 3-arm, non-randomized, open-label, post-marketing study to obtain data on the efficacy and tolerability of TU in patients with osteoporosis secondary to paraplegia.

Approximately 30 hypogonadal paraplegia patients were to be actively treated with TU. Ten hypogonadal paraplegia patients were to serve as an untreated control, and 10 eugonadal paraplegia subjects were to be included as a 3rd cohort arm.

Safety Results

There were 4 SAEs reported in 3 patients: 1 death due to sepsis associated with hip surgery; 1 peritoneal adhesion; and 1 case of osteomyelitis and pelvic decubitus. There were no reports of POME or allergic reactions reported.

Czech NEO (conducted entirely in Czechoslovakia; at 1 site, an ongoing study). This study involves 23 hypogonadal patients, each treated with all 4 planned doses for a total of 92 injections of TU 1000mg at the time of the Complete Response.

Study Design

This is a post-marketing surveillance, open-label study designed to obtain general efficacy and safety data. The study was intended to allow for eligible patients to receive up to 4 injections (7 months). CIOMS case report forms were provided to record study data.

Efficacy: Assessed by the Aging Male Symptom questionnaire, which is not included in this interim study report.

Safety: AEs assessed at each visit by patient questioning, and AEs occurring directly after injections were assessed. SAEs include; death, danger to life, hospitalization, significant injury or disability.

Safety Results

There were no AEs reported during this study. There were no POME or hypersensitivity reactions reported.

Study 303934 (conducted entirely in Finland; 1 at site. (This study was discontinued due to serious recruitment difficulties) Dates of study: May, 2001-February, 2002. This study involved 15 andropause patients who were to receive 15 injections of TU 1000mg.

Study Design

This prospective, randomized, double-blind, parallel-group, placebo-controlled, long-term study was to determine the possible benefit of TU on andropause-related symptoms in 200 subjects as assessed by the Aging Male Symptoms rating scale and the Turku 3-item questionnaire.

Safety Results

There were no AEs reported between start of treatment in this study and the premature discontinuation of the study.

The following 5 completed studies involve TU used for male contraception.

Study 97028 (study conducted entirely in Germany; at 1 site). This study involved 28 subjects receiving 112 injections of TU 1000mg ± levonorgestrel (LNG).

Study Design

This was a prospective, double-blind, randomized, 2-arm, placebo-controlled comparison of spermatogenesis in healthy men treated with TU plus LNG vs TU plus placebo.

Safety: Assessments included AEs, PSA, injection site tolerability, standard clinical-chemical parameters, testes examination, and prostate ultrasonography. Documentation was performed via case report forms.

Safety Results

Reported AEs included; flu, URI, migraine, sinusitis, increased sweating, rhinitis, gastritis, bronchitis, acne, headache, and pain. There were no POME or hypersensitivity reactions reported. There were no SAEs reported.

Study 97173 (conducted entirely in Italy; at 1 site). This study involved 24 subjects receiving 32 injections of TU 1000mg plus sequential cyproterone acetate.

Study Design

The study was conducted to determine whether after achieving satisfactory suppression of spermatogenesis, a lower hormone dose would be sufficient to maintain suppression of spermatogenesis without untoward AEs.

Safety Results

There were a total of 64 AEs reported in 18 of the 24 volunteers. AEs assessed as probably or possibly related to treatments were acne, 1; post-injection convulsion, 1; and post-injection collapse, 1. The latter 2 events occurred immediately after the respective TU injections and lasted for about 2 and 10 minutes, respectively, and the volunteers recovered. The subject with convulsion had a history of such symptoms.

There were 3 reported SAEs; MS, colitis, and arrhythmia, all assessed as not related to study drug.

> ***Reviewer's Comments:*** *In the opinion of this reviewer, the reports of post-injection convulsion (Patient #001-0011) and post-injection collapse (Patient #001-0017) should have been included in the listing of SAEs, and raises concern of possible POME or hypersensitivity reactions. The*

information provided for these 2 cases is sparse, but this reviewer does not agree to discount these cases based upon sparse information.

Study 99015 (study conducted entirely in Germany; at 1 site). This study involved 42 subjects receiving 166 injections of TU 1000mg plus norethisterone ethanate (NET-EN) 200 or 400mg, or noresthisterone acetate (NET-A) 10mg.

Study Design

This study was intended to determine the suppression of spermatogenesis via sperm counts in an open-label, prospective, randomized, 3-arm trial design, and to assess continued efficacy and safety throughout the 24 week treatment and observational phase. Case Report Forms were used to document results. Adverse events were monitored by history, physical examinations, vital signs, general laboratory variables, and prostate and testes ultrasonography.

Safety Results

There were 148 reported AEs. The most frequently reported AEs were flu symptoms, sweating, and breast pain. There were no POME or hypersensitivity reactions. There were 2 reported SAEs; shoulder capsule surgery, and Campylobacter jejuni infection.

Study 98016 (study conducted entirely in Germany; at 1 site). This study involved 14 subjects receiving 56 injections of TU 1000mg plus norethisterone ethanate over 24 weeks of treatment and 28 weeks of recovery period.

Study Design

This was a prospective, uncontrolled, 1-arm study to investigate the efficacy and safety of male contraception using TU plus norethisterone ethanate. Safety monitoring included; PSA, AEs, local tolerability, ultrasonography of testes and prostate, and standard clinical-chemical parameters. Results were documented on Case Report Forms.

Safety Results

A total of 37 AEs were reported in 10 of the 14 volunteers. The most frequently reported AEs were; acne, flu, sweating, and migraine. There were no POME or hypersensitivity reactions reported. There were 2 reported SAEs; psychotic depression, and nasal septum disorder.

Study 42306 (study conducted in Germany, the UK, Netherlands, Italy, Denmark, and Finland). This study involved 198 subjects receiving 860 injections of TU 750mg plus an etonogestrel implant, and 100 subjects receiving 372 injections of TU 1000mg plus an etonogestrel implant.

Study Design

This was a phase-2, double-blind, placebo-controlled, randomized, multicenter, multidose trial of the safety and efficacy TU plus an etonogestral implant for male fertility control.

Safety monitoring included; AEs, physical examinations, vital signs, status of implant and injection sites, and laboratory variables. Results were documented on Case Report Forms.

Safety Results

A total of 33 subjects discontinued due to an AE. Most discontinuations (n=24) were in the group receiving the implant. Acne, hyperhydrosis, and night sweats were the adverse events reported most frequently. There were 13 SAEs reported in 9 subjects (including 3 in the placebo groups). Two SAEs were reported in a single subject; acute myocardial ischemia and papillary muscle hypertrophy, were regard as possibly related to study drug. The other reported SAEs were considered unlikely or not related to study drug. There were no POME or allergic reactions reported.

> ***Reviewer's Comments:*** *Of the 11 new clinical study reports submitted in the Complete Response, just 2 cases were suspect for serious post-injection POME or post-injection anaphylaxis (the report of post-injection convulsion in Patient #001-0011 and post-injection collapse in Patient*

#001-0017 in Study 97173) . There were surprisingly few adverse events reported in all 11 trials, and several trials had no AEs reported at all. It was also surprising to find few cases reported with characteristics commonly seen with POME, such as cough or dyspnea.

There are 6 remaining trials, all submitted with the Original NDA.

- ***Study IP157-001*** *is the pivotal study, consisting of Parts A and C. This study has been extensively reviewed in previous sections of this review. There was one case of post-injection POME described in* Patient 050-7006 *in Part C (a 10 minute coughing fit). This cases has been counted by Sponsor. There was one case of interest in Part A: Patient #025-4187 who experienced post-injection pre-syncopal symptoms. There was one case of interest in Part B: Patient #011-6089 who experienced mild shortness of breath after his first injection that was accompanied by erythema of the neck.*

- ***Study JPH01495*** *- This was an open-label, Phase 1, single dose study conducted at a single site in Germany in 14 subjects. Safety was monitored by adverse events, local site examinations, prostate exams, PSA, uroflow, lipids, clinical labs, and vital signs. There were no reports of post-injection reactions.*

- ***Study JPH04995*** *– This was an open-label, Phase 2, multiple dose (four) study conducted at a single site in Germany in 14 subjects. It was followed by an open-label extension of up to 14 injections. Safety was monitored by adverse events, local site examinations, prostate exams, PSA, uroflow, lipids, and clinical labs. One patient experienced a skin disorder on the legs, arms and abdomen, which was diagnosed as leukocyoclastic vasculitis and required hospitalization. A skin test to TU was negative in this patient. Nonetheless, TU was stopped. The patient recovered. One patient in the short-term study (Patient #5) reported dizziness after his 1st injection that required him to be placed in supine position with legs raised.*

Another patient in the long-term follow-up part of this study experienced 2 events highly suspicious for post-injection reaction: Patient #004 had "circulatory collapse" immediately after his first injection of the extension period. Hypotension was documented. The patient again experienced "circulatory collapse" after his 9th injection. On both occasions, the patient was placed in Trendelenburg's position and recovered in 10 minutes.

- ***Study ME97029*** *– This was a PK comparator study versus T enanthate, conducted in 36 patients. There were 2 cases reported in this study that might reflect post-injection reaction. Patient #26 was reported to experience a serious AE of syncope at 12 weeks after his 9th injection. Table 29 in the text shows the time of this event to be the 10th injection. It is unclear if this occurred soon after the 10th injection. Patient #35 experienced "circulatory collapse" at the time of the 9th injection.*

- *Study ME98096 – This was a Phase 2 repeat-dose PK study conducted at a single site in Germany in total of 26 patients. Safety was monitored in the usual fashion. There were no reports suspicious for post-injection reaction.*

- *Study 306605 was a Phase 3 study conducted at 16 sites in Germany. A total of 100 patients were evaluable and 96 were analyzed. Safety was assessed in the usual fashion. There was one notable post-injection reaction. Patient #159 experienced stomach pain after each injection believed probably related to TU intramuscular.*

Therefore, in these 6 studies, there are 3 additional cases of particular relevance: Patient #001-0004 from Study JPH04995 (circulatory collapse after 1st injection of extension phase and again after 9th injection), Patient #26 from Study 97029 (post-injection syncope) and Patient #35 from Study 97029 (post-injection circulatory collapse).

7.5.3 Recent Suspect Adverse Reaction Reports

7.5.3.1 Final Safety Update Submitted by Sponsor on August 29, 2009

On August 29, 2009, at the Division's request, MedWatch reports of likely or possible post-injection reactions for the time period November, 2008-August, 2009 were submitted. Eighteen cases were included. Of these, 7 cases were non-serious and 11 cases were serious. Of the non-serious cases, cough was reported in 6 patients, chest pain in 3 patients, and dyspnea, sweating, burning in mouth, acid taste in mouth, and funny feeling in 1 patient each. One patient reported a "fur ball in throat". One patient received an antihistamine, another oxygen and reassurance. One non-serious case was notable: A 71 year old female-to-male transsexual had a positive skin reaction to a single substance, benzyl benzoate. The allergists's report documents a Type IV hypersensitivity reaction with erythema and blister. There were 8 serious cases suspect of POME or allergy:

2009-10048BNE. A 39 y/o was reported to have experienced "anaphylactic shock" which was reported as life threatening and required hospitalization. He was given 2 doses of adrenaline. Outcome unknown.

2009-10221BNE. A 44 y/o experienced throat and chest tightness, cough and sweats. No other information provided.

2009-12293BNE. A 53 y/o who had previously received 5 doses of TU, had 2 episodes reported as "anaphylactic shock" at an 11 week interval between injections. The 1st episode consisted of burning of throat, flushing and difficulty in breathing, from which he recovered. During the 2nd episode he experienced shortness of breath, feeling hot, sweaty, flushing, red face, and a thready and irregular pulse which lasted between 5 and 30 minutes. A consultant recommended that an alternative T replacement be considered, however a nurse confirmed that additional TU injections had been given without further reactions.

2009-12294-BNE. A 33 y/o experienced tightening of throat, feeling odd, shortness of breath, flushing, bronchospasm, and panic attack. Recovered. No additional information provided.

2009-16799LA. Age not stated. Patient developed an acute skin rash and breathing difficulty. He was treated with IV hydrocortisone and recovered.

2009-19013LA. A 75 y/o experienced dysgeusia, malaise, a hot feeling on body, a burning sensation and formication on skin. He recovered the same day after parenteral adrenaline and corticosteroids.

2009-19765LA. A 33 y/o experienced difficulty in breathing during his 1st TU injection. The difficulty intensified, cyanosis developed and administration of drug was stopped. IV hydrocortisone and antihistamine was given and patient improved within minutes. The patient also had a crying spell, cough and vomiting. That evening at 8 pm he reported fever which was treated with an unspecified NSAID and fever abated by midnight.

2009-24735GPV. A 22 y/o. experienced dyspnea, swollen mouth and throat, shivering and reported feeling scared, during injection by sister-in-law in his apartment. Recovered after treatment with IV antihistamine, adrenaline and SoluCortef, in addition to use of bronchodilator inhaler.

One non-serious case is shown here due to relevance:

2009-12132GPV. A 62 y/o experienced a burning sensation and dysgeusia in mouth, a feeling of a fuzz ball in his throat, a hacking cough, and sweating during the injection. No further information provided.

7.5.3.2 Postmarketing Case Submitted on September 21, 2009

On September 21, 2009, the Sponsor submitted a MedWtach report of a 16 year old Australian male receiving TU intramuscular injection who experienced an anaphylactic reaction less than 3 minutes after treatment with Reandron (TU intramuscular injection). The event was described as life-threatening and included "classical itching of the palms, groin and feet, followed by widespread/generalized uritcaria, tightening in the throat, angioedema of the lips and face, shortness of breath, constriction of the chest, hypotension, cough and dizziness. The reaction occurred after the patient's third injection of TU. The attending general practitioner administered IV adrenaline, IV antihistamines, IV steroid, IV fluids, and oxygen. He was hospitalized overnight and recovered. The patient had no history of allergy and had tolerated Sustanone (T) injections without previous incident. An

allergist conducted a skin test, which showed a very large Type I reaction to Reandron. The allergist felt that the causative substance was either the TU itself or benzyl benzoate.

> *Reviewer's Commment: The Sponsor believes that this is the first and only true cases of anaphylaxis to be "ruled in". This reviewer believes that many of the other postmarketing cases were anaphylactic reactions and this assessment is confirmed by our Division of Pulmonary And Allergy Products. The Sponsor still does not acknowledge the serious and life-threatening risks of TU intramuscular injection.*

7.5.3.3 Postmarketing Case of Death Submitted on June 16, 2009

On June 16, 2009, the Sponsor submitted a 7-day Safety Report describing a death in a 71 year old male in Germany who appears to have received 2 injections of TU. After the first injection, the patients developed peripheral edema and had a work-up to exclude venous thrombosis, which "proved unsuspicious". The patient received a 2nd dose and "died subsequently 12 days following the injection."
In a follow-up to the 7-day safety report dated July 1, 2009, The patient's spouse provided limited information to the physician-reporter, saying only that the death certificate indicated the cause of death was an unspecified foreign body in the respiratory tree, leading to respiratory failure. This was supported by what Sponsor understands to be a gross necropsy inspection of the body (external examination). No formal autopsy was conducted. A copy of the death certificate is expected to be received by mid-August, 2009.

> *Reviewer's Comment: This reviewer's assessment, made on the basis of the information received from Sponsor, is that the 12 day interval between the last injection and the death being attributed to a "bolus" of food aspirated into the respiratory tract, makes it highly unlikely that this event could be attributed to the TU injection. This reviewer concurs with the opinion of both Sponsor and their European partner (Bayer Schering Pharma) that the death is not related to this drug.*

7.6 Recent Consult from the Division of Pulmonary Allergy Products (DPAP)

In October 2009, DRUP again consulted DPAP to review 52 of the most recent postmarketing adverse event reports, including the November 2007 – November 2008 Bayer PSUR (inclusive of Appendix 8), the November 2008 – August 29, 2009 Safety Update, and the Additional Case received on September 21, 2009. DPAP conducted a detailed review and met with DRUP on November 3, 2009 to discuss. While their final consult is still pending, DPAP informed DRUP that they found a total of 9 definite cases of anaphylaxis in the group of 52 reports, 7 possible cases of anaphylaxis, 2 "borderline possible" cases, 4 allergic reactions, 8 cases of possible POME, 1 cases of injection site problem, 6 cases with nonspecific symptoms and 15 cases with too little information to ascribe an etiology. DPAP cautioned that most of the cases in the final category were reported as anaphylactic reaction, and these should not be summarily dismissed due to sparse information. DPAP noted that these cases were more concerning in terms of risk compared to then original 66 cases they had reviewed. DPAP felt that all reports of throat tightening, throat tickling and throat fullness, furriness, etc were signs of anigioedema, a mucosal swelling that can serve as a key symptoms for diagnosis of anaphylaxis.

> *Reviewer's Comment: This reviewer concurs with the DPAP assessment and strongly agrees that many cases were anaphylaxis. Many were serious POME. The risks of post-injection reactions can be life-threatening.*

8. Overall Safety Conclusion

Concerns regarding post-injection POME and anaphylactic reactions have not been allayed. Updated post-marketing data demonstrating numerous reported life-threatening post-injection reactions, many of which required on-site emergency treatment and/or hospitalization. Our consultants in allergy inform us that at least 22 cases of possible or definite anaphylaxis have been reported. Many more cases of angioedema have been reported. It appears that the incidence of the problem projected by Sponsor from clinical trials may be too low, based upon censoring of several cases possibly reflecting post-injection reaction. Taken together, the reviewer believes that the risks of the product outweigh its benefit.

9. Appendices

9.1 Labeling Recommendations

Although there have been some labeling discussions between Sponsor and DRUP, the reviewer recommends no further labeling discussions at this time as the reviewer's recommendation is not to approve the product at this time. Labeling which advises advice as to the management of post-injection reactions once they have occurred is considered inadequate. Efforts need to be made to reduce or eliminate the occurrence of these reactions.

9.2 Addendum

As a resource for the reader, a list of cases submitted by Sponsor from November, 25, 2008 through September 21, 2009 is provide herein:

BIN #1: Sept. 21, 2009 (CIOMS Form Submitted (n=1)

1. 2009 32012 GPV A 16 y/o with a history of testicular agenesis asthma, eczema, and food and drug allergies, who had previously received injections of TU without incident, had itching of his palms, groins and feet, widespread urticaria, tightening of throat, angioedema of lips and face, shortness of breath, constriction of chest, cough, dizziness and hypotension, less than 3 minutes after his 3rd dose. He required resuscitation by prednisolone, IV adrenaline, antihistamines and fluids, and oxygen by mask. This event was reported as a life threatening anaphylactic reaction, and subsequent skin testing showed a large positive type 1 reaction.

Reviewer's Comment: *This would appear to be a clear uncontested case of anaphylaxis by the Sampson criteria.*

BIN #2: Nov. 2008- Aug. 2009 (From individual MedWatch reports Submitted by Endo Pharmaceuticals on Aug. 29, 2009 (n=8)

1. 2009 10048 BNE A 39 y/o with Klinefelter's, experienced what was reported as "anaphylactic shock", approximately 16 months after starting treatment. Signs and symptoms were not stated. The event was reported as life threatening. He was treated with 2 doses of adrenaline 0.5 mg as an outpatient, then hospitalized. Outcome unknown.

Reviewer's Comment: *There is insufficient information to assess this event, however, the attending physician used the term anaphylactic reaction, called the event life-threatening and treated with adrenaline. This is meaningful information and the case should not be discounted.*

2. 2009 10221 BNE A 44 y/o with high prolactin, had chest tightness, throat tightness, cough and sweatiness on same day as his 1st dose. Treatment was not reported. He recovered the same day and the drug was withdrawn.

Reviewer's Comment: *Signs and symptoms in this case are suggestive of angioedema.*

3. 2009 12293 BNE. A 53 y/o who had previously received 5 doses of TU, had 2 episodes reported as "anaphylactic shock" at an 11 week interval between injections. The 1st episode consisted of burning of throat, flushing and difficulty in breathing, from which he recovered. During the 2nd episode he experienced shortness of breath, feeling hot, sweaty, flushing, red face, and a thready and irregular pulse which lasted between 5 and 30 minutes. A consultant recommended that an alternative T replacement be considered, however a nurse confirmed that additional TU injections had been given without further reactions.

Reviewer's Comment: *Signs and symptoms in this case are suggestive of an anaphylactic reaction (angioedema, skin flushing, and difficulty breathing).*

4. 2009 12294 BNE. A 33 y/o who had been taking TU for 2 years, experienced

tightening of throat, feeling odd, shortness of breath, flushing, bronchospasm, and panic attack. The event was reported as "possible anaphylactic reaction" Treatment was not stated. He recovered, and treatments have continued without further reactions.

Reviewer's Comment: *Signs and symptoms in this case are suggestive of anaphylactic reaction (angioedema, flushing and shortness of breath).*

5. 2009 16799 LA — Age not stated. Patient developed an acute skin rash and breathing difficulty immediately after his 2nd injection. Event was reported as "possible anaphylactic shock". He was treated with IV hydrocortisone and recovered. He refused further TU treatment.

Reviewer's Comment: *Signs and symptoms in this case are suggestive of anaphylactic reaction (skin rash and difficulty breathing).*

6. 2009 19013 LA — A 75 y/o who had been taking TU injections for 2 years, reported burning sensation on skin, body formication, hot feeling on body, bad taste in mouth, and malaise a few minutes after injection. He recovered the same day after parenteral adrenaline and corticosteroids.

Reviewer's Comment: *Signs and symptoms in this case are suggestive of an allergic reaction.*

7. 2009 19765 LA — A 33 y/o with a benign pituitary tumor experienced difficulty in breathing during his 1st TU injection. The difficulty intensified, cyanosis developed and administration of drug was stopped. IV hydrocortisone and antihistamine was given and patient improved within minutes. The patient also had a crying spell, cough and vomiting. That evening at 8 pm he reported fever which was treated with an unspecified NSAID and fever abated by midnight. This event was reported as an allergic reaction.

Reviewer's Comment: The case may reflect serious POME or an allergic reaction. *There is insufficient information to fully assess this event.*

8. 2009 2475 GPV A 22 y/o with Klinefelter's who had been taking TU for more than 3 years, experienced dyspnea, swollen mouth and throat, shivering and reported feeling scared, during injection by sister-in-law, a nurse, in his apartment. He was hospitalized for 1 day and recovered after treatment with IV antihistamine, adrenaline and SoluCortef, in addition to use of a bronchodilator inhaler.

Reviewer's Comment: *Signs and symptoms in this case are suggestive of an anaphylactic reaction (angioedema and dyspnea).*

BIN #3: Nov. 2007-Nov. 2008 (From listings in Attachment A to Appendix 8 of the Bayer PSUR, submitted with the Complete Response)[n=31]

1. 2008 15265 LA A 60 y/o who had been receiving TU for 1 year had an immediate post-injection injection reaction consisting of a cough, throat itching, glottis spasm and glottis edema. This was reported as an"anaphylactic reaction" and treated with adrenaline, oxygen, and IV saline, SoluCortef and antihistamine.

Reviewer's Comment: *Signs and symptoms in this case are suggestive of angioedema.*

2. 2008 18230 LA A 58 y/o was reported to have had an "anaphylactic reaction" 24 hours after receiving his dose. No further information was provided.

Reviewer's Comment: *There is insufficient information to assess this event. Nonetheless, the case was reported as an anaphylactic reaction and it should not be discounted.*

3. 2008 28604 GPV A 41 y/o with Klinefelter's who had been receiving TU for 6 years, was reported to have had an "anaphylactic reaction" during injection (feeling of tightness in region of thorax, burning eyes, flushing, tingling sensation in lungs ascending to nose, dry cough). Allergy testing planned.

Reviewer's Comment: *Signs and symptoms in this case are suggestive of an allergic reaction, although an anaphylactic reaction is possible (flushing,and dyspnea_).*

4. 2008 12947 GPV A 38 y/o with acute lymphoblastic leukemia, status- post radiotherapy, had 2 post-injection episodes. The 1st episode was reported as "mild allergic reaction" after 1st dose. 2nd episode 6 months later reported as "severe allergic reaction/potential heart failure" (severe throat swelling). Treatment was not reported.

Reviewer's Comments: *The 2nd episode is suggestive of anaphylaxis by the Sampson criteria. There is insufficient information to assess the 1st episode, although it was reported as an allergic reaction..*

5. DE 2005 008181 A 67 y/o obese patient, in whom "deep IM injection may have been difficult", developed circulatory collapse, hypotension, nausea, retching, and "fever attacks". "Reported as "allergic reaction". Treatment was not reported.

Reviewer's Comment: *Signs and symptoms in this case are suggestive of anaphylaxis by the Sampson criteria (an allergic reaction with hypotension).*

6. DE 2004 037302 A 38 y/o, reported hyperventilation during injection, and 2 minutes after injection, developed a red face, tachycardia, hypertension, feeling heat in thighs and upper arms, and "indisposition"). Reported as "allergic reaction" and treated with IV prednisone and oral antihistamine.

Reviewer's Comment: *Signs and symptoms in this case are suggestive of an allergic reaction.*

7. DE 2005 008140 A 56 y/o, reported immediate tickling of throat after removal of needle. This was his 1st injection of TU and was reported as an "allergic reaction". He was treated with an antihistamine.

Reviewer's Comment: *Signs and symptoms in this case are suggestive of angioedema.*

8. DE 2005 008146 A 57 y/o, developed post-injection headache, temporary visual field defect, and an injection site hemorrhage. Reported as "allergic reaction".

Reviewer's Comment: *There is insufficient information to assess this event. Nonetheless, the event was reported as an allergic reaction.*

9. DE 2005 008154 A 65 y/o, reported "pressing complaints after injection", and injection site discomfort. Reported as 'allergic reaction". Treatment or outcome not stated.

Reviewer's Comment: *There is insufficient information to assess this event. Nonetheless, the event was reported as an allergic reaction.*

10. DE 2005 008161 A 70 y/o, developed a post-injection "sensitive skin reaction". Reported as an "allergic reaction".

Reviewer's Comment: *There is insufficient information to assess this event, although it was reported as a sensitive skin reaction with sensitive skin. .*

11. DE 2005 008193 A 69 y/o, developed post-injection headaches, hot head, and pain at injection site. Reported as "allergic reaction". Treatment and outcome not stated.

Reviewer's Comment: *There is insufficient information to assess this event.*

12. DE 2005 008199 A 68 y/o, developed a post-injection short-term cough with

an “allergic sound”. Reported as “allergic reaction”. Patient is of the opinion that symptoms were more likely due to sprayed alcohol of disinfection than the injection.

Reviewer’s Comment: *There is insufficient information to assess this event. However, a cough with “allergic sound” was reported and may imply the stridor associated with angioedema.*

13. NO 2007 008557 Age not specified. Patient developed a dry cough, itching, and a tingling sensation. Reported as “hypersensitivity” No further information.

Reviewer’s Comment: *Signs and symptoms in this case are suggestive of an allergic reaction.*

14. NO 1007 008581 Age not specified. Patient developed post-injection “itching all over”. Reported as “hypersensitivity”.

Reviewer’s Comment: *Symptoms in this case are suggestive of an allergic reaction.*

15. DE 2005 014372 Age not specified. Patient developed post-injection edema. Attributed to an “allergic reaction”. No further information was provided.

Reviewer’s Comment: *There is insufficient information to assess this event.*

16. DE 2007 0047748 Age not specified. Patient developed urge to cough, and dyspnea. Reported as “suspicion of allergic event”.

Reviewer’s Comment: *Signs and symptoms in this case are suggestive of POME.*

17. DE 2006 009799 Age not specified. Patient developed post-injection dyspnea and a cold sweat shortly after injection. Reported as “suspected allergic reaction, no local symptoms”. Treatment and outcome not reported.

Reviewer's Comment: *There is insufficient information to assess this event, however dyspnea and cold sweating may imply POME.*

18. 2008 21776 GPV A 33 y/o with nonseminoma testicular cancer, status-post unilateral orchiectomy, and radiotherapy to remaining testicle, "felt bad" had breathing problems and cough directly after injection. BP increased to 147/89. Reported as "allergic reaction". Treated with bronchodilator inhalation and antihistamines.

Reviewer's Comment: *Signs and symptoms in this case are suggestive of POME.*

19. 2008 13805 LA A 53 y/o with three post-injection episodes, including injection site pain, injection site mass, injection site warmth, injection site pruritis after first 2 injections. After 3rd injection, injection site pain, warmth and pruritis, dry throat, sinusitis, nocturnal dyspnea, breathlessness at night, and increased blood pressure.

Reviewer's Comment: *Symptoms in this case are suggestive of an allergic reaction*, although pruritis and breathlessness may signal an anaphylactic reaction.

20. BR 2006 019257 Age not specified. Patient reported as having had an "allergic reaction". No further information provided.

Reviewer's Comment: *There is insufficient information to assess this event.*

21. 2007 11462 BNE A 44 y/o who had been treated for 8 months with TU, had cough, shortness of breath and flushing immediately after injection. He recovered after 24 hours.

Reviewer's Comment: *Signs and symptoms in this case are suggestive of POME, although flushing and shortness of breath may signal an anaphylactic reaction.*

22. AT 2006 001317 A 64 y/o developed a severe hot flush, dyspnea, anxiety, tachycardia, (>109 bpm), fatigue, depression and sleep disorder after 2nd injection.

Reviewer's Comment: *Symptoms in this case are suggestive of an allergic reaction.*

23. SE 2007 002541 Age not specified. Patient had cough, redness of face, and feeling of warmth over chest and head. No further information.

Reviewer's Comment: *Symptoms in this case are suggestive of an allergic reaction or POME. However, redness of face and feeling of warmth with cough may signal an anaphylactic reaction.*

24. SE 2006 039053 Age not specified. Patient developed post-injection palpitations, rash, whole body itching and trembling. He also had erection failure, intensive migraine and weight gain during 1st week after injection.

Reviewer's Comment: *Symptoms in this case are suggestive of an allergic reaction.*, although whole body itching, rash and palpitations may signal an anaphylactic reaction.

25. SE 2007 002515 Age not specified. Patient had post-injection urticaria over whole body, and itching. Other suspected drug: Plavix (clopidrogel sulfate).

Reviewer's Comment: *Symptoms in this case are suggestive of an allergic reaction.*

26. CH 2005 002386 A 33 y/o, with patchy reddening of whole integument (less in face) and mild pruritis after 1st injection. Treatment with antihistamine was ineffective, and rash abated immediately after cortisone injection.

Reviewer's Comment: *Symptoms in this case are suggestive of an allergic reaction.*

27. FR 2007 035024 Age not specified. Patient developed redness and pruritis on face and chest 1 week after 1st injection. A topical prescription was given to treat the rash. No further information was provided.

Reviewer's Comment: *Symptoms in this case are suggestive of an allergic reaction.*

28. 2008 16799 GPV Age not specified. Patient had nervousness, hot flushes, sweats, rash around neck, unusual head hair, excessive hair growth, headache, difficulty sleeping, rosacea, slight depression and no sex drive, one week after 1st dose.

Reviewer's Comment: *There is insufficient information to assess these events.*

29. 2008 15181 GPV A 52 y/o developed severe dyspnea, heat sensation in neck, muscle twitching, tickling in throat, and loss of consciousness. Reported as "assumed microfat embolization".
CT scan: "no pathological findings, no infarction, no bleeding".
He recovered after 24 hours.

Reviewer's Comment: *Signs and symptoms in this case are suggestive of anaphylaxis by the Sampson criteria.*

30. 2008 19576 LA Age not specified. Patient had sweating, cough, face redness, and dizziness during injection. No further information.

Reviewer's Comment: *Symptoms and signs in this case are suggestive of an allergic reaction or POME, although reddened face, cough and dizziness may signal an anaphylactic reaction.*

31. 2008 12881 BNE A 27 y/o with Noonan syndrome (primary testicular failure) and asthma had, with cough, flushing, wheezing and bronchospasm immediately after 2nd injection. Recovered in 20 minutes after use of salbutamol nebulizer.

Reviewer's Comment: *Symptoms and signs in this case are suggestive of an* anaphylactic reaction (flushing and wheezing).

BIN #4 **Nov. 2007- Nov. 2008 (From body and line listings of the PSUR) [n=12]**

1. 2008 11461BNE A 55 y/o with history of hypopituitarism treated with somatotropin, developed heavy sweating, metallic taste in mouth, a "burning up" sensation, and a sharp increase BP ("soared to 275/175"), immediately after 3rd injection. Patient was hospitalized and drug was withdrawn.

Reviewer's Comment: *Symptoms and signs in this case are suggestive of an allergic reaction.*

2. 2008 20307 GPV A 72 y/o developed cyanosis, continuous coughing, dizziness and numbness of face, immediately after 4th injection. Treatment and outcome not reported.

Reviewer's Comment: *Symptoms and signs in this case are suggestive of an allergic reaction or POME.*

3. 2008 21519 GPV A 21 y/o had sudden chest pain radiating toward neck and throat, light cough and cold sweating after injection.

Reviewer's Comment: *Symptoms and signs in this case are suggestive of an allergic reaction or POME.*

4. 2008 26527 GPV A 72 y/o developed severe coughing, temporary palsy of mouth and face, facial dysesthesia, and a choking fit during injection. Treatment not stated. Drug was withdrawn

Reviewer's Comment: *Symptoms and signs in this case are suggestive of an allergic reaction or POME.*

5. 2008 26556 GPV A 76 y/o, had severe coughing, dyspnea and a choking fit during injection. Patient has a similar reaction previously. Event reported as POME. Drug was withdrawn.

Reviewer's Comment: *Symptoms and signs in this case are suggestive of POME.*

6. 2008 11355 GPV A 30 y/o with a history of 30 months of TU treatment developed a post-injection dry cough, severe burning in throat, scratching in throat, moderate dyspnea, and sensation of heat.

Reviewer's Comment: *Symptoms and signs in this case are suggestive of angioedema, but an anaphylactic reaction may be possible (angioedema and dyspnea).*

7. 2008 121366 GPV A 40 y/o had cough, sweating, dizziness, and prickly feeling in fingers and toes after each of 2 injections.

Reviewer's Comment: *Symptoms and signs in this case are suggestive of allergy.*

8. 2008 25110 GPV A 21 y/o who had a 2 year history of TU treatment, developed chest pain, a cold sweat, and pain in throat. He was treated with adrenaline and betamethasone.

Reviewer's Comment: *There is insufficient information to assess this event, although pain on the throat and cold sweat might imply angioedema.*

9. 2008 21057 GPV A 50 y/o developed a generalized rash on whole body 3 days after injection. Treated with antihistamine and recovered.

Reviewer's Comment: *Signs in this case are suggestive of a delayed hypersensitivity reaction.*

10. 2008 22564 GPV A 30 y/o developed urticaria at an unknown time after injection. He was treated with an antihistamine but has not recovered. He was also using Testogel.

Reviewer's Comment: *There is insufficient information to assess this event.*

11. 2008 12867 LA A 22 y/o developed red eyes, cough, malaise, and diarrhea 24 hours after an injection. Previously had been using Durteston.

Reviewer's Comment: *There is insufficient information to assess this event.*

12. 2008 19842 GPV Age not specified. A patient with pituitary hypogonadism, had sweating, a slight fall in BP, and "severe reaction" at unknown time after injection.

Reviewer's Comment: *There is insufficient information to assess this event.*

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22219	ORIG-1	ENDO PHARMACEUTICALS INC	NEBIDO

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/s/

HARRY HANDELSMAN
11/10/2009

MARK S HIRSCH
11/10/2009
I concur.

DIVISION OF PULMONARY AND ALLERGY PRODUCTS (DPAP)
MEDICAL OFFICER CONSULTATION

Date:	June 30, 2008
To:	Jeannie Roule, Project Manager Division of Reproductive and Urologic Products
From:	Lynne H. Wu, MD, Medical Reviewer, DPAP
Through:	Anthony Durmowicz, MD, Team Leader, DPAP
Through:	Badrul A. Chowdhury, MD, PhD, Director, DPAP
Subject:	Aveed (testosterone undecanoate) for intramuscular injection

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General Information

NDA/IND#:	NDA# 22-219
Sponsor:	Indevus Pharmaceuticals, Inc.
Drug Product:	Aveed (testosterone undecanoate) for intramuscular injection
Request From:	Jeannie Roule, Project Manager, Division of Reproductive and Urologic Products
Date of Request:	May 4, 2009
Date Received:	May 4, 2009
Materials Reviewed:	IND [redacted] (b) (4) testosterone undecanoate, protocol # IP157-003

DPAP has been a consultant to the Division of Reproductive and Urologic Products (DRUP) for Aveed (previously Nebido) (NDA 22-219) for evaluation of post injection anaphylaxis and pulmonary oil microembolism (POME) events since April 2008. The original NDA was submitted in August 2, 2007, and an approvable letter was issued in July 27, 2008, expressing safety concerns about serious post injection respiratory (POME) and allergic adverse reactions. Most recently in September 2008, we evaluated and made recommendations regarding the sponsor's proposed protocol [redacted] (b) (4) For this consult, we are asked to review the sponsor's revised protocol. For additional background information see the consult to DRUP by this reviewer dated September 18, 2008, and the original consult which addressed the potential respiratory and allergic adverse events by Dr. Charles Lee dated April 14, 2008.

BACKGROUND

Aveed contains testosterone undecanoate in castor oil and benzyl benozate and is administered as IM injection for testosterone replacement in hypogonadal men with testosterone deficiency. The injection contains 250 mg/ml and is to be given at 750 mg per dose, repeated at 1 month, then dosed every 10 weeks. Post injection respiratory and anaphylactic reactions have been noted. In the clinical trial population of approximately 600 subjects (4000 injections), 2 cases of POME were reported.

Aveed has been approved in Europe since 2004 with more than (b) (4) single dose ampules distributed. Sixty-six cases of either POME or anaphylaxis were reported in this post-marketing population. Of all the reported cases, 2 fulfilled the diagnostic criteria for anaphylaxis (see Sampson HA, et. al. J Allergy Clin Immunol 115:584-591, 2005 and Sampson HA, et. al. J Allergy Clin Immunol 117:391-397, 2006) and 2 demonstrated systemic allergic reactions but did not fulfill anaphylaxis criteria. The rest of the cases were felt to be attributable to POME.

In response to recommendations from the approvable letter of June 27, 2008, the sponsor proposed a protocol (b) (4)

THE CURRENT CYCLE OF SUBMISSION AND THE REVISED PROTOCOL

For the current cycle of the NDA application dated March 2, 2009, the sponsor submitted a revised anaphylaxis evaluation protocol and additional safety data from the ongoing clinical trials. It is notable that of the additional 15 studies submitted in the sponsor's latest Complete Response involving approximately 2,200 patients, no additional serious POME reactions or allergic reactions were reported.

Revised Study Description:

(b) (4)

(b) (4)

Reviewer's comment:
This revised protocol is very similar to the previous protocol evaluated in September 2008. One of the differences is that (b) (4) *minor difference and do not significantly change the protocol.*

SUMMARY

Overall, DPAP maintains its previous position that the clinical criteria of anaphylaxis[1,2] has been met after injection of the Aveed product and that if the product is to be approved, the risks of anaphylaxis should be stated in the labeling and that an appropriate risk management plan be developed for the product. The likelihood of the proposed re-challenge study to yield useful information regarding the mechanism through which the reactions occur is low. However, if the sponsor decides to conduct the study, we continue to recommend the study design changes previously conveyed to the sponsor which were outlined in the previous DPAP consult dated September 18, 2008. (b) (4)

[1]Sampson HA, et al. J Allergy Clin Immunol. 115 (3):584-591, 2005.
[2]Sampson HA, et al. J Allergy Clin Immunol. 117 (2):391-397, 2006.

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/s/

Lynne Wu
7/6/2009 04:24:46 PM
MEDICAL OFFICER

Anthony Durmowicz
7/7/2009 06:33:07 AM
MEDICAL OFFICER

Badrul Chowdhury
7/9/2009 03:47:36 PM
MEDICAL OFFICER
I concur

DIVISION OF PULMONARY AND ALLERGY PRODUCTS (DPAP)
MEDICAL OFFICER CONSULTATION

Date:	September 18, 2008
To:	Jeannie Roule, Project Manager Division of Reproductive and Urologic Products
From:	Lynne H. Wu, MD, Medical Reviewer, DPAP LW 9/19/08
Through:	Anthony Durmowicz, MD, Team Leader, DPAP AD 9/19/08
Through:	Badrul A. Chowdhury, MD, PhD, Director, DPAP B. Chowdhury 9/18/08
Subject:	Nebido (Testosterone undecanoate) for intramuscular injection

General Information

NDA/IND#:	NDA# 22-219
Sponsor:	Indevus Pharmaceuticals, Inc.
Drug Product:	Nebido (testosterone undecanoate) for intramuscular injection
Request From:	Jeannie Roule, Project Manager, Division of Reproductive and Urologic Products
Date of Request:	August 8, 2008
Date Received:	August 8, 2007
Materials Reviewed:	Pre-meeting briefing package dated 09/03/2008

I. Background

On June 27, 2008, the Division of Reproductive and Urologic Products (DRUP) took an approvable action on Nebido (testosterone undecanoate) for IM injections (NDA 22-219). The product contains testosterone undecanoate in castor oil and benzyl benzoate and was approved for use in Europe in 2004. It is administered as an intramuscular injection for testosterone replacement in hypogonadal adult men with conditions associated with deficiency of endogenous testosterone. The injection contains 250mg/mL and the proposed regimen is an initial dose of 750mg repeated at 1 month, then every 10 weeks thereafter. During the course of the NDA review DRUP became aware of "immediate post-injection reactions" in NDA-related clinical trials and in the post-marketing experience in the EU. The reactions were characterized by urge to cough, cough, dyspnea, and respiratory distress. In addition, some cases describe symptoms consistent with an allergic reaction, including: "anaphylactic reaction", angioedema, facial flushing, tightening of the throat, facial swelling, peri-oral paresthesia, and pruritis. The Sponsor attributed all these immediate post-injection reactions to pulmonary oil microembolism (POME) and recommended that these adverse reactions could be mitigated by slowly injecting the drug, following precautions for intramuscular injections in order to avoid penetration of a vessel, and, because the Sponsor felt that injection volume of castor oil may play a role in the incidence of reactions, (b) (4) (b) (4) 3 mL (750 mg) in injection volume.

DRUP consulted DPAP to help evaluate these immediate drug reactions (see DPAP consults by Dr. Charles Lee dated 4/14/08 and 5/27/08 for full details).

Dr. Lee reviewed 66 cases of immediate drug reactions, 28 were categorized as serious adverse events, 12 required emergency medical care (e.g., adrenaline, steroids, oxygen, antihistamines), and 6 required hospitalization. He concluded that, despite limited clinical information concerning the events, up to four adverse reactions could be viewed as potentially meeting recently proposed clinical diagnostic criteria for anaphylaxis. Most of the remaining cases were consistent with pulmonary oil microembolism (POME), a short-lasting reaction due to the direct vascular or lymphovascular delivery of oil-based preparation. DPAP recommended that the Sponsor characterize these anaphylactic events due to their unclear mechanism. In vitro testing was recommended for specific IgE and IgG antibody to the drug, both active and excipient ingredients, in patients who had anaphylactic events associated with the drug, those who have been exposed to the drug but who have not had anaphylaxis, as well as unexposed controls. DPAP also recommended that sponsor should develop a skin testing procedure to the product and excipients in the same populations.

In response to DPAPs recommendations (which were noted in the approvable action letter of June, 27, 2008), the Sponsor has now proposed (b) (4) [redacted] Following is a brief description of the proposed study followed by DPAPs responses to questions posed by DRUP as well as additional comments.

Study Description:

(b) (4) [redacted]

(b) (4)

[redacted]

Reviewer's Comments: We do not agree with the Sponsor's proposal. (b) (4)

(b) (4)

[redacted]

The Sponsor submitted three questions with the meeting package. DRUP requests DPAPs input on Question #2 regarding the Sponsor's proposed skin testing protocol and its interpretation.

Question 2: (b) (4)

(b) (4)

Response: No. (b) (4)

(b) (4)

(b) (4)

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/s/

Lynne Wu
9/18/2008 03:49:51 PM
MEDICAL OFFICER

Anthony Durmowicz
9/18/2008 03:55:31 PM
MEDICAL OFFICER

Badrul Chowdhury
9/19/2008 03:20:15 PM
MEDICAL OFFICER
I concur

NDA 22-219

Cross-Discipline Team Leader's Memorandum: New NDA

Date submitted:	August 24, 2007
Date received:	August 28, 2007
PDUFA goal date:	June 28, 2008
Date memo completed:	June 27, 2008
Sponsor:	Indevus Pharmaceuticals Lexington, MA
Drug product:	Nebido (testosterone undecanoate)
Route and formulation:	intramuscular injection (250mg per mL)
Dose:	750 mg Loading Regimen (3mL on Day 1, on Day 28, then every 10 weeks thereafter)

Indication: For replacement of testosterone in adult males with conditions associated with a deficiency of endogenous testosterone.

1. Executive Summary

The purpose of this memo is to convey my recommendation for regulatory action on this new drug application (NDA). I recommend that an **Approvable** action be taken for this application. There are ***Clinical*** and ***Chemistry*** deficiencies. The rationale for the ***Clinical*** recommendation is that a serious and unresolved safety problem remains for this product (immediate post-injection coughing fits and allergic reactions), and the Sponsor is being asked to submit additional information to further assess and manage it. Until such time as the safety concern is better assessed and better managed, the risk/benefit ratio is unacceptable for the proposed indication.

In summary, while the product has been shown to provide adequate efficacy at the 750mg Loading regimen as defined by average and maximum serum testosterone (T) parameters, and the safety profile was otherwise in line with its pharmacologic action as an exogenous androgen, there remains a serious and unresolved safety problem with the product - the occurrence of medically significant post-injection "coughing fits" and allergic reactions – with a yet to be adequately defined incidence, etiology, and risk management plan for these adverse reactions.

Post-injection cough reactions were reported in 2 patients in the Nebido clinical trials (out of approximately 673 total clinical trial patients) and in 66 patients in the post-marketing period in Europe for Nebido. These cough reactions ranged in severity from mild to severe. In greater than one third of the post-marketing "cough" cases, the event was described as serious (medically significant). In one out of 5 post-marketing cases, the event described active medical intervention or hospitalization. In some post-marketing cases, the event was described as "life-threatening" and required medical

intervention to prevent death or disability. These "cough" reactions tended to occur soon after or during the intramuscular injection, were described by patients as beginning with a sudden urge to cough, and some have also included shortness of breath, severe cough, laryngeal tightness, cyanosis, respiratory distress, circulatory collapse, and loss of consciousness. These events are clearly related to the drug product. It appears that pulmonary oil microembolism (POME) with resultant reduction in oxygen diffusion in the lungs plays the major role in causing these events, based upon the castor oil present in each 3 milliliter injection. In my opinion, the Sponsor does not appreciate the seriousness of these POME-related adverse events, does not acknowledge the impact of this risk on the overall risk: benefit profile for Nebido, and has not sufficiently defined, managed, or proposed an acceptable management plan for this potentially life-threatening, drug-related side effect for this product for testosterone replacement in hypogonadal adult males.

In addition, POME does not appear to be the only reason for these respiratory adverse reactions. In at least 4 post-marketing cases, the case narrative describes signs and symptoms consistent with a systemic allergic reaction. According to a formal consultation report from the Division of Pulmonary and Allergy Products (DPAP), at least 2 of these cases meet the current and generally accepted criteria for anaphylaxis. Several reports document the terms "angioedema" and "laryngeal tightness" with difficulty breathing. A few adverse event reports document concomitant periorbital swelling, rash, skin blotches, itching, and effects on blood pressure, giving the impression that these were systemic allergic reactions. Reasons for such allergic reactions could be: allergy to testosterone or to the excipients in the product – which include only purified castor oil and benzyl benzoate.

The incidence of the POME reactions and anaphylactic reactions remains unclear. The Sponsor lumps these events under the term "POME/POME-like" reactions and has argued that their incidence is "rare". Based upon total sales of (b) (4) vials of Nebido in Europe, the Sponsor argues that these 66 post-marketing cases reflect an incidence of less than 1 in approximately 10,000 injections. The Sponsor agrees that this is a rough estimate and that it is not possible to derive a per-patient incidence from these spontaneously reported post-marketing adverse events. In terms of clinical trial occurrences, there was 1 case reported in the pivotal U.S. efficacy study of 117 patients (referred to as "Part C") and 1 case in a supporting European clinical trial (Patient #184 in Study 306605). To my knowledge, then, the NDA and its amendments included data on approximately 673 patients and there were 2 reports of "cough reactions". The Sponsor has only recently (June 10, 2008) submitted scant additional summary information from a large European observational safety study (n=approximately 870), an ongoing European observational safety study (n= approximately 280), and an abridged study report for a completed Phase 2, male contraception study (n=approximately 220) which are purported to show no additional POME cases. This June 10, 2008 amendment would add an additional approximately 1400 patients to the clinical trials database. However, the information submitted for the 2 new observational studies, comprising most of the additional clinical trial subjects, was indeed scant and summary in nature, lacking sufficient detail to allow a reasonable interpretation of the design and conduct of the

studies or the methods used to collect and analyze adverse events. Therefore, in my opinion, the incidence of POME and of allergic reactions remains unclear at this point. I am unable to confirm the Sponsor's contention that the incidence of these potentially life-threatening POME/POME-like events is rare.

The etiology of the POME reactions is assumed to be the intravascular absorption and circulation of castor oil from the injection site. However, it is not clear why anaphylaxis has also been reported in at least 2 and perhaps 4 cases. It should be noted that additional cases were reported to CIOMS in Europe as "allergic reaction' or "anaphylaxis" and many, perhaps most, patients were treated as if an allergic reaction was occurring. Therefore, in my opinion, systemic allergic reactions to Nebido have been reported and their etiology remains unclear.

Finally, the management of these risks has not been approached in a careful and serious manner by the Sponsor. The Sponsor offers only to add these adverse reactions to product labeling with the caveat that the Nebido 3 mL injection should be delivered slowly and carefully to avoid accidental intravascular injection. The Sponsor agrees that there is no tangible evidence to show that such advice will reduce the incidence or mitigate the severity of the adverse reactions. There are no other steps outlined in terms of further risk minimization/risk management.

Taken together, it is my opinion that the risk of POME reactions and allergic reactions secondary to Nebido have not been sufficient assessed (specifically, the incidence of both reaction types, and the etiology of allergic reactions) nor sufficiently managed. Because of this safety deficiency, in my opinion, at this point the demonstrated benefits of this new testosterone replacement therapy do not outweigh its known and potential risks, and the application should receive an "*Approvable*" action. I propose the following verbiage for the *Clinical Deficiency* and *Information Needed to Resolve the Clinical Deficiency* sections of the action letter:

> *Deficiency*
> *Reports of serious post-injection respiratory and allergic adverse reactions in men who have received NEBIDO® raise significant safety concerns regarding the risk/benefit profile for the use of NEBIDO® for your proposed indication. The drug-related respiratory events, described as a sudden need to cough in the immediate post-injection period, have been reported in 2 patients in the Nebido clinical trial and in approximately 60 patients in the post-marketing period in Europe. In some of the cases, laryngeal tightness, respiratory distress, circulatory collapse, cyanosis, and loss of consciousness were also reported as part of the event. Pulmonary oil microembolism (POME) to the lungs, based upon the castor oil in the depot injection, appears to be causative for most of these cases. In at least 4 other cases, signs and symptoms of a clinically serious systemic allergic reaction have been reported, including 2 cases meeting criteria for anaphylaxis.*

1. *The likely incidence of these serious POME and allergic reactions in men who would be treated with NEBIDO®, should the drug product be approved for marketing, is not known. A precise estimate of the likely incidence of these serious adverse events is needed, to make a meaningful risk/benefit assessment for the use of NEBIDO® for your proposed indication.*
2. *The application does not include information regarding the underlying etiology of the anaphylaxis-like reactions. It is not known if these reactions are secondary to the active drug substance or excipients in the drug product, including the castor oil vehicle.*
3. *The application does not include an adequate plan to minimize or manage the risk of developing these potentially life-threatening events (both POME and anaphylaxis-like events).*

Information Needed to Resolve the Clinical Deficiencies

1. *Detailed safety information from clinical studies to determine the incidence of serious post-injection POME and allergic reactions.*

   At a minimum, the safety database should include (1) all subjects treated in Stage 2 of all parts of Study IP157 001, (2) all subjects in (a) Study NE0601 (IPASS), (b) the Non-Interventional Study (NIS), and (c) Study 42306, and (3) all additional foreign data of which you are aware. We consider the information that you provided in your submission of June 10, 2008, to be preliminary. Depending on the findings and the number of subjects and the number of injections of NEBIDO® from the studies listed above, the safety database may need to include data from additional clinical studies. You should propose the size of the safety database (i.e., total number of subjects exposed to NEBIDO® and total number of injections) and the rationale for the size of the proposed safety database.

2. *Information from clinical investigations intended to characterize the nature and etiology of the anaphylaxis-like events with NEBIDO®.*

   This information could be obtained by (1) skin testing procedures to the product and its excipients and (2) in vitro testing for the presence of specific IgG and IgE antibodies to both active and excipient components of the drug product.

3. *A plan to minimize the risks associated with the clinical use of Nebido, namely, to reduce incidence and/or severity of the serious POME and anaphylaxis-like adverse events.*

The rationale for the ***Chemistry*** recommendation is that the purity of the drug product is not assured from the sterility perspective until the drug master file (DMF) holder addresses the relevant deficiencies. For specific DMF deficiencies, as outlined by the

microbiologist and conveyed to the DMF holder on June 25, 2008, the reader is referred to the CMC section of this memo (Section 4.4).

2. Summary of Clinical Efficacy

2.1 Efficacy Background

Testosterone undecanoate (TU) is an ester prodrug of testosterone (T). TU is administered intramuscularly (IM) in the buttock. The dose being sought is 750 mg at start of therapy, 4 weeks later, and then every 10 weeks (± 3 days) (hereafter referred to as TU 750 mg LOADING regimen).

The NDA is supported by 2 phase 3 safety and efficacy studies (Study IP157-001 Part C and Study IP157-001 Part A). Study IP157-001 Part C evaluated the TU 750 mg LOADING regimen (n = 117) and study IP157-001 Part A evaluated doses of 750 mg (n=102) or 1000 mg (n=97) given every 12 weeks to hypogonadal men. The primary endpoints in the phase 3 studies were pharmacokinetic (PK) endpoints (serum T).

Results from five (5) other Phase 1, Phase 2, and Phase 3 European studies and their extension phases (including Study JPH01495, Study JPH04995 [with Follow-up], Study ME98096 [with Follow-up and Final Follow-up], Study ME97029 [with Follow-up and Final Follow-up], and Study 306605 [with Follow-up]) were provided in the NDA but were not reviewed in depth for efficacy because they employed dose regimens that are not being sought in this NDA. In addition, these older studies employed assay methods (radioimmunoassay or electrochemoluminescence immunoassay) that were regarded by Clinical Pharmacology as being not as accurate as the current HPLC/MS/MS method used in the primary studies IP157-001 Part A and Part C.

(b) (4)

in a teleconference dated January 15, 2008, the Sponsor requested that the Division consider for approval the **TU 750 mg LOADING regimen** studied in Study IP157-001 **Part C** (A study report for Part C was submitted to the Division via an NDA amendment on December 20, 2007). Due to this change, data from Study IP157-001 Part C were used as the source of steady state PK. Data from Study IP157-001 Part A was used as the source of first dose PK data because Part C did not evaluate first dose

PK. Part A also served as the primary source of data on serum TU and serum dihydrotestosterone undecanoate (DHTU) because these analytes were not measured in Study IP157-001 Part C.

2.2 Efficacy Results from Part C

Following IM administration to the buttock, TU is slowly released from the injection site. TU is metabolized to T via ester cleavage of the undecanoic acid group.

2.2.1 Assessment of Steady State Conditions in Part C

For the TU 750 mg LOADING regimen, as studied in Part C, the 3rd injection interval was determined to be the first injection interval that represented steady state conditions for serum total T concentration. Steady state was assessed based on trough serum total T concentration following the 2nd, 3rd, and 4th injections. The status of the steady-state during the 3rd injection interval is important because the 3rd injection interval was used for the primary efficacy assessment.

The mean data indicated that the serum T Ctrough values were similar at end of 2nd, 3rd, and 4th injection interval, as shown in *Figure 1* and *Table 1*. A comparison of serum total T concentration at several time points post injection during the 3rd and 4th injection intervals demonstrates similar concentration-time profiles, as seen in *Figure 2*. Taken together, these data indicate that steady state was achieved during the 3rd injection interval in Part C.

Figure 1: Mean (±SD) trough serum total T concentrations at each injection visit from pre-treatment through 5th injection – Steady state PK population, Study IP157-001 Part C

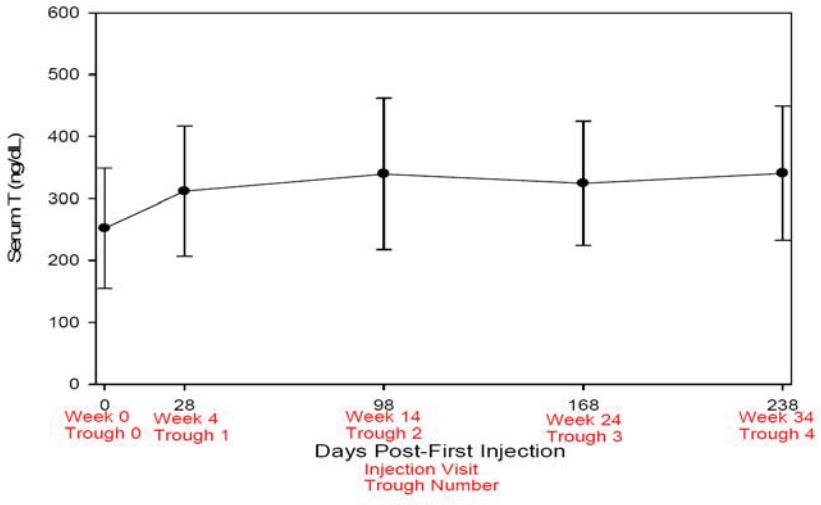
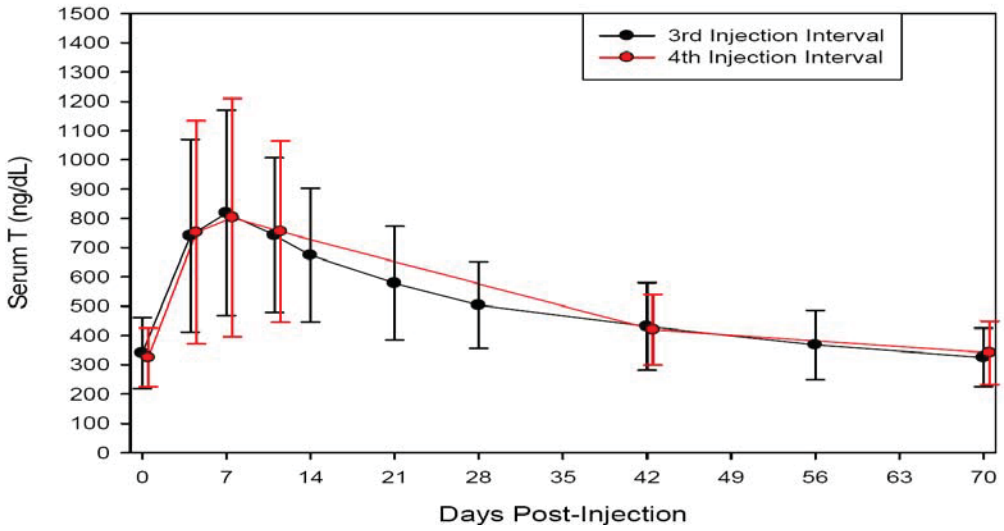


Table 1: Trough serum total T concentration at each injection visit from pre-treatment through 5th injection – Steady state PK population, Study IP157-001 Part C Stage 1 and Stage 2

	Serum Total Testosterone (ng/dL) (N=105)		
Time	**Mean**	**Standard Deviation**	**Range**
Week 0/Injection 1	251.3	96.79	0 to 538
Week 4/Injection 2	312.2	104.85	133 to 706
Week 14/Injection 3	340.1	122.17	141 to 754
Week 24/Injection 4	325.0	99.64	107 to 611
Week 34/Injection 5	340.9	108.09	148 to 634
Source: Table 9.2.1.2.1.1			

Figure 2: Comparison of serum total T concentrations between the 3rd and 4th injection intervals – Steady state PK population, Study IP157-001 Part C



2.2.2 Assessment of $C_{average}$ for Serum T (the primary endpoint) in Part C

Tables 2, 3 and 4 summarize the pharmacokinetic parameters of serum total T from the 3rd injection interval. The primary endpoint was Caverage.

Table 2. Serum total T pharmacokinetic parameters from the 3rd injection interval, TU 750mg LOADING regimen, from Study IP157-001 Part C

PK parameter	Mean (n=117)	Standard deviation
C_{avg} (ng/dL)	495	141
C_{max} (ng/dL)	891	345
T_{max} (days)	7 (median)	4 – 42 (range)

Table 3: PK parameters of serum total T (ng/dL) following the 3rd injection interval of TU 750 mg LOADING regimen - PK population, Study IP157-001 Part C

TU Dose	Pharmacokinetic Parameter	Number Patients	Mean	Standard Deviation	Minimum	Median	Maximum	CV (%)	Geometric Mean
TU 750 mg LOADING	$AUC_{(0-70)}$ (days*ng/dl)	117	34645.6	9902.45	13755.1	33342.2	70016.9	28.6	33263.6
	C_{Trough} (Day 70)	117	323.5	99.11	138.2	316.9	611.1	30.6	309.0
	C_{max} (ng/dL)	117	890.6	345.11	311.0	813.6	1758.5	38.8	826.8
	Dose-normalized C_{max}(ng/dL)[1]	117	1.2	0.46	0.4	1.1	2.3	38.8	1.1
	T_{Last} (days)	117	70.0	0.00	70.0	70.0	70.0	0.0	70.0
	T_{max} (days)	117	10.0	7.11	4.0	7.0	42.0	71.1	8.4
	Dose-normalized $AUC_{(0-70)}$ (days*ng/dl)[1]	117	46.2	13.20	18.3	44.5	93.4	28.6	44.4
	$C_{avg, 0-70}$ (ng/dL)[2]	117	494.9	141.46	196.5	476.3	1000.2	28.6	475.2

Reference: Section 14.2 Table 9.2.1.1.1
CV = Coefficient of Variation
[1] Statistics for the dose normalized AUC were derived by dividing the mean of the original parameter ($AUC_{(0-70)}$) by the dose amount (750 mg). Thus, no measures of variability, geometric mean, or CV are presented for the dose normalized AUC.
[2] C_{avg} derived as $AUC_{(0-70)}$/70 days

Table 4: Serum total T concentrations (ng/dL) over 70 day following the 3rd injection interval of TU 750 mg LOADING regimen - PK population, Study IP157-001 Part C

Treatment Group	Days Post-Injection	Number Patients	Mean	Standard Deviation	Minimum	Median	Maximum	CV%	Geometric Mean
TU 750 mg LOADING	0 (Pre-Injection)	117	339.5	122.69	141.4	303.0	754.1	36.1	319.8
	4	111	730.1	325.36	304.6	656.4	1715.0	44.6	662.9
	7	111	816.9	352.15	276.4	737.6	1758.5	43.1	747.5
	11	107	750.1	280.64	245.6	740.9	1757.0	37.4	697.9
	14	114	661.6	237.55	230.9	610.8	1352.3	35.9	619.2
	21	115	573.5	197.15	182.7	558.6	1350.4	34.4	541.3
	28	111	501.6	149.92	190.9	481.4	947.0	29.9	479.5
	42	109	432.3	152.16	171.3	399.8	1161.2	35.2	409.5
	56	115	367.0	120.67	144.5	349.8	780.8	32.9	348.7
	70[1]	116	323.8	99.51	138.2	317.2	611.1	30.7	309.2

Reference: Section 14.2 Table 9.2.1.2.1
[1] Note: As per the statistical analysis plan, for derivation of the PK parameters, if the concentration at the end (Day 70) of the 70-day dosing interval is missing, then the AUC was derived using λz as derived by curve-stripping. There was 1 patient who was missing a Day 70 concentration value; this table presents the data prior to the data imputation of Day 70 for this patient. However, the analysis for Table 25 was performed using the imputed data for the last value for that patient, and thus the C_{trough} value from that table will not match the Day 70 value from this table.

One patient was excluded from the PK analysis due to protocol violation. Patient 002-7022 was confirmed as taking concomitant DHEA, a known androgenic steroid hormone that was prohibited in this study.

Figures 3 and 4 show the mean and individual concentration-time profiles for serum T following the 3rd injection interval, respectively.

Figure 3: Mean (±SD) serum total T concentrations following the 3rd injection interval of TU 750 mg LOADING regimen, from Study IP157-001 Part C

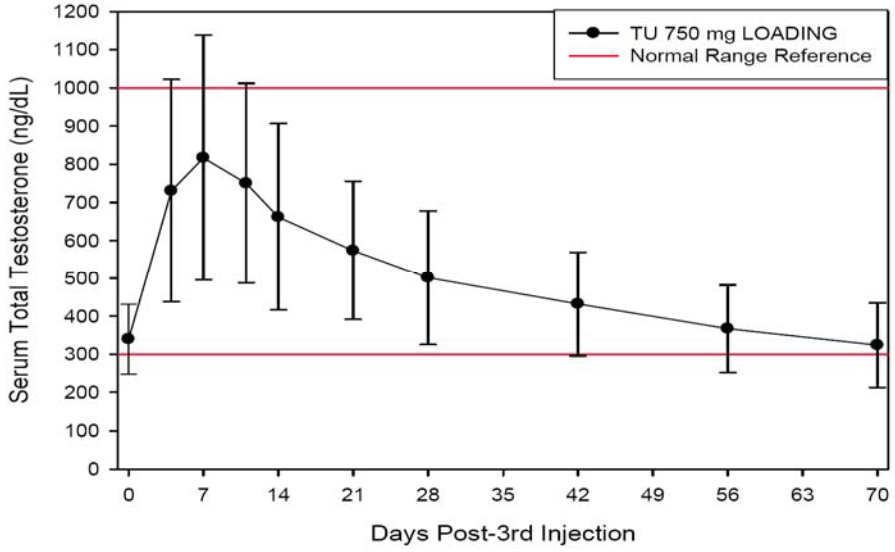
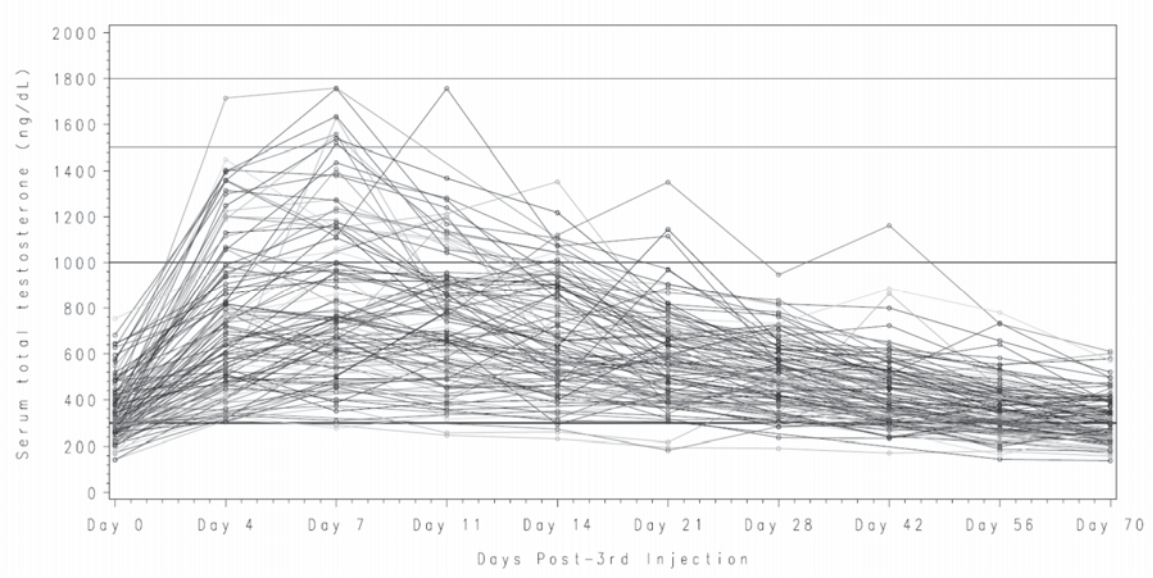


Figure 4: Composite of individual serum total T concentration following the 3rd injection of the TU 750 mg LOADING regimen – PK population, Study IP157-001 Part C



The primary efficacy endpoint in this study was the percentage of responders defined as Cavg within the normal range (300 – 1000 ng/dL). To meet the primary efficacy criterion, the point estimate for the pre-determined primary endpoint was set as at least 75% and the lower bound of the two-sided 95% confidence interval was set as not lower than 65%.

Ninety four percent of patients (110 of 117) had serum total T Cavg within the 300 – 1000 ng/dL range. The 95% confidence interval around this point estimate was 89.6 -

98.5. Of the 7 patients who did not meet this criterion, 6 failed due to Caverage below 300ng/dL and one failed due to a Caverage above 1000ng/dL.

Therefore, the data from Part C show that the primary efficacy objective was achieved.

2.2.3 Assessment of C_{max} for Serum T (an important secondary endpoint) in Part C

C_{max} was an important secondary efficacy endpoint in Part C. To meet the Cmax efficacy criterion, the criteria shown in *Table 5* were pre-set.

Table 5: Decision criteria for Cmax

Criteria for Serum Total Testosterone Maximum Concentration Observed	Criteria for Success	Not Meeting the Criteria for Success
≤ 1500 ng/dL	≥ 85% of Patients	< 85% of Patients
1800 - < 2500 ng/dL	≤ 5% of Patients	> 5% of Patients
≥ 2500 ng/dL	No Patients	At least 1 patient
All 3 criteria must be met in order to reject the null hypothesis in favor of the alternative hypothesis. If at least one of the 3 criteria is not met, the null hypothesis cannot be rejected. The time point for assessment of this secondary outcome is the post-3rd injection period (Weeks 14 - 24).		

The Sponsor excluded from the PK analysis those patients who weighed less than 65kg. One patient fell into this category in Part C (Patient 031-7021). This patient did experience a T concentration above 2500 ng/dL during the 3rd injection interval.

Otherwise, only nine of the 117 patients (7.7%) had Cmax > 1500 ng/dL and no patient had Cmax ≥ 1800 ng/dL.

> ***Reviewer's Comment***: *Based upon the excessive serum T parameters observed in Patient 031-7021, who weighed less than 65kg,* (b) (4) [redacted]

In summary, the data show that the Cmax efficacy objective was achieved in Part C in men weighing more than 65 kg.

2.2.4 Assessment of Free T, DHT, E2 and SHBG in Part C

In addition to the increase in serum total T concentration, the serum concentrations of free T and known downstream metabolites of T (dihydrotestosterone [DHT] and estradiol [E2]) were also increased. The increases in serum DHT and E2 were expected. TU administration did not affect concentration of sex hormone binding globulin (SHBG). With SHBG and albumin concentrations unchanged, the increase in free T concentration was also expected. The concentration versus time profiles for free T, DHT and E2

generally paralleled the T concentration-time profile. DHT:T and E2:T ratios were unchanged. The reader is referred to the medical officer's primary review and to the Clinical Pharmacology review for additional detail, tables and figures for these variables.

2.2.5 Other Efficacy Considerations in Part C

The Sponsor conducted exploratory correlation analyses of intrinsic factors and serum T showing that pre-injection T concentration, pre-treatment body mass index (BMI), and pre-treatment body weight were each predictive of T exposure. Higher serum T concentration can be expected from patients with higher pre-injection T concentration, lower BMI, or lower body weight. However, the data is not sufficient to predict serum T exposure following TU injections on an individual patient basis.

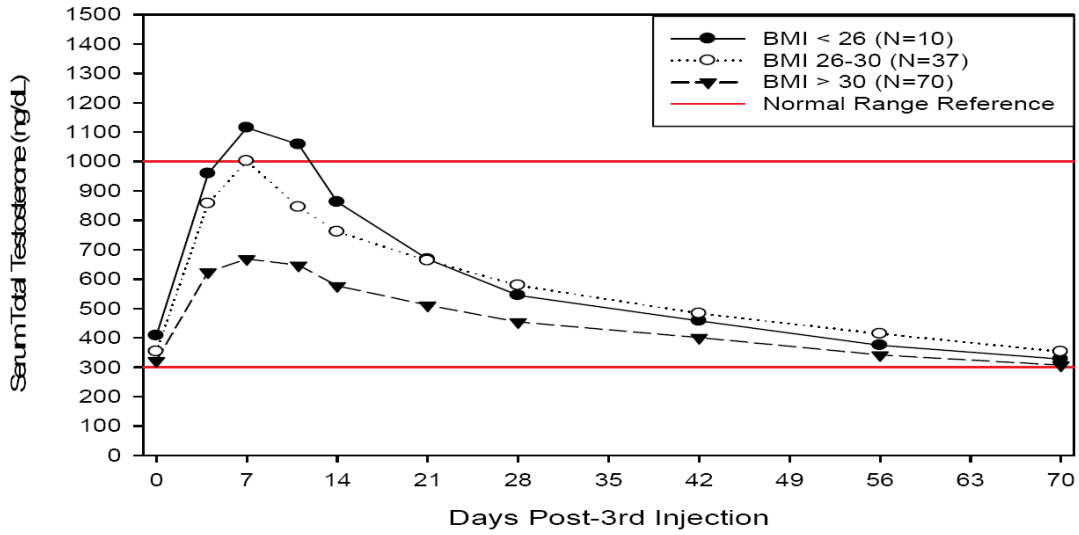
Table 6 shows the mean (SD) for serum total T C_{max} and C_{avg} stratified by BMI of <26, 26-30, and >30 kg/m^2. The group with the lowest BMIs had the highest mean T exposure and vice versa. Of note, patients in the BMI <26 group had BMI in the range of 22.9 – 25.9 kg/m^2.

Table 6: Mean (SD) serum total T C_{ave} and C_{max} during the 3rd injection interval by BMI subgroups – PK population, Study IP157-001 Part C

	TU 750 mg LOADING (N=117)		
	<26 kg/m^2 (N=10)	**26-30 kg/m^2 (N=37)**	**>30 kg/m^2 (N=70)**
	Mean (SD)	**Mean (SD)**	**Mean (SD)**
C_{max} (ng/dL)	1233.8 (339.57)	1061.5 (394.43)	751.2 (277.14)
C_{avg} (ng/dL)	578.8 (100.86)	566.7 (154.60)	445.0 (116.33)
Reference: Section 14.2 Table 9.2.1.8.3			

While the pre-dose and trough T concentrations were similar across the BMI subgroups, patients in the highest BMI category tended to have the lowest average T concentration through the majority of the steady state dosing interval. *Figure 5* provides the average concentration-time profiles for T by BMI subgroup.

Figure 5: Mean serum total T concentration by time point during 3rd injection interval by BMI subgroups – PK population, study IP157-001 Part C



<u>Reviewer's Comment</u>: This information is also relevant for future labeling discussions

2.3 Efficacy Results from Other Studies

The medical officer and Clinical Pharmacology team also assessed the efficacy data from Study IP157-001 Part A, which tested doses of 750mg (n=120) and 1000mg (n=117) given every 12 weeks (no loading doses).

(b) (4)

[redacted] (b) (4)

(b) (4) Sponsor decided (b) (4) to pursue approval only for the TU 750mg Loading regimen, as studied in Part C. This request was formally received on February 8, 2008.

Nonetheless, the medical officer and Clinical Pharmacologist reviewed the data from the 4th dosing interval in Part A and these data and analyses appear in their respective reviews in great detail. While the efficacy data from Part A provide some information relevant to the performance of the product and also have an indirect relationship to the TU 750mg Loading regimen, these data and analyses are not repeated here. The reader is referred to the medial officer's and clinical pharmacologist's reviews for more on Part A.

3. Summary of Clinical Safety

3.1 Background for Clinical Safety

Nebido (testosterone undecanoate) is a long-acting T ester. The rationale for development of this product was to provide testosterone replacement for hypogonadal adult men with the convenience of fewer administrations per year. The Sponsor's requested dose regimen is an intramuscular injection of 3mL on Days 1 and 28, followed by 3mL every 10 weeks thereafter. Thus, 7 injections are required for a 54 week period (approximately 1 year). The product is also purported to "smooth out" the serum T pharmacokinetic curve as compared to shorter acting T esters (such as T enanthate) which might theoretically improve clinical outcomes as compared to products requiring more frequent injections (such as T enanthate) or daily applications (such the topical T preparations).

Based on previous European Phase 1, Phase 2 and Phase 3 dose-finding studies, it was expected that Nebido would provide adequate T levels in hypogonadal men with a safety profile consistent with its pharmacological effect as an androgen. While Nebido did show a safety profile consistent with its androgen effect, it also induced respiratory adverse events (events related to pulmonary oil embolism [POME]) and allergic reactions (of unclear etiology) occurring during clinical trials and more obviously in the post-marketing period in Europe. The clinical review team took into consideration these less common but nonetheless medically significant drug-related adverse events in assessing the overall safety and overall risk to benefit profile for this product. The pharmacologically based androgen-related adverse events, the POME/POME-like adverse events, and the allergic adverse events are summarized in Section 3.2, Section 3.3 and Section 3.4 of this TL's memo, respectively, and are also described in detail in the medical officer's primary review.

3.1.1 Patient Exposure

The original NDA submitted August 24, 2007 contained safety data from a total of **422 adult male subjects** in clinical trials. These trials included: 1) the single U.S. pivotal Phase 3 study IP157-001 Part A comprising a total of 137 patients in two dose arms: TU 750mg every 12 weeks (*n=120*) and TU 1000mg every 12 weeks (*n=117*), and 2) six older European dose-finding trials comprising a total of *185* adult males subjects.

In Part A Stage 1, all patients received at least 4 injections (48 weeks exposure) and many received 5 injections (60 weeks exposure). The safety data submitted for Part A reflects a median follow-up period of approximately 48 weeks. Longer-term follow-up data was submitted for Part A Stage 2 in the 120-Day Safety Update.

> *Reviewer's Comment: The data from U.S. study IP157-001, including 237 subjects, was better documented and relied upon more heavily during the review as compared to the data from the 185 subjects in the older European dose-finding studies.*

On December 20, 2007, the Sponsor submitted a Clinical amendment containing a report for Part C of study IP157-001 including **117 adult male subjects** dosed with the TU 750 mg Loading regimen.

In Part C, Stage 1, all patients received at least 3 injections (24 weeks exposure) and the vast majority received 4 injections (34 weeks). The safety data submitted for Part C reflects a median follow-up period of 24 weeks.

On December 28, 2007, the Sponsor submitted the 120-Day Safety Update, containing: 1) Safety data from Study IP157-001 Part A Stage 2 (an extension study), and 2) A report for Study IP157-001 Part B which tested two new loading dose regimens. Part B included a total of **134 new adult male subjects** in two treatment groups: *112 patients* received an initial injection of TU 1000 mg, followed 8 weeks later with a loading injection of TU 1000 mg and then TU 1000 mg every 12 weeks thereafter, while *22 patients* received an initial injection of TU 1000 mg, followed 8 weeks later with a loading injection of TU 750 mg and then TU 750 mg every 10 weeks thereafter.

Therefore, for all clinical trials submitted in the original NDA through the 120-Day Safety Update, there were **a total of 673 subjects**, including data from a total of 488 U.S. patients in study IP157-001 Parts A, B and C.

On June 13, 2008 (two weeks prior to the PDUFA goal date), the Sponsor submitted a Clinical amendment containing safety information from additional subjects in clinical trials. The amendment included:

1) A brief summary of outcomes from 2 open-label, post-marketing observational studies (the NIS study and the IPASS study) conducted with Nebido.
   - The "Non-Interventional Study" [NIS] was conducted entirely in Germany and is apparently completed. For the NIS study, the Sponsor provided an overview of "*available data*" and a brief "*summary of outcomes*" from *870 patients*.
   - The IPASS study is entitled "*International, multi-center, post authorization, surveillance study on the use of Nebido to assess tolerability and treatment outcomes in daily clinical practice.*" [Study NE0601]. This study is apparently ongoing in countries in Europe, Asia, South America, and Australia. For the IPASS study, the Sponsor submitted a brief "*ad hoc interim analyses on raw data*" performed on *284 patients*, some of whom had completed the protocol and some who were still under treatment in the protocol.

2) A 188-page study report (without appendices or datasets) for Study 42306, a Phase 2 clinical trial using Nebido as part of a male contraception regimen. In this study, the Sponsor states that a total of *297 subjects* received multiple doses of TU (197 subjects received TU 750mg and 100 subjects received TU 1000mg).

<u>Reviewer's Comment</u>: Taken together, these 3 reports would add an additional 1,451 clinical trial patients to the 673 patients in the NDA. The Sponsor purports no cases of POME or POME-like events in any patient in this experience and only one local allergic reaction. The Sponsor states that this experience more than triples the original number of clinical trial subjects in the NDA without increasing the number of POME cases and thus strongly supports product safety.

In my opinion, the information submitted in this amendment for these observational studies, totaling <u>at least</u> an additional 1,154 clinical trial subjects (or 80% of the total number of new subjects submitted in the June 13, 2008 amendment), is too cursory to draw any reliable conclusions relevant to clinical safety. Important details related to study design, study conduct and procedures, patient accounting, missing data, and most importantly, adverse event collection, reporting and analysis methods are missing. It is not clear to me that the submitted overviews and data summaries report all adverse events occurring in all patients who participated in these trials. In my opinion, it is premature to draw conclusions about this critical safety issue for this NDA based upon the scant information that was submitted in the June 13 amendment.

In addition, it is important that ALL safety data from all completed and ongoing Nebido studies be submitted by Sponsor in order that we may conduct a rigorous and accurate safety assessment of the magnitude and severity of the POME/POME-like and allergy problems. In addition to full study reports and complete datasets for the NIS and IMPASS studies, and for Study 42306, complete safety data for the ongoing U.S. study IP157-001 Parts A, B, and C, with recent cut-off dates, should be submitted. If any other studies using Nebido are known to the Sponsor then these too should be submitted for our review.

3.2 Overall Adverse Reactions – Includes Adverse Reactions Related to the Androgen Pharmacological Effect

In general, treatment with Nebido was associated with adverse events and clinical laboratories expected for a testosterone replacement agent. However, there were reports of post-injection "coughing fit" reactions in the clinical trials (n=2) and in the post-marketing experience in Europe (n=66). The majority of these cases are believed to reflect pulmonary oil microembolism (POME), but there are also a few that meet criteria for anaphylaxis. These post-injection adverse reactions, which pose a serious and unresolved safety concern, are discussed in detail in the next two sections of this memo (Sections 3.3 and 3.4). The remainder of this section is reserved for the overall adverse events observed in clinical trials, which were predominantly related to the pharmacological effect of the product. This section summarizes the safety data for the two most important clinical trials: 1) study IP157-001 Part A Stage 1 and 2) study IP157-001 Part C.

3.2.1 Summary of Safety Results Study IP157-001 A

In Part A, adverse events reported in ≥ 1 % of subjects in the 750 mg and 1000 mg groups, respectively, and judged by the investigator to be *treatment-related* were:

- Injection site pain 1.7 % and 1.7 %
- Estradiol increase 0 % and 1.7 %
- Cholesterol increase 0 % and 1.7 %
- BPH 0.8 % and 1.7 %
- Fatigue 2.5 % and 0.9 %
- Insomnia 2.5 % and 0.9 %
- Libido decrease 1.7 % and 0.9 %
- PSA increase 3.3 % and 0 %
- Hypercholesterolemia 1.7 % and 0 %

These *treatment-related* adverse events are not unexpected for an injectable T replacement product.

"Adverse events of interest" in Part A included events attributable to androgen replacement and to injection site reaction. Such adverse events were reported in 24 subjects treated with TU 750 mg (20%) and 30 subjects treated with TU 1000 mg (26%), as shown in *Table 7*.

Table 7. Adverse events of interest in study IP157-001 Part A

Event Class	MedDRA System Organ Class	MedDRA Preferred term	Number of patients (%)	
			TU 750 (N=120)	TU 1000 (N=117)
Total Patients With At Least One TEAE of Interest			**24 (20.0)**	**30 (25.6)**
Endocrine Disorder	Investigations	Oestradiol increased	0 (0.0)	2 (1.7)
		Glycosylated haemoglobin increased	0 (0.0)	1 (0.9)
	Metabolism and nutrition disorders	Diabetes mellitus	1 (0.8)	1 (0.9)
Tolerability of Injection	General disorders and administration site conditions	Injection site erythema	0 (0.0)	1 (0.9)
		Injection site irritation	0 (0.0)	1 (0.9)
		Injection site pruritus	1 (0.8)	1 (0.9)
		Injection site pain	2 (1.7)	2 (1.7)
		Injection site reaction	0 (0.0)	1 (0.9)
Adverse Lipid Profiles	Investigations	Blood triglycerides increased	1 (0.8)	2 (1.7)
		Blood triglycerides abnormal	0 (0.0)	1 (0.9)
		Blood cholesterol increased	0 (0.0)	2 (1.7)
		High density lipoprotein decreased	1 (0.8)	0 (0.0)
	Metabolism and Nutritional disorders	Hypercholesterolaemia	3 (2.5)	1 (0.9)
		Hyperlipidemia	1 (0.8)	1 (0.9)
Erythropoiesis	Investigations	Haematocrit increased	0 (0.0)	1 (0.9)
		Haemoglobin increased	0 (0.0)	1 (0.9)
		Red blood cell count increased	0 (0.0)	1 (0.9)
	Blood and lymphatic system disorders	Polycythaemia	1 (0.8)	1 (0.9)
Aggression or depression	Psychiatric disorders	Depression	2 (1.7)	4 (3.4)
Urinary Symptoms	Renal and urinary disorders	Pollakiuria	0 (0.0)	2 (1.7)
		Urinary hesitation	0 (0.0)	1 (0.9)
		Urinary retention	1 (0.8)	2 (1.7)
		Urine flow decreased	1 (0.8)	2 (1.7)
		Nocturia	0 (0.0)	1 (0.9)
		Dysuria	1 (0.8)	2 (1.7)
	Infections and infestations	Urinary tract infection	3 (2.5)	3 (2.6)
Prostate health	Investigations	Prostatic specific antigen increased	4 (3.3)	1 (0.9)
		Prostate examination abnormal	2 (1.7)	1 (0.9)
	Reproductive system and breast disorders	Benign prostatic hyperplasia	2 (1.7)	3 (2.6)
		Prostatic intraepithelial neoplasia	1 (0.8)	2 (1.7)
		Prostatitis	0 (0.0)	2 (1.7)
		Prostatic disorder	1 (0.8)	0 (0.0)
Liver Abnormalities	Neoplasms benign, malignant and unspecified	Hepatic neoplasm malignant	0 (0.0)	1 (0.9)
	Investigations	Aspartate aminotransferase increased	1 (0.8)	0 (0.0)
Cerebrovascular events	Nervous system disorders	Cerebrovascular accident	0 (0.0)	1 (0.9)

Table 8 summarizes the adverse events reported in at least 2 % of subjects in both treatment groups in study IP157-001 Part A, *irrespective of relationship to study medication*, by preferred term in decreasing order based on incidence rates in the TU 1000 group.

Table 8. Incidence of All Adverse Events Regardless of Relationship to Study Medication, Reported in at Least 2.0% of Patients in Either Treatment Group, by Preferred Term, in Decreasing Frequency in TU 1000 mg arm, from study IP157-001 Part A

MedDRA Preferred term	Number of patients (%)	
	TU 750 (N=120)	TU 1000 (N=117)
Total patients with at least 1 TEAE	70 (58.3)	73 (62.4)
Upper respiratory tract infection	5 (4.2)	5 (4.3)
Diarrhoea	2 (1.7)	5 (4.3)
Pain in extremity	2 (1.7)	4 (3.4)
Nasopharyngitis	5 (4.2)	4 (3.4)
Hypertension	3 (2.5)	4 (3.4)
Sinusitis	3 (2.5)	4 (3.4)
Insomnia	3 (2.5)	4 (3.4)
Headache	2 (1.7)	4 (3.4)
Depression	2 (1.7)	4 (3.4)
Weight increased	3 (2.5)	4 (3.4)
Procedural pain	0 (0.0)	3 (2.6)
Arthralgia	2 (1.7)	3 (2.6)
Musculoskeletal pain	1 (0.8)	3 (2.6)
Urinary tract infection	3 (2.5)	3 (2.6)
Rash	1 (0.8)	3 (2.6)
Pain	0 (0.0)	3 (2.6)
Foot fracture	0 (0.0)	3 (2.6)
Muscle strain	0 (0.0)	3 (2.6)
Anxiety	0 (0.0)	3 (2.6)
Nasal congestion	0 (0.0)	3 (2.6)
Abdominal pain	0 (0.0)	3 (2.6)
Constipation	0 (0.0)	3 (2.6)
Vomiting	1 (0.8)	3 (2.6)
Gout	0 (0.0)	3 (2.6)
Benign prostatic hyperplasia	2 (1.7)	3 (2.6)
Cough	1 (0.8)	3 (2.6)
Fatigue	7 (5.8)	2 (1.7)
Bronchitis	5 (4.2)	2 (1.7)
Back pain	4 (3.3)	2 (1.7)
Nausea	3 (2.5)	2 (1.7)
Prostatic specific antigen increased	4 (3.3)	1 (0.9)
Hypercholesterolaemia	3 (2.5)	1 (0.9)

The majority of adverse events were judged by the investigator as mild or moderate in severity. Severe AEs were reported in 8.3% of TU 750 mg subjects and in 7.0% of TU 1000 mg patients. Atrial fibrillation was reported as a severe AE in 2 subjects in the TU 750 mg group; no other single event was reported as severe in more than 1 subject per treatment group. The other severe adverse events (regardless of investigator-attributed causality) were: cardiac failure, coronary artery disease, chest discomfort, irritability, sudden hearing loss, and PSA increased.

There were 3 deaths in the study. The causes of death were: homicide, fatal motorcycle accident, and sepsis in a subject with prior history of thrombocytopenia.

Eight (6.7%) subjects in the TU 750 group and ten (8.5%) subjects in the TU 1000 group experienced at least one SAE during the treatment period. Only two types of SAE were observed in more than 1 subject: atrial fibrillation in 2 subjects in the TU 750 mg group, and knee arthroplasty in 2 subjects in the TU 1000 mg group. No serious adverse events (SAEs) were judged by the investigator as being at least possibly related to study drug.

Study medication was permanently discontinued due to adverse events in 5.0 % of patients in the 750 mg group and 3.4 % of patients in the 1000 mg group. AEs judged by the investigator to be at least possibly related to study drug and leading to discontinuation were:

- Subject 027-4101 (TU 750 mg arm) - increased serum PSA.
- Subject 056-4077 (TU 1000 mg arm) - increased serum estradiol.
- Subject 040-4116 (TU 1000 mg arm) - increased red blood cell count.

There were a few (10) TEAEs of ECG abnormalities reported, and none were judged to be at least possibly related to study drug.

Several laboratory parameters changed from baseline during treatment with Nebido in Part A including red blood cell count parameters, serum hormones and serum PSA. From a safety perspective it is notable that average PSA increased with the TU 1000 mg dose by a median of 0.2 ng/mL during the 48-week treatment period. In addition, 5% of the 237 patients treated in this study had at least one on-treatment PSA concentration over 4 ng/mL.

3.2.2 Summary of Safety Results Study IP157-001 C

In Part C, adverse events reported in ≥ 2 % of subjects and judged by the investigator to be *treatment-related* were:

- Acne 4.6%
- Fatigue 4.6%
- Cough 3.1 %
- Injection site pain 3.1%
- Nasopharyngitis 3.1%
- Pharyngolaryngeal pain 3.1%
- Arthralgia 3.1%
- Insomnia 2.3%
- Prostatitis 2.3%
- Sinusitis 2.3%.

These *treatment-related* adverse events are not unexpected for an injectable T replacement product.

"Adverse events of interest" in Part C included events related to endocrine disorders, injection site reactions, adverse lipid profiles, erythropoiesis, aggression or depression, urinary symptoms, prostate health, liver abnormalities, sleep apnea syndrome,

cerebrovascular events and skin events. Such adverse events were reported in 28 subjects in Part C (21.5%) as shown in *Table 9*.

Table 9. Adverse events of interest in study IP157-001 Part C

Event Class	MedDRA System Organ Class	MedDRA Preferred term	Number of patients (%)
			TU 750 mg LOADING (N=130)
Total Patients With At Least One TEAE of Interest			28 (21.5)
Tolerability of Injection	General disorders and administration site conditions	Injection site irritation	2 (1.5)
		Injection site pain	4 (3.1)
		Injection site rash	2 (1.5)
Adverse Lipid Profiles	Investigations	Blood triglycerides increased	1 (0.8)
	Metabolism and Nutritional disorders	Hyperlipidemia	1 (0.8)
Erythropoiesis	Investigations	Haematocrit increased	1 (0.8)
		Haemoglobin increased	2 (1.5)
		Estradiol increased	2 (1.5)
Aggression or depression	Psychiatric disorders	Mood swings	2 (1.5)
		Aggression	2 (1.5)
Urinary Symptoms	Renal and urinary disorders	Urine flow decreased	1 (0.8)
		Nocturia	1 (0.8)
Prostate health	Investigations	Prostatic specific antigen increased	2 (1.5)
		Prostate examination abnormal	1 (0.8)
	Reproductive system and breast disorders	Prostatic intraepithelial neoplasia	1 (0.8)
		Prostatitis	3 (2.3)
		Paraesthesia of genital male	1 (0.8)
Skin	Skin and subcutaneous tissue disorders	Acne	6 (4.6)

Table 10 summarizes the adverse events reported in at least 2 % of subjects in study IP157-001 Part C, *irrespective of relationship to study medication*, by preferred term in decreasing order based on incidence rates in the TU 750 mg LOADING group.

Table 10. Incidence of All Adverse Events Regardless of Relationship to Study Medication, Reported in at Least 2.0% of Patients in Decreasing Frequency in study IP157-001 Part C

MedDRA Preferred term	Number of patients (%) TU 750 mg LOADING (N=130)
Total patients with at least 1 TEAE	70 (53.8)
Acne	6 (4.6)
Fatigue	6 (4.6)
Cough	4 (3.1)
Injection Site Pain	4 (3.1)
Nasopharyngitis	4 (3.1)
Pharyngolaryngeal Pain	4 (3.1)
Arthralgia	3 (2.3)
Insomnia	3 (2.3)
Prostatitis	3 (2.3)
Sinusitis	3 (2.3)

No subject died during the Part C study. Eight (6.2%) subjects experienced at least one SAE during the treatment period in Part C. No single SAE was observed in more than 1 subject. The SAE terms reported were: ischemic colitis, deep vein thrombosis (DVT), faecaloma, intervertebral disc protusion, myocardial infarction, prostatitis, spinal column stenosis, urinary tract infection and wrist fracture.

Study medication was permanently discontinued due to adverse events in 3.8 % of patients in Part C for the following reasons: acne, mood swings, myocardial infarction, increased estradiol and DVT. There was no single event resulting in discontinuation that was reported in more than one subject during this study. Of these, all but myocardial infarction were judged by the investigator to be at least possibly related to study drug.

Changes in several laboratory parameters were consistent with changes observed in Part A. From a safety perspective it is notable that PSA increased in this trial by approximately 0.3 ng/mL during the 24-week treatment period. Again, 4% of the 117 patients treated in this study had at least one on-treatment PSA concentration over 4 ng/mL.

There was one post-injection “cough event” reported in Part C. Patient 050-7006, a 53-year old white male who was diagnosed with primary hypogonadism in August 2006, received his 3rd injection on Day 98. The patient experienced a mild and non-serious “coughing fit lasting ~10 minutes following [the] injection”. The investigator reported the cough was non-productive, and that the patient experienced no wheezing or difficulty breathing. No intervention was given, and the patient recovered prior to leaving the office. The patient received his 1st, 2nd, and 4th injections with no associated cough event; further, the patient continued into Stage 2 where he is still receiving treatment with TU 750 mg every 10 weeks, and no further cough events were reported in Part C.

3.3 POME-Related Adverse Reactions

As described in Section 3.2 of this memo, treatment with Nebido was associated with adverse events and laboratory changes expected for a testosterone replacement agent. However, in addition, there were reports of "coughing fits" immediately following Nebido injection in the clinical trials (n=2) and in the European post-marketing experience (n=66). In my opinion, these adverse reactions pose a serious and unresolved safety concern. This section provides details on the POME adverse events.

In the original NDA submission (prior to the Sponsor's submission of data for Part C), a total of 422 adult male hypogonadal patients were treated in the Nebido drug development program, and there was 1 patient in whom an "immediate post-injection reaction" was reported. This case occurred in a European supporting study (Patient #184 in Study 306605) and was reported in the Clinical Summary of Safety in the original NDA. This 54 year old male received his 10th injection of Nebido on 3 April 2006 and shortly (1 minute) after the injection, the patient "experienced urge to cough associated with respiratory distress". Both symptoms lasted approximately 14-15 minutes. The event resolved without intervention and the subject continued in the study. The investigator and Sponsor both attributed the event to "pulmonary lipid (oil) microembolism" (POME) and cited the following possible reason: either too fast administration of the study drug or accidental intravascular placement of the study drug. The event was coded as an SAE (medically significant).

Upon submission of a clinical amendment containing the data from another 117 patients who participated in study IP157-001 Part C, the Division learned of one additional patient who experienced an "immediate post-injection reaction". As described in the previous section, this 53 year old white male received his 3rd injection on 12 July 2007 and experienced a "mild and not serious coughing fit lasting 10 minutes following the injection." The narrative describes the cough as not productive and the patient had no wheezing and no difficulty breathing. No intervention was given and the patient continued Nebido therapy without subsequent coughing event.

In addition to these 2 "coughing fit" cases from the clinical studies, the Clinical Summary of Safety in the original NDA contained six (6) cases of "immediate post-injection reactions" reported during the previous 7 months of post-marketing use of Nebido in Europe. The 120-Day Safety Update contained an additional four (4) cases reported in the previous 4 month of post-marketing use in Europe. Based upon the 2 cases reported in clinical trials and the 10 known cases from the post-marketing experience, the Division made request to Sponsor on January 15, 2008 to submit all known cases of "coughing fits" that followed an injection of Nebido. In response, on February 12, 2008, the Sponsor submitted a 28-page report entitled "*Immediate Post-Injection Reactions Suspect of Pulmonary Oil Microembolism*".

The report identified a total of **66 cases** suspect of these reactions from April 2004 to January 18, 2007. Of these, 28 cases (42%) were reported as serious adverse events.

Although there were no deaths in the combined post-marketing and clinical trial experience, review of the CIOMS forms submitted by Sponsor indicated that emergency medical care was provided or that the patient was hospitalized in 12 of the 66 patients (18 %).

Herein are provided brief narratives for 24 of these events. These 24 cases were selected based upon the medical seriousness of the event, including need for emergency medical care and/or hospitalization:

1. (AT-2006-020143) A 51 year old male experienced very severe irritative cough and dyspnea beginning during the intramuscular injection of Nebido. Cough resolved in 5 minutes and dyspnea persisted for 2 days.

2. (DE-2005-011567) A 48 year old male experienced "hypersensitivity reaction certainly to castor oil" described as dizziness, headaches, palpitation, vertigo, lump in throat, and tachycardia at an unspecified time after his second and third doses of Nebido. The reaction lasted 3 weeks. Tachycardia, palpitations and lump in throat resolved in 5 hours. The patient had a past history of "atopy" and reported similar events following treatment with Testoviron-Depot (containing castor oil).

3. (DE-2005-019516) A male (unknown age) experienced 3 hours of cough and dyspnea after the Nebido injection.

4. (DE-2006-002815) A 15 year old male experienced extremely severe urge to cough, retrosternal pain, mild dyspnea, eye redness, tachycardia and chest pain immediately after Nebido injection. He was treated with antihistamine and steroid (Solu-DecaCortin H).

5. (DK-2006-002013) A male (unknown age) experienced "massive coughing fit" 1 minute after Nebido injection lasting 1 hour – described as irritating hacking cough.

6. (20071127BNE) A male (unknown age) experienced immediate coughing, unable to catch breath, "collapse", severe dyspnea, burning sensation in mouth and chest upon Nebido injection (given by wife). Patient was hospitalized for 2 days and recovered. No reaction subsequent to Nebido when given by clinic nurse.

7. (200718455GPV) A 68 year old male experienced "allergic reaction" including sensation of numbness of mouth, tingling sensation mouth and lips ("paresthesias") during his 6th Nebido injection. Patient treated with H1 and H2 blockers. The complaints resolved after 6 hours.

8. (AT-2007-035468) A 46 year old male experienced "anaphylactic reaction" including "gagging", "tickle in throat" 30 seconds after administration of his 7th dose of Nebido. Patient was given an oral antihistamine and recovered within 15 minutes.

9. (AU-2007-014016) A male (unknown age) experienced "suspected allergic type reaction to the excipient (i.e. the oil)" including severe coughing and shivering during the 3rd Nebido injection. Patient was treated with oxygen, antihistamine, and prednisone and all symptoms subsided.

10. (BR-2007-005496) A 57 year old male experienced "anaphylactic shock" including "glottis edema", "breathlessness" and "malaise" immediately after injection. Breathlessness became

worse 30 minutes after injection. He was treated with corticosteroids and was "ventilated in the drug store".

11. (BR-2007-010933) A male (unknown age) experienced "fainted during injection" with "loss of consciousness for several minutes". The reporter suspected possible intravenous injection. A similar injection 6 months earlier was well tolerated.

12. (DE-2005-004016) A male (unknown age) experienced "circulatory collapse, nausea, cough, several minutes unconsciousness and encopresis" approximately 15 seconds after his 2nd dose of Nebido. The patient subsequently recovered.

13. (DE-2005-009-283) A 54 year old male with "suspected fat microembolism" described as "cough, red head, sweating attacks, trembling, dizziness, increased blood pressure, and dizziness" immediately after injection of 1st dose. Patient had previously tolerated Testosteron-Depot. Symptoms lasted longer than 20 minutes and patient was hospitalized. He was treated with cortisone and antihistamines and discharged home the same evening.

14. (DE-2006-00398) A 42 year old male experienced "idiosyncratic drug reaction possible oily microembolism" including 1-2 minutes of apnea, hot flush, paresthesias in area of mouth and head, dyspnea and cough 3 minutes after his 4th Nebido injection. Patient recovered after 10 minutes.

15. (DE-2007-004747) A 74 year old male experienced "pronounced urge to cough", "dyspnea" and "20 minutes of cyanosis" at 3 minutes after "slow injection" of Nebido. The event was described as "life-threatening". Nebido had been previously well-tolerated.

16. (DE-2007-023890) A 57 year old male experienced "suspected anaphylactoid reaction, possible oil microembolism" including dizziness, tingling sensation upper part of abdomen, hands and feet, weakness, pressure in head, headache, numbness sensation in fingers and toes after first dose of Nebido. Injection site was described as hot, hard, red and sensitive to pressure. Patient was treated with antihistamines and prednisolone and taken to emergency unit where symptoms persisted.

17. (DE-2007-00464) A 47 year old male experienced "laryngospasm", "severe dyspnea" and cough during 2nd Nebido injection. An emergency physician was called, however the patient recovered after a few minutes. The patient has a "cough reaction" to previous Nebido injection.

18. (GB-2006-006197) A 67 year old male experienced "acute anaphylactic reaction" including tightness in throat and coughing fit "minutes" after his 2nd injection. He was treated with epinephrine and chlorpheniramine. The event was considered life-threatening and involved hospitalization.

19. (GB-2007-000740) A 54 year old male experienced "anaphylactic reaction, including acute laryngeal edema, and near respiratory arrest", half-way through his 2nd Nebido injection. Patient began coughing, had tickle in throat, and the reaction worsened. He became sweaty, had trouble breathing, was given adrenaline and oxygen and was hospitalized.

20. (GB-2007-023826) A 46 year old male experienced "anaphylactic shock" including respiratory distress, coughing fit, T wave inversions, tightening of the throat, respiratory wheeze, rash on abdomen, itchy scalp, and raised blotches across the chest. Symptoms

began during his 2nd Nebido injection. He was treated with adrenaline, chlorpheniramine and oxygen, and his symptoms cleared upon arrival at the emergency room.

21. (SE-2006-014505) A 44 year old male experienced "burning pain lower sternum going up to the chin" and dyspnea during the 3rd Nebido injection. The administration was discontinued, symptoms lasted 2-3 minutes, and the patient was hospitalized.

22. (SE-2006-01516) A 47 year old male experienced "angioedema" including swollen throat, palpitations, difficulty breathing, cough and swelling of the neck immediately after his 2nd Nebido injection. The report describes an event of "serious swollen throat" and "non-serious palpitations" after his 1st Nebido injection.

23. (SE-2006-02230) A 38 year old male experienced "angioedema", pruritis, malaise, "swelling around the eyes", and itching in the throat after the 1st Nebido injection. Solu-Cortef and antihistamine were administered and the patient was discharged after a few hours observation.

24. (ZA-2007-035469) A 29 year old male experienced "life-threatening bronchospasm" and tachycardia, became hypotensive and collapsed within minutes after receiving Nebido. He received emergency medical care with nebulized epinephrine and recovered from the bronchospasm.

An additional case was reported on 29 February 2008, as follows:

(200812947GPV) A 38 year old male received Nebido twice. He experienced a "mild allergic reaction" following the 1st Nebido injection. Six months later a 2nd Nebido injection was administered in hospital and the patient experienced a "severe allergic reaction" including "severe throat swelling and potential heart failure". The patient recovered shortly thereafter.

In summary, in the Nebido clinical trial experience involving approximately 673 subjects (and more than 4000 injections) there were 2 post-injection cough reactions reported (0.30 %). For the post-marketing experience, Sponsor focused on the most recent 2 year period which they state includes more than 85% of all exposure to Nebido worldwide. According to the Sponsor, based solely on the number of Nebido units sold, the reporting of "post-injection cough reactions" was approximately 1/12,000 injections in 2006, and 1/15,000 injections in 2007. Therefore, there is a wide discrepancy in the incidence and severity of cough reactions as reported by Sponsor ("rare and self-limiting") versus what was observed in clinical trials reported in the NDA and in post-marketing reports. In the reviewer's opinion, the clinical trial data demonstrates an incidence that is neither rare, nor is the event uniformly self-limiting or not medically serious. Serious and non-serious post-injection cough reactions had been observed with Nebido. Although there were no deaths in the clinical trials or in the post-marketing experience, many of the 28 serious cases manifested life-threatening signs and symptoms, requiring emergency medical care and/or hospitalization.

In terms of etiology, the Sponsor continues to believe that most, perhaps all, these events are related to pulmonary oil microembolism (POME) and may be reduced in incidence or severity by lowering the injection volume (to 3 mL) and by careful, slow intramuscular injection. However, the Sponsor acknowledged that data to support these hypothetical

risk mitigation recommendations are not yet available. In addition, we continue to believe that at least a subset of these cases reported as POME showed signs and symptoms suggestive of systemic allergic reaction (n=4), which would not be resolved by reduction in dose from 4 cc to 3cc, nor by slower injection.

In order to fully evaluate these respiratory adverse events, we obtained a consultation from the Division of Pulmonary and Allergy Products (DPAP). Their conclusion and recommendations are discussed in the Section that follows (Section 3.4).

3.4 Allergy-Related Adverse Events (includes DPAP consult)

Of 66 cases submitted for review, DPAP concluded that two cases met the currently accepted diagnostic criteria for anaphylaxis (cases #20 and #24 in the preceding list). The Sponsor argued that neither of these two cases reflected anaphylaxis. After re-reviewing these 2 cases, DPAP disagreed with Sponsor, maintained that these cases met criteria for anaphylaxis, and offered the following additional comments:

Case GB-2007-023826 (Case #20 above) had respiratory distress, throat tightness, and a raised rash on the abdomen and chest. As noted previously, the case meets recently proposed diagnostic criteria for anaphylaxis. It is difficult to attribute the rash, whose onset was concurrent with the respiratory symptoms, to be due to use of testosterone patches and gels in the past.

Case ZA-3007-035469 (Case #24 above) had bronchospasm and a drop in blood pressure. This presentation is more consistent with anaphylaxis than POME. Additional information recently submitted noted the presence of tachycardia, an oxygen saturation of 94% at the onset of the event, and treatment of the bronchospasm with nebulized epinephrine. The additional information submitted by the sponsor adds additional support to anaphylaxis as the most likely interpretation of this event.

> *Reviewer's Comment: It should be noted that the sponsor states that the events in question are not inconsistent with a possible allergic or hypersensitivity reaction.*

In addition to these 2 cases, DPAP also made note of 2 other cases where anaphylaxis was possible:

Case GB-2006-006197 (Case #18 above) experienced coughing and tightness in the throat and the medical assessment at the time of the event was "acute anaphylactic reaction." In this case, despites Sponsor's contention that the case reflected POME, DPAP maintained that anaphylaxis could not be excluded, particularly in light of the assessment of the practitioner treating the event.

Case SE-2006-022330 (Case #23 above) experienced cutaneous itching, angioedema, ocular swelling, and itching of the throat. In their original consult, DPAP concluded that the case did not meet clinical criteria for anaphylaxis and that the case was consistent with acute urticaria and angioedema. DPAP later concurred with Sponsor that the patient

did not have urticaria. Nevertheless, DPAP maintained that the patient had manifestations of acute angioedema and cutaneous and mucosal itching.

> *<u>Reviewer's Comment</u>: Even with this small number of cases, evidence exists that post-injection anaphylaxis due to Nebido is possible. The extent of this risk and its etiology is not clear.*

In concluding their consult, DPAP made several additional comments:

- DPAP noted that IgE-mediated sensitivity to castor bean allergen in castor bean extract and castor wax extract had been reported in patients with occupational hypersensitivity to castor beans. Anaphylaxis had also been reported with use of polyethoxylated castor oil (Cremophor EL) when used as a solubilizing vehicle for various drugs.

- After considering the post-injection POME reactions and allergic reactions, DPAP noted that the decision to approve the product would be a risk versus benefit decision, and should be made in light of the degree of efficacy, the seriousness of the indication, the availability of alternative products for that indication, and the extent of the safety data.

- After considerable internal discussion, DPAP expressed the opinion in their consult to DRUP that it would be appropriate to characterize the frequency of the POME and POME-like events prior to, not after, approval. DPAP stated that the product is currently approved and marketed in Europe so it would be reasonable and appropriate to conduct these studies abroad prior to considering the product for approval in the United States.

- In addition, DPAP stated that given the unclear mechanism of the allergic reactions, they would also recommended consideration be given to advising Sponsor to characterize the nature of the anaphylaxis events. DPAP stated that establishing the mechanism of these allergic reactions could help to make a decision on the approvability of the drug more scientific and rational. DPAP recommended that DRUP consider asking the Sponsor to develop an in vitro test for specific IgE and IgG antibody to the drug, both active and excipient ingredients, and to evaluate the presence of antibodies in patients who have had anaphylaxis events associated with the drug, those who have been exposed to the drug but who have not had anaphylaxis, as well as unexposed controls. In addition, DPAP recommended that the Sponsor develop a skin testing procedure to the product and its excipients to evaluate the same populations to be studied with in vitro testing.

4. Summary of Clinically Relevant Items from Other Disciplines/ Consults

4.1 Clinical Pharmacology

In their final review, dated May 5, 2008, Drs. Tran and Kim concluded

"*We find this NDA acceptable from a Clinical Pharmacology perspective, pending labeling discussion.*"

Of the notable items from the Clinical Pharmacology review, most have already been discussed in the preceding sections of this memo. To briefly summarize:

1. The TU 750mg Loading regimen successfully achieved the Cavg and Cmax pre-set criteria at steady-state.
2. (b) (4) [redacted]
3. The assays of T and DHT for the primary analysis were valid.
4. While TU is generally converted to T, serum TU was shown to increase with all regimens tested. The concentration-time profile showed that Tmax was approximately 4 days for TU and serum concentrations were generally short-lived.
5. Serum DHTU was also observed in blood sampling, but most attempts to measure this analyte showed concentrations below the limit of quantification.
6. Patients with lower body weight and lower BMI had higher exposure to T with Nebido. Clinical Pharmacology advises that this finding be conveyed in labeling.
7. One patient with a body weight less than 65 kg was excluded from the PK analysis. He had excessive Cmax (approximately 3000 ng/dL). (b) (4) [redacted]

4.2 Biostatistics

In his final review, dated June 24, 2008, Dr. Sobhan concluded:

"*The results support the efficacy of Nebido TU 750 mg LOADING in the treatment of hypogonadism in adult male as indicated by the attainment of steady state by the 3rd injection. The intensive sampling for PK outcomes (Cavg and Cmax) also met FDA threshold for approvability and, therefore, can be extrapolated to represent PK outcomes under extended dosing beyond 3 injections.*"

> *Reviewer's Comment: Dr. Sobhan's review and conclusion are consistent with those of the Clinical Pharmacology team and the Medical Officer*

4.3 Pharmacology/Toxicology

In their final review dated April 18, 2008, Drs Andreason and Reid concluded:

"*Nonclinical data support approval*".

The review also included recommendations for revisions to the proposed labeling including adding sections on: use in women (5.10), affects on spermatogenesis (5.11), drug interactions with anticoagulants (7.5), use in pregnant or nursing women (8.1, 8.3), use in pediatrics (8.4,) use in patients with impaired renal or hepatic function (8.6). The proposed edits are documented in the Executive Summary and Appendix to the PharmTox review.

Items of note from the nonclinical review included:

1. The safety of testosterone is well known. The review stated: "*No additional safety concerns associated with TU were identified in the nonclinical program.*"
2. Testosterone undecanoate is an ester of testosterone. TU is an inactive pro-drug which upon in vivo hydrolysis of the ester bond releases testosterone and undecanoic acid. To insure that non-hydrolyzed TU itself had little potential for pharmacological activity, the ability of TU to bind to the human androgen receptor was assessed. The results suggested that TU does not have significant pharmacological activity since its relative binding affinity was only 1.3% of testosterone.
3. A local tolerance study in pigs was conducted comparing intramuscular administered TU and testosterone enanthate. Drug related adverse affects were not observed, however, large injection volumes (3-4 ml) did cause tissue necrosis, fibrosis, inflammation and hemorrhaging which tended to recover 7-42 days after dosing.
4. Testosterone undecanoate was negative in a battery of in vitro and in vivo genotoxicity assays assessing mutagenicity and clastogenicity.
5. A 14 week bridging study was conducted in male rats to compare physiological responses to testosterone undecanoate (TU) with another approved testosterone ester, testosterone cypionate (Depo® –Testosterone, TC). Rats were dosed intramuscularly with TU or TC every two weeks. TU exposures were 2 to 20 times the exposure in men dosed with 1000 mg TU. Exposures and results in the high dose TU group were similar to the TC group. The NOEL for this study was less than 50 mg/kg (approximately 2 times the exposure in men dosed with 1000 mg TU) based upon reduced feed intake, weight loss, exophthalmus, lacrimation, aggressive behavior, slight alterations in hematology, altered organ weights, thymic atrophy and inflammation observed at that dose. However, with the exception of the injection site cysts and local inflammatory response the findings were generally mild and could be considered effects of exaggerated pharmacology.
6. The reviewer noted that the following histopathologic findings were observed in the TU animals but not in the TC group:

1) Non-dose responsive and non-recoverable decrease in testicular weight (8-26%).
2) Low incidence of reversible adverse renal and bladder histopathology (transitional cell hyperplasia [14% of HD group]), degeneration and necrosis of the renal proximal tubule and dilation of the renal pelvis (7% of HD group).

As stated in the PharmTox conclusion, these observations were not believed to be show additional safety concerns for TU as compared to TC

4.4 Chemistry, Manufacturing and Controls (CMC)

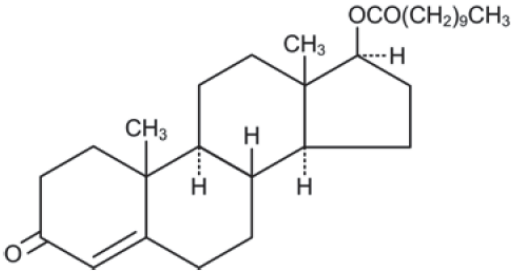
In their final review dated, June 26, 2008, Drs. Sun and Rhee, concluded:

"*This NDA has not provided sufficient CMC information to assure the purity of the drug product. Therefore, from a CMC perspective, this NDA is recommended for* ***Approvable****" pending resolution of the issues delineated in the deficiency letter issued on June 25 for DMF #* (b) (4)

The Items of note from the nonclinical review included:

1. The drug substance used in the drug products of this NDA is testosterone undecanoate, which is an ester of the naturally-occurring androgen, testosterone. The active form, testosterone, is formed by cleavage of the undecanoic acid side chain. Testosterone undecanoate is a white to off-white crystalline substance. Detailed CMC information was referred to DMF # (b) (4) which was reviewed and found adequate for supporting the use of Testosterone undecanoate in NDA 22-219.

Figure 7: Chemical structure and molecular weight of testosterone undecanaoate



$C_{30}H_{48}O_3$

MW: 456.7

2. Nebido® is the drug product that contains 3 mL of 250 mg/mL of Testosterone undecanoate oily solution in each (b) (4) amber glass vial with a grey stopper. Nebido® is a clear, yellowish, sterile oil solution for intramuscular injection. Testosterone undecanoate oily solution consists of testosterone undecanoate (750 mg/vial), refined castor oil (885 mg/vial) and benzyl benzoate (1500 mg/vial).

Each mL of 250 mg/mL testosterone undecanoate solution provides 157.9 mg testosterone. Detailed CMC information was referred to DMF # (b) (4) which was reviewed and found adequate except for missing information about the microbiological attributes of the drug product (see next section of this memo).

3. The Establishment Evaluation Request Summary Report for this NDA stated that the overall Compliance recommendation was ACCEPTABLE on 26 June 2008.

4. This NDA has provided sufficient CMC information to assure the identity, strength, and quality of the drug product, but not its purity (sterility). Labels were reviewed and have adequate information as required. Therefore, from a CMC perspective, this NDA is recommended for "Approvable" pending resolution of the microbiology deficiencies cited for DMF (b) (4) in the regulatory letter dated 25 June 2008. (see next section of this memo)

Reviewer's Comment:

On June 23, 2008, the Microbiology consultation was finalized and on June 25, 2008, a deficiency letter was conveyed to the holder of the DMF based upon the microbiologist's review. The next section of this memo (Section 4.4.1) provides a summary of the Microbiology Consult and the specific DMF deficiencies.

4.4.1 Microbiology Consult

In their final review dated June 20, 2008, Drs. Pawar and Hussong concluded that:

"*The application is recommended for **approvable** pending resolution of items listed as deficiencies in the DMF* (b) (4)

The microbiologist's review stated that (b) (4)

The microbiologist found the following DMF deficiencies. These deficiencies were conveyed to the DMF holder on June 25, 2008.

(b) (4)

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4.5 Division of Medication Error Prevention (DMEP)

In their final consultation report, dated May 13, 2008, Mr Fava and Drs. Kim-Jung and Toyer concluded that the tradename was acceptable, as follows:

"The results of the proprietary name risk assessment found that the proposed name, Nebido, has some similarity to other proprietary and established drug names, but the findings of the (tradename) analysis indicates that the proposed name does not appear to be vulnerable to name confusion that could lead to medication errors. *Thus, the Division of Medication Error Prevention does not object to the use of the name, Nebido, for this product.*"

However, the DMEP review of container and carton labeling revealed a need for labeling revisions in order to avoid medication errors. In this regard, the review stated:

"*The results of the label and labeling risk assessment found that the presentation of information and design of the proposed container labels and carton labeling appears to be vulnerable to confusion that could lead to medication errors. Specifically, the presentation of important information (e.g., established name, dosage form, route of administration, and product strength), is not optimal for easy readability and comprehension by practitioners. The Division of Medication Error Prevention believes the risks we have identified can be addressed and mitigated prior to drug approval, and provides recommendations (in Section 6 of the consult report) that aim at reducing the risk of medication errors.*"

Therefore, the DMEP review included the following recommendations for revision to container and carton labeling:

For the Container Label

1. Use a darker color font to display the proprietary name name, the established name, the dosage form, the strength, the route of administration, as well as other important information.
2. Delete [redacted] (b) (4)
3. Include the product concentration, 250 mg/mL, in parentheses on a separate line immediately following the total drug content statement.
4. Delete the word [redacted] (b) (4) from the dosage form statement below the established name.
5. Relocate and increase the prominence of the route of administration statement, [redacted] (b) (4)
6. Revise the [redacted] (b) (4) statement to read: 'Single Use Vial – Discard Unused Portion'. Relocate this statement to appear below the route of administration statement and above the 'Store at room temperature' statement.

For the Carton Labeling

1. See comments 1-6 above.
2. Include a quantitative statement following each inactive ingredient in accordance with 21 CFR 201.100 (b)(5)(iii).
3. Decrease the prominence of the name of the Applicant, [redacted] (b) (4), located at the bottom portion of the principal display panel.

Reviewer's Comment: These DME comments were sent to Sponsor on May 13, 2008. According to Dr. Sun's final CMC review, the carton and container labels are "acceptable". Therefore, it appears that Sponsor responded to the DMEP labels and these responses were found acceptable by Chemistry.

4.6 Division of Drug Marketing, Advertising and Communication (DDMAC)

In her final review dated January 7, 2008, Amy Toscano of DDMAC provided comments and edits to the proposed Nebido package insert. These proposed revisions were not conveyed to Sponsor as labeling discussions were not held during this cycle. Therefore, the DDMAC comments and proposals will need to be addressed in the next cycle.

Of note, DDAMC objected to the trade name [redacted] (b) (4) They stated:

[redacted] (b) (4)

Reviewer's Comment: In my opinion, the trade name [redacted] (b) (4) *is acceptable. DMEP also offered no objection to the trade name.*

4.7 Division of Pulmonary and Allergy Products (DPAP)

In order to fully evaluate the POME and POME-like respiratory adverse events reported in clinical trials and in European post-marketing, we obtained a consultation from the Division of Pulmonary and Allergy Products (DPAP). Their conclusion and recommendations are discussed in Section 3.4 of this memo, and are not repeated here.

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/s/

Mark S. Hirsch
6/27/2008 12:58:25 PM
MEDICAL OFFICER

Scott Monroe
6/27/2008 02:09:53 PM
MEDICAL OFFICER
I concur with Dr. Hirsch’s overall assessment of the safety and efficacy of testosterone undecanoate intramuscular injection for the proposed indication and his recommendation that this NDA is Approvable.

DIVISION OF REPRODUCTIVE AND UROLOGIC PRODUCTS (DRUP)

DIVISION DIRECTOR MEMORANDUM

NDA	NDA 22-219
Type of Application	Original
Applicant	Indevus Pharmaceuticals, Inc. Lexington, MA
Proprietary Name (Proposed)	NEBIDO
Established Drug Name	(Testosterone undecanoate) intramuscular injection
Drug Class	Androgen
Indication (Proposed)	[redacted] (b) (4) testosterone indicated for replacement therapy in males for conditions associated with a deficiency or absence of endogenous testosterone"
Route of administration	Intramuscular
Dosage Form	Injection
Dosage Strength	Testosterone undecanoate (250 mg/mL) in castor oil and benzyl alcohol
Dosing Regimen	One 3 mL injection (750 mg) on Day 1, on Day 28, and every 10 weeks thereafter
PDUFA Goal Date	June 28, 2008
Date of Memorandum	June 27, 2008
Division Director	Scott E. Monroe, MD Division Director, DRUP

1. RECOMMENDATIONS

1.1 Recommendation regarding Approvability

I concur with the primary Medical Reviewer (Harry Handelsman, DO) and the Clinical Team Leader (Mark Hirsch, MD, also referred to as the Cross-Discipline Team Leader in this Memorandum) that NDA 22-219 for testosterone undecanoate intramuscular injection is **Approvable** for the indication of replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous testosterone. Eventual approval of testosterone undecanoate intramuscular injection for the proposed indication is contingent upon the Applicant's satisfactorily addressing and resolving the clinical safety and chemistry, manufacturing, and controls (CMC) issues described in Sections 1.2 and 1.3 of this Memorandum and the Approvable Letter dated June 27, 2008

1.2 Basis for Recommendation regarding Approvability and Information Needed to Address Deficiencies

1.2.1 Clinical Issues

Deficiencies

Reports of serious post-injection respiratory and allergic adverse reactions in men who have received testosterone undecanoate intramuscular injection raise significant safety concerns regarding the risk/benefit profile for the use of testosterone undecanoate intramuscular injection for the proposed indication. The drug-related respiratory events, generally described as a sudden need to cough in the immediate post-injection period, have been reported in 2 patients in the testosterone undecanoate intramuscular injection clinical trials and in approximately 60 patients in the postmarketing period in Europe. In some of the cases, laryngeal tightness, respiratory distress, circulatory collapse, cyanosis, and loss of consciousness were also reported as part of the event. For most of these cases, pulmonary oil microembolism (POME), based upon the castor oil in the depot injection, appears to be causative. In at least 4 other cases, signs and symptoms of a clinically serious systemic allergic reaction have been reported, including 2 cases meeting criteria for anaphylaxis.

1. The likely incidence of these serious POME and allergic reactions in men who would be treated with testosterone undecanoate intramuscular injection, should the drug product be approved for marketing, is not known. A precise estimate of the likely incidence of these serious adverse events is needed to make a meaningful risk/benefit assessment for the use of testosterone undecanoate intramuscular injection for the proposed indication.
2. The application does not include information regarding the underlying etiology of the anaphylaxis-like reactions. It is not known if these reactions are secondary to the active drug substance or excipients in the drug product, including the castor oil vehicle.
3. The application does not include an adequate plan to minimize or manage the risk of developing these potentially life-threatening events (both POME and anaphylaxis-like events).

Information Needed to Resolve the Deficiencies (to be provided prior to possible approval)

1. *Detailed safety information from clinical studies to determine the incidence of serious post-injection POME and allergic reactions.*

   At a minimum, the safety database should include (1) all subjects treated in Stage 2 of all parts of Study IP157-001, (2) all subjects in (a) Study NE0601 (IPASS), (b) the Non-Interventional Study (NIS), and (c) Study 42306, and (3) all additional foreign data of which the Applicant is aware. Depending on the findings and the number of subjects and the number of injections of testosterone undecanoate from the studies listed above, the safety database may need to include data from additional clinical studies. The Applicant should propose the size of the safety database (i.e., total number of subjects exposed to testosterone undecanoate intramuscular injection and total number of injections) and the rationale for the size of the proposed safety database.

2. I*nformation from clinical investigations intended to characterize the nature and etiology of the anaphylaxis-like events with testosterone undecanoate intramuscular injection*.

   This information could be obtained by (1) skin testing procedures to the product and its excipients and (2) *in vitro* testing for the presence of specific IgG and IgE antibodies to both active and excipient components of the drug product.

3. *A plan to minimize the risks associated with the clinical use of testosterone undecanoate intramuscular injection, namely, to reduce the incidence and/or severity of the serious POME and anaphylaxis-like adverse events*.

1.2.2 Chemistry, Manufacturing, and Controls (CMC) Issue

The Microbiology Reviewer identified deficiencies in the Drug Master File (DMF) No. (b) (4) for the drug product. These deficiencies concerned a lack of sufficient detail in the DMF regarding the processes to ensure sterility of the final drug product. Because the Applicant is not the holder of the DMF for the drug product, specific information regarding deficiencies could not be conveyed to the Applicant. The deficiencies were outlined in a communication to the DMF holder (b) (4) The Applicant (Indevus) will be notified in the Action Letter that deficiencies identified in the DMF were conveyed to the DMF holder and that these will need to be satisfactorily resolved and submitted to the DMF prior to approval to support the CMC section of NDA 22-219.

1.3 Recommendation on Risk Management Steps and/or Phase 4 Studies

1.3.1 Recommendation on Risk Management Steps

The Applicant will need to develop a plan to minimize the risks associated with the clinical use of testosterone undecanoate intramuscular injection, namely, to reduce the incidence and/or severity of the serious POME and anaphylaxis-like adverse events observed following IM administration of testosterone undecanoate. The specifics of the risk management plan will be dependent, in part, on the additional safety data that the Applicant will need to provide to support approval of testosterone undecanoate intramuscular injection for the proposed indication.

1.3.2 Phase 4 Studies

No Phase 4 studies are requested at this time.

2. PRODUCT DESCRIPTION

The drug product is a long-acting depot formulation of testosterone undecanoate (TU) in castor oil and benzyl benzoate. Testosterone undecanoate is an ester of testosterone that is metabolized to active testosterone by cleavage of the undecanoic acid side chain, presumably via serum esterases. The dosage form is an oily solution of 250 mg TU/mL (equivalent to 157.9 mg testosterone/mL) intended for intramuscular (IM) injection. An injection volume of 3 mL contains 750 mg of testosterone undecanoate.

Testosterone undecanoate intramuscular injection (with the tradename of NEBIDO in most markets) was first approved for marketing in November 2003 in Finland. Testosterone undecanoate intramuscular injection has subsequently been approved for marketing in at least 13 other Western European countries and in more than 50 countries worldwide.

3. REVIEW ISSUES

Three major issues were identified during the review of NDA 22-219. These were (1) (b) (4) serum concentration of testosterone in Phase 3 clinical Trial IP157-001A, (2) reports of serious post-injection respiratory and allergic adverse reactions in men treated with testosterone undecanoate intramuscular injection, and (3) inadequate information in DMF No. (b) (4) to ensure the sterility of the final drug product.

3.1 (b) (4) Serum Testosterone Concentrations

Clinical Trial IP157-001A was one of two principal Phase 3 trials intended to support the safety and efficacy of testosterone undecanoate intramuscular injection in castor oil. The Division of Reproductive and Urologic Products (DRUP) has accepted pharmacokinetic (PK) data (i.e., serum concentrations of testosterone) from a single adequate clinical trial as sufficient to support the efficacy of drug products for testosterone replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous testosterone.

(b) (4)

In a teleconference on January 15, 2008, the Applicant requested that DRUP consider for approval an alternative dosing regimen (referred to as the "750 mg TU LOADING regimen"), which was investigated in Study IP157-001C (report submitted on December 20, 2007). Because of this request to change the dosing regimen for which approval was sought, data from Study IP157-001C were used as the primary source of steady state PK data to support the efficacy of testosterone undecanoate intramuscular injection. Data from Study IP157-001A (750 mg TU dosing regimen), however, were used as the source of first-dose PK data because Study IP157-001C did not evaluate first-dose pharmacokinetics.

Division Director's Comment

- *I agree with the Applicant's request and the decision of the clinical pharmacology and clinical review teams to use the dosing regimen and PK data from Study IP157-001C as the primary basis of support for the efficacy of testosterone undecanoate intramuscular injection for the proposed indication.*

3.2 Reports of Serious Post-Injection Respiratory and Allergic Adverse Reactions

With one exception, the overall safety profile of testosterone undecanoate intramuscular injection in the clinical trials submitted in support of NDA 22-219 was comparable to other testosterone drug products and acceptable for the indication of testosterone replacement therapy in males for conditions associated with a deficiency or absence of endogenous testosterone. The one exception concerned reports of serious post-injection respiratory and allergic adverse reactions in

men who received testosterone undecanoate by intramuscular injection. These reports raised significant safety concerns regarding the risk/benefit profile for the use of testosterone undecanoate intramuscular injection for the proposed indication. The drug-related respiratory events, generally described as a sudden need to cough in the immediate post-injection period, have been reported in 2 patients in the testosterone undecanoate intramuscular injection clinical trials and in approximately 60 patients in the post-marketing period in Europe. In some of the cases, laryngeal tightness, respiratory distress, circulatory collapse, cyanosis, and loss of consciousness were also reported as part of the event. Most of these events appear to be caused by pulmonary oil micro embolism (POME), based upon the castor oil in the depot injection. In at least 4-5 other cases, all based on postmarketing reports, signs and symptoms of a clinically serious systemic allergic reaction have been reported, including 2 cases meeting the currently accepted criteria for anaphylaxis.

The following description of the range of clinical severity of these post-injection respiratory and allergic adverse reactions is taken from the Executive Summary of the Review of the Cross-Discipline Team Leader:

> *"These cough reactions ranged in severity from mild to severe. In greater than one third of the post-marketing "cough" cases, the event was described as serious (medically significant). In one out of 5 post-marketing cases, the event described active medical intervention or hospitalization. In some post-marketing cases, the event was described as "life-threatening" and required medical intervention to prevent death or disability. These "cough" reactions tended to occur soon after or during the intramuscular injection, were described by patients as beginning with a sudden urge to cough, and some have also included shortness of breath, severe cough, laryngeal tightness, cyanosis, respiratory distress, circulatory collapse, and loss of consciousness….. In my opinion, the Sponsor does not appreciate the seriousness of these POME-related adverse events, does not acknowledge the impact of this risk on the overall risk: benefit profile for Nebido, and has not sufficiently defined, managed, or proposed an acceptable management plan for this potentially life-threatening, drug-related side effect for this product for testosterone replacement in hypogonadal adult males."*

The actual incidence of the POME reactions and anaphylactic reactions is uncertain because all but 2 of the cases are based on postmarketing reports. The Applicant has argued that these events are "rare." Based upon total sales of (b) (4) vials of testosterone undecanoate intramuscular injection (i.e., Nebido) in Europe, the Applicant concluded that these 64 post-marketing cases reflect an incidence of less than 1 in approximately 10,000 injections. The Applicant also acknowledged that this value is a rough estimate and that it is not possible to derive a per-patient incidence from these post-marketing reports.

Division Director's Comments

- *I concur with the assessments of the Cross-Discipline Team Leader (provided above) and the primary Medical Reviewer that many of the reported cases were clinically serious events and possibly life-threatening.*
- *I also concur that it is not possible to make a meaningful risk/benefit assessment for the use of testosterone undecanoate intramuscular injection for the proposed indication because of the serious nature of these events and the uncertainty as to their true incidence.*

On June 10, 2008, the Sponsor submitted preliminary new clinical data from 3 studies that included approximately 1,450 subjects treated with a total of approximately 7,200 injections of testosterone undecanoate intramuscular injection. These new data were derived from (1) a completed clinical trial studying testosterone undecanoate intramuscular injection for suppression of male spermatogenesis (2) an ongoing observational safety study being conducted in Germany, and (3) an ongoing observational safety study being conducted in several European countries and Australia.

Division Director's Comments

- *Although the new information does not include any reports of immediate post-injection respiratory or systemic allergic adverse events, the submitted data are, for the most part, preliminary. The data do not appear to have undergone the level of verification required to support a NDA and final reports for these 3 additional studies have not been submitted for review.*
- *Because it is not possible to make a meaningful risk/benefit assessment for the use of testosterone undecanoate intramuscular injection for the proposed indication, the drug product cannot be approved for marketing at this time. Other deficiencies in the Application related to these serious post-injection adverse events include:*
  - *A lack of information regarding the underlying etiology of the anaphylaxis-like reactions. It is not known if these reactions are secondary to the active drug substance or excipients in the drug product, including the castor oil vehicle.*
  - *The absence of an adequate plan to minimize or manage the risk of developing these potentially life-threatening events (both POME and anaphylaxis-like events).*
- *Before this Application could be approved, the Applicant will need to provide the additional information identified in Section 1.2.1 under the clinical subheading "Information Needed to Resolve the Deficiencies."*

3.3 Inadequate Information to Ensure the Sterility of the Final Drug Product

The Microbiology Reviewer identified deficiencies in the Drug Master File (DMF) No. (b) (4) for the drug product. These deficiencies concerned a lack of sufficient detail in the DMF regarding the processes to ensure sterility of the final drug product. Because the Applicant is not the holder of the DMF for the drug product, specific information regarding the deficiencies could not be conveyed to the Applicant. The deficiencies were outlined in a communication to the DMF holder (b) (4) The Applicant (Indevus) will be notified in the Action Letter that deficiencies identified in the DMF were conveyed to the DMF holder and that these will need to be satisfactorily resolved and submitted to the DMF to support the CMC section of NDA 22-219.

4. CLINICAL PROGRAM – OVERVIEW AND SUBJECT EXPOSURE

The original NDA submitted on August 24, 2007, contained safety data from a total of 422 adult male subjects in clinical trials. These trials consisted of (1) a single U.S. Phase 3 Study (Study IP157-001A, Stage 1) that included of a total of 137 patients in 2 dose arms (750 mg TU by IM injection every 12 weeks [n=120] and 1000 mg TU by IM injection every 12 weeks [n=117]) and (2) 6 older European dose-finding trials that included a total of 185 adult males subjects. In Study IP157-001A, Stage 1, all patients received at least 4 injections of IM

testosterone undecanoate (48-weeks exposure) and many received 5 injections (60 weeks exposure). The safety data submitted for Study IP157-001A reflected a median follow-up period of approximately 48 weeks. Longer follow-up safety data were submitted for Stage 2 of Study IP157-001A in the 120-Day Safety Update.

On December 20, 2007, the Applicant submitted a report for Study IP157-001C containing data from 117 adult male subjects dosed with the 750 mg TU LOADING regimen. In Study IP157-001C, all subjects received at least 3 injections of testosterone undecanoate (on Day 1, on Day 28, and Day 98), reflecting 24 weeks of exposure and the vast majority received 4 injections, reflecting 34 weeks of exposure. The safety data submitted for this Study reflects a median follow-up period of 24 weeks.

On December 28, 2007, the Applicant submitted the 120-Day Safety Update, containing (1) safety data from Study IP157-001A, Stage 2 (an extension of the primary study) and (2) a report for Study IP157-001B, which tested two new loading dose regimens. This latter study included a total of 134 new male subjects in 2 treatment groups (a 1000 mg TU group and a 750 mg TU group).

In summary, for all clinical trials submitted in the original NDA through the 120-Day Safety Update, there were data from a total of 673 subjects treated with various dosing regimens of testosterone undecanoate intramuscular injection. Among these subjects were data from a total of 488 U.S. subjects treated in Study IP157-001A, Study IP157-001B, and Study IP157-001C.

Division Director's Comment

- *The scope of the clinical trials (derived from [1] the number of subjects studied with the proposed to-be-marketed dosing regimen [i.e., 750 mg TU LOADING regimen] and duration of treatment with this regimen and [2] overall number of treated subjects and duration of treatment with all dosing regimens) would normally meet DRUP's exposure requirements for a testosterone drug product for replacement therapy in males for conditions associated with a deficiency or absence of endogenous testosterone.*
- *Because of safety concerns based primarily on postmarketing reports of serious post-injection respiratory and allergic adverse reactions in men who have received testosterone undecanoate intramuscular injection, additional clinical safety data will be required to make a meaningful risk/benefit assessment for the use of IM testosterone undecanoate for the proposed indication.*

5. OVERVIEW OF EFFICACY

5.1 Primary Efficacy Endpoint and Efficacy Analysis

DRUP has accepted PK data (i.e., serum concentrations of testosterone) from a single adequate clinical trial as sufficient to support the efficacy of drug products for testosterone replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous testosterone. The primary PK efficacy endpoint for such a study is the average total serum testosterone concentration (i.e., Cave) over the dosing interval. A successful outcome for a study subject is a Cave value for total testosterone that is within the range of 300-1000 ng/dL. To meet the overall efficacy criteria for a successful clinical trial, at least 75% of subjects must have a total testosterone Cave within the range of 300-1000 ng/dL, and the lower bound of the two-sided 95% confidence interval about the point estimate must not be lower than 65%.

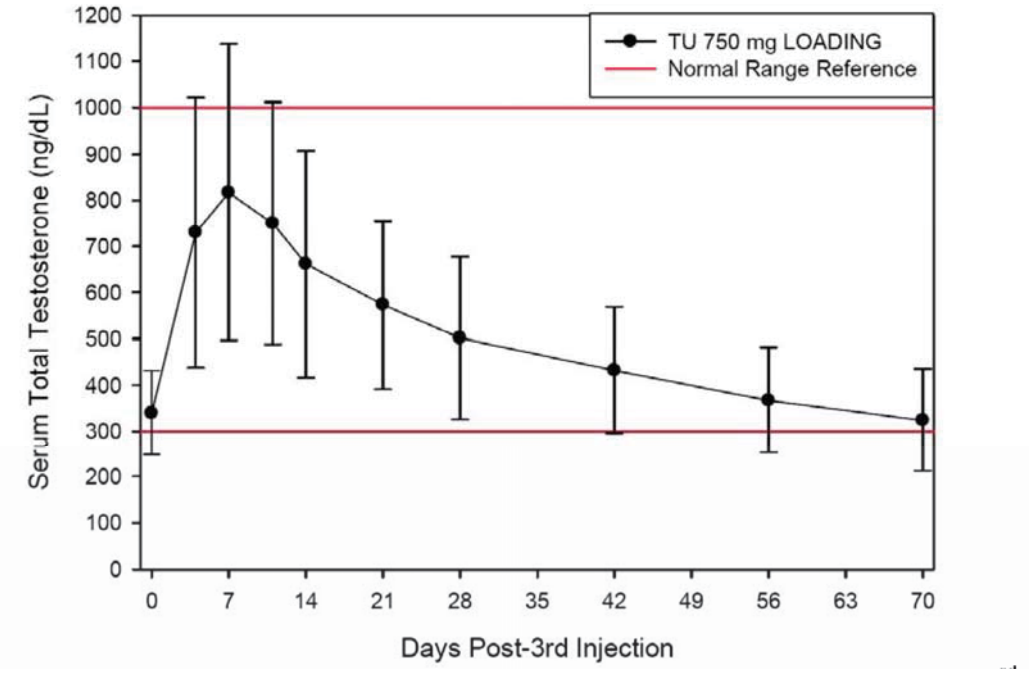
Additionally, there are several secondary endpoints. One of the most important of these is based on the total serum testosterone Cmax values. For a clinical trial to be considered successful, the following also should be observed: (1) ≥ 85% of subjects with a Cmax value of ≤ 1500 ng/mL; (2) ≤5% subjects with a Cmax value of 1800 to < 2500 ng/mL, and (3) no subjects with a Cmax value ≥ 2500 ng/dL.

The primary Medical Reviewer has described in detail the efficacy findings for Study IP157-001A (dosing regimens of 750 mg TU and 1000 mg TU every 12 weeks and Study IP157-001C (750 mg TU LOADING regimen). Because the Applicant is seeking approval only for the 750 mg TU LOADING regimen, the following discussion reviews only the findings from Study IP157-001C.

5.2 Efficacy Findings

The primary and secondary endpoints for Study IP157-001C were based on pharmacokinetic data obtained from the 3rd injection interval of 750 mg TU. Figure 1 shows the mean serum total testosterone concentrations following the 3rd injection of 750 mg TU. Mean serum testosterone concentrations at all sampling times fell within the target range of 300-1000 ng/dL.

Figure 1 Mean (±SD) Serum Total Testosterone Concentrations following the 3rd Injection Interval of 750 mg TU (Study IP157-001C)



Source: Clinical Pharmacology Review, Figure 4, pg. 9.

5.2.1 Primary Efficacy Endpoint (Cave)

The primary efficacy endpoint was defined as the percentage of subjects that had a total serum testosterone Cave within the normal range (300–1000 ng/dL). Ninety four percent (94%) of subjects (110 of 117) had serum total testosterone Cave values within the 300-1000 ng/dL range. The 95% confidence interval around this point estimate was 89.6%-98.5%. Of the 7 patients

who did not meet this criterion, 6 failed due to a Cave below 300 ng/dL, and one failed due to a Cave above 1000 ng/dL.

Division Director's Comment

- *The above findings indicate that the primary efficacy objective for Study IP157-001C was achieved.*

5.2.2 Assessment of Cmax (Important Secondary Endpoint)

The percentages of Cmax values for serum total testosterone that fell into predefined ranges are listed in Table 1.

Table 1 Distribution of Cmax Values for Serum Total Testosterone Concentrations during the 3rd Injection Interval (Study IP157-001C)

	Number of Patients Exceeding/Number of Patients Assessed (Percent of Patients Exceeding)
C_{max} Outcome	TU 750 mg LOADING (N=117)
> 1500 ng/dL[1]	9 of 117 (7.7%)
≥ 1800 ng/dL and < 2500 ng/dL	0 of 117 (0%)
≥ 2500 ng/dL	0 of 117 (0%)
Did Dose Meet Threshold Limits?	**Yes**

Source: Clinical Pharmacology Review, table 4, pg. 11.

Division Director's Comments

- *The Applicant excluded from the PK analysis subjects who weighed less than 65 kg. One subject (Patient 031-7021) fell into this category. This subject (not represented in Table 1) had a testosterone concentration above 2500 ng/dL during the 3rd injection interval. Otherwise, only 9 of the 117 patients (7.7%) had Cmax values >1500 ng/dL and no patient had a Cmax value ≥1800 ng/dL.*
- *In summary, the data show that the Cmax efficacy objective was achieved in men weighing more than 65 kg.*

5.3 Overall Assessment of Efficacy

In his final review, dated June 24, 2008, Dr. Sobhan (FDA statistician) concluded:

> *"The results support the efficacy of Nebido TU 750 mg LOADING in the treatment of hypogonadism in adult males as indicated by the attainment of steady state by the 3rd injection. The intensive sampling for PK outcomes (Cave and Cmax) also met FDA threshold for approvability and, therefore, can be extrapolated to represent PK outcomes under extended dosing beyond 3 injections."*

Division Director's Comment

- *Dr. Sobhan's conclusion is consistent with that of the Clinical Pharmacology and Medical Review teams. Pharmacokinetic data provided in NDA 22-219 for testosterone undecanoate intramuscular injection (750 mg TU LOADING regimen) have met DRUP's criteria for efficacy for a testosterone drug product for replacement therapy in adult men for conditions associated with a deficiency or absence of endogenous testosterone.*

6. SAFETY FINDINGS

6.1 General Comments

The primary Medical Reviewer and the Clinical Team Leader have thoroughly reviewed the safety data submitted in support of the use of testosterone undecanoate intramuscular injection for the proposed indication (see the primary Medical Review [signed June 16, 2008] and the Cross-Discipline Team Leader Memorandum [signed June 27, 2008]). During their safety reviews of this Application, both initially focused on the safety data from the 2 Phase 3 clinical trials (Study IP157-001A and Study IP157-001C). These 2 studies contained only a single report of an immediate systemic post-injection adverse event (a non-serious case of POME). Review of the postmarketing safety reports submitted in the original submission and in the 120 Day Safety update, however, revealed several additional cases of serious post-injection respiratory and allergic adverse reactions. These cases prompted further inquires from the Division to the Applicant, eventually resulting in the identification of 66 cases (64 of which were obtained from postmarketing reports).

Division Director's Comment

- *With one exception, reported adverse events and changes in laboratory values from subjects treated with testosterone undecanoate intramuscular injection in the clinical trials described in NDA 22-219 were similar to those reported in clinical trials for other approved testosterone drug products. The one exception was the reports, almost entirely from postmarketing information, of serious post-injection respiratory and allergic adverse reactions in men who had received testosterone undecanoate IM injections. These serious events are discussed in Section 3.2 and Section 6.4 of this Memorandum.*

6.2 Clinical Trial Safety Database

The original NDA submitted on August 24, 2007, contained safety data from a total of 422 adult male subjects in clinical trials. These trials consisted of (1) Study IP157-001A, Stage 1, which included of a total of 137 patients in 2 dose arms and (2) 6 older European dose-finding trials that included a total of 185 adult male subjects. In Study IP157-001A, Stage 1, all patients received at least 4 injections of IM testosterone undecanoate (48-weeks of exposure). The Applicant subsequently submitted a report for Study IP157-001C that included data from 117 adult male subjects dosed with the 750 mg TU LOADING regimen. In this study, all subjects received at least 3 injections of testosterone undecanoate (on Day 1, on Day 28, and Day 98), reflecting 24 weeks of exposure, and the vast majority received 4 injections reflecting 34 weeks of exposure. Additional clinical trial data were included in the 120-Day Safety Update.

Division Director's Comments

- *For all clinical trials submitted in the original NDA through the 120-Day Safety Update, there were data from a total of 673 subjects treated with various dosing regimens of testosterone undecanoate intramuscular injection. Among these subjects were data from a total of 488 U.S. subjects treated in Study IP157-001A, Study IP157-001B, and Study IP157-001C.*
- *Were it not for the reports of serious post-injection respiratory and allergic adverse reactions, the safety data and safety findings from these 673 subjects would have been*

sufficient to support the approval of testosterone undecanoate intramuscular injection for the proposed indication.

6.3 Deaths and Other Serious Adverse Events

Deaths. There were 3 deaths in Study IP157-001A. The causes of death were: homicide, fatal motorcycle accident, and sepsis in a subject with prior history of thrombocytopenia. None of the deaths were attributed to treatment with testosterone undecanoate intramuscular injection by the investigators. No subject died during Study IP157-001C.

Other Serious Adverse Events (SAEs)

Study IP157-001A. Eight (6.7%) subjects in the 750 mg TU group and 10 (8.5%) subjects in the 1000 mg TU group experienced at least one SAE during the treatment period. Only 2 SAEs were observed in more than 1 subject: atrial fibrillation in 2 subjects in the 750 mg TU group, and knee arthroplasty in 2 subjects in the 1000 mg TU group. One instance each of the following SAEs were reported in the 750 mg TU group: cervical spinal stenosis, parathyroid tumor, congestive cardiac failure, tinnitus, acute pancreatitis, and sepsis. One instance each of the following SAEs were reported in the 1000 mg TU group: coronary artery disease, enterococcal bacteremia, malignant hepatic tumor, renal artery stenosis, viral gastroenteritis, spinal column stenosis, arthritis, cerebrovascular accident, prostatitis, and tendon rupture. None of the SAEs were judged by the investigators as being at least possibly related to study drug.

Study IP157-001C. Eight (6.2%) subjects experienced at least one SAE during the treatment period. No single SAE was observed in more than 1 subject. The SAEs reported were ischemic colitis, deep vein thrombosis (DVT), faecaloma, intervertebral disc protrusion, myocardial infarction, prostatitis, spinal column stenosis, urinary tract infection, and wrist fracture. None of these events were considered by the investigators as being at least possibly related to study drug.

Withdrawals due to Adverse Events

Study IP157-001A. Study medication was prematurely discontinued due to an adverse event in 6 (5.0%) subjects in the 750 mg TU group and 4 (3.4%) subjects in the 1000 mg TU group. Adverse events judged by the investigator to be at least possibly related to study drug and leading to discontinuation of treatment were increased serum PSA (750 mg TU group), increased serum estradiol (1000 mg TU group), and increased red blood cell count (1000 mg TU group).

Study IP157-001C. Study medication was prematurely discontinued in 4 (3.8%) patients for the following adverse events: acne, mood swings, myocardial infarction, increased estradiol, and DVT. Of these adverse events, all but myocardial infarction were judged by the investigators to be at least possibly related to treatment with study drug.

Division Director's Comment

- *The numbers and types of reported serious adverse events and the numbers of withdrawals because of adverse events in these studies do not raise any safety concerns.*

6.4 Consultation with the Division of Pulmonary and Allergy Products

To more fully evaluate the nature and clinical significance of the immediate post-injection respiratory and allergic adverse events, the Division of Pulmonary and Allergy Products (DPAP) was consulted. Of the 66 cases submitted for their review, the DPAP concluded that 2 cases (GB-2007-023826 and ZA-3007-035469) met the currently accepted diagnostic criteria for anaphylaxis. In addition to these 2 cases, the DPAP also identified 2 other cases where

anaphylaxis could not be excluded. Of the remaining 62 cases, the DPAP stated that "51 clearly did not meet the clinical criteria for the diagnosis of anaphylaxis. The majority of these 51 cases were consistent with POME.

The DPAP's initial consultation response (dated April 14, 2008) included the following comment and recommendations:

> *Ultimately, the decision to approve the product will be a risk versus benefit decision, and should be made in light of the degree of efficacy, the seriousness of the indication, the availability of alternative products for that indication, and the extent of the safety data.*
>
> *The following are recommendations for your consideration if the product is to be approved.*
>
> 1. *It would be appropriate to note in the product label that it should be administered only in a practitioner's office.*
> 2. *Most of these adverse events occurred immediately after injection. It would be also be appropriate to consider a labeling recommendation that there be a waiting period after injection.*
> 3. *The sponsor should attempt to provide as much detail as possible in any postmarketing reports suggestive of anaphylaxis. Follow-up requests for additional medical information may be necessary to provide the additional detail necessary to interpret the adverse event.*

In a follow up communication (dated May 27, 2008), the DPAP provided the following additional recommendations:

- *..... it would be appropriate to characterize the frequency of these events* (b) (4) [redacted] *we would recommend that these studies be conducted prior to approval.*
- *Given the unclear mechanism of these reactions, we also recommend that consideration be given to advising the sponsor to characterize the nature of the anaphylaxis events. Establishing the mechanism of these allergic reactions can help to make a decision on the approvability of the drug more scientific and rational.*

Division Director's Comment

- *The primary clinical review team and I concur with the assessments and recommendations of the DPAP reviewer.*

6.5 Overall Assessment of Safety

The systemic safety profile of approved testosterone drug products for replacement therapy in hypogonadal men is well established. Mean serum testosterone concentrations in men treated with 750 mg TU LOADING regimen were, for the most part, within the normal male range for serum testosterone (i.e., 300-1000 ng/dL) and were within the range of values produced by previously approved testosterone products. Local tolerance to the testosterone undecanoate IM injections in the clinical trials was acceptable. With one exception, reported adverse events and changes in laboratory values for men treated with IM testosterone undecanoate were similar to those reported in clinical trials for other approved testosterone drug products. The one exception

concerned reports, almost entirely from postmarketing information, of serious post-injection respiratory and allergic adverse reactions in men who had received IM testosterone undecanoate. These reports raise significant safety concerns regarding the risk/benefit profile for the use of testosterone undecanoate intramuscular injection for the proposed indication.

7. RECOMMENDATIONS FROM OTHER DISCIPLINES

The findings from each of the non-medical review disciplines are well-summarized in the review of the Cross-Discipline Team Leader. Only the recommendations from these other review disciplines are provided in this section.

- There are no unresolved toxicology or clinical pharmacology issues.
- The drug product manufacturing facility has been inspected and has received an "Acceptable" recommendation from the Office of Compliance. There is, however, one unresolved CMC (chemistry, manufacturing, and control) issue that concerns a microbiology deficiency in DMF No. (b) (4) (see Section 1.2.2). The CMC Reviewer made the following statement: "*This NDA has provided sufficient CMC information to assure the identity, strength, and quality of the drug product, but not its purity (sterility).*"
- The proposed trade name (b) (4) was found acceptable by the Division of Medication Error Prevention (DMEDP). The Division of Drug Marketing, Advertising, and Communication (DDMAC), however, objected to the name (b) (4)

Division Director's Comment

- *The primary Medical Review Team and I find the proposed tradename acceptable.*

8. LABELING

Labeling was not addressed during the present review cycle.

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/s/

Scott Monroe
6/27/2008 10:39:54 PM
MEDICAL OFFICER

MEDICAL OFFICER'S REVIEW
NDA 22-219 Nebido (testosterone undecanoate)

Application Information:	
NDA #	**22-219**
Sponsor	**Indevus Pharmaceuticals, Inc.**
Primary Efficacy Study:	**Protocol #IP157-001**
Submission Date:	**August 24, 2007**
PDUFA Goal Date:	**June 24, 2008**
Review Status:	**Standard**
Drug Name	**Testosterone undecanoate**
Generic Name	**Testosterone undecanoate**
Proposed Trade Name	**Nebido**
Drug Categorization:	
Pharmacological Class	**Androgen**
Proposed Indication	**Treatment of male hypogonadism**
Proposed Dose Regimen	**750 mg loading regimen, then 750 mg every 10 weeks**
Strength and Dosage Form	**250 mg/mL in castor oil and benzyl benzoate**
Route of Administration	**Intramuscular**

Reviewer Information:	
Clinical Reviewer	**Harry Handelsman, DO**
Medical Team Leader	**Mark Hirsch, MD**
Division Director	**Scott Monroe, MD**

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I. Executive Summary

1. Conclusions and Recommendation:

In the opinion of this reviewer, the evidence presented in the submission of this NDA is adequate in support of the effectiveness of **Nebido 750 mg Loading Regimen** (administered at baseline, week 4 and every 10 weeks thereafter) [redacted] (b) (4) in patients 18 years of age and older. However, safety concerns derived from clinical trial and post-marketing data, and the opinion of our FDA consultants from the Division of Pulmonary and Allergy Products related to the risks, risk/benefit, and management of serious post-injection reactions, preclude approval of this product until such time as these issues are resolved.

2. Summary of Clinical Findings

A. Brief Overview of the Clinical Program

Testosterone undecanoate (TU) is a member of the endogenous androgens drug class, which includes both testosterone and dihydrotestosterone, responsible for normal growth and development of the male sex organs and the maintenance of secondary male sex characteristics, in addition to playing a role in numerous other normal physiologic and metabolic functions. Normal serum total testosterone concentrations in healthy males generally range from 300 to 1000 ng/dL. Various administration routes are used in testosterone replacement therapy, including oral, transdermal, and buccal formulations, as well as subcutaneous and intramuscular formulations, all of which have associated advantages and disadvantages. The inconvenience of frequent physician visits, application site reactions, and fluctuations in T concentrations are among the disadvantages of currently approved T products that the Sponsor purports as the rationale for preferential use of Nebido.

In support of this **NDA 22-219**, the sponsor submitted data from 2 pivotal Phase-3 trials **IP157-001 Part A, Stage 1** involving 220 subjects at 54 U.S. study sites, and **IP157-001 Part C, Stage 1** involving 130 subjects at 31 U.S. study sites In addition, this NDA also contains data from earlier PK studies, including data from 4 completed European studies (185 subjects) and an ongoing study in Germany (**ME97029**) designed to assess the effects of Nebido 1000 mg in 95 subjects over the course of 3 years. The reviewer chose to focus primarily on the study reports from the 2 pivotal Phase-3 trials and the ongoing German study. Nonetheless, safety data from all sources werereviewed in detail.

The **Part A** study was a 2-arm, open-label, randomized, multi-center PK and long-term safety study of intramuscular (IM) injections of Nebido 750 mg and 1000 mg in hypogonadal men. The Part A submission reflects only data through the 5th injection visit. The Part C submission reflects data up to 9 injections (20 months).

The primary objective in Part A was to evaluate the PK of Nebido 750 mg and 1000 mg given every 12 weeks, over the 12 week interval following the 4th injection, in approximately 110 subjects per treatment arm.

The primary objective in **Part C** was to evaluate the PK of the Nebido 750 mg loading regimen (the to-be-marketed dose regimen) in approximately 130 hypogonadal men.

The secondary objectives in **Part A** were 1) to evaluate the PK of the 750 mg and 1000 mg doses of Nebido over the 12 week intervals following the 1st, 2nd and 3rd injections in a subset of 20 subjects per treatment arm, and 2) to compare the simultaneous serum levels of total T to levels of DHT, E2, SHBG, TU, and DHTU.

The secondary objectives in **Part C** were 1), to evaluate the PK of the Nebido 750 mg loading regimen given at baseline, 4 weeks and every 10 weeks thereafter, over 10 week intervals following the 4th dose, 2) to compare the simultaneous serum levels of total T to levels of DHT, E2, SHBG, TU, and DHTU, and 3) to evaluate safety at baseline, week 4, and every 10 weeks through 9 injections.

B. Efficacy

(b) (4)

(b) (4)

[redacted] (b) (4) (b) (4) The Sponsor subsequently decided to apply only for approval of the 750mg Loading Regimen, involving two loading doses (Day 1, then Day 28), followed by injections every 10 weeks thereafter, as studied in Part C.

The Sponsor's efficacy conclusions in the **Part C** study were as follows:

> Nebido 750 mg Loading Regimen provided satisfactory average and maximum T concentrations in hypogonadal men. C_{avg} was within the normal range and the C_{max} profile did not exceed the FDA thresholds.

The Clinical Pharmacology team reviewed the information from Part C and found adequate support for the Sponsor's conclusion. In the opinion of this Clinical reviewer, the Part C study results, supported by the Part A data, provide substantial evidence in support of the effectiveness of Nebido when used in the 750mg Loading Regimen for testosterone replacement in men aged 18 years and older with clinical conditions associated with hypogonadism. The percent of subjects having C_{avg} within the normal range in Part C was 94%.

C. Safety

Safety data is drawn from a total of 367 subjects enrolled in the 2 completed pivotal studies in the U.S., additional subjects in European clinical trials, and the European post-marketing experience from April, 2004 through January, 2007. The safety evaluation in this database is considered adequate for the number of subjects exposed to Nebido and the duration of exposure. The average safety follow-up in the pivotal studies was over 43 weeks.

Nebido was generally well tolerated in the pivotal studies, and no clinically meaningful treatment differences were noted between race or age subgroups. The reported significant adverse events are primarily those related to known side effects of other approved testosterone formulations used to treat male hypogonadism. No significant cardiovascular, hepatic, renal, or hematologic toxicities were identified. However, there were reports of "coughing fits" in 2 patients immediately post-injection in the pivotal trials (one in a European study and one in a U.S. pivotal trial). In addition to the 2 post-injection cough reactions reported in clinical studies, there were 66 individual European post-marketing adverse event reports of post-injection "cough reactions", some of which were medically serious and required urgent care and/or hospitalization. These "coughing fits" are the basis for the unresolved safety concern for Nebido.

Safety-related Findings:

In **Study A**, treatment-related-adverse-events (TEAEs) reported in ≥ 1.0 % of subjects in the 750 mg and 1000 mg groups respectively were as follows: injection site pain, 1.7 % and 1.7 %; estradiol increase, 0 % and 1.7 %; cholesterol increase, 0 % and 1.7 %; BPH, 0.8 % and 1.7 %; fatigue, 2.5 % and 0.9 %; insomnia, 2.5 % and 0.9 %; libido decrease, 1.7 % and 0.9 %; PSA increase 3.3 % and 0 %; hypercholesterolemia, 1.7 % and 0 %. These adverse events were not unexpected for an injectable T replacement product.

Study medication was permanently discontinued due to TEAEs in 5.0 % in 750 mg group and 3.4 % in the 1000 mg group.

There were 3 deaths in the study. Two of the deaths were secondary to a homicide and a fatal motorcycle accident, and the third death was secondary to sepsis in a subject that had a prior history of thrombocytopenia. There were no Serious Adverse Events (SAEs) judged as being at least possibly related to study drug.

There were a very few (10) TEAEs of ECG abnormalities reported, and none were judged to be at least possibly related to study drug.

Excepting changes in erythropoietic parameters, serum hormones and a few other laboratory parameters, the mean and median changes from baseline to endpoint for clinical laboratory tests were generally small and similar in both treatment groups. Liver function tests, BUN and serum calcium demonstrated slight average decreases from baseline to endpoint, and these were judged to be not clinically meaningful. The most notable changes from baseline to endpoint were the 60 % decreases in serum FSH and LH, which reflect the fact that the majority of subjects in the study had primary hypogonadism and testicular failure and therefore, had higher average serum FSH and LH than subjects with secondary hypogonadism.

In **Study C,** treatment-related-adverse-events (TEAEs) reported in ≥ 2.0 % of subjects in the 750 mg loading regimen were as follows: acne, 4.6%; fatigue, 4.6%, cough, 3.1 %; injection site pain, 3.1%; nasopharyngitis, 3.1%; pharyngolaryngeal pain, 3.1%; arthralgia, 3.1%; insomnia, 2.3%; prostatitis, 2.3%; sinusitis, 2.3%. Again, these adverse events were not unexpected for an injectable T replacement product.

Study medication was discontinued due to TEAE's in 3.8% of subjects.

There were no deaths during the Part C study. There was one SAE judged by the investigator to be at least possibly related to study drug: a DVT, resulting in discontinuation from study.

There were no TEAE's of ECG abnormalities reported in this study.

The analysis of laboratory measurements in Part C indicated expected changes in parameters known to be affected by T replacement and no clinically relevant changes in parameters thought to be generally unaffected by T replacement. These outcomes were similar to those observed in Part A of the study.

In the **Post-marketing Experience,** immediate post-injection reactions characterized by symptoms of cough, dyspnea, and respiratory distress were reported in 66 cases, 28 of which were reported as serious or life-threatening, 12 required emergency medical care, and 6 required hospitalization. The majority of these reactions were transient and have been attributed to the phenomenon of pulmonary oil microembolism (POME). However, our FDA consultant concluded that 2 of these events met diagnostic criteria for anaphylaxis, another case was consistent with urticaria and angioedema, and in an additional case anaphylaxis could not be excluded. In addition, some of the POME events were not short-lived and were medically severe.

Reviewer's Comments: Except for the occurrence of life-threatening "cough reactions", treatment with Nebido generally resulted in safety outcomes consistent with those expected with other T replacement therapies. Safety outcomes were for the most part the same for all treatment groups, and reflected a low overall incidence of TEAEs. However, the occurrence of life-threatening "cough" reactions associated with this product presents a significant and unresolved safety concern.

D. Dosing

The dosing regimens selected for Phase 3 were based on modeling and simulations using data from earlier clinical studies of 1000 mg to provide steady state C_{max} T values that would not exceed 2500 ng/dL in any subject, would not exceed 1800 mg/dL in more than 5 % of subjects, and would not exceed 1500 ng/dL in more than 15 % of subjects. Dosing regimens selected were expected to provide steady state C_{avg} values within the range of 300-1000 ng/dL for at least 75 % of subjects (with a lower bound for the 95 % confidence interval about the proportion being no lower than 65 %).

(b) (4)

Data from Part C demonstrates that steady-state was more rapidly achieved using the 750 mg Loading Regimen, while not providing excessive C_{max} (>1500 ng/dL,7.7 % and no subject ≥ 1800 ng/dL).

E. Special Populations:

There were no clinical meaningful differences between the treatment groups with respect to the incidence of adverse events (AE's) or differences in efficacy by age or race subgroups.

II. Integrated Summary of Efficacy (ISE)

A. Brief Statement of Conclusions

The pivotal Phase-3 studies **IP157-001 Parts A and C** were adequate efficacy, PK, and long-term safety studies conducted in multiple US sites. They provide substantial evidence of efficacy of the 750mg Loading Regimen of Nebido, in meeting the primary and secondary protocol efficacy objectives. The proposed indication, therefore, is well supported by the efficacy data.

B. Method of Efficacy Review

The reviewer's basic approach to the efficacy review involved:

- Review of the proposed indication, protocols, regulatory and scientific background.
- Identification and review of the well-controlled studies to support the indication.
- Conduct of a detailed review of each study for efficacy.
- Generate conclusions regarding efficacy from the pivotal and supporting studies.

C. List of Studies, Designs, Population and Efficacy Variables

The following studies were analyzed during the review process:

IP157-001 - Pivotal studies Parts A and C, Phase-3
JPH01495 - a PK study (single injection)
JPH04995 - a PK study (multiple injections)
ME97029 - a Supporting PK Comparator Study
ME98096 - a PK study (multiple injections)

The 2 pivotal trials were Phase 3, randomized, multi-center, open-label, studies of efficacy and safety of Nebido conducted in the US for terms of up to 48 weeks.

The supporting study (ME970029) was a single-center, open-label, controlled, 2-arm, parallel study in 40 hypogonadal men of the safety and efficacy of multiple injections of Nebido 1000 mg given at 6-week intervals for 3 doses followed by a final injection after a 9-week interval, compared to T enanthate 250 mg injections for 10 doses given at 3-week intervals.

Key study entry criteria for the pivotal trials included:

1. Males 18 years and older.
2. Screening serum T concentration <300 ng/dL.

D. Statistical Methods:

In study **IP157-001 Part A**, a total of 237 subjects were randomized to receive Nebido 750 mg (N=120) or1000 mg (N=117). In **Part C**, a total of 130 subjects were enrolled to receive Nebido 750 mg Loading Regimen.

Descriptive methods were used to present the data, reflecting baseline characteristics and exposure in the pivotal studies. Pharmacokinetics were presented via descriptive statistics and figures demonstrating the concentration-time profile. Incidence rates, including assessment of C_{max} success criteria, were presented in concordance with study objectives.

E. Integrated Review of Efficacy Results:

1. Study IP157-001 Part A

In Part A, of the 237 subjects enrolled at the 54 sites, 193 completed the study (81.4 %). The primary reasons for dropouts were AE's and withdrawal of consent, and the treatment groups (750mg and 100mg) were generally similar for the rates and reasons for discontinuation. Treatment groups were well matched for demographic and baseline characteristics. The majority of subjects were White (87.4 %), mean age was 55.

1.1 Basic study design and outcome measures in Part A

The baseline characteristics of the treatment groups in the pivotal Part A study are shown in Table1.

Table 1: Demographic and Baseline Characteristics – Total Patient Sample (Study IP157-001 Part A Stage 1)

Characteristic	TU 750 (N=120)	TU 1000 (N=117)
Age (in years)		
Mean ± SE	55.0 ± 0.97	55.9 ± 1.00
Median (range)	54 (30, 82)	56 (23, 83)
Age Categories, N (%)		
< 30	0 (0.0)	1 (0.9)
30 - <40	9 (7.5)	5 (4.3)
40 - <50	23 (19.2)	28 (23.9)
50 - <60	48 (40.0)	36 (30.8)
60 - <70	28 (23.3)	40 (34.2)
70 - <80	10 (8.3)	4 (3.4)
≥ 80	2 (1.7)	3 (2.6)
Gender, N (%)		
Male	120 (100.0)	117 (100.0)
Race, N (%)		
White	101 (84.2)	106 (90.6)
Black	11 (9.2)	8 (6.8)
Hispanic	3 (2.5)	3 (2.6)
Asian	2 (1.7)	0 (0.0)
Other	3 (2.5)	0 (0.0)
Height (in cm)		
Mean ± SE	178.5 ± 0.72	179.4 ± 0.70
Weight (in kg)		
Mean ± SE	101.4 ± 1.68	101.7 ± 1.89
BMI (kg/m^2)[1]		
Mean ± SE	31.8 ± 0.47	31.5 ± 0.51

SE = Standard Error
Note: A few patients did not have values reported for some parameters, and thus the number of patients contributing to some descriptive statistics may vary.
[1]BMI was derived from the reported weight and height.

The population was characterized by a majority of patients who had been diagnosed with primary or secondary hypogonadism 2 to 7 years prior to entry into this study; thus, most patients in this study were not newly-diagnosed. This characteristic was consistent with the finding that 80% of patients in each treatment group had received prior TRT before enrolling into the study; thus, few patients were naïve to the effects of testosterone

Reviewer's Comment: *The demographics for the population sample for Part C were essentially the same as those in Part A, excepting the category of race where the percentage of Whites were 74.6%; Blacks, 12.3%; and Hispanics 10.8 %.*

Inclusion Criteria

1. Male with primary or secondary hypogonadism at least 18 years of age.
2. Morning screening serum testosterone concentration < 300 ng/dL.
3. If receiving other endocrine replacement hormones (e.g., thyroid), antihypertensives, lipid lowering agents, antidepressants or anxiolytic medications, the dose must be stable for least 28 days prior to entry OR is not currently on such medications.
4. Able to consent to participate by signing an Informed Consent Form following an explanation of the nature and purpose of this study.

Exclusion Criteria

1. Participation in another clinical trial within the 30 days preceding the first of the study drug.
2. Simultaneous participation in another clinical trial.
3. AUA Symptom Score ≥ 15.
4. Blood donation (including plasmapheresis) or blood loss of =500 mL in the last 30 before the beginning of the study or in the 30 days preceding a visit which includes a determination of serum hormone levels.
5. Prostatic symptoms, tumors or induration of the prostate or the male mammary gland including suspicion of cancer. In case of serum PSA levels ≥ 4 ng/mL or hyperplasia of prostate (size = 25 cm^3 as measured by transrectal ultrasonography), the investigator may include the respective patient if a carcinoma of the prostate has been ruled out (e.g., by biopsy).
6. Past or present liver tumors or acute or chronic hepatic disease with impairment of function; liver function tests (AST, ALT) exceeding 1.5 times upper limit of normal (normal range provided by central laboratory).
7. History of deep vein thrombosis in the past 5 years or any history of cerebrovascular accident.
8. Severe acne.
9. Serious psychiatric disease or uncontrolled medical illness, as suspected from medical history and/or the clinical examination.
10. Significant hypertension (systolic blood pressure >160 mmHg and diastolic >95 mmHg) or coronary heart disease not stabilized by therapy as assessed by the investigator.
11. Insulin-dependent diabetes mellitus or uncontrolled non-insulin-dependent diabetes mellitus.
12. Use of any sex hormones within 28 days (for injectable testosterone preparations) or 7 days (for oral, gel, patch testosterone preparations, etc.) prior to Screening serum testosterone collection for PK assessment, and at any time throughout the study.
13. Biochemical and/or hematological laboratory values outside the normal ranges, unless the investigator confirms that the deviations are of no clinical relevance.
14. Any chronic use of drugs and/or alcohol abuse.

15. Use of steroidal anabolic drugs or supplements (e.g., DHEA) by any application method within the 28-days prior to the first administration of the study drug and throughout the study (exclusive of the administered study drug).
16. Medication with substances which might interfere with testosterone metabolism within 28 days before the first administration of the study drug and throughout the study.
17. Use of anticoagulants (with the exception of low-dose aspirin) within 28 days before the first administration of the study drug and throughout the study.
18. Use of antiandrogens, estrogens, p450 enzyme inducers, barbiturates or antidepressant concomitant medication therapy.
19. Clinical history suggestive of allergy to Testosterone Undecanoate or to the excipients and/or severe intolerances, allergies or idiosyncrasies to other drugs.
20. History of sleep apnea.

Subject Discontinuation

If a subject was discontinued from the study prematurely, the Investigator was to select a reason for discontinuation on the End of Study Phase Status eCRF. In addition, every effort was made to complete the assessments listed under the End of Study visit.

Subjects withdrawn from the study were generally considered evaluable for statistical assessments, but may have been excluded from some assessments (e.g., PK) if insufficient data was present to warrant inclusion in the analysis.

The study protocols and amendments listed the following reason for why a subject may have been removed from the study:

• Adverse Event: If a subject experienced an adverse event that the subject found unacceptable or that, in the judgment of the Principal Investigator, Indevus Pharmaceuticals, Inc., or the Medical Monitor presented an unacceptable or risk to the subject , the subject may have been discontinued from further study.

• Administrative Discontinuation: After consultation with the Sponsor or Monitor, a subject may have been discontinued from the study for failure to comply protocol requirements. All instances of noncompliance must be documented eCRF.

• Refusal of Treatment: If for any reason the subject refused treatment during the study, the subject was to be discontinued from the study and the reasons for refusal documented on the eCRF. Reasonable efforts were to be made to monitor the adverse events following such discontinuation. Such efforts shall be documented in the eCRF.

Early Discontinuation Criteria

In the event a subject experienced any of the following events, or a significant change in status was detected by the investigator, the evaluation should have been repeated and if confirmed, the subject should have been terminated from the study:

1. Hemoglobin > 21.0 gm/dL

2. Uncontrolled hypertension, defined as blood pressure with systolic blood pressure and diastolic blood pressure ≥ 95

3. PSA > 4 ng/mL and ≤ 10 ng/mL, unless prostate cancer is ruled out by new testing

4. PSA > 10 ng/mL.

1.2 Efficacy Results from Pivotal Study Part A

The primary objective of this study was to evaluate the pharmacokinetics of Nebido 750 mg and 1000 mg given every 12 weeks, over the 12-week interval following the 4th injection (b) (4) Secondary objectives included the comparison of other serum hormone levels (including DHT, E2, and SHBG) to simultaneous levels of serum total T.

(b) (4)

(b) (4)

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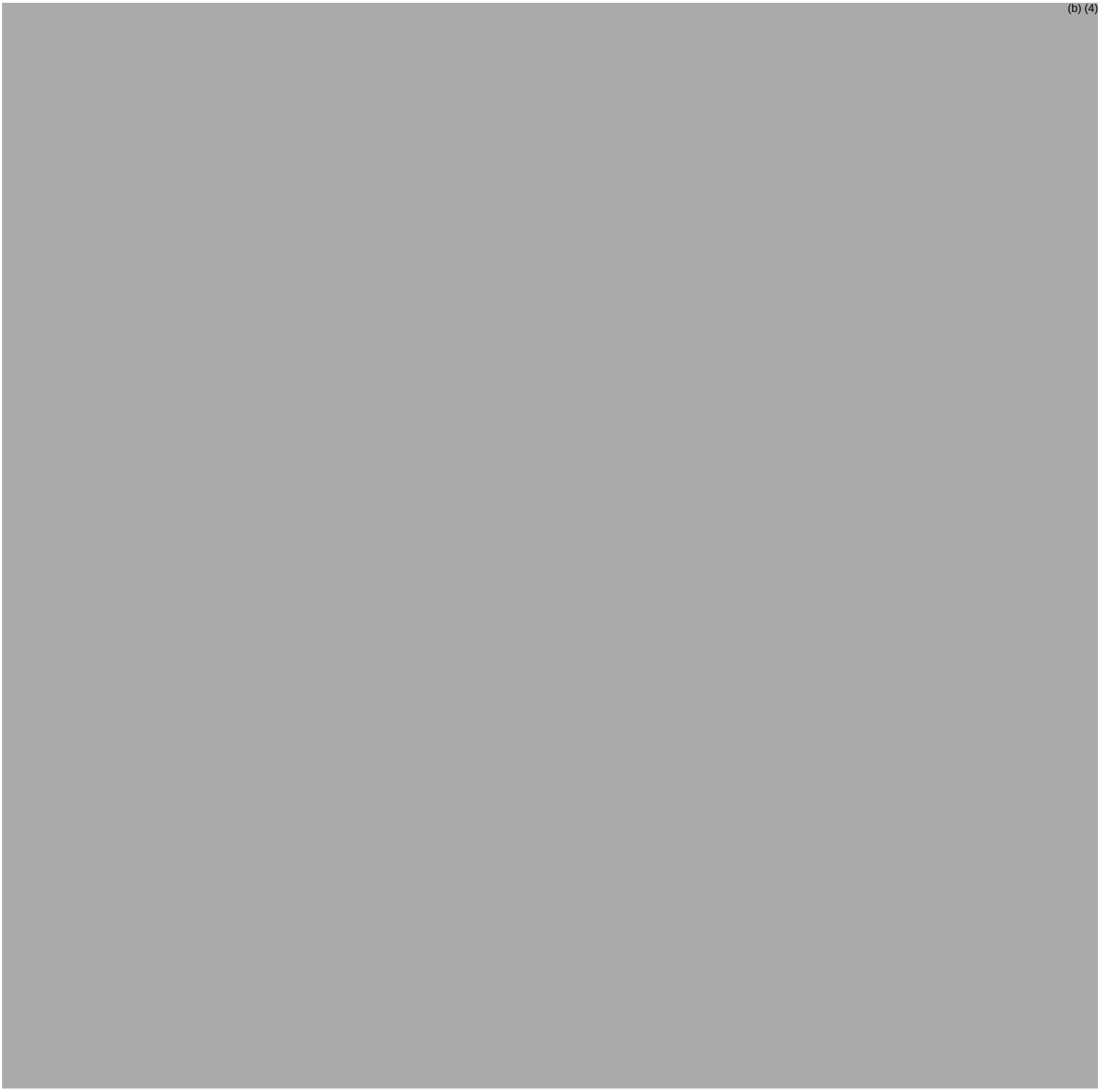
(b) (4)

1.3. Secondary Efficacy Results in Part A

(b) (4)



Secondary objectives included the comparison of other serum hormone levels to simultaneous levels of serum total T, which can be seen in Figures 2 (serum free T), 3 (serum DHT), 4 (estradiol), and 5 (sex hormone globulin binding globulin).

Figure 2.

Free Testosterone and Ratio of Free Testosterone to Total Testosterone Following the 1st and 4th Injections

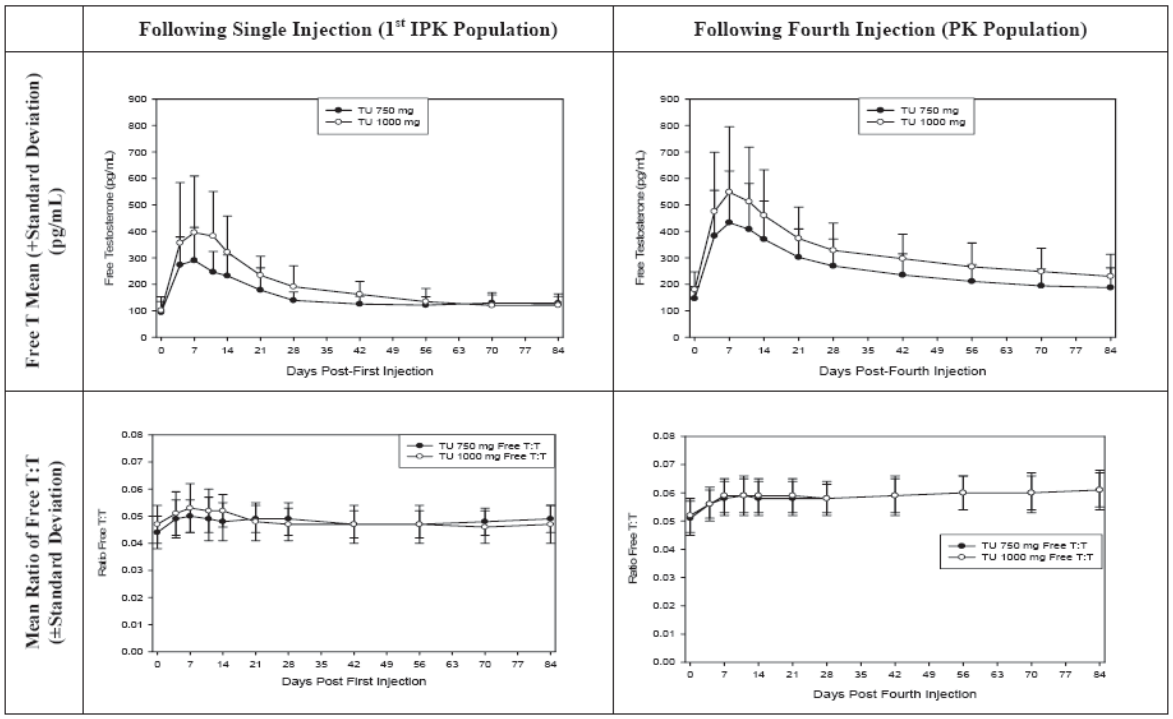


Figure 3.

Dihydrotestosterone and Ratio of Dihydrotestosterone to Total Testosterone Following the 1st and 4th Injections

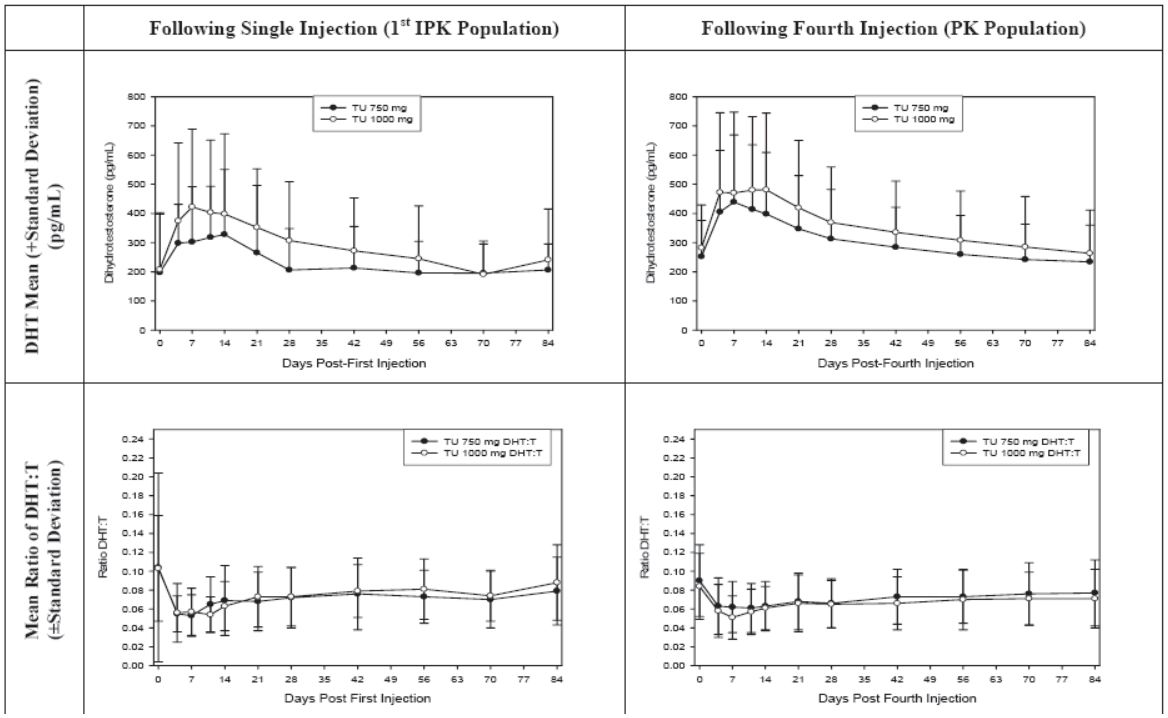


Figure 4. Estradiol and Ratio of Estradiol to Total Testosterone Following the 1st and 4th Injections of TU

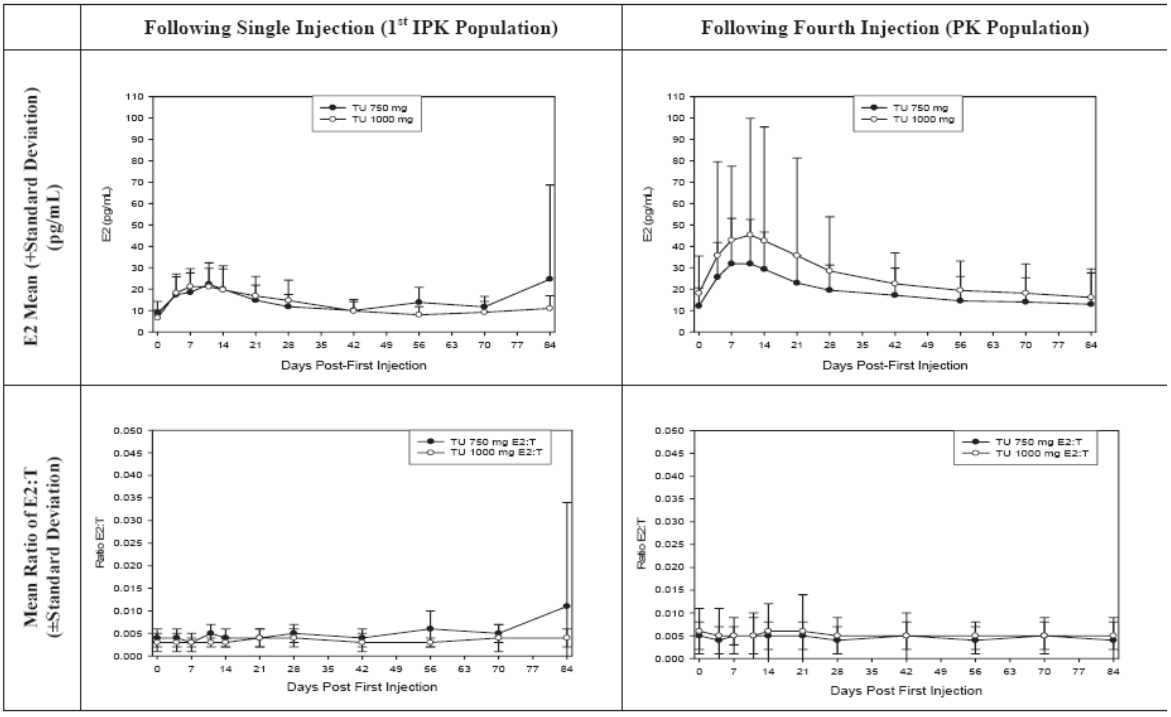
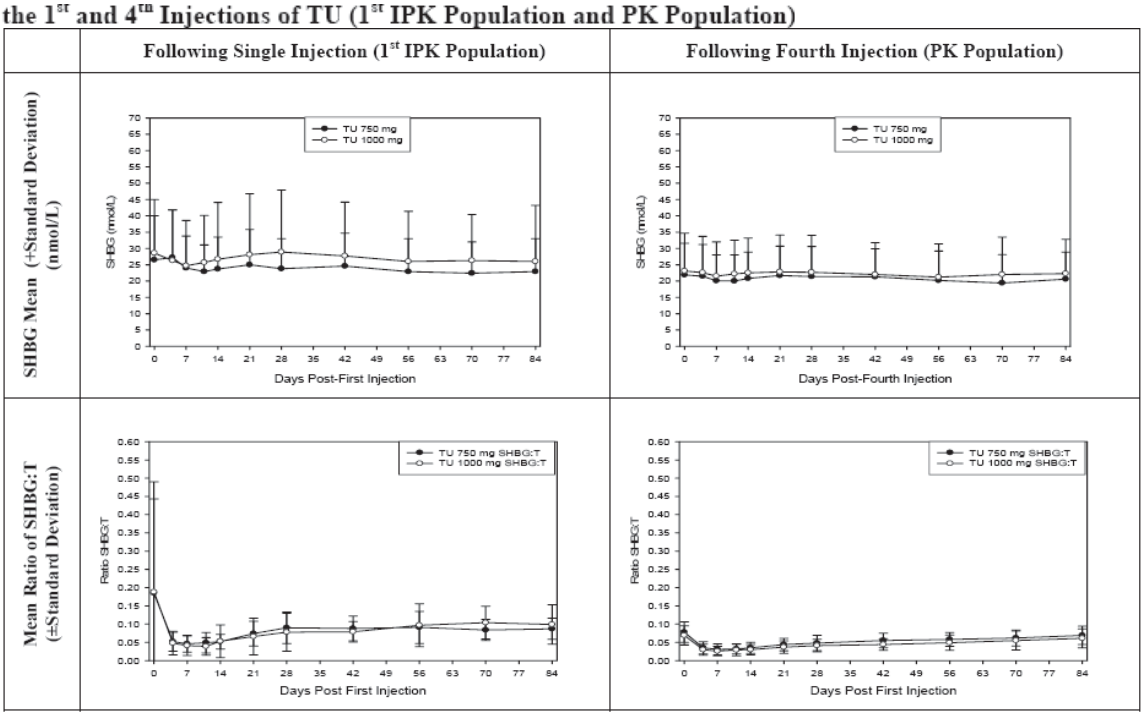


Figure 5.

Sex Hormone Binding Globulin and Ratio of Sex Hormone Binding Globulin to Total Testosterone Following the 1st and 4tn Injections of TU (1st IPK Population and PK Population)

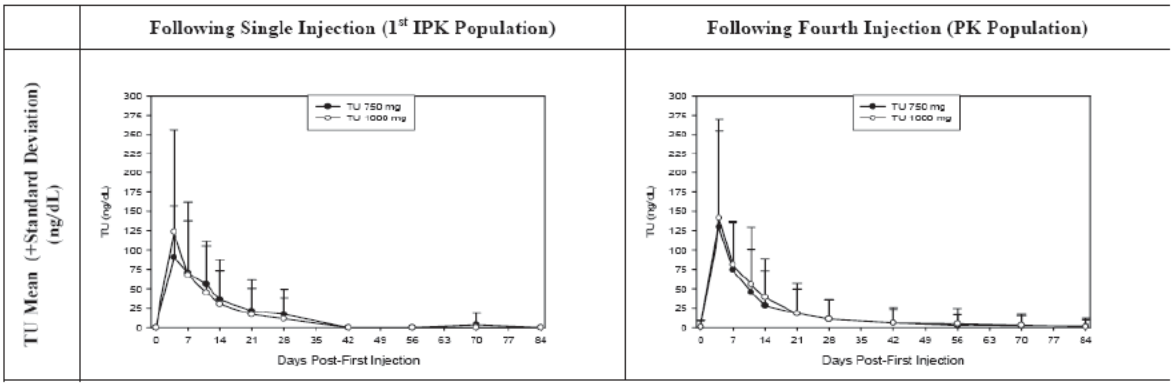


These figures demonstrate acceptable levels of serum free T, DHT, estradiol and SHBG, and acceptable ratios for DHT:T and estradiol:T for both dose regimens.

TU and DHTU concentrations over time were also assessed. However, excepting for a few samples, levels of DHTU were below the limit of quantification of the assay, making this analysis inappropriate. Figure 6 provides 2 plots summarizing the concentrations of TU during the 1st and 4th injection intervals.

Figure 6.

Testosterone Undecanoate Following the 1st and 4th Injections of TU (1st IPK Population and PK Population)



Reviewer's Comments: (b) (4) [redacted]

2. Pivotal Study Part C

The primary objective of this study was to evaluate the pharmacokinetics of Nebido 750 mg given at baseline, at 4 weeks, and every 10 weeks, over the 10-week interval following the 3rd injection. This dose schedule is referred to as the 750mg Loading Regimen,

Secondary objectives included the comparison of other serum hormone levels (including DHT, E2, and SHBG) to simultaneous levels of serum total T over the 3rd injection interval.

Figure 7 provides the steady-state group-mean concentration-time profile for T following the 3rd injection of Nebido 750 mg given with the loading injection.

2.1 Primary Efficacy Results from Part C – 750mg Loading Regimen

Figure 7. Steady-state group-mean concentration-time profile for T following the 3rd injection of Nebido 750 mg Loading Regimen

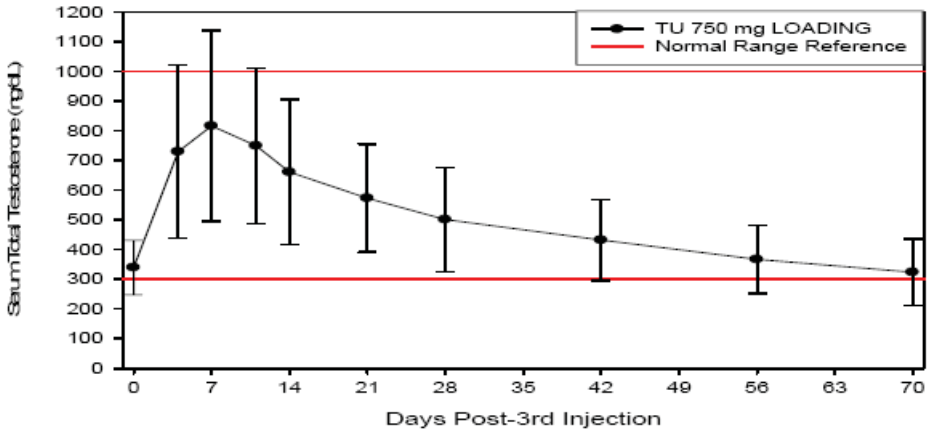


Table 7 presents a summary of PK parameters during the 3rd injection interval.

Table 7. Summary of PK parameters during the 3rd injection interval of the 750mg Loading Regimen.

TU Dose	Pharmacokinetic Parameter	Number Patients	Mean	Standard Deviation	Minimum	Median	Maximum	CV (%)	Geometric Mean
TU 750 mg LOADING	$AUC_{(0-70)}$ (days*ng/dl)	117	34645.6	9902.45	13755.1	33342.2	70016.9	28.6	33263.6
	C_{Trough} (Day 70)	117	323.5	99.11	138.2	316.9	611.1	30.6	309.0
	C_{max} (ng/dL)	117	890.6	345.11	311.0	813.6	1758.5	38.8	826.8
	Dose-normalized C_{max}(ng/dL)[1]	117	1.2	0.46	0.4	1.1	2.3	38.8	1.1
	T_{Last} (days)	117	70.0	0.00	70.0	70.0	70.0	0.0	70.0
	T_{max} (days)	117	10.0	7.11	4.0	7.0	42.0	71.1	8.4
	Dose-normalized $AUC_{(0-70)}$ (days*ng/dl)[1]	117	46.2	13.20	18.3	44.5	93.4	28.6	44.4
	$C_{avg, 0-70}$ (ng/dL)[2]	117	494.9	141.46	196.5	476.3	1000.2	28.6	475.2

Reviewer's Comment: *When compared with outcomes from Part A, treatment with the Nebido loading dose regimen provided Cavg and Cmax estimates* (b) (4) *The levels achieved with the 750mg Loading Regimen are acceptable.*

Table 8 provides a summary of selected secondary efficacy outcome results during the 3rd injection interval. This table includes the Division's pre-defined safety criteria for Cmax.

Table 8. Summary of selected secondary efficacy outcome results during the 3rd injection interval for the 750mg Loading Regimen

Secondary Outcome Parameter	TU 750 mg LOADING (N=117)
Number Patients with C_{avg} < 300, 300 - 1000, > 1000 ng/dL	
<300 ng/dL	6 (5.1)
300 to 1000 ng/dL	110 (94.0)
>1000 ng/dL	1 (0.9)
Number Patients with C_{avg} ≥ 300 ng/dL	
<300 ng/dL	6 (5.1)
≥300 ng/dL	111 (94.9)
Number Patients with at least one serum total testosterone below 300 ng/dL	
At least one concentration < 300 ng/dL	61 (52.1)
No concentration < 300 ng/dL	56 (47.9)
Number Patients with C_{max} ≤1500, > 1500 - < 1800, 1800 - <2500, ≥ 2500 ng/dL	
≤ 1500 ng/dL	108 (92.3)
> 1500 - < 1800 ng/dL	9 (7.7)
1800 - <2500 ng/dL	0 (0.0)
≥ 2500 ng/dL	0 (0.0)
Number Patients with at least one serum total testosterone > 1000 ng/dL	
At least one T concentration > 1000 ng/dL	35 (29.9)
No T concentration > 1000 ng/dL	82 (70.1)

Figure 8 provides a presentation of the mean T concentrations at each trough time point - demonstrating that steady state was achieved as early as Week 4 and definitely by the 3rd dosing interval for the 750mg Loading Regimen, which was the pre-determined timepoint of interest for the primary endpoints.

Figure 8. Mean T concentrations at each trough time point in Part C – 750mg Loading Regimen

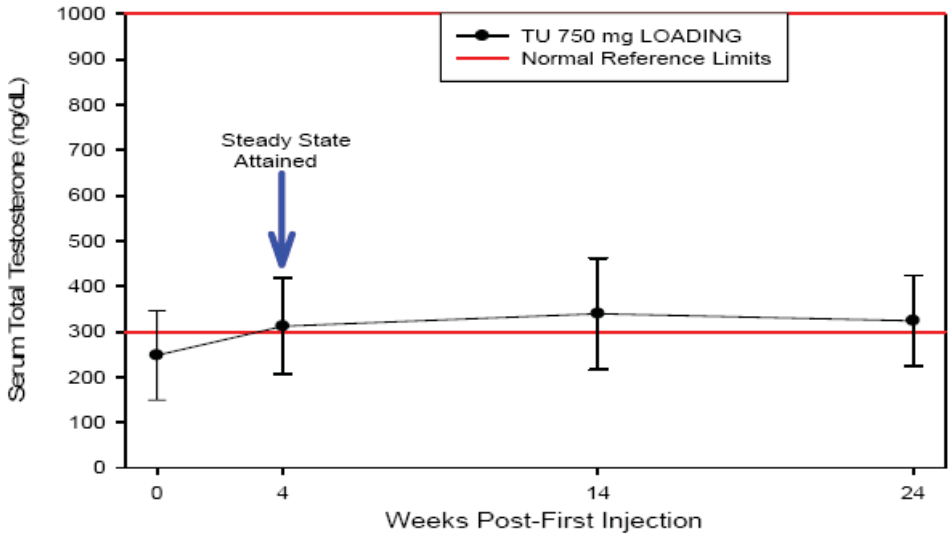


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Table 9 presents a summary of C_{max} assessments of T concentrations during the 3rd injection interval in Part C.

Table 9. Summary of Cmax assessments of T concentrations during the 3rd injection interval in Part C – 750mg Loading Regimen

	Number of Patients Exceeding/Number of Patients Assessed (Percent of Patients Exceeding)
C_{max} Outcome	**TU 750 mg LOADING (N=117)**
> 1500 ng/dL[1]	9 of 117 (7.7%)
≥ 1800 ng/dL and < 2500 ng/dL	0 of 117 (0%)
≥ 2500 ng/dL	0 of 117 (0%)
Did Dose Meet Threshold Limits?	**Yes**

2.2. Secondary Efficacy Outcomes in Part C – 750mg Loading Regimen:

The Sponsor summarized the results of secondary efficacy assessments as follows:

Secondary efficacy objectives included the assessment of clinical markers related to changes in T concentrations, ie, changes in body weight and patient satisfaction with the treatment. Objectives also included the study of changes in clinical laboratory parameters as related to changes in T, specifically outcomes related to erythropoiesis, lipids, and hormones.

Average changes from pre-treatment to on-treatment in both hematocrit and hemoglobin as they related to changes in T concentrations over time were as expected for a TRT. Erythropoiesis outcomes demonstrated that:

- Average values of hemoglobin and hematocrit increased slightly from pre-treatment to Week 24 as average T concentrations increased; however, the average increases in these erythropoietic markers were small in magnitude and well within the normal range.
- Slight changes from pre-treatment in hemoglobin or hematocrit were seen at the Week 24 time point.

Hemoglobin and hematocrit demonstrated low variability across treatments and visits, and thus were relatively stable during the treatment period.

Lipid changes were as expected, with minor changes in the parameters from pre-treatment to the Week 24 time point.

Average changes from pre-treatment to on-treatment in hormones as they related to changes in T concentrations over time were as expected for a TRT. Hormone outcomes were marked by:

- Average Free T concentrations closely paralleled T concentrations and tended to remain within or above the normal range. Mean ratios of Free T:T remained relatively constant throughout.
- Average DHT concentrations closely paralleled T concentrations and tended to remain within the lower end of the normal range. Mean ratios of DHT:T remained relatively constant.
- Average E2 concentrations closely paralleled T concentrations and tended to remain within the middle of the normal range. Mean ratios of E2:T remained relatively constant. The average on-treatment ratios remained similar to the average pre-treatment ratios.
- Average SHBG concentrations remained constant and tended to remain within the middle of the normal range. Mean ratios of SHBG:T tended to drop immediately following the injection (at the Day 4 time point); this was due to changes in T concentrations (and not changes in SHBG concentrations).

Outcomes from the patient assessment of satisfaction are summarized as follows:

- As collected via the M-PGA, the majority of patients had improvements in confidence/self esteem, moods/behavior, satisfaction with performance, feeling of well-being, and were satisfied with the treatment.
- Over 92% of patients expressed satisfaction with treatment with TU.
    - In this study population of hypogonadal men (62% of whom had used prior TRT before entering this study), satisfaction with treatment with TU was very high.

There were no notable changes in body weight or BMI in this study.

The reviewer analyzed the data in support of these conclusions relevant to the secondary efficacy parameters in Part C and is in agreement with Sponsor.

3. Overall Efficacy Conclusions

The Sponsor summarized the efficacy results from Part C as follows:

The TU 750 mg LOADING regimen (TU 750 mg given with a 4-week loading injection and every 10 weeks thereafter) was found to provide adequate TRT (as measured by T C_{avg}) while not providing excessive TRT (as measured by C_{max}). The dosing regimen demonstrated a C_{avg} within the normal range and a C_{max} profile that did not exceed the approvability thresholds provided. Thus, the primary objectives of this study were met. And finally, though importantly, the vast majority of patients expressed satisfaction with the treatment.

The reviewer is in agreement with Sponsor's efficacy conclusion for the results of Part C. The 750mg Loading Regimen was shown to provide adequate testosterone replacement at steady-state (as measured by Cavg) without providing excessive testosterone (as measured by Cmax).

(b) (4)

[redacted]

(b) (4) Part C TU 750 mg loading regimen was clearly demonstrated to have reached steady state by the 2nd injection. Thus, treatment with TU 750 mg loading regimen resulted in attainment of steady state (b) (4)

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III. Integrated Summary of Safety (ISS)

A. Brief Statement of Conclusions

Both phase-3 pivotal studies were adequate and well-controlled. When data from these studies are combined with data from the previous European experience, this NDA contains substantial evidence to assess safety. The safety data is derived from monitoring adverse events, clinical laboratory tests, vital signs, physical examination, ECGs, PSA, and prostate volume. In general, treatment with Nebido was associated with adverse events and laboratory changes expected for a testosterone replacement agent. However, there were reports of "coughing fits" immediately following injection in the clinical trials (n=2) and in the postmarketing experience in Europe (n=66). These adverse reactions pose a serious and unresolved safety concern.

Prior to the Sponsor's submission of data for Part C, a total of 422 hypogonadal patients were treated in the Nebido drug development program, and there was 1 patient in whom an "immediate post-injection reaction" was reported. This case occurred in a European supporting study and was reported in the Clinical Summary of Safety in the original NDA. This 54 year old male received his 10th injection of Nebido on 3 April 2006 and shortly (1 minute) after the injection, the patient "experienced urge to cough associated with **respiratory distress**". Both symptoms lasted approximately 14-15 minutes. The event resolved without intervention and the subject continued in the study. The investigator and Sponsor both attributed the event to "pulmonary lipid microembolism" and cited the following possible reason: either too fast administration of the study drug or accidental intravascular placement of the study drug.

Upon submission of an amendment to the NDA containing the data from another 117 patients who participated in the second pivotal study (Part C), the Division learned of one additional patient who experienced an "immediate post-injection reaction". This 53 year old white male received his 3rd injection on 12 July 2007 and experienced a "mild and not serious **coughing fit** lasting 10 minutes following the injection." The narrative describes the cough as not productive and the patient had no wheezing and no difficulty breathing. No intervention was given and the patient continued Nebido therapy without subsequent coughing event.

In addition to these 2 "coughing fit" cases, the Clinical Summary of Safety in the original NDA contained six (6) cases of "immediate post-injection reactions" reported during the previous 7 months of post-marketing use of Nebido in Europe. The 120-Day Safety Update contained an additional four (4) cases reported in the previous 4 month of post-marketing use in Europe. Based upon the 2 cases reported in clinical trials and the 10 known cases from the post-marketing experience, the Division made request to Sponsor to submit all known cases of "coughing fits" following injection of Nebido, and in response, the Sponsor provided CIOMS reports for a total of **66 individual cases** reported in the post-marketing period.

Table ISS.A below summarizes the six CIOMS reports of "post-injection reaction" for the period between November 25, 2006 and June 30, 2007 – as submitted in the Clinical Summary of Safety of the original NDA

Table ISS.A. CIOMS reports for the period between November 25, 2006 and June 30, 2007 (as submitted in the original NDA).

Case Number	Event onset date	AE Term(s)	Time to onset (from injection)	Time to worse symptom level	Treatment given	Injection Number	Outcome	Comment
DE-2007-004747	8-Dec-06	Dyspnea, cough, cyanosis	3 minutes	Unk	None listed	Unk - first dose Jan 2005	Resolved	Dyspnea and cyanosis lasted 20 minutes
GB-2007-000740	(b) (6)	Anaphylactic reaction, laryngeal edema, respiratory arrest, dyspnoea, cough, throat irritation, hyperhidrosis	Halfway through injection	Progressively worse - transferred to hospital	Adrenaline and oxygen	2nd injection	Resolved	Physician stated that possible some Nebido may have gone IV and into circulation
BR-2007-005496	5-Feb-07	Anaphylactic shock, malaise, dyspnea	Immediately	30 minutes	Corticosteroids	First injection	Resolved	
BR-2007-010933	Unk-Jan-07	Syncope	After injecting 3 of 4ml TU	Immediately	None listed	3rd injection	Resolved	States that pt. Recovered and received the 1mL remainder.
AU-2007-014016	Unk[1]	Suspected allergic type reaction – Hypersensitivity, cough, chills	Shortly after injection of Reandron (TU)	Unk	Prednisolone and oxygen	2nd injection	Resolved	
GB-2007-023826	Unk[1]	Anaphylactic shock, respiratory distress, T-wave inversion, cough	Unk	Unk	Epinephrine and chlorphenamine maleate	2nd injection	Unk	

Unk=Unknown.
Case number based on CIOMS reporting system from Bayer Schering Pharma.
[1]Minimal information is available for these events, as they were only recently reported.

Table ISS.B below shows the four CIOMS reports of "post-injection reaction" for the period between June 30, 2007 and October 12, 2007 – as submitted in the 120-Day Safety Update to the NDA.

Table ISS.B. CIOMS reports for the period between June 30, 2007 and October 12, 2007 (as submitted in the 120-Day Safety Update).

Case Number	Event Term(s) Verbatim	Onset Date	Relatedness to Nebido	Initial Report	Follow-up Report(s)
DE-2007-023890	Anaphylactic reaction	(b) (6)	possible	4-Jul-2007	13-Jul-2007, 11-Sep-2007
CO-2007-025007	Cardiac failure	unk	possible/unlikely	13-Jul-2007	18-Jul-2007
BR-2007-028116	Retinal detachment	unk-Jun-2007	none	1-Aug-2007	7-Sep-2007
AU-2007-029476	Lymphoedema	8-Aug-2007	none	14-Aug-2007	
DE-2007-030464	Dyspnea, cough, laryngospasm	(b) (6)	possible	20-Aug-2007	
RU-2007-031850	PSA level increased	26-Jun-2007	unclassifiable	28-Aug-2007	3-Sep-2007
AT-2007-035468	Anaphylactic reaction, retching, throat irritation	13-Jun-2007	possible	25-Sep-2007	
ID-2007-032962	Tooth disorder	13-Aug-2007	none	7-Sep-2007	
ZA-2007-035469	Bronchospasm	(b) (6)	certain/unclassifiable	24-Sep-2007	
The lymphoedema and the tooth disorder were considered serious events; no other event was considered serious.					

The CIOMS reports in the 120-Safety Update, containing 4 events possibly related to pulmonary oil microembolism (POME), coupled with the 8 previously identified cases (2 in clinical trials and 6 in the post-marketing period), raised serious concerns regarding the risk/benefit ratio for the use of this product in the intended population.

As previously stated, the Sponsor was contacted on January 15, 2008 about this unresolved concern. A discussion was held in regard to possible etiologies for the immediate post-injection reactions and number of total cases known to Sponsor. The Sponsor was aware of additional cases reported to CIOMS during the post-marketing period in Europe and they agreed to forward all the case narratives for review by FDA.

On February 12, 2008, the Sponsor submitted a 28-page report entitled "I*mmediate Post-Injection Reactions Suspect of Pulmonary Oil Microembolism*". The report identified a total of **66 cases suspect of these reactions** from April 2004 to January 18, 2007. Of these, 28 cases (42%) were reported as serious adverse events. Although there were no deaths in the combined post-marketing and clinical trial experience, review of the CIOMS forms submitted by Sponsor indicated that emergency medical care was provided or hospitalization occurred in 12 patients (18 %).

Herein are provided brief narratives for 24 of these events. These cases were selected based upon the seriousness of the event, including need for emergency medical care and/or hospitalization:

1. (AT-2006-020143) A 51 year old male experienced **very severe irritative cough and dyspnea** beginning during the intramuscular injection of Nebido. Cough resolved in 5 minutes and dyspnea persisted for 2 days.

2. (DE-2005-011567) A 48 year old male experienced "**hypersensitivity reaction certainly to castor oil**" described as dizziness, headaches, palpitation, vertigo, lump in throat, and tachycardia at an unspecified time after his second and third doses of Nebido. The reaction lasted 3 weeks. Tachycardia, palpitations and lump in throat resolved in 5 hours. The patient had a past history of "atopy" and reported similar events following treatment with Testoviron-Depot (containing castor oil).

3. (DE-2005-019516) A male (unknown age) experienced 3 hours of **cough and dyspnea** after the Nebido injection.

4. (DE-2006-002815) A 15 year old male experienced extremely s**evere urge to cough, retrosternal pain, mild dyspnea, eye redness, tachycardia and chest pain** immediately after Nebido injection. He was treated with antihistamine and steroid (Solu-DecaCortin H).

5. (DK-2006-002013) A male (unknown age) experienced "**massive coughing fit**" 1 minute after Nebido injection lasting 1 hour – described as irritating hacking cough.

6. (20071127BNE) A male (unknown age) experienced **immediate coughing, unable to catch breath, "collapse", severe dyspnea, burning sensation in mouth and chest** upon Nebido injection (given by wife). Patient was hospitalized for 2 days and recovered. No reaction to subsequent Nebido when given by clinic nurse.

7. (200718455GPV) A 68 year old male experienced "**allergic reaction**" including sensation of **numbness of mouth, tingling sensation mouth and lips ("paresthesias"**) during his 6th Nebido injection. Patient treated with H1 and H2 blockers. The complaints resolved after 6 hours.

8. (AT-2007-035468) A 46 year old male experienced "**anaphylactic reaction**" including "**gagging", "tickle in throat**" 30 seconds after administration of his 7th dose of Nebido. Patient was given an oral antihistamine and recovered within 15 minutes.

9. (AU-2007-014016) A male (unknown age) experienced "s**uspected allergic type reaction to the excipient (i.e. the oil)**" including **severe coughing and shivering** during the 3rd Nebido injection. Patient was treated with oxygen, antihistamine, and prednisone and all symptoms subsided.

10. (BR-2007-005496) A 57 year old male experienced **"anaphylactic shock" including "glottis edema", "breathlessness" and "malaise"** immediately after injection. Breathlessness became worse 30 minutes after injection. He was treated with corticosteroids and was "ventilated in the drug store".

11. (BR-2007-010933) A male (unknown age) experienced "**fainted during injection**" with "**loss of consciousness for several minutes**". The reporter suspected possible intravenous injection. A similar injection 6 months earlier was well tolerated.

12. (DE-2005-004016) A male (unknown age) experienced "**circulatory collapse, nausea, cough, several minutes unconsciousness and encopresis**" approximately 15 seconds after his 2nd dose of Nebido. The patient subsequently recovered.

13. (DE-2005-009-283) A 54 year old male with "suspected fat microembolism" described as "**cough, red head, sweating attacks, trembling, dizziness, increased blood pressure, and dizziness**" immediately after injection of 1st dose. Patient had previously tolerated Testosteron-Depot. Symptoms lasted longer than 20 minutes and patient was hospitalized. He was treated with cortisone and antihistamines and discharged home the same evening.

14. (DE-2006-00398) A 42 year old male experienced "**idiosyncratic drug reaction possible oily microembolism**" including **1-2 minutes of apnea, hot flush, paresthesias in area of mouth and head, dyspnea and cough** 3 minutes after his 4th Nebido injection. Patient recovered after 10 minutes.

15. (DE-2007-004747) A 74 year old male experienced "**pronounced urge to cough", "dyspnea" and "20 minutes of cyanosis**" at 3 minutes after "slow injection" of Nebido. The event was described as "life-threatening". Nebido had been previously well-tolerated.

16. (DE-2007-023890) A 57 year old male experienced "**suspected anaphylactoid reaction, possible oil microembolism**" including **dizziness, tingling sensation upper part of abdomen, hands and feet, weakness, pressure in head, headache, numbness sensation in fingers and toes** after first dose of Nebido. Injection site was described as hot, hard, red and sensitive to pressure. Patient was treated with antihistamines and prednisolone and taken to emergency unit where symptoms persisted.

17. (DE-2007-00464) A 47 year old male experienced "**laryngospasm", "severe dyspnea" and cough** during 2nd Nebido injection. An emergency physician was called, however the patient recovered after a few minutes. The patient has a "cough reaction" to previous Nebido injection.

18. (GB-2006-006197) A 67 year old male experienced "**acute anaphylactic reaction" including tightness in throat and coughing fit** "minutes" after his 2nd injection. He was treated with epinephrine and chlorpheniramine. The event was considered life-threatening and involved hospitalization.

19. (GB-2007-000740) A 54 year old male experienced "**anaphylactic reaction, including acute laryngeal edema, and near respiratory arrest**", half-way through his 2nd Nebido injection. Patient began coughing, had tickle in throat, and the reaction worsened. He became sweaty, had trouble breathing, was given adrenaline and oxygen and was hospitalized.

20. (GB-2007-023826) A 46 year old male experienced "**anaphylactic shock" including respiratory distress, coughing fit, T wave inversions, tightening of the throat, respiratory wheeze, rash on abdomen, itchy scalp, and raised blotches across the chest**. Symptoms began during his 2nd Nebido injection. He was treated with

adrenaline, chlorpheniramine and oxygen, and his symptoms cleared upon arrival at the emergency room.

21. (SE-2006-014505) A 44 year old male experienced "**burning pain lower sternum going up to the chin" and dyspnea** during the 3rd Nebido injection. The administration was discontinued, symptoms lasted 2-3 minutes, and the patient was hospitalized.

22. (SE-2006-01516) A 47 year old male experienced "**angioedema" including swollen throat, palpitations, difficulty breathing, cough and swelling of the neck** immediately after his 2nd Nebido injection. The report describes an event of "**serious swollen throat" and "non-serious palpitations**" after his 1st Nebido injection.

23. (SE-2006-02230) A 38 year old male experienced "**angioedema", pruritis, malaise, "swelling around the eyes", and itching in the throat** after the 1st Nebido injection. Solu-Cortef and antihistamine were administered and the patient was discharged after a few hours observation.

24. (ZA-2007-035469) A 29 year old male experienced "**life-threatening bronchospasm" and tachycardia, became hypotensive and collapsed** within minutes after receiving Nebido. He received emergency medical care with nebulized epinephrine and recovered from the bronchospasm.

An additional case was reported on 29 February 2008 (200812947GPV) in which a 38 year old male received Nebido twice. He experienced a "**mild allergic reaction**" following the 1st Nebido injection. Six months later a 2nd Nebido injection was administered in hospital and the patient experienced a **"severe allergic reaction" including "severe throat swelling and potential heart failure"**. The patient recovered shortly thereafter.

In summary, in the Nebido clinical trial experience involving approximately 600 subjects (and more than 4000 injections) there were 2 post-injection cough reactions reported (0.3 %). For the post-marketing experience, Sponsor focused on the most recent 2 year period which they state includes more than 85% of all exposure to Nebido worldwide. According to the Sponsor, based solely on the number of Nebido units sold, the reporting of "post-injection cough reactions" was approximately 1/12,000 injections in 2006, and 1/15,000 injections in 2007. Therefore, there is an extremely wide discrepancy in the incidence and severity of cough reactions as reported by Sponsor ("rare and self-limiting") versus what was observed in clinical trials. In the reviewer's opinion, the clinical trial data demonstrates an incidence that is neither rare, nor is the event uniformly self-limiting or medically not serious. Serious and non-serious post-injection reactions had been observed with Nebido. Although there were no deaths in the clinical trials or in the postmarketing experience, many of the 28 serious cases manifested life-threatening signs and symptoms, requiring emergency medical care and/or hospitalization.

In terms of etiology, the Sponsor continues to believe that most, perhaps all, these events are related to pulmonary oil microembolism (POME) and may be reduced in incidence or severity by lowering the injection volume (to 3 mL) and by careful, slow intramuscular injection. However, the Sponsor acknowledged that data to support these hypotheses are not yet available. In addition, we continue to believe that at least a subset of these cases

reported as POME showed signs and symptoms suggestive of severe allergic reaction, which would not be resolved by reduction in dose from 4 cc to 3cc, nor by slower injection.

At this time, the available information suggests that this product should not be approved and this reviewer believes that additional research is necessary in the pre-marketing phase to further evaluate and satisfactorily resolve this safety issue. Some pathways for resolving the issue might include: change in vehicle, further lowering the dose, and lowering the volume.

A consultation from the Division of Pulmonary and Allergy Products (DPAP) concluded:

Adverse events characterized by sudden onset of cough, dyspnea, and respiratory distress occurring shortly after injection were noted in clinical trials and post-marketing spontaneous adverse event reports for Nebido. Of 66 cases submitted by the sponsor, DPAP concluded that two met recently proposed diagnostic criteria for anaphylaxis (cases #20 and #24 in the preceding list above). Most of the remaining cases were consistent with pulmonary oil microembolism (POME), a short-lasting reaction due to the direct vascular or lymphovascular delivery of oil-based preparations.

DPAP noted that the decision to approve the product would be a risk versus benefit decision, and should be made in light of the degree of efficacy, the seriousness of the indication, the availability of alternative products for that indication, and the extent of the safety data.

DPAP strongly believed that post-marketing cases of anaphylaxis had been reported for Nebido – that these cases met the currently accepted criteria for definition of anaphylaxis. Further, DPAP noted that IgE-mediated sensitivity to castor bean allergen in castor bean extract and castor wax extract had been reported in patients with occupational hypersensitivity to castor beans. Anaphylaxis had also been reported with use of polyethoxylated castor oil (Cremophor EL) when used as a solubilizing vehicle for various drugs.

Therefore, after considerable internal discussion, DPAP expressed the opinion that it would be appropriate to characterize the frequency of these events prior to, not after, approval. DPAP stated that the product is currently approved and marketed in Europe so it would be reasonable and appropriate to conduct these studies abroad prior to considering the product for approval in the United States. In addition, DPAP stated that given the unclear mechanism of these reactions, they would also recommended consideration be given to advising Sponsor to characterize the nature of the anaphylaxis events. DPAP stated that establishing the mechanism of these allergic reactions could help to make a decision on the approvability of the drug more scientific and rational. DPAP recommended that DRUP consider asking the Sponsor to develop an in vitro test for specific IgE and IgG antibody to the drug, both active and excipient ingredients, and to evaluate the presence of antibodies in patients who have had anaphylaxis events associated with the drug, those who have been exposed to the drug but who have not had anaphylaxis, as well as unexposed controls. In addition, DPAP recommended that the Sponsor develop a skin testing procedure to the product and its excipients to evaluate the same populations to be studied with in vitro testing.

Taken together, the information and recommendation from the DPAP consult and subsequent DPAP addendum support the reviewer's decision that additional research and information is needed in the pre-marketing phase to inform and manage this unresolved safety concern. These post-marketing adverse events, including 66 reports of immediate post-injection reactions, some of which were life-threatening, pose a serious unresolved safety concern for the risks associated with use of this product.

B. Method of Safety Review

1. Review of the proposed indication, study protocols, regulatory and scientific background.
2. Review of the pivotal and supporting studies.
3. A detailed review of safety parameters.
4. Generate safety conclusions from the available data.
5. Review of the post-marketing experience.
6. Review of the consultations from the Division of Pulmonary and Allergy Drug Products.

C. List of Controlled Studies Assessing Safety Variables

IP57-001 Parts A and C - Phase-3 Pivotal studies
ME97029 - a Phase-3 Supporting study

D. Summarized Safety Results from the Controlled Studies

D.I Summarized Safety Results from Study IP157-001 Part A

1.0 Extent of Exposure and Overall Adverse Events in Part A

In Part A, exposure to TU averaged approximately 375 days in both treatment groups; over 80% of patients in each group received 5 injections, and thus patients were exposed to treatment with TU for over a year. However, consistent with the study design, safety outcomes in this study report reflect an actual median follow-up period of 334 days (47.7 weeks) for each treatment group.

• The planned duration of exposure to study medication was calculated as number of days from first injection to the last injection, plus 84 days. For most patients, the last injection was the 5th injection (48 weeks following the first injection). Exposure to TU would have been derived as 60 weeks.

• Exposure as measured by the duration of safety follow-up was calculated as through the 5th injection visit, and is limited to approximately 48 weeks. Procedures employed in this study to evaluate safety included prostate health assessment via the measurement of PSA and performance of digital rectal examinations. Further, laboratory measurements and urological data (e.g., via the AUA scale) were collected every 6 months; lipid profiles were collected every 12 weeks; and monitoring of adverse events was performed in an ongoing manner throughout the course of the study. Very few serious events were reported.

Table 10 summarizes treatment-emergent-adverse-events (TEAEs) reported in at least 2 % of subjects in both groups irrespective of relationship to study medication, by preferred term in decreasing order based on incidence rates in the TU 1000 group.

Table 10.

Incidence of All TEAEs Regardless of Relationship Reported in at Least 2.0% of Patients in Either Treatment Group by Preferred Term in Decreasing Frequency in TU 1000 mg arm – Total Patient Sample (Study IP157-001 Part A Stage 1)

MedDRA Preferred term	Number of patients (%)	
	TU 750 (N=120)	TU 1000 (N=117)
Total patients with at least 1 TEAE	70 (58.3)	73 (62.4)
Upper respiratory tract infection	5 (4.2)	5 (4.3)
Diarrhoea	2 (1.7)	5 (4.3)
Pain in extremity	2 (1.7)	4 (3.4)
Nasopharyngitis	5 (4.2)	4 (3.4)
Hypertension	3 (2.5)	4 (3.4)
Sinusitis	3 (2.5)	4 (3.4)
Insomnia	3 (2.5)	4 (3.4)
Headache	2 (1.7)	4 (3.4)
Depression	2 (1.7)	4 (3.4)
Weight increased	3 (2.5)	4 (3.4)
Procedural pain	0 (0.0)	3 (2.6)
Arthralgia	2 (1.7)	3 (2.6)
Musculoskeletal pain	1 (0.8)	3 (2.6)
Urinary tract infection	3 (2.5)	3 (2.6)
Rash	1 (0.8)	3 (2.6)
Pain	0 (0.0)	3 (2.6)
Foot fracture	0 (0.0)	3 (2.6)
Muscle strain	0 (0.0)	3 (2.6)
Anxiety	0 (0.0)	3 (2.6)
Nasal congestion	0 (0.0)	3 (2.6)
Abdominal pain	0 (0.0)	3 (2.6)
Constipation	0 (0.0)	3 (2.6)
Vomiting	1 (0.8)	3 (2.6)
Gout	0 (0.0)	3 (2.6)
Benign prostatic hyperplasia	2 (1.7)	3 (2.6)
Cough	1 (0.8)	3 (2.6)
Fatigue	7 (5.8)	2 (1.7)
Bronchitis	5 (4.2)	2 (1.7)
Back pain	4 (3.3)	2 (1.7)
Nausea	3 (2.5)	2 (1.7)
Prostatic specific antigen increased	4 (3.3)	1 (0.9)
Hypercholesterolaemia	3 (2.5)	1 (0.9)

There were no clinically meaningful differences in the incidence of any TEAE noted across the age, BMI, prior T replacement, or C_{max} subgroups.

1.1 TEAEs by Severity in Part A

TEAEs were categorized by investigator-judged severity (mild, moderate, and severe).

The majority of TEAEs were judged as mild or moderate in severity; 10 (8.3%) TU 750 mg subjects and 7 (6.0%) TU 1000 mg patients experienced at least one severe TEAE. Atrial fibrillation was reported as severe in 2 (1.7%) subjects in the TU 750 mg group; no other event was reported as severe in more than 1 patient per treatment group. Severe events (regardless of investigator-attributed causality) included cardiac failure, coronary artery disease, chest

discomfort, irritability, sudden hearing loss, and PSA increased. In the reviewer's opinion, it is not possible to directly attribute any of these individual severe adverse events to Nebido, although there may be some relationship between androgen replacement in general and such adverse events as "PSA increased", "irritability", "cardiac failure", "coronary artery disease" and "chest discomfort".

1.2 TEAEs of Interest in Part A

Adverse events attributable to androgen replacement in general, and injection site AEs were designated TAES of interest. TEAEs of interest were experienced by 24 (20.0%) of subjects treated with TU 750 mg and 30 (25.6 %) of subjects treated with TU 1000 mg, as seen in Table 11.

Table 11. TEAEs of Interest in Part A

Event Class	MedDRA System Organ Class	MedDRA Preferred term	Number of patients (%)	
			TU 750 (N=120)	TU 1000 (N=117)
Total Patients With At Least One TEAE of Interest			**24 (20.0)**	**30 (25.6)**
Endocrine Disorder	Investigations	Oestradiol increased	0 (0.0)	2 (1.7)
		Glycosylated haemoglobin increased	0 (0.0)	1 (0.9)
	Metabolism and nutrition disorders	Diabetes mellitus	1 (0.8)	1 (0.9)
Tolerability of Injection	General disorders and administration site conditions	Injection site erythema	0 (0.0)	1 (0.9)
		Injection site irritation	0 (0.0)	1 (0.9)
		Injection site pruritus	1 (0.8)	1 (0.9)
		Injection site pain	2 (1.7)	2 (1.7)
		Injection site reaction	0 (0.0)	1 (0.9)
Adverse Lipid Profiles	Investigations	Blood triglycerides increased	1 (0.8)	2 (1.7)
		Blood triglycerides abnormal	0 (0.0)	1 (0.9)
		Blood cholesterol increased	0 (0.0)	2 (1.7)
		High density lipoprotein decreased	1 (0.8)	0 (0.0)
	Metabolism and Nutritional disorders	Hypercholesterolaemia	3 (2.5)	1 (0.9)
		Hyperlipidemia	1 (0.8)	1 (0.9)
Erythropoiesis	Investigations	Haematocrit increased	0 (0.0)	1 (0.9)
		Haemoglobin increased	0 (0.0)	1 (0.9)
		Red blood cell count increased	0 (0.0)	1 (0.9)
	Blood and lymphatic system disorders	Polycythaemia	1 (0.8)	1 (0.9)
Aggression or depression	Psychiatric disorders	Depression	2 (1.7)	4 (3.4)
Urinary Symptoms	Renal and urinary disorders	Pollakiuria	0 (0.0)	2 (1.7)
		Urinary hesitation	0 (0.0)	1 (0.9)
		Urinary retention	1 (0.8)	2 (1.7)
		Urine flow decreased	1 (0.8)	2 (1.7)
		Nocturia	0 (0.0)	1 (0.9)
		Dysuria	1 (0.8)	2 (1.7)
	Infections and infestations	Urinary tract infection	3 (2.5)	3 (2.6)
Prostate health	Investigations	Prostatic specific antigen increased	4 (3.3)	1 (0.9)
		Prostate examination abnormal	2 (1.7)	1 (0.9)
	Reproductive system and breast disorders	Benign prostatic hyperplasia	2 (1.7)	3 (2.6)
		Prostatic intraepithelial neoplasia	1 (0.8)	2 (1.7)
		Prostatitis	0 (0.0)	2 (1.7)
		Prostatic disorder	1 (0.8)	0 (0.0)
Liver Abnormalities	Neoplasms benign, malignant and unspecified	Hepatic neoplasm malignant	0 (0.0)	1 (0.9)
	Investigations	Aspartate aminotransferase increased	1 (0.8)	0 (0.0)
Cerebrovascular events	Nervous system disorders	Cerebrovascular accident	0 (0.0)	1 (0.9)

1.3 TEAEs of ECG Abnormalities in Part A

Based upon the potential effect of androgen replacement on the cardiovascular system, ECGs were obtained and results assessed. There were very few TEAEs of ECG abnormalities reported in this study, and none of these events included as ECG abnormalities were judged to be at least possibly related to study medication by the investigator.

2.0 Deaths and Other Serious or Significant AEs in Part A

2.1 Deaths in Part A

There was 1 patient who died during this study. A 54 year old Caucasian male who received 2 injections of TU 750 mg died of injuries sustained from being stabbed. The patient died 165 days following his first injection; the death was considered unrelated to study treatment.

2.2 Other Serious Adverse Events in Part A

Serious AEs (SAEs) were defined as those events that led to death, were immediately life-threatening, resulted in a persistent or significant disability or incapacity, required or prolonged hospitalization, involved congenital anomaly, or required intervention to prevent one of the prior conditions from occurring. Eight (6.7%) subjects in the TU 750 group and 10 (8.5%) subjects in the TU 1000 group experienced at least one treatment-emergent SAE during the treatment period. Only 2 SAEs were observed in more than 1subject: Atrial fibrillation was reported in 2 subjects in the TU 750 mg group, while knee arthroplasty was reported in 2 subjects in the TU 1000 mg group. No treatment-emergent SAEs judged by the investigator as at least possibly related to study medication were observed in either treatment group.

2.3 Other Significant Adverse Events in Part A

AEs were defined as "other significant events" if they met 1 or more of the following criteria: led to discontinuation of study medication, led to temporary interruption of study medication, or required dose reduction. Table 12 summarizes these events.

Table 12.

Incidence of Other Significant TEAEs by Criterion Regardless of Relationship – Total Patient Sample (Study IP157-001 Part A Stage 1)

	Number of patients (%)	
Other significant TEAE criterion	TU 750 (N=120)	TU 1000 (N=117)
Led to discontinuation of study medication	6 (5.0)	4 (3.4)
Led to temporary interruption of study medication	2 (1.7)	1 (0.9)
Required dose reduction of study medication	0 (0.0)	0 (0.0)

AEs Leading to Discontinuation

Those AEs judged by the investigator to be at least possibly related to study drug and leading to discontinuation were:

• Subject 027-4101 (TU 750 mg arm) was discontinued from the study due to an increased PSA.

• Subject 056-4077 (TU 1000 mg arm) was discontinued from the study due to increased estradiol.

• Subject 040-4116 (TU 1000 mg arm) was discontinued from the study due to an increased red blood cell count.

3.0 Clinical Laboratory Evaluation in Part A

Clinical laboratory data were collected at screening, baseline (1st injection visit), Week 12 (2nd injection visit) and Week 36 (4th injection visit). Lipids (total cholesterol, LDL, HDL, triglycerides) and PSA data were collected at screening, baseline, and at every injection visit (Weeks 12, 24, 36 and 48).

Laboratory data were reviewed for changes that occurred from baseline to each protocol-scheduled time point. In addition, laboratory data were analyzed using predefined criteria to identify potentially clinically significant abnormal laboratory values.

The Sponsor's analysis of average changes from pre-treatment to endpoint is summarized as follows:

• With the exception of changes in erythropoiesis, hormones, and a few other outcomes, the mean and median changes from baseline to endpoint were generally small in magnitude and similar between the treatment groups for most laboratory parameters.

• Liver function tests (e.g., alkaline phosphatase, ALT, and AST) demonstrated slight average decreases from pre-treatment to endpoint; these reductions in these enzymes were judged to be not clinically meaningful.

• Blood urea nitrogen (BUN) and calcium decreased from pre-treatment in both treatment groups; the average decreases were similar between the treatment groups. Sodium, potassium, and phosphorus did not demonstrate meaningful changes in average values from pre-treatment in either treatment group.

The Sponsor believes that decreases in calcium and phosphorus are to be expected, as E2 is known to regulate bone resorption; the Sponsor believes that higher levels of E2 would be expected to lead to lower resorption (and thus lower serum calcium and phosphorus levels).

• The most notable changes from pre-treatment to endpoint were the decreases in average FSH and LH. Average FSH and LH each decreased approximately 60% from pre-treatment to the endpoint in both treatment arms. The TU 1000 mg arm had a slightly higher pre-treatment mean LH, and the Sponsor believes that the slightly larger decrease to the endpoint is possibly a result of the higher pre-treatment mean, as compared to the TU 750 mg arm.

Subjects with primary hypogonadism are marked by testicular failure, and thus these subjects may have higher average LH and FSH values than subjects with secondary hypogonadism (who are marked by a systemic failure of the pituitary-hypothalamic-gonadal axis, and thus by generally lower LH and FSH). In this study; there were slightly more subjects diagnosed with primary hypogonadism than with secondary hypogonadism. Therefore, the Sponsor believes that the changes in LH and FSH values observed in this study reflect the fact that the majority of subjects in this study were diagnosed with primary hypogonadism (per the medical history data). Pre-treatment concentrations of both LH and FSH were in the middle of their normal ranges for both treatment groups, but there were many subjects with elevated (above-normal) LH and FSH values pre-treatment. By Week 36 of treatment, average LH and FSH values had dropped to near the

lower limits of normal for both hormones, and the majority of subjects had both LH and FSH values within the normal range.

Reviewer's Comment: The Sponsor's conclusions relevant to "clinical laboratories" are all considered to be reasonable.

Table 13 provides a summary of the average changes for most laboratory parameters in Part A.

Table 13.

Changes from Pre-Treatment to Endpoint in Clinical Laboratory Parameters (Hematology, Serum Chemistry, and Lipids) – Total Patient Sample (Study IP157-001 Part A Stage 1)

Laboratory Parameter	TU 750 (N=120)			TU 1000 (N=117)		
	Pre-Treatment	Endpoint	Change	Pre-Treatment	Endpoint	Change
Hematology						
WBC (10^3/uL) N	119	119	119	114	114	114
Mean (SE)	6.7 (0.16)	6.8 (0.18)	0.01(0.14)	6.5 (0.15)	6.8 (0.18)	0.3 (0.15)
Median	6.4	6.5	-0.0	6.4	6.5	0.3
Range	2.3, 14.9	2.6, 15.7	-4.2, 7.6	2.9, 11.7	3.6, 15.4	-5.1, 8.6
Lymphocytes (%) N	119	119	119	114	114	114
Mean (SE)	30.2 (0.73)	29.5 (0.73)	-0.7 (0.56)	29.7 (0.66)	29.2 (0.66)	-0.5 (0.60)
Median	29.7	28.4	-1.2	28.6	28.8	-0.1
Range	12.5, 54.2	11.2, 53.8	-16.9, 19.4	9.8, 53.9	17.3, 50.4	-18.6, 19.0
Monocytes (%) N	119	119	119	114	114	114
Mean (SE)	6.0 (0.14)	6.2 (0.17)	0.2 (0.18)	6.2 (0.16)	6.3 (0.15)	0.0 (0.16)
Median	5.8	6.1	0.1	6.1	6.2	0.2
Range	1.0, 12.2	0.0, 15.0	-7.0, 8.5	2.7, 11.5	3.0, 10.9	-6.8, 4.0
Basophils (%) N	119	119	119	114	114	114
Mean (SE)	0.9 (0.04)	0.9 (0.04)	0.0 (0.05)	0.8 (0.04)	0.9 (0.06)	0.1 (0.07)
Median	0.8	0.8	0.0	0.8	0.8	0.0
Range	0.0, 2.5	0.0, 3.0	-1.3, 2.1	0.0, 2.6	0.0, 3.0	-1.9, 2.5
Eosinophils (%) N	119	119	119	114	114	114
Mean (SE)	2.6 (0.14)	3.0 (0.18)	0.4 (0.15)	2.6 (0.13)	2.9 (0.16)	0.2 (0.15)
Median	2.2	2.7	0.2	2.5	2.5	0.2
Range	0.3, 9.4	0.0, 13.2	-6.4, 9.9	0.4, 7.0	0.0, 8.5	-4.4, 5.1
Neutrophils (%) N	119	119	119	114	114	114
Mean (SE)	60.3 (0.74)	60.4 (0.78)	0.1 (0.65)	60.6 (0.73)	60.6 (0.72)	0.0 (0.71)
Median	60.2	61.4	0.7	60.8	60.6	-0.4
Range	37.4, 81.7	36.9, 77.4	-25.4, 16.4	39.5, 82.2	39.3, 76.4	-27.4, 20.6
RBC (10^6/uL) N	119	119	119	114	114	114
Mean (SE)	5.2 (0.04)	5.1 (0.04)	-0.1 (0.03)	5.2 (0.04)	5.2 (0.04)	-0.0 (0.04)
Median	5.2	5.2	-0.1	5.3	5.2	0.0
Range	4.0, 6.3	3.9, 5.9	-1.0, 0.8	4.1, 6.5	3.9, 6.6	-0.9, 1.0
Hematocrit (%) N	119	119	119	114	114	114

Mean (SE)	45.0 (0.36)	45.1 (0.36)	0.1 (0.32)	44.8 (0.34)	45.9 (0.36)	1.0 (0.34)
Median	45.0	45.0	0.0	45.0	46.0	1.0
Range	28.0, 56.0	30.0, 55.0	-15.0, 11.0	35.0, 52.0	34.0, 61.0	-7.0, 12.0
Hemoglobin (g/dL) N	119	119	119	114	114	114
Mean (SE)	15.0 (0.12)	15.3 (0.12)	0.3 (0.11)	14.9 (0.13)	15.5 (0.13)	0.6 (0.11)
Median	15.0	15.5	0.3	15.0	15.5	0.5
Range	9.9, 17.8	10.4, 18.3	-3.4, 4.0	11.2, 18.2	11.2, 18.9	-3.0, 4.0
Platelet Count (10^3/uL) N	117	117	117	114	114	114
Mean (SE)	240.8 (5.34)	240.2 (5.59)	-0.6 (3.43)	244.3 (5.33)	241.5 (5.59)	-2.9 (2.97)
Median	234.0	232.0	-1.0	239.5	232.0	-3.5
Range	122.0, 392.0	114.0, 384.0	-94.0, 164.0	120.0, 416.0	138.0, 463.0	-80.0, 89.0
PT Value (sec) N	115	115	115	112	112	112
Mean (SE)	12.0 (0.07)	12.4 (0.08)	0.4 (0.09)	12.1 (0.07)	12.3 (0.07)	0.2 (0.07)
Median	11.9	12.3	0.4	12.0	12.2	0.2
Range	10.6, 17.3	10.9, 16.6	-4.6, 5.5	10.7, 15.8	10.9, 14.6	-3.9, 1.6
PTT Value (sec) N	115	115	115	112	112	112
Mean (SE)	23.8 (0.29)	24.9 (0.27)	1.1 (0.27)	24.0 (0.37)	24.8 (0.34)	0.8 (0.39)
Median	23.1	24.6	1.1	23.4	24.4	1.0
Range	18.4, 42.7	20.0, 36.6	-16.2, 10.1	18.5, 54.5	17.8, 48.4	-31.1, 20.1
INR Value N	115	115	115	112	112	112
Mean (SE)	1.0 (0.01)	1.1 (0.01)	0.0 (0.02)	1.1 (0.01)	1.1 (0.01)	-0.0 (0.01)
Median	1.0	1.1	0.0	1.0	1.0	0.0
Range	0.8, 2.1	0.8, 1.9	-1.0, 1.0	0.8, 1.7	0.8, 1.6	-0.8, 0.3
Serum Chemistry						
Total Protein (g/dL) N	119	119	119	114	114	114
Mean (SE)	7.3 (0.04)	7.3 (0.04)	0.0 (0.03)	7.3 (0.04)	7.3 (0.04)	0.0 (0.03)
Median	7.2	7.3	0.0	7.3	7.3	0.0
Range	6.0, 8.3	6.2, 8.1	-0.8, 1.2	6.2, 8.5	6.4, 8.3	-1.0, 0.8
Albumin (g/dL) N	119	119	119	114	114	114
Mean (SE)	4.3 (0.03)	4.2 (0.03)	-0.1 (0.02)	4.3 (0.03)	4.2 (0.03)	-0.1 (0.02)
Median	4.2	4.1	-0.1	4.3	4.2	-0.1
Range	3.5, 5.5	3.6, 5.3	-0.9, 0.8	3.4, 4.8	3.5, 4.9	-0.6, 0.7

Laboratory Parameter	**TU 750 (N=120)**			**TU 1000 (N=117)**		
	Pre-Treatment	**Endpoint**	**Change**	**Pre-Treatment**	**Endpoint**	**Change**
Creatinine (mg/dL) N	119	119	119	114	114	114
Mean (SE)	1.0 (0.02)	1.1 (0.02)	0.1 (0.01)	1.0 (0.02)	1.1 (0.02)	0.1 (0.01)
Median	1.0	1.1	0.1	1.0	1.0	0.1
Range	0.6, 1.6	0.6, 1.7	-0.2, 0.8	0.7, 1.6	0.7, 1.9	-0.3, 0.5
Urea Nitrogen (BUN) (mg/dL) N	119	119	119	114	114	114
Mean (SE)	17.5 (0.42)	16.9 (0.42)	-0.6 (0.32)	19.4 (0.52)	17.5 (0.42)	-1.9 (0.35)
Median	17.0	16.0	-1.0	19.0	17.0	-2.0
Range	7.0, 31.0	7.0, 30.0	-8.0, 7.0	7.0, 43.0	9.0, 34.0	-13.0, 9.0
Uric Acid (mg/dL) N	119	119	119	114	114	114
Mean (SE)	6.5 (0.12)	6.3 (0.13)	-0.2 (0.10)	6.9 (0.14)	6.5 (0.15)	-0.4 (0.11)
Median	6.4	6.2	-0.2	6.7	6.2	-0.4
Range	3.3, 10.1	3.7, 10.7	-3.3, 4.6	3.9, 12.8	3.9, 16.4	-4.1, 3.6
Direct Bilirubin (mg/dL) N	119	119	119	114	114	114
Mean (SE)	0.1 (0.01)	0.1 (0.01)	0.0 (0.01)	0.1 (0.01)	0.2 (0.01)	0.0 (0.01)
Median	0.1	0.1	0.0	0.1	0.1	0.0
Range	0.1, 0.3	0.1, 0.4	-0.2, 0.1	0.1, 0.3	0.1, 0.4	-0.1, 0,2
Total Bilirubin (mg/dL) N	119	119	119	114	114	114
Mean (SE)	0.6 (0.05)	0.6 (0.05)	0.1 (0.02)	0.6 (0.02)	0.6 (0.02)	0.1 (0.02)
Median	0.5	0.5	0.0	0.5	0.6	0.1
Range	0.2, 5.5	0.2, 6.2	-0.5, 0.7	0.2, 1.3	0.2, 1.8	-0.6, 0.9
Alkaline Phosphatase (U/L) N	119	119	119	114	114	114
Mean (SE)	72.4 (1.92)	69.8 (1.77)	-2.6 (0.86)	73.9 (1.88)	71.1 (1.76)	-2.8(0.97)
Median	68.0	67.0	-2.0	73.0	68.5	-2.0
Range	27.0, 140.0	25.0, 124.0	-38.0, 19.0	25.0, 143.0	23.0, 126.0	-39.0, 33.0
SGPT (ALT) (U/L) N	119	119	119	114	114	114
Mean (SE)	32.0 (1.25)	31.1 (1.31)	-0.9 (0.98)	30.0 (1.13)	28.4 (1.00)	-1.6 (1.06)
Median	30.0	27.0	-1.0	27.0	26.0	0.5
Range	11.0, 87.0	13.0, 95.0	-48.0, 34.0	8.0, 84.0	11.0, 66.0	-56.0, 30.0
SGOT (AST) (U/L) N	119	119	119	114	114	114
Mean (SE)	26.8 (0.74)	25.6 (0.86)	-1.2 (0.68)	26.6 (1.17)	24.5 (0.88)	-2.2 (1.22)
Median	25.0	23.0	-1.0	24.5	23.0	-1.0
Range	15.0, 62.0	13.0, 81.0	-27.0, 39.0	16.0, 139.0	13.0, 103.0	-110.0, 56.0

Creatine Phosphokinase (U/L) N	119	119	119	114	114	114
Mean (SE)	172.8 (10.92)	184.8 (17.90)	12.0 (16.71)	191.5 (34.35)	170.3 (12.84)	-21.2 (33.86)
Median	136.0	139.0	0.0	123.0	139.0	-1.5
Range	44.0, 715.0	40.0, 1944.0	-374.0, 1633.0	28.0, 3922.0	26.0, 930.0	-3686.0, 566.0
Fasting Glucose (mg/dL) N	96	96	96	106	106	106
Mean (SE)	105.8 (3.00)	110.2 (3.39)	4.4 (2.20)	104.1 (2.16)	109.0 (2.82)	4.9 (2.20)
Median	97.5	102.0	4.0	100.0	101.0	3.0
Range	71.0, 260.0	48.0, 264.0	-92.0, 81.0	74.0, 212.0	79.0, 243.0	-58.0, 135.0
Calcium (mg/dL) N	119	119	119	114	114	114
Mean (SE)	9.8 (0.04)	9.7 (0.03)	-0.1 (0.04)	9.8 (0.03)	9.7 (0.03)	-0.1 (0.04)
Median	9.8	9.7	-0.1	9.8	9.7	-0.1
Range	8.9, 11.4	9.0, 10.6	-1.1, 1.2	9.1, 11.0	8.8, 10.4	-1.7, 0.9
Phosphorus (mg/dL) N	119	119	119	114	114	114
Mean (SE)	3.4 (0.05)	3.2 (0.06)	-0.2 (0.06)	3.5 (0.05)	3.3 (0.05)	-0.2 (0.06)
Median	3.4	3.2	-0.1	3.5	3.3	-0.1
Range	1.8, 5.6	1.6, 5.1	-2.2, 1.4	2.2, 5.6	2.3, 4.5	-2.0, 1.1
Sodium (mEq/L) N	119	119	119	114	114	114
Mean (SE)	140.6 (0.24)	140.4 (0.24)	-0.2 (0.24)	140.5 (0.24)	140.7 (0.21)	0.2 (0.23)
Median	140.0	140.0	0.0	140.0	140.0	0.0
Range	133.0, 151.0	133.0, 152.0	-8.0, 7.0	134.0, 153.0	136.0, 150.0	-7.0, 7.0
Potassium (mEq/L) N	119	119	119	114	114	114
Mean (SE)	4.3 (0.04)	4.3 (0.03)	0.0 (0.04)	4.3 (0.04)	4.3 (0.04)	0.1 (0.03)
Median	4.2	4.3	0.0	4.3	4.3	0.0
Range	3.0, 5.4	3.4, 5.6	-0.9, 1.3	3.3, 5.5	3.2, 5.7	-0.9, 1.2
Chloride (mEq/L) N	119	119	119	114	114	114
Mean (SE)	102.9 (0.23)	102.6 (0.22)	-0.3 (0.23)	102.3 (0.27)	102.2 (0.24)	-0.1 (0.27)
Median	103.0	102.0	0.0	103.0	102.0	0.0
Range	99.0, 112.0	96.0, 112.0	-11.0, 7.0	94.0, 110.0	93.0, 111.0	-7.0, 9.0
Bicarbonate (mEq/L) N	119	119	119	114	114	114
Mean (SE)	26.2 (0.23)	25.8 (0.24)	-0.3 (0.25)	26.3 (0.24)	26.1 (0.26)	-0.2 (0.23)
Median	26.2	26.3	-0.4	26.4	25.8	-0.4
Range	18.2, 34.1	18.8, 32.8	-7.6, 6.9	18.3, 32.0	19.6, 33.7	-6.4, 7.7

Laboratory Parameter	TU 750 (N=120)			TU 1000 (N=117)		
	Pre-Treatment	Endpoint	Change	Pre-Treatment	Endpoint	Change

Laboratory Parameter	TU 750 (N=120)			TU 1000 (N=117)		
	Pre-Treatment	Endpoint	Change	Pre-Treatment	Endpoint	Change
FSH (mIU/dL) N	119	119	119	114	114	114
Mean (SE)	9.4 (1.11)	3.6 (0.67)	-5.8 (0.78)	9.9 (1.27)	2.9 (0.85)	-7.0 (0.72)
Median	6.0	1.0	-3.0	6.0	1.0	-5.0
Range	1.0, 71.0	1.0, 66.0	-62.0, 3.0	1.0, 113.0	1.0, 92.0	-41.0, 2.0
LH (mIU/dL)	119	119	119	114	114	114
Mean (SE)	5.7 (0.57)	2.1 (0.41)	-3.5 (0.44)	6.4 (0.89)	1.6 (0.31)	-4.7 (0.66)
Median	4.0	1.0	-2.0	4.0	1.0	-2.5
Range	1.0, 34.0	1.0, 44.0	-29.0, 10.0	1.0, 82.0	1.0, 34.0	-48.0, 2.0
Lipids[1]						
Triglycerides (mg/dL) N	98	98	98	107	107	107
Mean (SE)	204.6 (13.17)	193.3 (16.64)	-11.4 (12.59)	192.9 (15.17)	169.6 (11.74)	-23.2 (15.67)
Median	170.0	155.5	-9.0	165.0	146.0	-12.0
Range	47.0, 776.0	50.0, 1391.0	-396.0, 615.0	49.0, 1333.0	47.0, 1044.0	-1158.0, 639.0
Total Cholesterol (mg/dL) N	98	98	98	107	107	107
Mean (SE)	190.5 (4.17)	187.1 (4.22)	-3.4 (3.32)	190.1 (3.62)	181.4 (3.78)	-8.7 (3.34)
Median	191.0	187.5	-2.5	193.0	180.0	-11.0
Range	100.0, 327.0	91.0, 345.0	-107.0, 94.0	106.0, 281.0	103.0, 328.0	-112.0, 101.0
HDL (mg/dL) N	98	98	98	107	107	107
Mean (SE)	44.3 (1.07)	41.4 (1.08)	-2.9 (0.85)	44.9 (0.94)	43.1 (0.95)	-1.7 (0.70)
Median	44.0	40.0	-2.0	43.0	42.0	-1.0
Range	25.0, 71.0	21.0, 86.0	-48.0, 15.0	30.0, 75.0	29.0, 77.0	-35.0, 34.0
LDL (mg/dL) N	89	89	89	106	106	106
Mean (SE)	105.9 (3.57)	108.5 (3.40)	2.6 (2.89)	109.1 (3.11)	105.9 (3.37)	-3.2 (2.81)
Median	104.0	110.0	3.0	109.5	104.0	-2.0
Range	40.0, 200.0	43.0, 206.0	-81.0, 90.0	27.0, 197.0	33.0, 228.0	-79.0, 85.0

3.1 Individual Potentially Clinically Significant Abnormalities (PCS) in Clinical Laboratory Parameters in Part A

3.1.1 Hematology PCS Values in Part A

A summary of hematology PCS values in Part A is shown in Table 14.

Table 14.

Hematology: PCS Abnormal Values Reported in at least 2 Patients in Either Treatment Group at Endpoint – Total Patient Sample (Study IP157-001 Part A Stage 1)

Hematology PCS abnormal value	TU 750 (N=120)		TU 1000 (N=117)	
	n/N (%)	Normal at BL n/N (%)	n/N (%)	Normal at BL n/N (%)
Number of patients with at least 1 Hematology PCS abnormal value	7/119 (5.9)	4/119 (3.4)	4/114 (3.5)	2/114 (1.8)
Eosinophils – High (≥ 10%)	2/119 (1.7)	2/119 (1.7)	0/114 (0.0)	0/114 (0.0)
Hematocrit – Low (≤ 37%)	2/119 (1.7)	0/115 (0.0)	2/114 (1.8)	0/111 (0.0)
PT Value – High (≥ 16 seconds)	2/116 (1.7)	2/114 (1.8)	0/113 (0.0)	0/112 (0.0)

3.1.2 Serum Chemistry PCS Values (Including FSH, LH, and Lipids) in Part A

Table 15 summarizes serum chemistry abnormal PCS values in Part A.

Table 15.

Serum Chemistry, FSH, LH, and Lipids: PCS Abnormal Values Reported in at least 2 Patients in Either Treatment Group at Endpoint – Total Patient Sample (Study IP157-001 Part A Stage 1)

Chemistry PCS abnormal value	TU 750 (N=120)		TU 1000 (N=117)	
	n/N (%)	Normal at BL n/N (%)	n/N (%)	Normal at BL n/N (%)
Number of patients with at least 1 Chemistry PCS abnormal value	9/119 (7.6)	5/119 (4.2)	5/114 (4.4)	0/114 (0.0)
Urea Nitrogen (BUN) – High (≥ 30 mg/dL)	1/119 (0.8)	0/118 (0.0)	2/114 (1.8)	0/110 (0.0)
Phosphorus – Low (≤ 1.7 mg/dL)	2/119 (1.7)	2/119 (1.7)	0/114 (0.0)	0/114 (0.0)
Follicle Stimulating Hormone – High (> 20 mIU/mL)	2/119 (1.7)	0/107 (0.0)	2/114 (1.8)	0/103 (0.0)
Luteinizing Hormone – High (>18 mIU/mL)	2/119 (1.7)	0/112 (0.0)	1/114 (0.9)	0/107 (0.0)
Fasting Triglycerides – High (>600 mg/dL)	2/109 (1.8)	1/97 (1.0)	1/110 (0.9)	1/105 (1.0)
Fasting HDL – Low (≤ 30 mg/dL)	14/109 (12.8)	7/90 (7.8)	6/110 (5.5)	4/104 (3.8)
Fasting LDL – High (≥ 200 mg/dL)	2/105 (1.9)	2/88 (2.3)	1/109 (0.9)	1/106 (0.9)

3.1.3 Hormone PCS Values in Part A

PCS criteria for serum hormone levels were defined as follows:

- DHT > 1300 pg/mL
- E2 > 70 pg/mL
- Free T > 800 pg/mL
- SHBG > 70 nmol/L
- DHT:T Ratio > 0.25

• E2:T Ratio > 0.025

Using these definitions, abnormal hormone PCS values in Part a are summarized in Table 16.

Table 16.

Hormone PCS abnormal value	TU 750 (N=120)		TU 1000 (N=117)	
	n/N (%)	Normal at BL n/N (%)	n/N (%)	Normal at BL n/N (%)
Number of patients with at least 1 Hormone PCS abnormal value	3/118 (2.5)	3/118 (2.5)	1/113 (0.9)	1/113 (0.9)
E2 – High (> 70 pg/mL)	2/117 (1.7)	2/116 (1.7)	0/113 (0.0)	0/112 (0.0)
DHT – High (> 1300 pg/mL)	0/118 (0.0)	0/118 (0.0)	0/113 (0.0)	0/113 (0.0)
Free T – High (> 800 pg/mL)	0/118 (0.0)	0/118 (0.0)	1/113 (0.9)	1/113 (0.9)
SHBG – High (> 70 nmol/L)	0/118 (0.0)	0/116 (0.0)	0/113 (0.0)	0/110 (0.0)
DHT:T Ratio – High (> 0.25)	1/117 (0.9)	1/109 (0.9)	0/112 (0.0)	0/106 (0.0)
E2:T Ratio – High (> 0.025)	1/116 (0.9)	1/106 (0.9)	0/113 (0.0)	0/103 (0.0)
Free T:T Ratio – High (> 0.08)	0/117 (0.0)	0/114 (0.0)	0/113 (0.0)	0/110 (0.0)

4.0 Vital Signs, Physical Findings and Other Safety Related Observations in Part A

4.1 Vital Signs in Part A

A summary of mean changes in vital signs in Part A is shown in Tables 17 and 18.

Table 17.

Changes from Pre-Treatment to Endpoint in Vital Sign Parameters – Total Patient Sample (Study IP157-001 Part A Stage 1)

Vital Sign Parameter	TU 750 (N=120)			TU 1000 (N=117)		
	Pre-Treatment	Endpoint	Change	Pre-Treatment	Endpoint	Change
Systolic BP (mm Hg) N	113	113	113	106	106	106
Mean (SE)	127.0 (1.11)	128.6 (1.28)	1.5 (1.22)	126.8 (1.16)	129.1 (1.37)	2.3 (1.30)
Median	127.0	126.0	2.0	126.0	130.0	2.0
Range	96.0 to 154.0	86.0 to 175.0	-46.0 to 36.0	94.0 to 163.0	90.0 to 185.0	-35.0 to 70.0
Diastolic BP (mm Hg) N	113	113	113	106	106	106
Mean (SE)	79.3 (0.69)	80.1 (0.75)	0.8 (0.79)	78.3 (0.73)	79.4 (0.90)	1.1 (0.91)
Median	80.0	80.0	0.0	79.5	80.0	0.0
Range	58.0 to 97.0	46.0 to 96.0	-20.0 to 28.0	60.0 to 99.0	58.0 to 114.0	-16.0 to 38.0
Pulse (bpm) N	113	113	113	106	106	106
Mean (SE)	72.1 (0.88)	71.4 (0.85)	-0.7 (0.96)	70.2 (0.80)	71.0 (0.95)	0.8 (0.91)
Median	72.0	70.0	0.0	70.0	72.0	0.0
Range	54.0 to 100.0	48.0 to 96.0	-42.0 to 20.0	52.0 to 88.0	52.0 to 97.0	-26.0 to 23.0

Pre-defined potential clinically significant changes in vital signs in Part A are shown in table 18.

Table 18.

Vital Signs: PCS Abnormal Values Occurring at Endpoint in at least 2 Patients in Either Treatment Group – Total Patient Sample (Study IP157-001 Part A Stage 1)

Vital signs PCS abnormal value	TU 750 (N=120)		TU 1000 (N=117)	
	n/N (%)	Normal at BL n/N (%)	n/N (%)	Normal at BL n/N (%)
Systolic blood pressure:				
Low: < 90 or decrease ≥ 20 mmHg	7/113 (6.2)	7/113 (6.2)	4/106 (3.8)	4/106 (3.8)
High: >180 or increase ≥ 20 mm Hg	6/113 (5.3)	6/113 (5.3)	11/106 (10.4)	11/106 (10.4)
Diastolic blood pressure:				
Low: < 50 or decrease ≥ 15 mm Hg	3/113 (2.7)	3/113 (2.7)	6/106 (5.7)	6/106 (5.7)
High: >105 or increase ≥ 15 mm Hg	9/113 (8.0)	9/113 (8.0)	7/106 (6.6)	7/106 (6.6)
Pulse				
Low: Decrease ≥ 15 bpm	9/113 (8.0)	9/113 (8.0)	7/106 (6.6)	7/106 (6.6)
Low: <50, Decrease ≥15 bpm or both	10/113 (8.8)	10/113 (8.8)	7/106 (6.6)	7/106 (6.6)

Reviewer's Comment: While there are no mean or median changes from baseline of note in Part A, it is interesting that individual PCS increases from baseline in systolic BP appeared to be dose-related (5.3% for the 750mg dose versus 10.4% for the 100mg dose). This may reflect an androgen replacement effect.

4.2 Physical Examinations in Part A

There were no meaningful changes in any physical examination assessments of abnormalities from pre-treatment to the 4th injection visit; further, the treatment groups were similar in the incidence of abnormal findings at both pre-treatment and the 4th injection visit.

4.3 ECG Data in Part A

Descriptive statistics for changes in ECG parameters in Part A are provided in Table 19.

Table 19.

Changes from Pre-Treatment to Endpoint in ECG Parameters – Total Patient Sample (Study IP157-001 Part A Stage 1)

Vital Sign Parameter	TU 750 (N=120)			TU 1000 (N=117)		
	Pre-Treatment	Endpoint	Change	Pre-Treatment	Endpoint	Change
PR Interval (msec) N	109	109	109	103	103	103
Mean (SE)	165.7 (2.30)	166.0 (2.22)	0.3 (1.10)	166.2 (2.85)	165.9 (2.69)	-0.3 (2.09)
Median	164.0	164.0	0.0	162.0	162.0	-1.0
Range	110.0 to 252.0	128.0 to 256.0	-50.0 to 50.0	82.0 to 284.0	118.0 to 256.0	-90.0 to 76.0
QRS Interval (msec) N	111	111	111	103	103	103
Mean (SE)	92.3 (2.10)	95.3 (1.31)	3.0 (1.77)	94.0 (1.86)	97.1 (1.60)	3.0 (1.56)
Median	94.0	96.0	0.0	96.0	94.0	0.0
Range	6.0 to 174.0	33.0 to 160.0	-75.0 to 95.0	21.0 to 166.0	60.0 to 164.0	-22.0 to 99.0
QTcF (msec) N	111	111	111	103	103	103
Mean (SE)	405.9 (2.03)	403.6 (1.94)	-2.3 (1.96)	408.4 (2.29)	403.1 (2.71)	-5.4 (2.39)
Median	406.2	402.1	-4.2	404.7	401.9	-5.5
Range	336.9 to 490.4	344.7 to 490.4	-48.1 to 91.1	338.8 to 477.3	242.1 to 485.6	-155.2 to 48.1
Heart Rate (bpm) N	111	111	111	103	103	103
Mean (SE)	67.5 (1.01)	68.2 (0.98)	0.7 (0.92)	65.6 (1.00)	67.7 (1.02)	2.1 (0.92)
Median	67.0	66.0	2.0	66.0	66.0	3.0
Range	47.0 to 108.0	45.0 to 95.0	-39.0 to 29.0	41.0 to 92.0	44.0 to 97.0	-23.0 to 31.0

Reviewer's Comment: There do not appear to be any significant changes from baseline in mean ECG parameters

4.4 Prostate Health Parameters in Part A

Special attention was given to the prostate health of subject in Part A. Subjects were excluded from this study if they had a screening serum PSA level > 4 ng/mL or hyperplasia of the prostate (defined as prostate volume > 75 cm3 as measured by transrectal ultrasonography). During the study, PSA and digital rectal examinations (DRE) were performed at every injection visit, and prostate biopsies were to have been performed for any subject with a PSA > 4 ng/dL.

4.4.1 Serum PSA in Part A

There were 9 subjects in the 750 mg arm and 4 in the 1000 mg arm with at least one post-baseline PSA value > 4 ng/mL during this study. There were elevated PSA values observed at each post-baseline injection visit during the study.

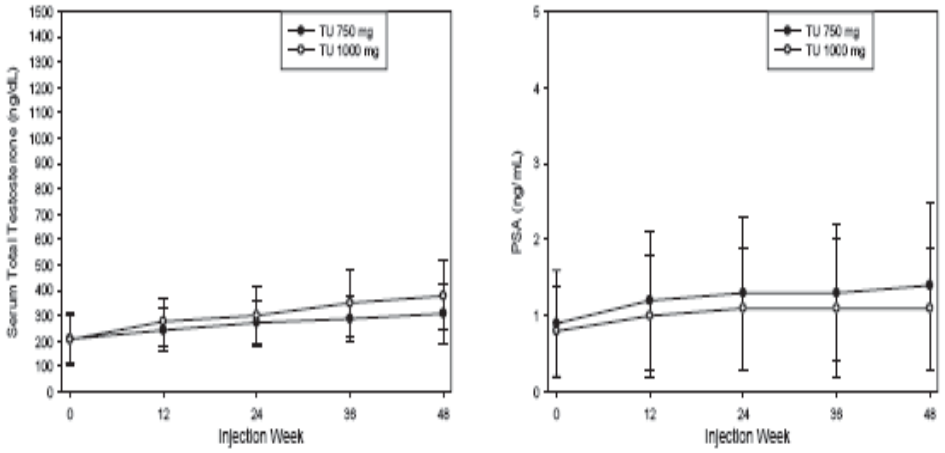
Table 20 provides the number (%) of patients who had PSA value > 4 ng/mL at each injection visit and at any time during this study.

Table 20.

Time (Visit)	Relation to normal range	Number (%) of Patients	
		TU 750 (N=120)	TU 1000 (N=117)
Screening	Within 0 to 4 ng/mL	120 (100.0)	116 (100.0)
	Above 4 ng/mL	0 (0.0)	0 (0.0)
Baseline (1st Injection Visit)	Within 0 to 4 ng/mL	116 (100.0)	116 (100.0)
	Above 4 ng/mL	0 (0.0)	0 (0.0)
Week 12 (2nd Injection Visit)	Within 0 to 4 ng/mL	109 (97.3)	114 (100.0)
	Above 4 ng/mL	3 (2.7)	0 (0.0)
Week 24 (3rd Injection Visit)	Within 0 to 4 ng/mL	99 (96.1)	104 (100.0)
	Above 4 ng/mL	4 (3.9)	0 (0.0)
Week 36 (4th Injection Visit)	Within 0 to 4 ng/mL	99 (97.1)	95 (99.0)
	Above 4 ng/mL	3 (2.9)	1 (1.0)
Endpoint - Week 48 (5th Injection Visit) or Early Discontinuation	Within 0 to 4 ng/mL	112 (94.1)	111 (97.4)
	Above 4 ng/mL	7 (5.9)	3 (2.6)
Any Time[1]	Within 0 to 4 ng/mL	110 (92.4)	110 (96.5)
	Above 4 ng/mL	9 (7.6)	4 (3.5)

Figure 9 provides a plot of the by-treatment mean PSA values over time in Part A, from the screening visit through the Injection 5 visit, and the corresponding mean (standard deviation) T concentrations at the same time points.

Figure 9. Mean (Standard Deviation) Serum Total Testosterone – PK Population Compared to Mean (Standard Deviation) PSA over Time by Treatment in Part A



4.4.2. Prostate-Related TEAEs in Part A

Table 21 presents a list of the incidence rates of prostate related TEAEs in Part A.

Table 21. **Incidence of TEAEs related to Prostate Health by Preferred Term – Total Patient Sample (Study IP157-001 Part A Stage 1)**

MedDRA System Organ Class	MedDRA Preferred term	Number of patients (%)	
		TU 750 (N=120)	TU 1000 (N=117)
Investigations	Prostatic specific antigen increased	4 (3.3)	1 (0.9)
	Prostate examination abnormal	2 (1.7)	1 (0.9)
Reproductive system and breast disorders	Benign prostatic hyperplasia	2 (1.7)	3 (2.6)
	Prostatic intraepithelial neoplasia	1 (0.8)	2 (1.7)
	Prostatitis	0 (0.0)	2 (1.7)
	Prostatic disorder	1 (0.8)	0 (0.0)

4.4.3 Summary of Prostate Health Outcomes in Part A

The Sponsor provides the following summary of prostate health assessments in Part A:

• Approximately 5% of the 237 subjects treated in this study had at least one on-treatment PSA concentration >4 ng/mL.

A higher percentage of subjects in the low-dose arm (TU 750 mg) had at least one elevated PSA (as compared to the TU 1000 mg arm).

There were 6 subjects with a pre-treatment PSA between 3 ng/mL and 4 ng/mL; 3 (50%) of these subjects had at least one on-treatment PSA >4 ng/mL.

• Rigorous tracking of PSA was performed in this study, with an average of 4 on-treatment PSA assessments performed per subject in this study (a PSA sample was collected once every 12 weeks while the subjects were on-treatment). Given this high level of rigor in the assessment of PSA (and given the physical manipulation of the prostate during the DREs that were performed on every patient at every injection visit), the incidence of elevated PSA concentrations was likely well within the normal rate for a population of men with an average age of 55 years.

• PSA increased, as expected, with the TU 1000 mg pre-treatment median PSA 0.6 ng/mL and the endpoint median PSA 0.9 ng/mL (the median increase was 0.2 ng/mL during the 48-week treatment period). This reflects an approximate PSA velocity over the 48 week treatment period of < 4 ng/mL for the TU 1000 mg arm.

• There were no prostate cancers reported in this 48 week study. There were a number of AEs related to the prostate reported in both treatment groups (PSA increased, prostate examination abnormal, benign prostatic hyperplasia, prostatic intraepithelial neoplasia, prostatitis, and prostate disorder).

• The incidence of on-treatment visit-wise DRE findings were similar to the incidence observed pre-treatment.

A higher percentage of subjects in the low-dose arm (TU 750 mg) had at least one DRE finding (as compared to the TU 1000 mg arm).

Prostate health outcomes in this study were considered to be clinically consistent with those expected in a population of hypogonadal men receiving testosterone replacement; there was no evidence that treatment with TU 750 mg or with TU 1000 mg resulted in unexpected prostate health outcomes.

4.5 Changes in Mood States (POMS) in Part A

Both study arms demonstrated similar mood disturbance scores as seen in Table 22.

Table 22.

Summary Statistics For Changes in POMS: Change from Pre-Treatment to 5th Injection Visit (or End of Study) – PK Population (Study IP157-001 Part A Stage 1)

POMS Parameter	TU 750 (N=102)			TU 1000 (N=97)		
	Pre-Treatment	5th Injection Visit	Change	Pre-Treatment	5th Injection Visit	Change
Total Mood Disturbance N	100	100	100	95	95	95
Mean (SE)	34.0 (3.37)	14.1 (2.60)	-19.8 (2.82)	28.2 (3.05)	14.6 (2.89)	-13.6 (2.98)
Median	27.0	10.0	-13.0	25.0	7.0	-13.0
Range	-20.0 to 115.0	-24.0 to 90.0	-106.0 to 49.0	-19.0 to 133.0	-24.0 to 100.0	-85.0 to 94.0
Subscales						
Tension-anxiety N	100	100	100	95	95	95
Mean (SE)	10.4 (0.57)	7.5 (0.44)	-2.9 (0.51)	9.8 (0.56)	7.8 (0.51)	-2.0 (0.50)
Median	8.5	7.0	-3.0	8.0	7.0	-2.0
Range	2.0 to 26.0	2.0 to 23.0	-17.0 to 15.0	2.0 to 24.0	0.0 to 25.0	-16.0 to 11.0
Depression-dejection N	100	100	100	95	95	95
Mean (SE)	10.2 (1.02)	5.8 (0.70)	-4.3 (0.83)	9.0 (0.92)	6.4 (0.88)	-2.5 (0.94)
Median	7.0	4.0	-2.0	6.0	3.0	-2.0
Range	0.0 to 39.0	0.0 to 28.0	-31.0 to 10.0	0.0 to 46.0	0.0 to 35.0	-33.0 to 25.0
Anger-hostility N	100	100	100	95	95	95
Mean (SE)	9.0 (0.87)	5.6 (0.66)	-3.4 (0.73)	7.8 (0.79)	5.9 (0.73)	-1.9 (0.90)
Median	6.0	3.5	-1.5	5.0	3.0	-1.0
Range	0.0 to 37.0	0.0 to 25.0	-32.0 to 11.0	0.0 to 33.0	0.0 to 31.0	-23.0 to 29.0
Vigor-activity N	100	100	100	95	95	95
Mean (SE)	14.8 (0.59)	17.5 (0.64)	2.6 (0.61)	16.2 (0.61)	18.7 (0.67)	2.5 (0.58)
Median	14.0	18.0	2.0	16.0	20.0	2.0
Range	0.0 to 32.0	1.0 to 32.0	-13.0 to 18.0	2.0 to 31.0	1.0 to 32.0	-10.0 to 16.0
Fatigue-inertia N	100	100	100	95	95	95
Mean (SE)	11.9 (0.70)	6.8 (0.56)	-5.1 (0.62)	10.8 (0.65)	7.1 (0.56)	-3.7 (0.63)
Median	12.0	6.0	-4.0	10.0	6.0	-3.0
Range	0.0 to 27.0	0.0 to 21.0	-19.0 to 14.0	0.0 to 26.0	0.0 to 21.0	-20.0 to 12.0
Confusion-bewilderment N	100	100	100	95	95	95
Mean (SE)	7.4 (0.39)	5.9 (0.32)	-1.5 (0.32)	7.0 (0.37)	6.1 (0.34)	-0.9 (0.39)
Median	6.0	5.0	-1.0	6.0	5.0	-1.0
Range	0.0 to 18.0	0.0 to 15.0	-11.0 to 6.0	2.0 to 16.0	1.0 to 17.0	-11.0 to 13.0

4.6 Urologic Health Parameters in Part A

Urological health was assessed via measurement of changes in urological symptoms via the AUA, and via the review of AEs related to urological health. Table 23 presents summary statistics for the AUA scores.

Table 23.

Summary Statistics For AUA: Baseline, Post-4th Injection Day 21 and Change from Baseline to Post-4th Injection Day 21 - PK Population (Study IP157-001 Part A Stage 1)

AUA Parameter	TU 750 (N=102)			TU 1000 (N=97)		
	Baseline	Day 21 of 4th Injection Interval	Change	Baseline	Day 21 of 4th Injection Interval	Change
Overall Total N	98	98	98	93	93	93
Mean (SE)	6.1 (0.42)	6.2 (0.60)	0.1 (0.42)	6.2 (0.44)	6.7 (0.57)	0.6 (0.44)
Median	5.0	4.0	0.0	6.0	6.0	0.0
Range	0.0 to 17.0	0.0 to 28.0	-13.0 to 15.0	0.0 to 14.0	0.0 to 27.0	-8.0 to 16.0
Subscales						
Incomplete Emptying N	98	98	98	93	93	93
Mean (SE)	0.8 (0.10)	0.7 (0.10)	-0.1 (0.08)	0.9 (0.12)	0.9 (0.12)	-0.0 (0.13)
Median	0.5	0.0	0.0	1.0	0.0	0.0
Range	0.0 to 4.0	0.0 to 4.0	-2.0 to 2.0	0.0 to 5.0	0.0 to 4.0	-5.0 to 3.0
Frequency N	98	98	98	93	93	93
Mean (SE)	1.2 (0.10)	1.4 (0.14)	0.2 (0.10)	1.3 (0.11)	1.4 (0.11)	0.1 (0.10)
Median	1.0	1.0	0.0	1.0	1.0	0.0
Range	0.0 to 4.0	0.0 to 5.0	-3.0 to 3.0	0.0 to 4.0	0.0 to 4.0	-3.0 to 3.0
Intermittency N	98	98	98	93	93	93
Mean (SE)	0.5 (0.08)	0.6 (0.09)	0.0 (0.07)	0.6 (0.08)	0.7 (0.11)	0.1 (0.08)
Median	0.0	0.0	0.0	0.0	0.0	0.0
Range	0.0 to 3.0	0.0 to 5.0	-2.0 to 3.0	0.0 to 3.0	0.0 to 4.0	-2.0 to 3.0
Urgency N	98	98	98	93	93	93
Mean (SE)	0.7 (0.10)	0.9 (0.13)	0.2 (0.11)	0.8 (0.10)	0.8 (0.12)	0.1 (0.11)
Median	0.0	0.0	0.0	0.0	0.0	0.0
Range	0.0 to 4.0	0.0 to 5.0	-2.0 to 4.0	0.0 to 4.0	0.0 to 5.0	-3.0 to 3.0
Weak stream N	98	98	98	93	93	93
Mean (SE)	0.9 (0.12)	0.9 (0.12)	-0.0 (0.10)	0.8 (0.12)	1.0 (0.14)	0.1 (0.11)
Median	1.0	0.0	0.0	0.0	0.0	0.0
Range	0.0 to 5.0	0.0 to 5.0	-5.0 to 3.0	0.0 to 5.0	0.0 to 5.0	-3.0 to 3.0
Straining N	98	98	98	93	93	93
Mean (SE)	0.4 (0.08)	0.4 (0.09)	-0.1 (0.09)	0.4 (0.08)	0.6 (0.10)	0.2 (0.09)
Median	0.0	0.0	0.0	0.0	0.0	0.0
Range	0.0 to 5.0	0.0 to 5.0	-5.0 to 4.0	0.0 to 5.0	0.0 to 4.0	-2.0 to 4.0
Nocturia N	98	98	98	93	93	93
Mean (SE)	1.5 (0.10)	1.5 (0.12)	-0.0 (0.12)	1.4 (0.10)	1.3 (0.12)	-0.1 (0.11)
Median	1.0	1.0	0.0	1.0	1.0	0.0
Range	0.0 to 5.0	0.0 to 5.0	-3.0 to 4.0	0.0 to 5.0	0.0 to 5.0	-3.0 to 5.0
Urinary Condition	98	98	98	93	93	93
Mean (SE)	1.7 (0.14)	1.5 (0.14)	-0.2 (0.09)	1.6 (0.14)	1.5 (0.13)	-0.1 (0.10)
Median	1.0	1.0	0.0	1.0	1.0	0.0
Range	0.0 to 5.0	0.0 to 5.0	-2.0 to 3.0	0.0 to 5.0	0.0 to 4.0	-2.0 to 3.0

4.7 Local Tolerability Assessments in Part A

Local tolerability was assessed via the use of a local tolerance questionnaire given approximately 10 minutes following each injection. Table 24 presents a list of the incidence rates of these TEAEs.

Table 24.

Incidence of TEAEs related to Local Tolerability by Preferred Term – Total Patient Sample (Study IP157-001 Part A Stage 1)

MedDRA System Organ Class	MedDRA Preferred term	Number of patients (%)	
		TU 750 (N=120)	TU 1000 (N=117)
Total patients with at least 1 TEAE Associated with Local Tolerability		2 (1.7)	5 (4.3)
General disorders and administration site conditions	Injection site erythema	0 (0.0)	1 (0.9)
	Injection site irritation	0 (0.0)	1 (0.9)
	Injection site pruritus	1 (0.8)	1 (0.9)
	Injection site pain	2 (1.7)	2 (1.7)
	Injection site reaction	0 (0.0)	1 (0.9)

Reviewer's Comments: *Regarding safety, this pivotal study was characterized by a low incidence of individual AEs consistent with those expected with other T replacement therapies. Safety outcomes were generally the same for both doses of Nebido and appear to be both safe and well tolerated, and strongly supported by the submitted data from this trial.*

D.II Summarized Safety Results from Study IP157-001 Part C

1.0 Extent of Exposure:

Exposure to TU in Part C averaged approximately 226 days; over 94% of patients received 4 injections, and thus patients were exposed to treatment with TU for almost 6 months. However, consistent with the study design, safety outcomes in this study report reflect an actual median follow-up period of 168 days (24 weeks).

• The planned duration of exposure to study medication was calculated as number of days from first injection to the last injection, plus 70 days. For most patients, the last injection was the 4th injection (24 weeks following the first injection). Exposure to TU would have been derived as 34 weeks.

• Exposure as measured by the duration of safety follow-up was calculated as through the 4th injection visit, and is limited to approximately 24 weeks.

• Patients receiving their 4th injection continued into ongoing Stage 2 of the Part C study; Safety outcomes following the 4th injection were planned to be reported in a separate Stage 2 clinical study report.

Duration of exposure in Part C is seen in Table 25.

Table 25. Duration of exposure in Part C

Duration[1] of Exposure (Weeks)	Number (%) of Patients
	TU 750 mg LOADING (N=130)
0 ≤ Duration ≤ 12 weeks	4 (3.1)
12 < Duration ≤ 24 weeks	112 (86.2)
24 < Duration ≤ 36 weeks	14 (10.8)
36 < Duration ≤ 48 weeks	0 (0.0)
> 48 weeks	0 (0.0)

2.0 Brief Summary of TEAE's in Part C:

Approximately 53.8% of patients experienced at least one AE during the Part C study, with acne and fatigue being the AEs reported with the highest incidence; each was reported in 6 (4.6%) patients. Cough, injection site pain, nasopharyngitis, and pharyngolaryngeal pain were each reported in 4 (3.1%) patients. Thus, the types of events reported tended to be of a minor (and non-serious) nature.

There was one "cough event" that immediately followed an injection with TU. Patient 050-7006 is a 53-year old white male who was diagnosed with primary hypogonadism in August 2006. [The patient had been briefly treated with a transdermal TRT (Androgel) but discontinued that treatment due to lack of efficacy.] He received his 3rd injection on Day 98, and immediately experienced a mild and non-serious "coughing fit lasting ~10 minutes following

[the] injection". The investigator reported the cough was non-productive and that the patient experienced no wheezing or difficulty breathing; no intervention was given, and the patient recovered prior to leaving the office. The patient received his 1st, 2nd, and 4th injections with no associated cough event; further, the patient has continued into Stage 2 where he is still receiving treatment with TU 750 mg every 10 weeks, with no further cough events having been reported. During treatment the patient has demonstrated T concentrations generally within the eugonadal range; his Cmax was 1067.35 ng/dL during the 3rd injection interval. This event was similar to the post-marketing "coughing fit" events that have been reported; these events are suspected to be associated with pulmonary oil microembolism.

There were no other coughs associated with the IM injection of TU during any office visit in Part C.

No AE was reported with an incidence higher than 6 patients, and thus the overall incidence of individual AEs was relatively low in this 24 week study. Table 26 below summarizes TEAEs reported in at least 2.0% of patients, irrespective of relationship to study medication, by preferred term in decreasing order based on incidence rate.

The Sponsor's analysis of AE'S in Part C is provided herein:

• The events reported as at least possibly related were generally consistent with those expected for a population treated with a TRT. For instance, hemoglobin increased, mood swings, prostatic specific antigen increase, and irritability have been reported to be sometimes related to TRT.

• There were only 3 types of at least possibly related TEAEs reported in more than 2 patients: acne, fatigue, and injection site pain. All other events were reported in 2 or fewer patients. Injection site pain was reported in 4 (3.1%) patients, and this incidence of injection site pain was not unexpected.

• The only hormone parameter with an associated TEAE was estradiol; estradiol increased was reported in 2 (1.5%) patients.

There were no deaths in this study.

Table 26 presents a summary of the incidence of treatment-emergent SAE's in Study C.

Table 26. Incidence of treatment-emergent SAE's in Part C.

MedDRA Preferred term	Number of patients (%) TU 750 mg LOADING (N=130)
Total patients with at least 1 TEAE	70 (53.8)
Total patients with at least 1 Treatment-emergent SAE	8 (6.2)
Colitis ischaemic	1 (0.8)
Deep vein thrombosis	1 (0.8)
Faecaloma	1 (0.8)
Intervertebral disc protrusion	1 (0.8)
Myocardial infarction	1 (0.8)
Prostatitis	1 (0.8)
Spinal column stenosis	1 (0.8)
Urinary tract infection	1 (0.8)
Wrist fracture	1 (0.8)

Table 27 presents the incidence of TEAE's leading to discontinuation.

Table 27. Incidence of TEAE's leading to discontinuation in Part C.

MedDRA Preferred term	Number of patients (%) TU 750 mg LOADING (N=130)
Total patients with at least 1 TEAE	70 (53.8)
Total patients with at least 1 TEAE Leading to Discontinuation of Study Medication	5 (3.8)
Acne	1 (0.8)
Mood swings	1 (0.8)
Myocardial infarction	1 (0.8)
Estradiol increased	1 (0.8)
Deep vein thrombosis	1 (0.8)

3.0 Summary of Laboratory Outcomes in Part C

The analysis of clinical laboratory data for Part C reveals changes in lipids, red cells, and other parameters over the treatment period that were consistent with those changes that have been reported for other testosterone replacement medications. The outcomes from the analysis of laboratory data reveal that treatment with TU 750 mg loading regimen resulted in expected changes in parameters known to be affected by testosterone replacement, and in no clinically relevant changes in parameters thought to be generally unaffected by testosterone replacement.

4.0 Safety Conclusions from Part C

Patient safety was monitored during this 24-week study. In addition to the assessment of measured serum free testosterone and other hormones, regular collection of data for PSA, DRE, clinical laboratory data (including serum chemistry, coagulation, lipids, hematology, and urinalysis), vital signs (including pulse, blood pressure, and temperature), and adverse event monitoring were performed. Further, tolerability at the injection site was assessed at every injection visit, following the injection.

Average safety follow-up was over 160 days (i.e., 23 weeks), with the majority of patients completing all 4 injections (and thus completing the 24-week treatment period). The safety of treatment with TU 750 mg given with a 4-week loading injection and every 10 weeks thereafter was demonstrated using these data. The Sponsor's summary of the key safety conclusions follows:

In regard to clinical AE's in Part C

Approximately 53.8% of patients experienced at least one AE during the study; acne and fatigue were the AEs reported with the highest incidence, each in 6 (4.6%) patients. Cough, injection site pain, nasopharyngitis, and pharyngolaryngeal pain were each reported in 4 (3.1%) patients. Thus, the types of events reported tended to be of a minor (and non-serious) nature. No AE was reported with an incidence higher than 6 patients, and thus the overall incidence of individual AEs was relatively low in this 24 week study. General disorders and administration site conditions, infections and infestations, and respiratory, thoracic and mediastinal disorders were the 3 system organ class reported with the highest incidence.

There was one cough event that immediately followed an injection with TU. Patient 050-7006, a 53-year old white male who was diagnosed with primary hypogonadism in August 2006 [and who had previously discontinued treatment with transdermal TRT (Androgel) due to lack of efficacy], received his 3rd injection on Day 98. The patient experienced a mild and non-serious "coughing fit lasting ~10 minutes following [the] injection". The investigator reported the cough was non-productive, and that the patient experienced no wheezing or difficulty breathing. No intervention was given, and the patient recovered prior to leaving the office. The patient received his 1st, 2nd, and 4th injections with no associated cough event; further, the patient continued into Stage 2 where he is still receiving treatment with TU 750 mg every 10 weeks, and no further cough events were reported in Part C.

The proportion of patients experiencing at least one TEAE was similar across age, race, BMI, prior TRT, and Cmax subgroups, with no notable trends observed. Importantly no clinically meaningful difference in the incidence of any type of individual TEAE was noted across these subgroups.

Approximately 23.8% of patients experienced at least one TEAE that was judged to be at least possibly related to study medication. In summary:

• The events reported as at least possibly related were generally consistent with those expected for a population treated with a TRT. For instance, haemoglobin increased, mood swings, and irritability have been reported to be sometimes related to TRT.

• There were only 3 types of at least possibly related TEAEs reported in more than 2 patients: fatigue, acne, and injection site pain. All other events were reported in 2 or fewer patients. Injection site pain was reported in 4 (3.1%) of patients, this overall incidence of injection site pain was not unexpected.

• The only hormone parameter with an associated TEAE was estradiol; estradiol increased was reported in 2 (1.5%) patients.

In general, this study was characterized by a low incidence of individual AEs; given the 24-week treatment period and the rigorous assessment of clinical laboratory outcomes, local tolerability assessments, and the other safety markers, the safety of TU 750 mg given with a 4-week loading injection and every 10 weeks thereafter, the Sponsor believes that safety is strongly supported by the data collected in this study.

There were no deaths in this study. Eight (6.2%) patients experienced at least one treatment-emergent SAE during the treatment period. No SAE was observed in more than 1 patient. There were 5 (3.8%) patients who experienced TEAEs that led to discontinuation from the study medication (and from the study). Four AEs that resulted in discontinuation from the study were judged by the investigator as at least possibly related to study medication: a deep vein thrombosis, estradiol increased, mood swings, and acne. There were no patients who had their study medication temporarily interrupted due to AEs.

The extensive safety monitoring procedures employed in this study included prostate health assessment via the measurement of serum PSA and performance of digital rectal examinations (DREs) at injection visit. Further, laboratory measurements, urological data, and lipid profiles

were collected. Monitoring of adverse events was performed in an ongoing manner throughout the course of the study. There were very few serious events reported.

In regard to clinical laboratory assessments in Part C

Changes in laboratory values over the treatment period in Part C were consistent with those changes that have been reported for other testosterone replacement medications. The outcomes from the analysis of laboratory data reveal that treatment with TU 750 mg loading regimen resulted in expected changes in parameters known to be affected by testosterone replacement. These data are generally consistent with those observed in Part A.

In regard to vital signs and other observations related to safety in Part C

Included here is a summary of outcomes for vital signs, prostate health, mood states, and local tolerability in Part C.

There were no clinically meaningful changes in average blood pressure or pulse from pre-treatment to endpoint; average (median) systolic BP increased approximately 0.4 (0.0) mmHg, while average (median) diastolic BP increased approximately 0.8 (0.0) mmHg. No clinically relevant changes in pulse rate were noted.

A summary of prostate health in this study is as follows:

• There were 5 (3.9%) patients with at least one post-baseline PSA value over 4 ng/mL during this study. However, 2 of these patients had a baseline (pre-1st injection) PSA of 4.2 ng/mL. Thus, there were 3 (3.2%) patients who had a new-onset PSA value over 4 ng/mL.

• Patients with a higher pre-treatment PSA were more likely to exceed the 4 ng/mL threshold during the study than those patients with a lower pre-treatment PSA. Notably, there were 7 patients with pre-treatment PSA concentrations between 3 and 4 ng/mL. Of these 7 patients, 2 (33.3%) exceeded the 4 ng/mL PSA threshold at some time in this study. In contrast, patients who had a pre-treatment PSA < 3 ng/mL rarely exceeded the 4 ng/mL threshold while under treatment with TU.

• Average PSA values did not increase by more than 0.3 ng/mL from pre-treatment to the end of the 24 week treatment period. According to the Sponsor, treatment with other TRT preparations has been reported to increase PSA by approximately 0.5 ng/mL per year, and this study demonstrated consistent PSA as that reported for other preparations.

• Average PSA velocity was = 0.3 ng/mL over the 24-week treatment period, and a few individual patients in this study had a PSA velocity that exceeded 2 ng/mL.

• A review of TEAEs was performed to identify any events related to prostate health. Events included prostatitis, benign prostatic hyperplasia, PSA elevations and other events associated with prostate health. The most commonly reported AE associated with prostate health was prostatitis, reported for 3 (2.3%) patients. PSA increased was reported by 2 (1.5%) patients. Note that some of the prostate health-related events were judged by the investigator to be at least possibly related to study treatment.

• The incidence of abnormal prostate findings varied from visit to visit. The screening visit had the highest incidence of abnormal prostate findings, with 17 (13.1%) patients having an abnormal outcome on the screening DRE. Of these 17 patients with abnormal findings, 16 (94.1%) patients had an enlarged prostate at the screening visit. The incidence of on-treatment abnormal prostates was generally the same across the on-treatment weeks.

• There was a low incidence of any abnormal prostate findings on DRE during the treatment period. Only 11 (8.5%) of patients had, at any given time post-1st injection, an abnormal prostate finding based on their DRE; most of these 11 patients had an enlarged prostate as their abnormality. When compared to the incidence rate of abnormal prostate outcomes pre-treatment, the incidence on-treatment was unremarkable.

These data are generally consistent with those observed in Part A.

In order to assess changes in mood states, a review of TEAEs was performed to identify any events related to changes in mood during the course of the study. TEAEs related to mood states included mood swings, aggression, anxiety, and irritability. There were no reports of anger or depression in the Part C study.

Urological health was assessed via the review of AEs related to urological health. A review of TEAEs was performed to identify any events related to urinary health, and specifically bothersome urinary symptoms. Events that the data were reviewed for included pollakiuria, urinary hesitation, urinary retention, urine flow decreased, and nocturia. Bothersome urinary symptoms were reported in a total of 2 (1.5%) patients; no individual event of this type was reported in more than 1 patient.

Approximately half of patients in this study reported mild pain following at least one of their injections; however, only 4 (3.1%) patients reported injection site pain as an adverse event during the study. Further, only 2 (1.5%) patients reported moderate pain, while no patient reported severe pain associated with the injection in this study.

5.0 Overall Safety Conclusion, Part C

Treatment with TU 750 mg loading regimen resulted in safety outcomes consistent with those expected for a TRT provided to men with primary or secondary hypogonadism. Treatment resulted in a low overall incidence rate of TEAEs in all system organ classes, with some reports of expected TEAEs. Changes in laboratory parameters were generally minor and not clinically meaningful, while changes in lipids, erythropoiesis, and hormone parameters were consistent with those changes that have been reported for other testosterone replacement medications. Prostate health was carefully monitored, and no unexpected incidence rates of any untoward event were observed. PSA concentrations increased slightly, as expected. No clinically meaningful changes in vital sign or other safety outcomes were noted, and the injections were well-tolerated. Average safety follow-up was over 160 days, with the majority of patients completing all 4 injections. One patient reported a “coughing fit” event in the Part C study. Overall, reasonable safety and tolerability of treatment with TU 750 mg loading regimen was demonstrated in Part C.

D.III Summarized Safety Results from Study ME97029, (A Synopsis)

1.0 General study design and outcome measures.

This was a single-center, open-label, controlled 2-arm parallel study of the safety and efficacy of multiple injections of TU 1000 mg or testosterone enanthate (TE) 250 mg. Forty hypogonadal men were randomized between the 2 arms. TU was administered at 6-week intervals (3 doses) and a final injection after a 9-week interval. TE was administered at 3-week intervals. T was sampled at 3-week intervals during the 30-week study. Primary efficacy variables were hemoglobin, hematocrit, and grip strength. Secondary efficacy variables included serum levels of T and other hormones, sexual activity, well-being, bone density and metabolism, and body composition and lipids. In a follow-up extension, 36 subjects were offered treatment and 32 completed through 8 additional injections. TU subjects received injections for 8 additional injection cycles, and TE subjects were crossed over to TU 1000 mg treatment. All subjects completing the 1st extension entered a 2nd follow-up extension and 26 completed through their 10th injection (exceeding 4 years exposure).

2.0 Demographic and baseline characteristics.

Participants were hypogonadal Caucasians 18-64 years old. Treatments groups were similar with respect to age, height, weight, BMI and other characteristics.

3.0 Extent of Exposure

All 20 subjects receiving TU 1000 mg had a cumulative exposure of 4000 mg during the 30-week treatment period.

4.0 Clinical AEs

There were no deaths or SAEs during this study. In the TU group, 12 AEs involved 8 of 20 subjects, with the causal association listed as probable in 1 (injection site pain), possible in 1 (increased snoring), improbable in 1 (unspecified), and none in 9. The most frequent AEs were upper respiratory infection (4 AEs in 3 subjects) and headache (2 AEs in 2 subjects).

The investigator in this study was not required to document abnormal laboratory findings, however 2 subjects in the TU group had abnormal laboratory values (unspecified).

Vital signs and physical findings at the final examination did not change as compared to data acquired at the screening examinations. TU displayed good local tolerability: there was only 1 subject from the TU treatment group with mild reddening, swelling and induration 3 weeks after the first administration, and no other signs of intolerability occurred in the course of treatment.

During the treatment period, sporadic episodes of supraphysiological serum T levels were detected at individual measurement times in 5 patients receiving TU; aberrant values were confirmed by the final T assay in 2 patients. In view of the fact that in the two patients abnormal T values were found after the last TU administration (week 24 to 30), the Sponsor determined that a prolongation of this 9-week dosing interval could be advantageous in order to minimize episodes of supraphysiological serum T concentrations.

In this small study, the subjects tolerated this formulation well, while not exhibiting more AEs than the comparator formulation.

Appendices

E. Study IP157-001 Part A

1.0 Introduction

TU is a long-acting depot formulation of testosterone undecanoate in castor oil and benzyl benzoate solution intended as replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous testosterone. The dosage form is an oily solution of 250 mg/mL TU, with 4 mL [redacted] (b) (4) intended for intramuscular injection. An injection of 3 mL yields 750 mg TU, and an injection of 4 mL yields 1000 mg TU.

In this study, 2 treatment regimens were studied:

• 3 mL of 250 mg/mL TU (ie, TU 750 mg) given intramuscularly (IM) every 12 weeks, and;

• 4 mL of 250 mg/mL TU (ie, TU 1000 mg) given IM every 12 weeks.

1.1 Testosterone Replacement Therapy (TRT) with TU

Intramuscular administration of T esters is currently used as a well-established approach to hormone replacement therapy (HRT) in hypogonadal men. Testosterone enanthate (TE) or testosterone cypionate (TC) are commercially available preparations for this indication. Using these preparations, levels of total testosterone (TT) within the normal physiological range can be achieved for 2-3 weeks following a single injection.

Testosterone undecanoate has been developed in order to provide a convenient option for long term replacement therapy. It is a depot formulation which allows the extension of the injection interval almost by perhaps a factor of 5, from a 2- to 3-week interval for the standard replacement therapy with TE (ie, 17 to 26 injections per year) to up to 12-week intervals with testosterone undecanoate (ie, 4 to 5 injections per year).

[redacted] (b) (4)

The first marketing authorization for Nebido was granted in Finland on 25 November 2003. Under the trade names Nebido® and Reandron®, it is currently approved for marketing in over 70 countries (other than the US) and is actively marketed in 36 countries.

1.1 Dose Selection

The doses used in this study were designed to address the need to provide T concentrations within the FDA thresholds for both Cmax and Cavg. Specifically, the dosing regimens selected were expected, based on modeling and simulations using data from earlier clinical studies of TU 1000 mg, to provide steady state Cmax values that would not exceed 2500 ng/dL for any subject, would not exceed 1800 ng/dL in more than 5% of subjects, and would not exceed 1500 ng/dL in more than 15% of subjects. Further, the dosing regimens selected were expected to provide steady state Cavg values within the normal range (300 to 1000

ng/dL) for at least 75% of subjects (with a lower bound for the 95% confidence interval about the proportion being no lower than 65 %).

2.0 Design of Study IP157-001, Part A

2.1 Study Objectives

The primary objective of this study was to evaluate the pharmacokinetics of T from TU 750 mg and TU 1000 mg IM injections given every 12 weeks, via measurements of T concentrations in up to approximately 110 hypogonadal men per treatment group. T was to be assessed during the 4th injection dosing interval (i.e., after the 4th injection).

Secondary objectives were:

• To evaluate the pharmacokinetics (of T) from TU following the 1st, 2nd, and 3rd injections of TU 750 mg or TU 1000 mg IM dose, over the 12-week dosing intervals in 20 hypogonadal men per treatment group.

• To compare serum levels of DHT, E2, SHBG, TU, and DHTU to simultaneous levels of T.

• To evaluate long-term safety in all patients via extended (up to 3 years) treatment with TU 750 mg or TU 1000 mg IM dose, given every 12 weeks in hypogonadal men.

Safety assessment included:

• Serum levels of prostate-specific antigen (PSA, by enzyme-linked immunoassay [EIA])

• Prostate assessment via digital rectal exam (DRE)

• AUA Symptom Score

• Local Tolerability at Injection Site

• Adverse Events

• Standard clinical laboratory parameters

• Sex hormones, including measurement of serum free testosterone, TU, DHTU, SHBG, DHT and estradiol at every time point T was to be measured (with the limited exception of the sparse PK assessments where 6 T/DHT assessments were to be collected in the 1st 20 subjects in each treatment group during the 2nd and 3rd dosing intervals) and LH and FSH with clinical laboratory parameters

• Vital Signs

• Physical Examination

Additional clinical assessments included:

• Hip-to-waist ratio

• Hand Grip Strength

• International Index of Erectile Function

• Profile of Mood States (POMS)

• Male Patient Global Assessment (M-PGA)

• Psychosexual Daily Questionnaire

2.2 Study Design in Detail

There were 2 arms in this study, TU 750 mg and TU 1000 mg, each given every 12 weeks. Approximately 110 subjects were to be randomized to each of these 2 arms. Stage 1 was completed and was the basis for the study report in the original NDA. Stage 2 is ongoing, and data from Stage 2 were not included in the original study report.

This was a multicenter, 2-arm, randomized, open-label part of the study. Treatment arms were:

• 750 mg testosterone undecanoate (250 mg/mL) in 3 mL oily solution (TU 750 mg), injected every 12 weeks

• 1000 mg testosterone undecanoate (250 mg/mL) in 4 mL oily solution (TU 1000 mg), injected every 12 weeks

Approximately 110 subjects were to be randomized into each treatment dose arm for a total of up to approximately 220 subjects. The randomization schedule for subjects was to be stratified by the screening T concentration level as follows:

• testosterone < 150 ng/dL, and;

• testosterone = 150 to < 250, and;

• testosterone = 250 < 300 ng/dL.

The last screening T measurement prior to randomization was used to determine the subject stratification level.

The first 40 subjects (20 per treatment group) were to be included as the sub-group of subjects who would undergo intensive pharmacokinetic (IPK) assessments during both the 1st and 4th injection intervals with sparse additional T/DHT PK assessments post 2nd and 3rd injection, while the remaining 180 subjects were to have IPK captured after only the 4th injection.

The primary analysis was performed following the completion of the post-injection IPK collections.

Subjects were to have a trough PK at the 2nd and 3rd injection and were to continue to have trough PK captured thereafter (following the 5th injection, i.e., during the extension portion of the study) at each 12-week dosing interval visit through the remainder of the study. Additionally, the first 40 subjects were to have testosterone and DHT levels assessed at three timepoints each post 2nd and 3rd injection.

2.3 Intensive Pharmacokinetic Collection

Intensive pharmacokinetic assessment was to be performed in this study. The pharmacokinetic sampling schedule reflected the 12-week dosing interval of TU. Sampling for PK was to be performed as follows:

• In the first 20 subjects in each treatment group after the 1st injection at Day 0 (pre-injection), Day 4, 7, 11, 14, 21, 28, 42, 56, 70, and the end of the injection interval at Day 84, ie, at injection visit 2, and; Day 42, 56, 70 post 2nd injection and Day 42, 56, 70 post 3rd injection (ie, the sparse PK assessments)

• After the 4th injection at 36 weeks post-first injection, PK draws were planned at Day 0 (pre-injection), 4, 7, 11, 14, 21, 28, 42, 56, 70, and Day 84, where the 5th injection visit was defined as the end of the injection interval.

The 1st injection IPK data was to be used to characterize the single-injection concentration-time profile for each treatment group, and is included in the Stage 1 analysis in this study report. Additionally, the first 40 subjects were to have sparse PK assessment of testosterone and DHT levels assessed at three time points each post 2nd and 3rd injection, and these data are included in this study report.

The 4th injection IPK data will be used to determine the primary pharmacokinetic outcomes.

Reviewer's Comment: Unfortunately, the interval after the fourth injection was not at steady-state, as Sponsor had anticipated.

2.3.1 Inclusion Criteria

To be considered eligible to participate in this study, the subject must have met the following requirements:

1. Male with primary or secondary hypogonadism at least 18 years of age

2. Morning screening serum testosterone concentration < 300 ng/dL

3. If receiving endocrine replacement hormones (e.g., thyroid), antihypertensives, lipid lowering agents, antidepressants or anxiolytic medications, the dose must be stable for at least 28 days prior to entry OR is not currently on such medications.

4. Able to consent to participate by signing an Informed Consent Form following an explanation of the nature and purpose of this study.

2.3.2 Exclusion Criteria

Subjects were not eligible for entry into this study if they met any of the following criteria:

1. Participation in another clinical trial within the 30 days preceding the first administration of the study drug

2. Simultaneous participation in another clinical trial

3. AUA Symptom Score ≥ 15

4. Blood donation (including plasmapheresis) or blood loss ≥ 500 mL in the last 30 days before the beginning of the study or in the 30 days preceding a visit which includes a determination of serum hormone levels

5. Prostatic symptoms, tumors or induration of the prostate or the male mammary gland including suspicion thereof. In case of serum PSA levels ≥ 4 ng/mL or hyperplasia of the prostate as measured by transrectal ultrasonography), the investigator can include the respective patient if a carcinoma of the prostate has been ruled out by other means (e.g., biopsy)

6. Past or present liver tumors or acute or chronic hepatic disease with impairment of liver function; liver function tests (AST, ALT) exceeding 1.5 times upper limit of normal (normal range provided by central laboratory)

7. History of deep vein thrombosis in the past 5 years or any history of cerebrovascular accident

8. Severe acne

9. Serious psychiatric disease or uncontrolled medical illness, as suspected from the history and/or the clinical examination

10. Hypertension (systolic blood pressure >160 mmHg and diastolic >95 mmHg) or coronary heart disease not stabilized by therapy as assessed by the investigator

11. Insulin-dependent diabetes mellitus or uncontrolled non-insulin-dependent diabetes mellitus

12. Use of any sex hormones within 28 days (for injectable testosterone preparations) or 7 days (for oral, gel, patch testosterone preparations, etc.) prior to Screening serum testosterone collection for PK assessment, and at any time throughout the study

13. Biochemical and/or hematological laboratory values outside the normal ranges, unless the investigator confirms that the deviations are of no clinical relevance

14. Any chronic use of drugs and/or alcohol abuse

15. Use of steroidal anabolic drugs or supplements (e.g., DHEA) by any application method within the 28-days prior to the first administration of the study drug and throughout the study (exclusive of the administered study drug)

16. Medication with substances which might interfere with testosterone metabolism within 28 days before the first administration of the study drug and throughout the study

17. Use of anticoagulants (with the exception of low-dose aspirin) within 28 days before the first administration of the study drug and throughout the study

18. Use of antiandrogens, estrogens, p450 enzyme inducers, barbiturates or antidepressant concomitant medication therapy

19. Clinical history suggestive of allergy to testosterone undecanoate or the excipient and/or severe intolerances, allergies or idiosyncrasies to other drugs

20. History of sleep apnea

2.3.3. Subject Discontinuation

If a subject was discontinued from the study prematurely, the Investigator was to select a reason for discontinuation on the End of Study Phase Status eCRF. In addition, every effort was to be made to complete the assessments listed under the End of Study visit.

Subjects withdrawn from the study were generally considered evaluable for statistical assessments, but may have been excluded from some assessments (eg, PK) if insufficient data was present to warrant inclusion in the analysis.

The study protocols and amendments listed the following reason for why a subject may have been removed from the study:

• Adverse Event: If a subject experienced an adverse event that the subject finds unacceptable or that, in the judgment of the Principal Investigator, Indevus Pharmaceuticals, Inc., or the Medical Monitor presents an unacceptable consequence or risk to the patient, the subject may be discontinued from further participation in the study.

• Administrative Discontinuation: After consultation with the Sponsor or Medical Monitor, a subject may be discontinued from the study for failure to comply with protocol requirements. All instances of noncompliance must be documented in the eCRF.

• Refusal of Treatment: If for any reason the subject refuses treatment during the study, the subject shall be discontinued from the study and the reasons for refusal documented on the eCRF. Reasonable efforts shall be made to monitor the subject for adverse events following such discontinuation. Such efforts shall be documented on the eCRF.

2.3.4. Early Discontinuation Criteria

In the event a subject experienced any of the following or a significant change in status as judged by the investigator was detected, the evaluation should have been repeated on a separate day and, if confirmed, the subject should have been terminated from the study.

1. Hemoglobin > 21.0 gm/dL

2. Uncontrolled hypertension, defined as blood pressure with systolic blood pressure ≥ 160 and diastolic blood pressure ≥ 95

3. PSA ≥ 4 ng/mL unless prostate cancer is ruled out by new biopsy

4. PSA ≥ 10 ng/mL.

The schedules for PK sampling and protocol events are shown in Appendix A Tables 1 and 2.

Appendix A Table 1.

Schedule of Pharmacokinetic Intensive Sampling and Additional Clinical Outcomes Events (Study IP157-001 Part A)

Intensive PK Collection Time Points (Post-Injection 1[a] ,2[a] ,3[a] ,and 4[b] Only)											
	Day										
Assessments	0[c]	4	7	11	14	21	28	42	56	70	84[c,d]
Serum Total Testosterone[e]	X	X	X	X	X	X	X	X	X	X	X
DHT[e]	X	X	X	X	X	X	X	X	X	X	X
TU	X	X	X	X	X	X	X	X	X	X	X
DHTU	X	X	X	X	X	X	X	X	X	X	X
Estradiol	X	X	X	X	X	X	X	X	X	X	X
SHBG	X	X	X	X	X	X	X	X	X	X	X
Free T (measured)	X	X	X	X	X	X	X	X	X	X	X
Psychosexual Daily Questionnaire (7-day diary)						X (start on Day 21)	X (return on Day 28)				
International Index of Erectile Function & AUA Symptom Score						X					
Profile of Mood States						X					
Male Patient Global Assessment						X					
Local tolerability assessment			X Post injection 4 only								

Appendix A Table 2.

Schedule of Events (Study IP157-001 Part A)

	Injection Number and Week															
	Screening Phase		1	2	3	4	5	6	7	8	9	10	11	12	13	EOS
	Days -35 to -7	Post-Washout	Day 0	12	24	36	48	60	72	84	96	108	120	132	144	156[5]
Informed Consent	X															
Eligibility	X		X[1]													
Medical History	X		X[1]													
Physical Exam	X					X		X				X				X
Digital Rectal Examination	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital Signs (includes pulse, blood pressure, temperature)	X		X			X		X				X				X
12 Lead ECG	X					X		X				X				X
Hematology, Coagulation, Chemistry, Urinalysis, FSH, LH	X		X	X		X		X				X				X
Lipid Profile - Preferred Fasting (Total, LDL, HDL cholesterol & triglycerides) and PSA	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Prostate Volume (via TRUS)[2]	X															
Pharmacokinetic Sampling (T, DHT, FREE T,TU, DHTU, E2, SHBG) TU/DHTU are not collected at screening	X only if Washout NOT Required	X if Washout Required	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events			X	X	X	X	X	X	X	X	X	X	X	X	X	X
Prior/Concomitant Medications	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Injection (includes drug accountability)			X	X	X	X	X	X	X	X	X	X	X	X	X	
Local tolerability assessment[3]			X	X	X	X	X	X	X	X	X	X	X	X	X	X
Body Measurements (hip-and-waist circumference, hand grip strength and weight; height is captured at Baseline only; DEXA[4])			X			X		X				X				X
Profile of Mood States			X	X	X	X	X	X	X	X	X	X	X	X	X	X
Psychosexual Daily Questionnaire (7-day diary to begin 7 days prior to Baseline)	X only if Washout NOT Required	X if Washout Required	Patient Returns Diary													
International Index of Erectile Function			X	X		X		X				X				X
AUA Symptom Score	X		X	X		X		X				X				X
Male Patient Global Assessment				X		X		X				X				X

2.4 Statistical Methods

Descriptive methods were used to present all the data from both treatment arms.
In agreement with the primary objectives of the study, the primary analysis was the Stage 1 assessment of T pharmacokinetics during the 4th injection interval. The Stage 1 analysis included all subjects and all data (including baseline characteristics, pharmacokinetic assessment of 1st through 4th injection intervals, and safety data) through the 5th injection visit for each subject.

2.5 Sample Size

The sample size was based on the primary efficacy outcome parameter, the proportion of subjects in each treatment group "responding to treatment" during the 4th injection interval as defined by Cavg within the normal range [ie, the proportion of subjects with a Cavg value falling within the normal reference range for T (300 – 1000 ng/dL)]. When the sample size is 73 in a treatment group, a two-sided 95% confidence interval using the large sample normal approximation to the binomial will extend 0.10 from the observed proportion, based on an assumed expected proportion of 0.75. Thus, assuming a response rate of 75% or greater in a treatment group, the lower bound of the 95% confidence interval will fall no lower than 65% in that treatment group. The treatment groups will be independently assessed in the analysis.

2.6 Primary Efficacy Variable

The primary efficacy variable upon which the null hypothesis was to be tested was the proportion of subjects "responding to treatment" post protocol-defined 4th injection interval (Weeks 36 - 48). A subject was to be defined as a responder if his average concentration of T (Cavg) fell within the normal range of 300 to 1000 ng/dL, where Cavg was to be derived as the AUC of the dose interval divided by the duration of the dosing interval.

Thus:
• A subject was to be considered a responder if his Cavg was in the interval [300,1000] ng/dL.

• A subject was to be considered NOT a responder if his Cavg was either < 300 ng/dL or > 1000 ng/dL.

A full PK analysis of the concentrations was also included in the assessment of the primary efficacy analysis.

2.7 Secondary Efficacy Variables

• Additional serum T pharmacokinetic assessments, as follows

o The number (and percent) of subjects with T concentration values outside the normal range (below 300 ng/dL or above 1000 ng/dL), both separately for high/low values, and pooled (high and/or low values), for each time point following the 4th injection.

o The number (%) of subjects for whom the T concentration values were within the normal range for each time point following the 4th injection.

o “Clinical Success”. This was defined based on Cavg and Ctrough concentrations during the 4th injection interval. Subjects were classified as a ‘Clinical Success’ if both their Cavg and Ctrough values fell within the normal range of 300 to 1000 ng/dL.

• Steady state assessment of T concentrations during the 4th injection interval

• Serum T Cmax outcomes compared to the FDA thresholds

• 1st injection interval serum T concentrations

• 2nd and 3rd injection interval serum T concentrations

o Correlation assessments of serum T concentrations with clinical outcome (POMS, PSDQ, IIEF and M-PGA) changes from pre-treatment to the 4th injection interval.

o Changes from pre-treatment in body measurement characteristics (including weight, BMI and hip-to-waist ratio) and grip strength (from the pre-4th injection time point) assessed for correlation (Pearson coefficients) with T concentration PK parameters (Cmax, Cavg, and Ctrough) obtained from the 4th injection interval.

o The impact of T concentrations on erythropoiesis assessed via plots of the time course of hemoglobin and hematocrit versus T concentrations for the Stage 1 period.

o The impact of T concentrations on lipid markers (HDL, LDL, total cholesterol) assessed via plots of their time course versus T concentrations for the Stage 1 period.

o Exploration of factors that may be predictive of T Cmax or Cavg during the 4th Injection interval, including:

.. Age

.. Baseline (pre-1st injection) serum T

.. Baseline BMI and weight

.. Prior TRT use

.. Other variables as warranted

• Other hormone concentration assessments over time and their association with changes in T concentrations (including Free T, DHT, SHBG, E2 and their ratios to T over time)

• Drug (TU) and metabolite (DHTU) concentration assessments over time and their association with T concentrations.

2.8 Clinical Efficacy

Clinical markers of T replacement therapy included:

• Body Composition (eg, weight, BMI, grip strength)

• Psychosexual Daily Questionnaire

• International Index of Erectile Function

°Male Patient Global Assessment

3.0 Safety Assessments

All safety data collected were to be included in the data listings sorted by domain, subject and time point. Mean changes from baseline (pre-treatment) to on-treatment were generally tabulated by protocol-specified time points, while the incidence of shifts from baseline of values from the pre-defined potentially clinically significant ranges (with individual values categorized as low, normal or high based on those ranges) were presented for endpoint/final values. For those subjects missing a baseline value for a particular parameter, the screening value was used as the pre-treatment value for that parameter.

For purposes of safety assessment, the 'endpoint' and 'final' value are both defined as the last observed value for a subject during the Stage 1 treatment period (up to and including the 5th Injection visit). This value represented the point at which the patient has had the longest exposure to TU.

Generally, safety assessments were performed using the Total Subject Sample. Additional analyses were performed using the PK Population or other subgroups of patients. Potentially clinically significant ranges were defined for clinical laboratory parameters, vital signs and ECG outcomes.

3.1 Adverse Events

Tabulations included an overall incidence of at least one adverse event, incidence within body system, and incidence by preferred term. Each subject only contributed once (ie, first occurrence) to each of the incidence rates, regardless of the number of occurrences.

Events occurring prior to the first injection were to be reported in the medical history section of the eCRF. The incidence of adverse events for the Stage 1 analysis was presented as follows:

The incidence of treatment-emergent adverse events was tabulated by treatment for the Stage 1 Treatment Phase. Treatment-emergent was defined as any adverse event with an onset date greater than or equal to the study medication first injection date.

Subjects with serious adverse events (including deaths) and subjects who discontinued due to adverse events were listed. Subjects who had other significant serious adverse events deemed to

be of special interest because of clinical importance were also listed. Narratives were included in the clinical study report for these subjects.

3.2 PSA Serum Levels

PSA levels in serum were to be determined by the Central laboratory. Blood samples were to be collected at Screening, Baseline, and on-treatment as noted in the schedules of events (see Table 2). Generally, the last pre-treatment value prior to the injection was used in the analysis for assessment of changes over time. Descriptive statistics at baseline (pre-treatment), endpoint, and change from pre-treatment were calculated for the subjects who had both pre-treatment and on-treatment evaluations. Shifts from pre-treatment to endpoint were examined, and when applicable, PSA samples were to be obtained prior to digital rectal examinations being performed.

3.3 Prostate Volume

Transrectal ultrasonography (TRUS) of the prostate was to be performed during screening (prior to randomization) to determine the volume of the organ and if necessary to clarify abnormal findings of palpation if present. These data were to be listed.

3.4 Clinical Laboratory Tests

Clinical laboratory tests were to be performed as noted in the schedule of events in the study protocol. Parameters were to include:

• CLINICAL CHEMISTRY - Total protein, albumin, serum creatinine, blood urea nitrogen (BUN), uric acid, bilirubin (total & direct), alkaline phosphatase, alanine aminotransferase (ALT, SGPT), aspartate aminotransferase (AST, SGOT), creatine phosphokinase (CPK), glucose, calcium, phosphorus, sodium, potassium, chloride, bicarbonate, follicle stimulating hormone (FSH), and luteinizing hormone (LH)

• LIPID PANEL - Triglycerides, total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL). Best attempts were to be made to collect FASTING LIPIDs, where the fast was to have begun at least 8 hours prior to lipid assessment.

• HEMATOLOGY - White blood cell (WBC) count, differential white cell count (lymphocytes, monocytes, basophils, eosinophils, neutrophils), red blood cell (RBC) count, hematocrit, hemoglobin, platelet count, PT, PTT and INR

• URINALYSIS - Color, specific gravity, pH, glucose, ketones, blood, protein, leukocyte esterase, RBC, WBC.

These data were analyzed as follows:

• Descriptive statistics at pre-treatment, on-treatment, and change from pre-treatment were calculated for the patients who had both pre-treatment and on-treatment evaluations. These values were assessed at each protocol-specified time point.

• Shifts from pre-treatment to the last (endpoint) value were tabulated.

• The number of patients with potentially clinically significant values at pre-treatment and at the last (endpoint) value were tabulated

o Special attention was given to markers of erythropoiesis (eg, hematocrit, hemoglobin) and lipids.

3.5 and 3.6 Vital signs and ECGs

Vital sign and ECG data were analyzed as follows:

• Descriptive statistics at pre-treatment, on-treatment, and change from pre-treatment were calculated for the subjects who had both pre-treatment and on-treatment evaluations. These values were assessed at each protocol-specified time point.

• Shifts from pre-treatment to the last (endpoint) value were be tabulated.

• The number of subjects with potentially clinically significant values at pre-treatment and at the last (endpoint) value was tabulated.

3.7 Digital Rectal Examinations

DREs were conducted at screening, baseline, and on-treatment as noted in the schedule of events (see Table 2). Descriptive statistics at baseline (pre-treatment), on-treatment, and change from pre-treatment were to be calculated for the subjects who had both pre-treatment and on-treatment evaluations.

3.8 AUA Symptom Score

The AUA Symptom Score is a self-reported 7 item validated instrument. The score is the sum of questions 1 to 7. The lowest score is 0 and the maximum total score is 35 with higher scores indicating more bothersome urinary symptoms. Seven response domains include incomplete emptying, frequency, intermittency, urgency, weak stream, straining, and nocturia. Changes in these assessments over time (from baseline) were tabulated. If, for a particular subject, there were approximately 30% or more missing items, the score was set to missing for that patient.

3.9 Local Tolerability

Pain, color change, swelling/induration, and tenderness were assessed. These data were to be tabulated by response category. Clinically significant finding(s) as judged by the investigator were to be recorded as Adverse Events; thus, tolerability symptoms reported on the questionnaire were not considered to be AEs unless assessed by the investigator as such.

4.0 Physical Examinations

Physical examinations were to be performed at screening and on-treatment as noted in the schedule of events (see Appendix A Table 2). Descriptive statistics were to be calculated for subjects who had both Baseline and on treatment evaluations, where appropriate.

4.1 Body Measurements

Body measurements were to be performed at baseline and on-treatment. Descriptive statistics were to be calculated for subjects who had both baseline and on treatment evaluations. Mean changes over time (from baseline) were to be tabulated. Similar assessments of grip strength were to be tabulated. Hand grip strength assessments will be averaged within each hand (left/right) within each subject.

5.0 Profile of Mood States (POMS)

This questionnaire consists of 65 adjectives that describe feelings and mood (e.g. aggression, depression, etc.). There are six subscales: tension-anxiety; depression-dejection; anger-hostility; vigor-activity; fatigue-inertia; and confusion-bewilderment. The subscales were used to an overall Total Mood Disturbance score. Higher scores represented higher tension-anxiety, depression-dejection, etc. For the Vigor subscale, higher scores represented 'better' functioning.

Changes in these assessments over time (from baseline) were to be tabulated by visit. If, for a particular subject, a subscale had 30% or more missing items, that domain was set to missing for that subject. If any one (or more) of the subscales was missing, the Total Mood Disturbance score was not derived.

5.2 Psychosexual Daily Questionnaire

The Psychosexual Daily Questionnaires (PSDQ) was to be completed daily by the subject approximately 7 days prior to Baseline and on-treatment as noted in the schedule of events in the study protocol. This questionnaire is a validated self-report diary designed to assess psychosexual function in hypogonadal men. Parameters are measured to assess 3 different domains:

• sexual desire, sexual enjoyment and sexual performance;

• sexual activity; and;

• moods (positive or negative).

5.3 International Index of Erectile Function (IIEF)

Subjects were to complete the IIEF at the start of the study (baseline visit) and again at intermittent follow-up visits. Changes in these assessments over time (from baseline) for each

domain and the total were tabulated. The five response domains include erectile function, orgasmic function, sexual desire, intercourse satisfaction, and overall satisfaction.

5.4 Male Patient Global Assessment (M-PGA)

Global self-evaluation of change in hypogonadal symptoms and overall well-being were to be assessed using the M-PGA questionnaire starting on treatment at Week 12 and as noted in Schedule of Events. The M-PGA is a 5-item self-report questionnaire designed to assess patient perception of change from pre-treatment or baseline in their hypogonadal symptoms including confidence/self-esteem, sexual performance, moods/behavior, overall feeling of well-being, and satisfaction with the study treatment.

M-PGA responses were to be tabulated by treatment group by original responses and by a collapsed set of categories. For the first 4 questions, the proportion of subjects in each treatment group with improvement (eg, 'Very Much Improved', 'Much Improved', or 'Minimally Improved') were collapsed into a single category, while the proportion of the corresponding group with worsening ('Very Much Worse', 'Much Worse', or 'Minimally Worse') was collapsed into a second category. 'No Change' responses were the third category. Similar categories were derived for the Patient Satisfaction question. Note that the subject satisfaction with study treatment was measured and tabulated by the response to the question: "Please, rate your satisfaction with the study treatment according to the following scale:

• (1 = very much satisfied to 7 = very much dissatisfied)."

5.5 Pharmacokinetic T Assessments

As previously stated, the main PK assessment objectives were:

• To characterize the T pharmacokinetics from TU 750 mg and TU 1000 mg given every 12 weeks (during the 4th injection interval) in patients with hypogonadism at each dose level.

• To characterize, in a subgroup of approximately 20 patients per arm, the single-injection pharmacokinetics of TU 750 mg and TU 1000 mg during a 12 week interval.

T was to be measured at all injection visits during the course of the study and at the last study visit. IPK monitoring was to be performed in all subjects of both treatment arm doses after the 4th injection, and was to include the following time points: Day 0 (pre-4th-injection), Day 4, 7, 11, 14, 21, 28, 42, 56, 70 and the end of the injection interval at Day 84 (pre-5th-injection), ie, at the 5th injection visit.

Similar sampling after the 1st injection was to be performed in the first 20 subjects randomized to each treatment arm, to allow for characterization of the single-injection T concentration-time profile for each treatment arm. Additional T and DHT levels were to be assessed in this subset of subjects following the 2nd and 3rd injections on Days 42, 56 and 70 and these sparse data were to be included in the Stage 1 analysis.

5.6 Other Hormone Assessments

Selected hormones were assessed for serum levels during all protocol-scheduled time points that T was measured. Hormone data, including free testosterone, DHT, estradiol and SHBG were presented using concentration-time plots. Ratios of DHT:T and E2:T were presented over the dosing interval. TU (the parent compound) and DHTU (a metabolite) levels were also assessed.

6.0 Study Subjects

6.1 Disposition

Subjects that were considered for enrollment in the study but who did not meet eligibility criteria (i.e., inclusion or exclusion criteria) were considered screen failures. Of the 692 subjects screened by the sites, 455 (65.8%) subjects were screen failures. The majority of screen failures were due to one of 2 reasons: too high of a T concentration (ie, a screening T = 300 ng/dL), or study enrollment completed. A large number of subjects did not necessarily fail screening; however, these subjects were not randomized because the enrollment target had been completed (and thus enrollment into the study was terminated prior to these subjects entering the study).

The remaining 237 subjects were enrolled (i.e., randomized and treated with at least one injection of study medication). Of the 120 TU 750 mg subjects that were enrolled, 99 (82.5%) subjects completed Stage 1 (through the 5th injection visit), while of the 117 TU 1000 mg subjects that were enrolled, 94 (80.3%) subjects completed Stage 1. These completing subjects all continued into Stage 2 of the study.

Table 3 and Table 4 summarize the subject accounting and primary screen failure reasons.

Appendix A Table 3. Patient Accounting (Study IP157-001 Part A Stage 1)

	Number of patients		
	TU 750	**TU 1000**	**Total**
Screened	N/A	N/A	692
Enrolled[1]	120	117	237
Completing 5th Injection Visit N (% Based on Enrolled Patients)	99 (82.5)	94 (80.3)	193 (81.4)
Premature Discontinuation N (% Based on Enrolled Patients)	21 (17.5)	23 (19.7)	44 (18.6)

Appendix A Table 4. Number (%) of Patients by Screen Failure Reason

Reason for Screen Failure	**Number (%) of Patients**
Total Number Patients Screen Failure	**455**
Screening testosterone ≥ 300 ng/dL	184 (40.4)
Study enrollment completed	164 (36.0)
History of sleep apnea	21 (4.6)
Prostate-Related (includes high PSA and prostate abnormalities)	18 (4.0)
Other reasons[1]	68 (14.9)

7.0 Efficacy Evaluation

7.1 Demographic and Other Baseline Characteristics

Baseline Characteristics

The patients averaged approximately 55 years of age, were predominantly white with an average BMI of approximately 31.5 kg/m2; over half the patients had a BMI over 30 kg/m2, and thus patients in this study tended to be, on average, overweight. The average screening serum total testosterone (T) was 185.9 for patients in the TU 750 mg arm and 188.4 ng/dL for patients in the TU 1000 mg arm. The demographic and baseline characteristics of the Total Patient Sample are summarized in Table 5.

Appendix A Table 5. Baseline Demographics in Part A

Characteristic	TU 750 (N=120)	TU 1000 (N=117)
Age (in years)		
Mean ± SE	55.0 ± 0.97	55.9 ± 1.00
Median (range)	54 (30, 82)	56 (23, 83)
Age Categories, N (%)		
< 30	0 (0.0)	1 (0.9)
30 - <40	9 (7.5)	5 (4.3)
40 - <50	23 (19.2)	28 (23.9)
50 - <60	48 (40.0)	36 (30.8)
60 - <70	28 (23.3)	40 (34.2)
70 - <80	10 (8.3)	4 (3.4)
≥ 80	2 (1.7)	3 (2.6)
Gender, N (%)		
Male	120 (100.0)	117 (100.0)
Race, N (%)		
White	101 (84.2)	106 (90.6)
Black	11 (9.2)	8 (6.8)
Hispanic	3 (2.5)	3 (2.6)
Asian	2 (1.7)	0 (0.0)
Other	3 (2.5)	0 (0.0)
Height (in cm)		
Mean ± SE	178.5 ± 0.72	179.4 ± 0.70
Weight (in kg)		
Mean ± SE	101.4 ± 1.68	101.7 ± 1.89
BMI (kg/m^2)[1]		
Mean ± SE	31.8 ± 0.47	31.5 ± 0.51
Screening Inclusion Serum Total Testosterone (ng/dL)		
Mean ± SE	185.9 (7.2)	188.4 (7.11)
Median (range)	201.1 (0.0 to 300.0)	208.9 (0.0 to 295.7)

7.2 Prior T Replacement Therapy (TRT)

Prior TRT use was reported by 103 (85.8%) TU 750 mg subjects, and by 92 (78.6%) TU 1000 mg subjects prior to study entry. Androgel was by far the most frequently reported prior TRT medication, with over 40% of subjects in both treatment arms having taken Androgel at least once prior to study entry. Other TRT medications used by at least 20% of subjects in either treatment group included Depo-Testosterone, Androderm and Testim.

A summary of prior TRT use is seen in Appendix A Table 6.

Appendix A Table 6. Number (%) of Patients Reporting Having Used Testosterone Therapy Prior to Study Enrollment - Total Patient Sample

	Number (%) of patients	
Prior Testosterone Replacement Therapy	**TU 750 (N=120)**	**TU 1000 (N=117)**
At least one prior testosterone replacement therapy	**103 (85.8)**	**92 (78.6)**
Androgel	55 (45.8)	48 (41.0)
Depo-Testosterone	36 (30.0)	35 (29.9)
Testim	24 (20.0)	27 (23.1)
Androderm	24 (20.0)	15 (12.8)
Testosterone Enanthate (generic or Delatestryl)	15 (12.5)	14 (12.0)
Testosterone Cypionate (generic)	7 (5.8)	6(5.1)
Striant Buccal	4 (3.3)	3 (2.6)
Other	8 (6.7)	8 (6.8)

4.0 Primary Efficacy Results

(b) (4)

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11.0 Correlation Assessments of T with Clinical Outcome Measures

Clinical outcome measures included in this assessment were the POMS (mood states), PSDQ (psychosexual functioning), IIEF (erectile function), and M-PGA (patient global assessment), and the subscores for each of these measures. Appendix A Table 14 provides a summary of these correlation assessments.

Appendix A Table 14. Correlation Coefficients of Serum Total Testosterone Pharmacokinetic Parameters with Clinical Outcome Measures Collected on Day 0 (Pre-4th Injection) and Day 21 (Week 3) of 4th injection interval – PK Population

Clinical Outcome Measure	Pharmacokinetic Parameter	Correlation Coefficient (P-Value[1])			
		Day 0		Day 21	
		TU 750 mg (N=102)	TU 1000 mg (N=97)	TU 750 mg (N=102)	TU 1000 mg (N=97)
POMS Total Score	C_{avg}	0.061 (0.544)	0.022 (0.831)	0.071 (0.486)	-0.004 (0.973)
	C_{max}	0.021 (0.832)	0.007 (0.944)	0.014 (0.888)	-0.006 (0.954)
	C_{Trough} (Day 84 Value)	0.059 (0.558)	0.045 (0.665)	0.033 (0.743)	-0.047 (0.650)
POMS Tension-anxiety	C_{avg}	-0.006 (0.949)	0.035 (0.731)	0.095 (0.351)	0.061 (0.557)
	C_{max}	-0.024 (0.813)	-0.024 (0.814)	-0.016 (0.872)	0.076 (0.466)
	C_{Trough} (Day 84 Value)	0.052 (0.601)	0.081 (0.431)	0.106 (0.295)	-0.042 (0.690)
POMS Depression-Dejection	C_{avg}	0.005 (0.959)	0.125 (0.223)	0.003 (0.975)	0.020 (0.847)
	C_{max}	-0.033 (0.740)	0.084 (0.412)	-0.042 (0.679)	-0.006 (0.956)
	C_{Trough} (Day 84 Value)	0.060 (0.548)	0.125 (0.224)	0.016 (0.876)	0.011 (0.918)
PSDQ Sexual Desire	C_{avg}	N/A	N/A	0.212 (0.039)	-0.038 (0.726)
	C_{max}	N/A	N/A	0.194 (0.058)	-0.124 (0.248)
	C_{Trough} (Day 84 Value)	N/A	N/A	0.115 (0.263)	-0.001 (0.990)
PSDQ Sexual Enjoyment without Partner	C_{avg}	N/A	N/A	0.046 (0.658)	-0.036 (0.742)
	C_{max}	N/A	N/A	-0.057 (0.585)	-0.079 (0.469)
	C_{Trough} (Day 84 Value)	N/A	N/A	-0.025 (0.813)	0.052 (0.633)
PSDQ Sexual Enjoyment with Partner	C_{avg}	N/A	N/A	0.157 (0.130)	-0.111 (0.305)
	C_{max}	N/A	N/A	0.107 (0.301)	-0.054 (0.621)
	C_{Trough} (Day 84 Value)	N/A	N/A	0.031 (0.768)	-0.184 (0.087)
PSDQ Sexual Activity	C_{avg}	N/A	N/A	0.132 (0.202)	0.032 (0.767)
	C_{max}	N/A	N/A	0.068 (0.514)	-0.003 (0.976)
	C_{Trough} (Day 84 Value)	N/A	N/A	-0.031 (0.766)	0.046 (0.670)

Clinical Outcome Measure	Pharmacokinetic Parameter	Correlation Coefficient (P-Value[1])			
		Day 0		Day 21	
		TU 750 mg (N=102)	TU 1000 mg (N=97)	TU 750 mg (N=102)	TU 1000 mg (N=97)
PSDQ Positive Moods	C_{avg}	N/A	N/A	0.178 (0.089)	-0.138 (0.203)
	C_{max}	N/A	N/A	0.131 (0.209)	-0.111 (0.304)
	C_{Trough} (Day 84 Value)	N/A	N/A	0.131 (0.209)	-0.061 (0.573)
PSDQ Negative Moods	C_{avg}	N/A	N/A	0.087 (0.409)	0.146 (0.176)
	C_{max}	N/A	N/A	0.103 (0.324)	0.080 (0.462)
	C_{Trough} (Day 84 Value)	N/A	N/A	0.082 (0.433)	0.099 (0.364)
PSDQ Satisfactory Duration	C_{avg}	N/A	N/A	-0.003 (0.979)	-0.081 (0.513)
	C_{max}	N/A	N/A	-0.054 (0.672)	-0.037 (0.764)
	C_{Trough} (Day 84 Value)	N/A	N/A	0.131 (0.299)	-0.063 (0.612)
IIEF Erectile Function	C_{avg}	0.231 (0.019)	0.079 (0.447)	0.121 (0.232)	0.167 (0.107)
	C_{max}	0.248 (0.012)	0.116 (0.262)	0.199 (0.049)	0.155 (0.137)
	C_{Trough} (Day 84 Value)	0.153 (0.124)	-0.064 (0.536)	0.025 (0.808)	-0.003 (0.978)
IIEF Orgasmic Function	C_{avg}	0.091 (0.364)	-0.039 (0.702)	0.037 (0.716)	0.047 (0.650)
	C_{max}	0.172 (0.085)	-0.007 (0.948)	0.187 (0.065)	-0.001 (0.993)
	C_{Trough} (Day 84 Value)	0.024 (0.812)	-0.082 (0.422)	-0.057 (0.578)	-0.009 (0.933)
IIEF Sexual Desire	C_{avg}	0.063 (0.529)	0.175 (0.086)	0.214 (0.034)	0.237 (0.021)
	C_{max}	0.098 (0.328)	0.078 (0.449)	0.234 (0.020)	0.127 (0.224)
	C_{Trough} (Day 84 Value)	0.045 (0.653)	-0.019 (0.851)	0.050 (0.626)	0.038 (0.714)
IIEF Intercourse Satisfaction	C_{avg}	0.122 (0.222)	0.130 (0.204)	0.087 (0.392)	0.191 (0.065)
	C_{max}	0.139 (0.164)	0.114 (0.265)	0.168 (0.099)	0.125 (0.232)
	C_{Trough} (Day 84 Value)	0.137 (0.171)	-0.022 (0.832)	0.038 (0.712)	0.068 (0.517)
IIEF Overall Satisfaction	C_{avg}	0.092 (0.375)	-0.022 (0.831)	0.055 (0.601)	0.072 (0.495)
	C_{max}	0.115 (0.267)	-0.090 (0.390)	0.062 (0.554)	0.016 (0.882)
	C_{Trough} (Day 84 Value)	0.119 (0.249)	-0.006 (0.956)	0.090 (0.392)	-0.009 (0.931)
M-PGA Confidence/Self-Esteem	C_{avg}	-0.147 (0.141)	-0.014 (0.889)	-0.179 (0.077)	-0.103 (0.323)
	C_{max}	-0.159 (0.109)	-0.045 (0.663)	-0.124 (0.220)	-0.083 (0.424)
	C_{Trough} (Day 84 Value)	-0.237 (0.017)	0.061 (0.550)	-0.292 (0.003)	-0.116 (0.266)
M-PGA Sexual Performance	C_{avg}	-0.084 (0.401)	-0.053 (0.604)	-0.209 (0.038)	-0.180 (0.082)
	C_{max}	-0.074 (0.461)	-0.121 (0.239)	-0.149 (0.142)	-0.218 (0.034)
	C_{Trough} (Day 84 Value)	-0.237 (0.016)	0.014 (0.895)	-0.264 (0.008)	-0.052 (0.620)
M-PGA Moods/Behavior	C_{avg}	-0.083 (0.409)	-0.064 (0.536)	-0.122 (0.231)	-0.091 (0.382)
	C_{max}	-0.089 (0.373)	-0.114 (0.267)	-0.105 (0.302)	-0.169 (0.103)
	C_{Trough} (Day 84 Value)	-0.254 (0.010)	0.031 (0.764)	-0.263 (0.009)	-0.066 (0.530)
M-PGA Overall Feeling of Well-Being	C_{avg}	-0.103 (0.305)	-0.062 (0.544)	-0.245 (0.015)	-0.132 (0.203)
	C_{max}	-0.096 (0.335)	-0.090 (0.379)	-0.174 (0.085)	-0.161 (0.121)
	C_{Trough} (Day 84 Value)	-0.259 (0.009)	0.026 (0.799)	-0.233 (0.020)	-0.060 (0.566)
M-PGA Satisfaction with Study Treatment	C_{avg}	0.033 (0.740)	-0.067 (0.517)	-0.112 (0.268)	-0.178 (0.086)
	C_{max}	0.013 (0.898)	-0.078 (0.445)	-0.086 (0.399)	-0.112 (0.281)
	C_{Trough} (Day 84 Value)	-0.121 (0.225)	0.019 (0.852)	-0.165 (0.103)	-0.146 (0.162)

<u>Reviewer's Comment</u>: It is not possible to determine clear correlation between any clinical endpoint and T pharmacokinetics based upon this analysis.

12.0 Body Measurements and T

Changes in hip to waist ratios and in grip strength outcomes demonstrated no meaningful correlations with T exposure. However, for the TU 750 mg group, T concentrations were weakly inversely correlated with changes from pre-treatment in weight and BMI. Thus, in the TU 750 mg group, the observed decreases in body weight and BMI from pre-treatment to the 4th injection interval tended to be greater (i.e, more weight loss, lower BMI) in those subjects with higher T exposure than in those subjects with lower T exposure. The strength of the linear correlation was weak, with the Pearson correlation coefficients between 0 and 0.3. There was no correlation noted for subjects in the TU 1000 mg arm with respect to weight or BMI and T concentrations. Appendix A Table 15 provides the Pearson correlation coefficients and p-values for test of strength of linear association between the T PK parameters (from the 4th

injection interval) and changes from pre-treatment in weight, BMI, the hip to waist ratio and grip strength from Day 0 of the 4th injection interval (i.e, the pre 4th injection value).

Appendix A Table 15. Body Composition Changes from Pre-Treatment to Day 0 of 4th Injection Interval Correlated with Serum Total Testosterone Pharmacokinetic Parameters (from 4th Injection Interval)—PK Population

Body Measurement Parameter	Pharmacokinetic Parameter	Correlation Coefficient and P-Value[1]	
		TU 750 mg (N=102)	TU 1000 mg (N=97)
Weight	C_{avg}	-0.278 (0.005)	-0.027 (0.797)
	C_{max}	-0.121 (0.226)	-0.041 (0.693)
	C_{min} (Trough, Day 84 Value)	-0.090 (0.370)	0.024 (0.816)
BMI	C_{avg}	-0.264 (0.008)	-0.016 (0.879)
	C_{max}	-0.109 (0.276)	-0.031 (0.764)
	C_{min} (Trough, Day 84 Value)	-0.082 (0.417)	0.036 (0.730)
Hip to Waist Ratio	C_{avg}	-0.027 (0.787)	-0.045 (0.663)
	C_{max}	-0.050 (0.616)	0.085 (0.411)
	C_{min} (Trough, Day 84 Value)	-0.026 (0.799)	-0.164 (0.111)
Grip Strength (Right Hand)	C_{avg}	0.053 (0.600)	0.043 (0.683)
	C_{max}	0.002 (0.984)	0.020 (0.851)
	C_{min} (Trough, Day 84 Value)	0.225 (0.024)	0.127 (0.221)
Grip Strength (Left Hand)	C_{avg}	-0.015 (0.879)	0.072 (0.485)
	C_{max}	-0.104 (0.303)	0.039 (0.711)
	C_{min} (Trough, Day 84 Value)	0.149 (0.137)	0.149 (0.148)

13.0 Erythropoiesis Laboratory Parameters and T

Data demonstrated that for both treatment groups:

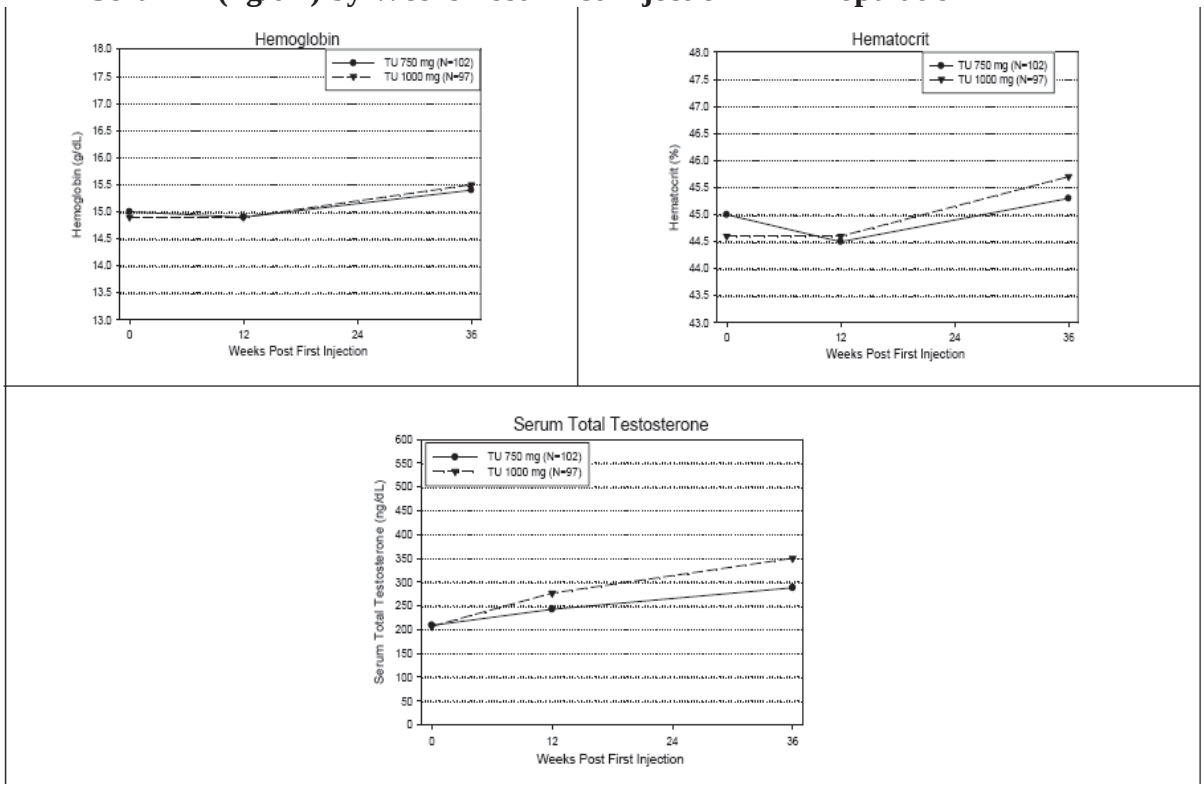
• Average values of hemoglobin and hematocrit increased slightly from pre-treatment to Week 36 as average T concentrations increased; however, the average increases in these erythropoietic markers were small in magnitude, with average values remaining well within the normal range.

• Changes in hemoglobin or hematocrit were not apparent at the Week 12 time point, but rather were seen only by the Week 36 time point, suggesting that more than 12 weeks of treatment with TU 1000 mg or TU 750 mg was required to manifest the small average increases in these parameters.

• Hemoglobin and hematocrit demonstrated low variability across treatments and visits, and thus were relatively stable during the treatment period.

Appendix A Figure 4 presents plots of the average hemoglobin and hematocrit values over time.

Appendix A Figure 4. Average Hemoglobin (g/dL) and Hematocrit (%) vs Average Serum T (ng/dL) by Weeks Post-First Injection—PK Population



14. Lipid Laboratory Parameters and T

Lipid changes were marked by:

• Reductions in average triglycerides as average T concentrations increased, noted for both treatment groups but slightly greater for the TU 1000 mg arm. Over the course of the 48 weeks of treatment, subjects in the TU 1000 mg group experienced an average reduction in triglycerides of 40 mg/dL.

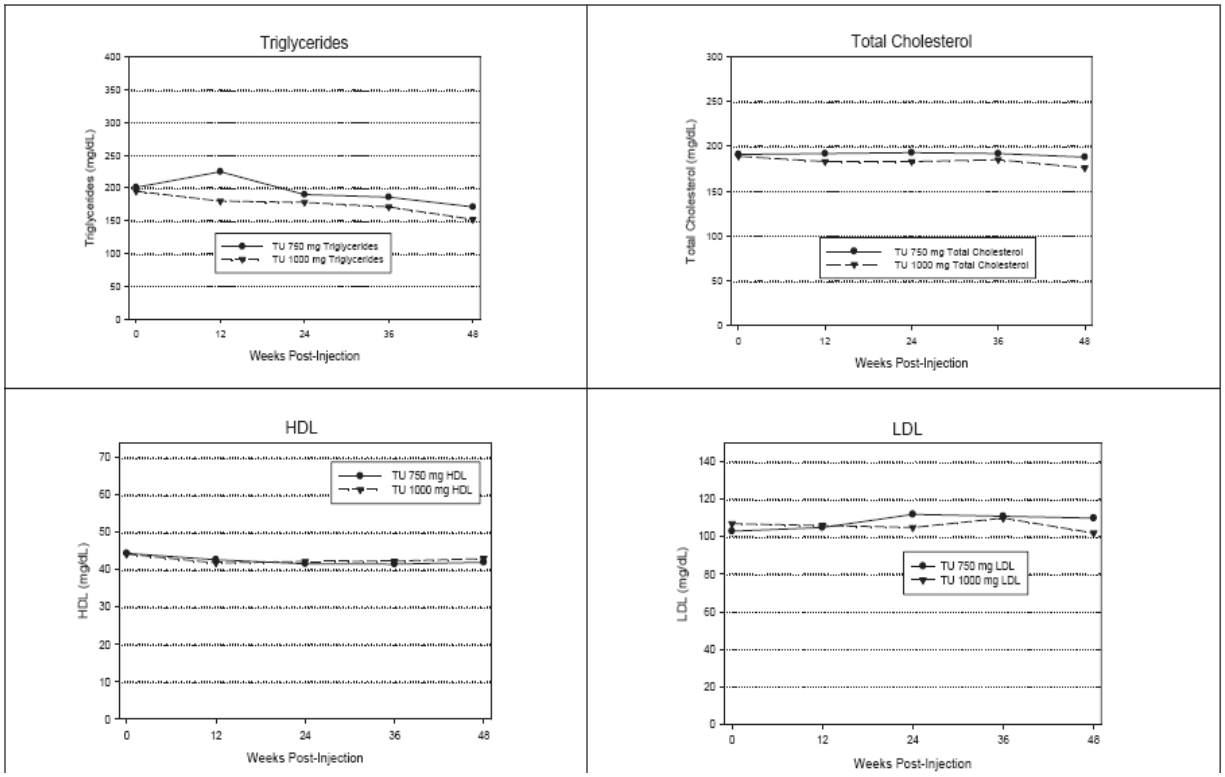
• Minor reductions in average total cholesterol and HDL were noted for both treatment groups. Over the course of the 48 weeks of treatment, patients in the TU 1000 mg group experienced an average reduction in total cholesterol of 12 mg/dL and an average reduction in HDL of 2 mg/dL.

• No meaningful changes in average LDL were observed in either treatment group.

Patients in the TU 750 mg group experienced reductions in triglycerides and total cholesterol with slightly less magnitude than for the TU 1000 mg subjects. Generally, average reductions in these lipid parameters (including HDL) became clear only after at least 24 weeks of treatment, with reductions continuing to be seen through the 48 week time point.

Appendix A Figure 5 presents the average lipids for PK population subjects who reported fasting prior to sample collection for the PK Population patients. Injection visits are denoted by the number of weeks post-first injection.

Appendix A Figure 5. Average Fasting Lipids by Weeks Post-1st Injection



15. Other Factors Associated with T Exposure

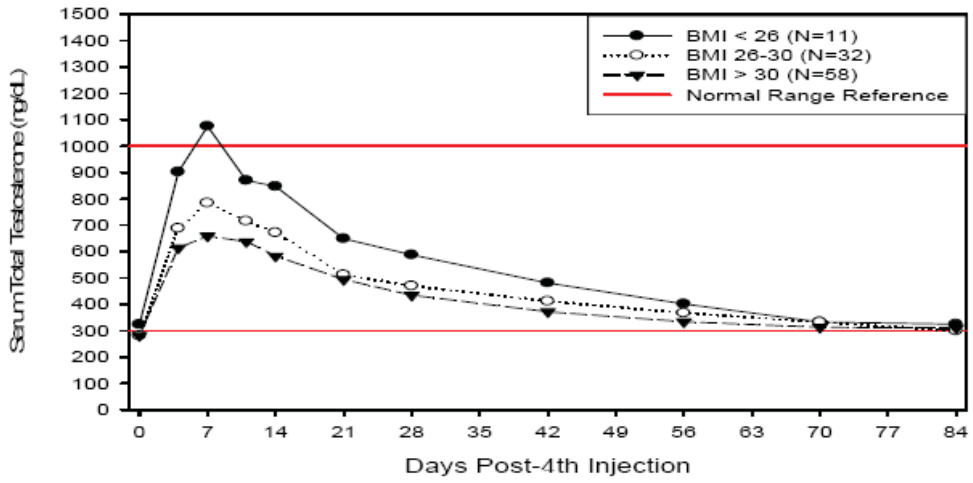
Appendix A Table16 provides a summary of the average Cmax and Cavg values by the pre-defined BMI subgroups. Note that the number of subjects in the subgroups varies, with the lowest BMI subgroup having the least subjects contributing data and the highest BMI subgroup having the most patients.

Appendix A Table 16. Summary of Average (Standard Deviation) Serum Total Testosterone Cavg and Cmax During 4th Injection Interval by BMI Subgroups – PK Population

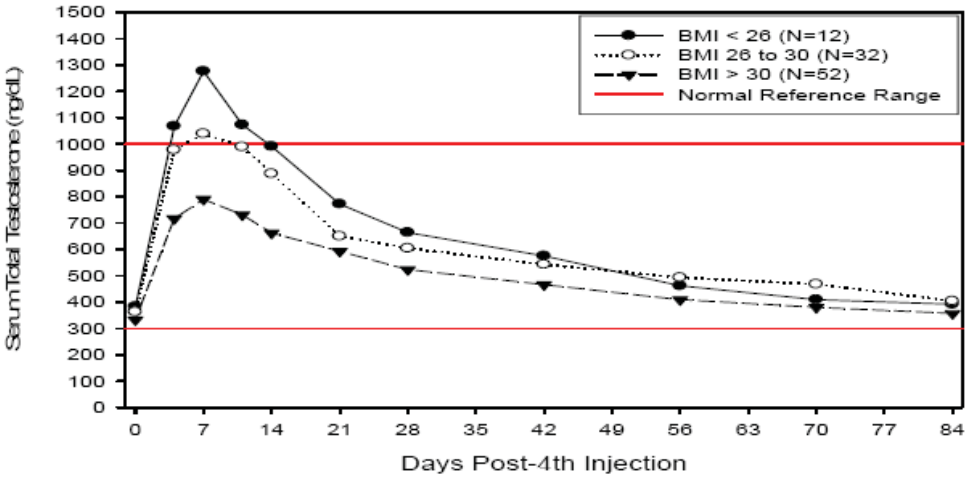
	TU 750 (N=102)			TU 1000 (N=97)		
	<26 kg/m^2 (N=11)	26-30 kg/m^2 (N=32)	>30 kg/m^2 (N=58)	<26 kg/m^2 (N=12)	26-30 kg/m^2 (N=32)	>30 kg/m^2 (N=52)
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
C_{max} (ng/dL)	1084.8 (344.96)	837.2 (333.17)	713.1 (260.57)	1271.5 (383.67)	1108.4 (396.81)	858.0 (344.27)
C_{avg} (ng/dL)	535.0 (99.49)	457.2 (150.42)	409.6 (110.78)	623.0 (131.88)	603.6 (167.86)	498.5 (164.22)

Appendix A Figures 5 and 6 provide the average concentration-time profiles for T by BMI subgroup for the TU 750 mg arm and the TU 1000 mg arm, respectively.

Appendix A Figure 5. TU 750 mg Average Serum Total Testosterone by Time Point During 4th Injection Interval by BMI Subgroups – PK Population



Appendix A Figure 6. TU 1000 mg Average Serum Total Testosterone by Time Point During 4th Injection Interval by BMI Subgroups

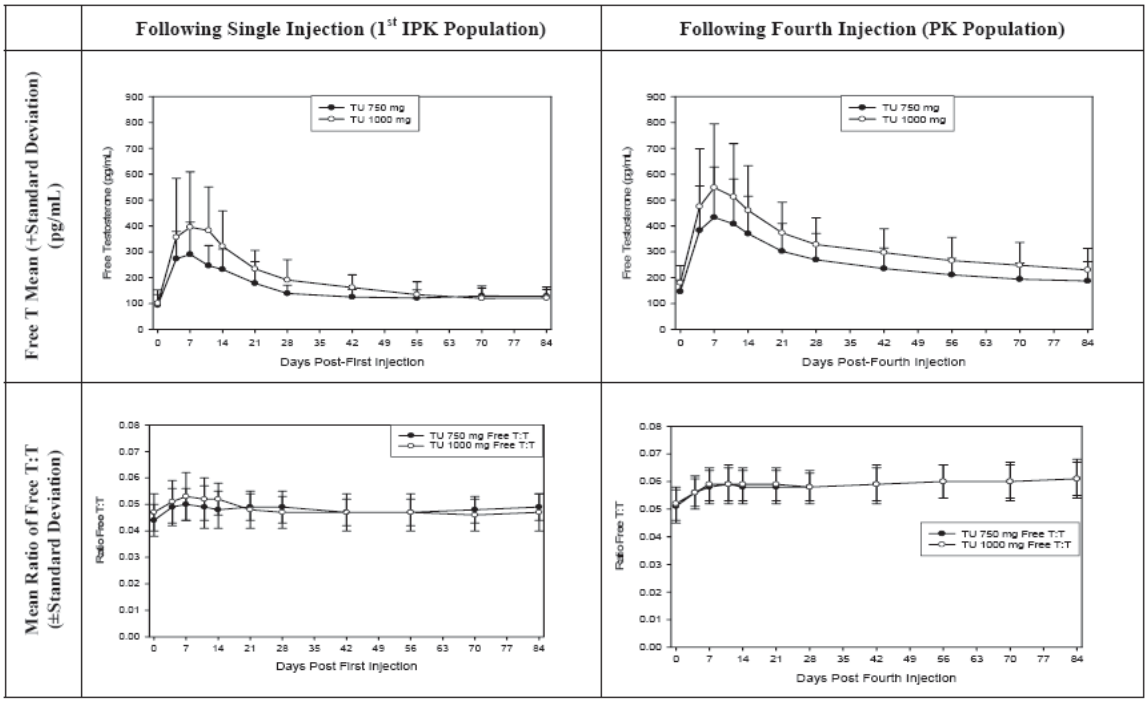


16. Other Hormones and T

Treatment with T has been shown to change concentrations of other hormones, and comprehensive assessments of the effects of treatment with TU on hormones is provided in this section. Of particular interest were the relationships between T concentrations and each hormone following either a single injection of TU or at steady state (b) (4) . Hormones were assessed for their average concentrations over time as well as how changes in their concentrations were associated with changes in T concentrations over time. Data from both the 1st injection interval (using the 1st IPK Population) and the 4th injection interval (using the PK Population) were included in the analysis.

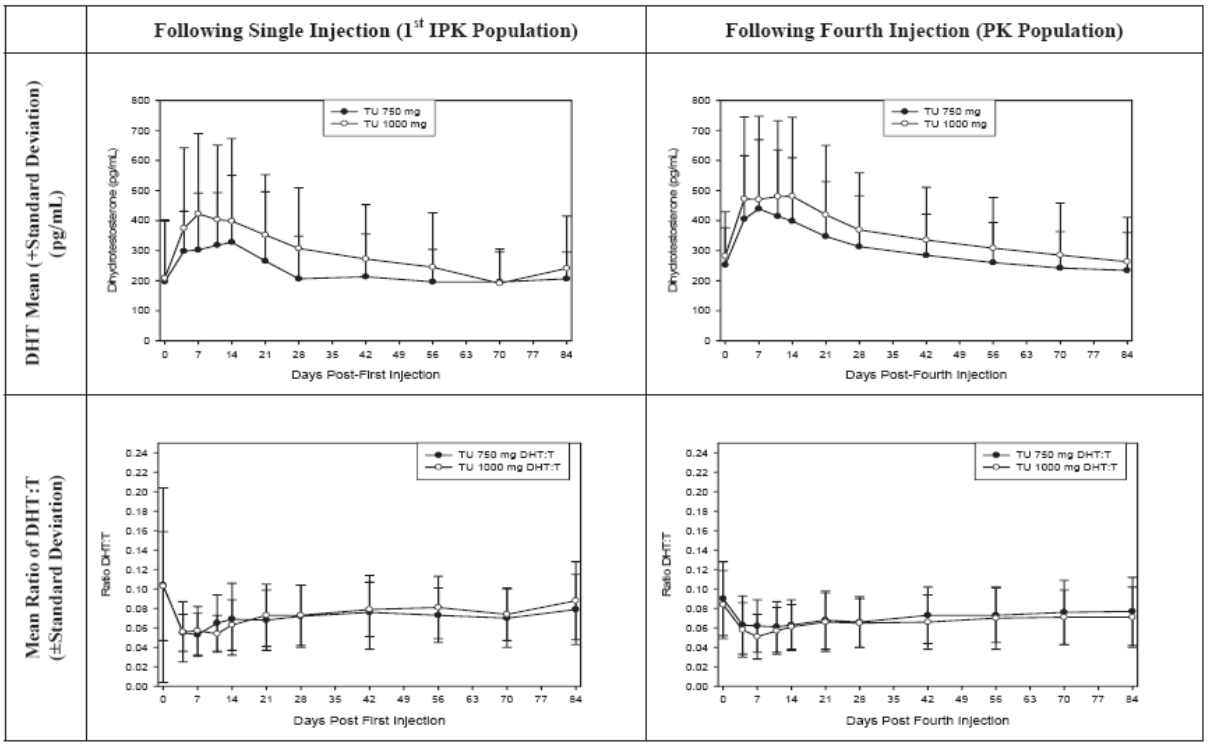
Appendix A Figure 7 provides 4 plots of Free T levels and demonstrates the relationship between Free T and T.

Appendix A Figure 7. Free T and the Relationship of Free T to Total T following the 1st and 4th Injections of TU



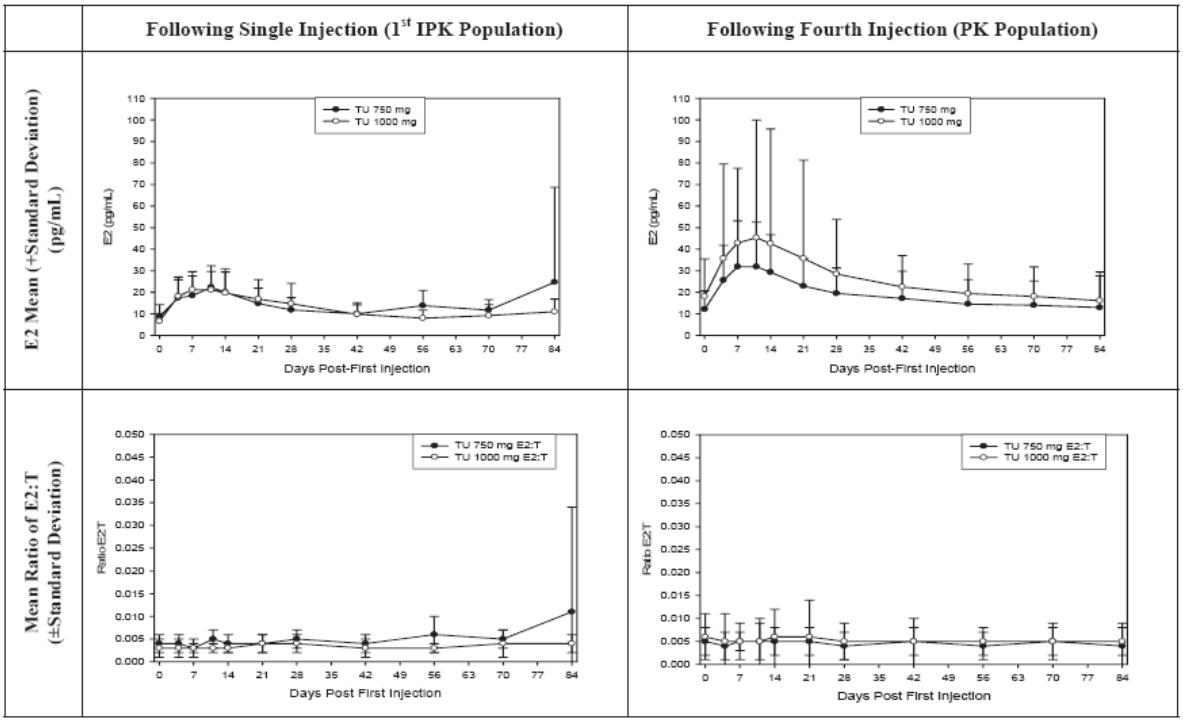
Appendix A Figure 8 provides 4 plots of DHT and demonstrates the relationship between DHT and T.

Appendix A Figure 8. DHT and the Ratio of DHT to Total T Following the 1st and 4th Injections of TU



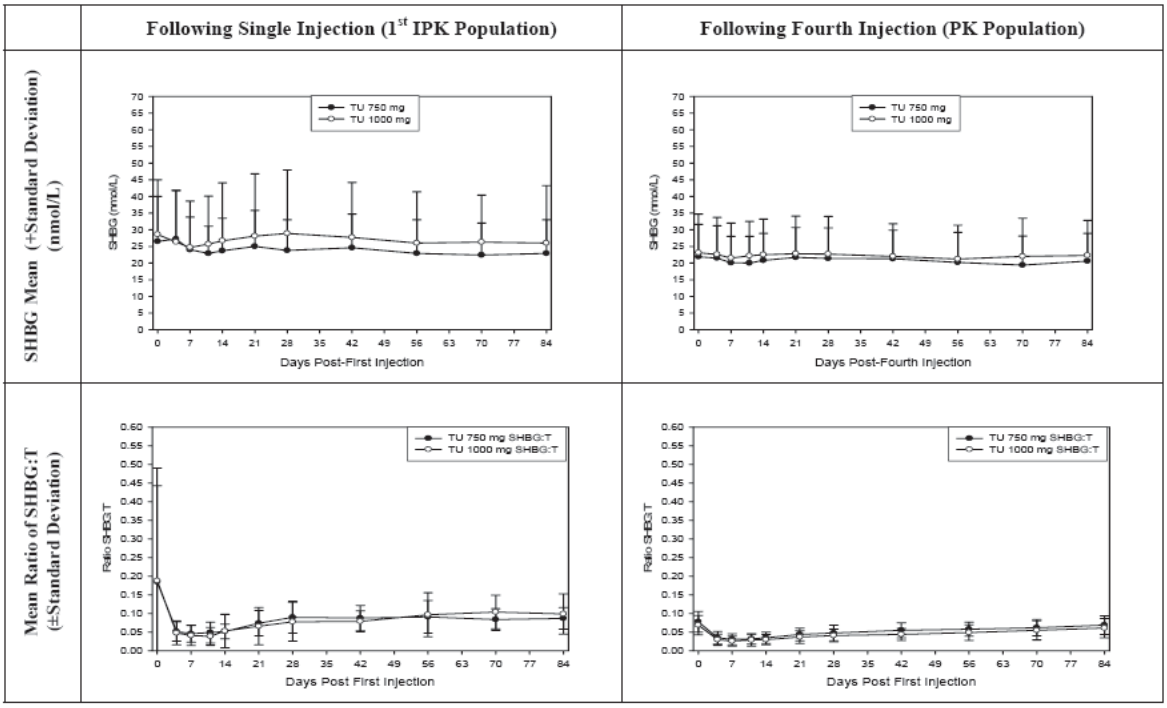
App A Figure 9 provides 4 plots of E2 and demonstrates the relationship between E2 and T.

Appendix A Figure 9. E2 and the Ratio of E2 to Total T Following the 1st and 4th Injections of TU



Appendix A Figure 10 provides 4 plots of SHBG and demonstrates the relationship between SHBG and T.

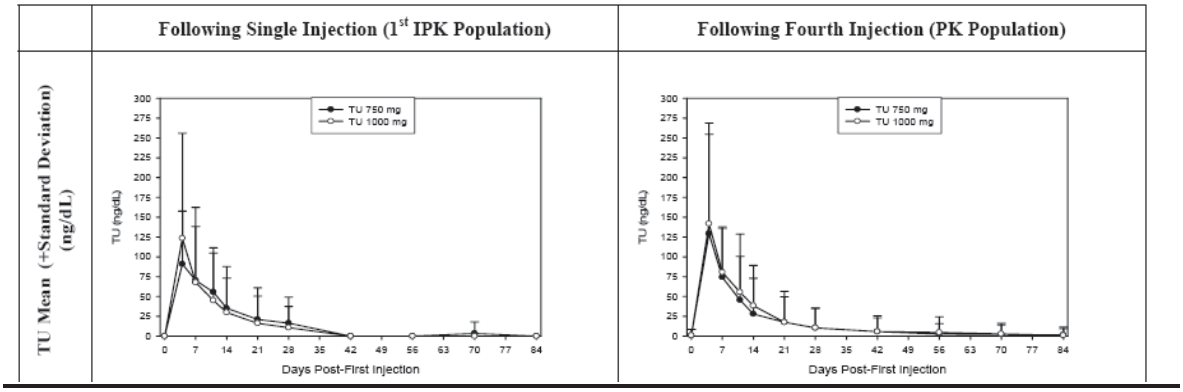
Appendix A Figure 10. SHBG and Ratio of SHBG to Total T Following 1st and 4th Injection of TU



Concentration values of DHTU were below the limit of quantification (BLQ was <100 ng/dL for the assay) at all but a few samples in this study, and thus an analysis of DHTU values is not possible. Thus, DHTU outcomes are not reported here, beyond remarking that the concentrations were BLQ for 99% of samples assayed.

A plot comparing the mean changes in serum testosterone undecanoate (TU) during the 1st and 4th injection interval is seen in Appendix A Figure 11.

Appendix A Figure 11. Testosterone Undecanoate Following the 1" and 4'" Injections of TU



17.0 Clinical Efficacy Results

Clinical efficacy includes the assessment of clinical markers of TRT and the assessment of body measurements, as follows:

- Psychosexual Daily Questionnaire (PSDQ)
- International Index of Erectile Function (IIEF)
- Male Patient Global Assessment (M-PGA)
- Weight
- BMI
- Hip to Waist Ratio
- Grip Strength

Appendix A Table 17 presents changes in the PSDQ and IIEF from pre-treatment to day 21 of the 4th injection interval.

Appendix A Table 17. Clinical Efficacy Outcomes for PSDQ and IIEF – Change from Pre- Treatment to Day 21 of 4th Injection Interval - PK Population

Clinical Outcome Measure	Descriptive Statistic	Pre-Treatment and Change from Pre-Treatment to On-Treatment					
		TU 750 mg (N=102)			TU 1000 mg (N=97)		
		Pre-Treatment	4th Injection Interval	Change to 4th Injection Interval	Pre-Treatment	4th Injection Interval	Change to 4th Injection Interval
PSDQ Outcomes							
PSDQ Sexual Desire	N	96	96	96	88	88	88
	Mean (SD)	2.1 (0.13)	3.6 (0.15)	1.5 (0.15)	2.2 (0.16)	4.0 (0.14)	1.8 (0.14)
	Median	2.3	3.8	1.3	2.0	4.1	1.7
	Range	0.0 to 4.6	0.0 to 7.0	-1.9 to 6.4	0.0 to 7.0	1.0 to 7.0	-0.9 to 5.6
PSDQ Sexual Enjoyment without Partner	N	94	94	94	87	87	87
	Mean (SD)	0.7 (0.10)	1.2 (0.15)	0.5 (0.14)	0.6 (0.10)	1.6 (0.21)	1.0 (0.17)
	Median	0.4	0.6	0.1	0.0	0.6	0.4
	Range	0.0 to 3.7	0.0 to 7.0	-2.6 to 6.4	0.0 to 4.0	0.0 to 7.0	-1.6 to 6.0
PSDQ Sexual Enjoyment with Partner	N	95	95	95	87	87	87
	Mean (SD)	1.3 (0.13)	2.3 (0.19)	1.0 (0.17)	1.2 (0.15)	2.1 (0.19)	0.9 (0.16)
	Median	1.0	2.4	0.9	0.7	1.7	0.9
	Range	0.0 to 4.0	0.0 to 7.0	-2.4 to 6.1	0.0 to 6.0	0.0 to 6.9	-4.0 to 5.3
PSDQ Sexual Activity	N	95	95	95	88	88	88
	Mean (SD)	3.7 (0.25)	5.1 (0.22)	1.4 (0.26)	3.8 (0.26)	5.7 (0.19)	1.9 (0.26)
	Median	4.0	6.0	1.0	4.0	6.5	1.5
	Range	0.0 to 7.0	0.0 to 7.0	-5.0 to 7.0	0.0 to 7.0	1.0 to 7.0	-4.0 to 7.0
PSDQ– Positive Moods	N	93	93	93	87	87	87
	Mean (SD)	4.3 (0.13)	4.9 (0.11)	0.6 (0.10)	4.5 (0.11)	5.1 (0.12)	0.5 (0.11)
	Median	4.2	4.9	0.6	4.6	5.2	0.5
	Range	1.5 to 6.9	2.5 to 7.0	-1.8 to 2.9	2.2 to 7.0	1.6 to 7.0	-2.3 to 3.2
PSDQ– Negative Moods	N	93	93	93	87	87	87
	Mean (SD)	2.0 (0.13)	1.2 (0.09)	-0.8 (0.12)	1.8 (0.12)	1.0 (0.09)	-0.8 (0.11)
	Median	1.6	0.9	-0.6	1.7	1.0	-0.7
	Range	0.1 to 5.3	0.0 to 3.7	-4.5 to 2.5	0.0 to 5.5	0.0 to 3.2	-3.6 to 2.9

Clinical Outcome Measure	Descriptive Statistic	Pre-Treatment and Change from Pre-Treatment to On-Treatment					
		TU 750 mg (N=102)			TU 1000 mg (N=97)		
		Pre-Treatment	4th Injection Interval	Change to 4th Injection Interval	Pre-Treatment	4th Injection Interval	Change to 4th Injection Interval
IIEF Outcomes							
IIEF Erectile Function	N	99	99	99	94	94	94
	Mean (SD)	15.8 (0.93)	20.0 (0.91)	4.1 (0.97)	15.8 (0.98)	21.2 (0.89)	5.4 (1.04)
	Median	17.0	23.0	3.0	16.5	23.0	5.0
	Range	1.0 to 30.0	1.0 to 30.0	-24.0 to 27.0	1.0 to 30.0	1.0 to 30.0	-22.0 to 27.0
IIEF Orgasmic Function	N	98	98	98	94	94	94
	Mean (SD)	6.5 (0.36)	7.7 (0.31)	1.2 (0.38)	6.0 (0.39)	7.7 (0.30)	1.7 (0.35)
	Median	8.0	8.5	0.0	8.0	8.5	1.0
	Range	0.0 to 10.0	0.0 to 10.0	-9.0 to 10.0	0.0 to 10.0	0.0 to 10.0	-8.0 to 10.0
IIEF Sexual Desire	N	99	99	99	94	94	94
	Mean (SD)	5.0 (0.18)	6.9 (0.18)	1.9 (0.21)	4.9 (0.21)	7.1 (0.18)	2.3 (0.21)
	Median	5.0	7.0	2.0	5.0	7.0	2.0
	Range	2.0 to 10.0	2.0 to 10.0	-4.0 to 8.0	2.0 to 10.0	3.0 to 10.0	-3.0 to 8.0
IIEF Intercourse Satisfaction	N	98	98	98	94	94	94
	Mean (SD)	6.6 (0.46)	8.6 (0.49)	1.9 (0.48)	6.5 (0.47)	8.9 (0.44)	2.4 (0.48)
	Median	8.0	10.0	1.0	8.0	10.0	2.0
	Range	0.0 to 15.0	0.0 to 15.0	-11.0 to 13.0	0.0 to 15.0	0.0 to 15.0	-12.0 to 12.0
IIEF Overall Satisfaction	N	93	93	93	91	91	91
	Mean (SD)	5.3 (0.25)	6.8 (0.23)	1.5 (0.26)	5.2 (0.25)	7.0 (0.25)	1.8 (0.25)
	Median	5.0	7.0	1.0	5.0	8.0	2.0
	Range	2.0 to 10.0	2.0 to 10.0	-6.0 to 8.0	2.0 to 10.0	2.0 to 10.0	-4.0 to 7.0
IIEF Total	N	98	98	98	94	94	94
	Mean (SD)	39.5 (1.83)	50.1 (1.80)	10.6 (1.98)	38.4 (2.01)	51.9 (1.82)	13.4 (2.02)
	Median	42.0	56.0	8.0	38.5	59.0	13.5
	Range	5.0 to 71.0	7.0 to 75.0	-42.0 to 57.0	5.0 to 75.0	7.0 to 75.0	-42.0 to 59.0

Reviewer's Comment: Lacking a placebo control, it is not possible to assess the independent effect of TU on these clinical parameters.

The M-PGA was collected at Week 12 and 36 (in addition to during the 1st and 4th injection intervals at Day 21). For the M-PGA, lower scores are better.

Outcomes from these analyses are summarized by the Sponor as follows:

• Following treatment with TU, over half of subjects in each treatment group reported improvement for each item on the M-PGA. The improvements were observed as early as Day 21 of the 1st injection interval, and these improvements increased from the first injection interval to the end of the treatment period (as evidenced by the higher proportions of subjects reporting improvements at the 4th injection visit and at Day 21 of the 4th injection interval).

o At Day 21 of the 4th injection interval, both treatment groups demonstrated at least 70% of patients with improved confidence/self esteem, moods/behavior, satisfaction with performance, feeling of well-being, and satisfaction with the treatment.

o Over 93% of subjects in the TU 1000 mg arm expressed satisfaction with treatment with TU, compared to 86% in the TU 750 mg arm. Thus, in this study population of hypogonadal men (80% of whom had used prior TRT before entering this study), satisfaction with treatment with TU was very high.

• For all 5 items on the M-PGA, the TU 1000 mg arm demonstrated higher satisfaction during the 4th injection interval, as compared to the TU 750 mg arm.

Appendix A Table 18 presents outcomes for the M-PGA for the 4th injection interval (Day 0 and Day 21).

Appendix A Table 18. Clinical Efficacy Outcomes for M-PGA – Change from Pre-Treatment to 4th Injection Interval (Day 0 and Day 21) - PK Population

M-PGA Item	Change from Pre-Treatment	TU 750 mg (N=102)		TU 1000 mg (N=97)	
		Day 0	Day 21	Day 0	Day 21
		N (%)	N (%)	N (%)	N (%)
Confidence/Self-Esteem	Improved	58 (56.9)	69 (69.7)	69 (71.1)	70 (74.5)
	No Change	37 (36.3)	26 (26.3)	25 (25.8)	22 (23.4)
	Worsened	7 (6.9)	4 (4.0)	3 (3.1)	2 (2.1)
Sexual Performance	Improved	71 (69.6)	74 (74.7)	74 (76.3)	74 (78.7)
	No Change	23 (22.5)	17 (17.2)	16 (16.5)	18 (19.1)
	Worsened	8 (7.8)	8 (8.1)	7 (7.2)	2 (2.1)
Moods/Behavior	Improved	73 (71.6)	70 (70.7)	69 (71.1)	70 (74.5)
	No Change	20 (19.6)	25 (25.3)	27 (27.8)	21 (22.3)
	Worsened	9 (8.8)	4 (4.0)	1 (1.0)	3 (3.2)
Overall Feeling of Well-Being	Improved	72 (70.6)	75 (75.8)	75 (77.3)	76 (80.9)
	No Change	25 (24.5)	20 (20.2)	20 (20.6)	17 (18.1)
	Worsened	5 (4.9)	4 (4.0)	2 (2.1)	1 (1.1)

Reviewer's Comment: Again, lacking a placebo control, it is not possible to assess the independent effect of TU on these clinical parameters.

Appendix A Table 19 provides a summary of the pre-treatment, Week 36 (Day 0 of the injection interval), and change from pre-treatment to Week 36 values for body measurement outcomes.

Appendix A Table 19. Body Measurement Changes from Pre-Treatment to Week 36 (Day 0 of 4th Injection Interval) Weight, BMI, Hip to Waist Ratio and Grip Strength – PK Population

		TU 750 mg N=102			TU 1000 mg N=97		
	Statistic	Pre-Treatment	Week 36	Change	Pre-Treatment	Week 36	Change
Body Measurements							
Weight (kg)	N	101	101	101	96	96	96
	Mean (SE)	100.8 (1.75)	100.9 (1.75)	0.0 (0.52)	102.1 (2.07)	102.3 (2.08)	0.2 (0.41)
	Median	99.9	99.4	0.5	98.1	99.4	0.7
	Range	67.6 to 148.9	70.0 to 144.4	-18.2 to 11.8	64.5 to 158.9	66.3 to 165.7	-12.7 to 10.0
BMI (kg/m^2)	N	101	101	101	96	96	96
	Mean (SE)	31.6 (0.51)	31.6 (0.50)	-0.0 (0.17	31.5 (0.55)	31.6 (0.55)	0.1 (0.13)
	Median	30.7	31.0	0.1	30.1	30.3	0.2
	Range	20.9 to 43.1	20.0 to 43.9	-5.9 to 3.5	23.9 to 51.4	24.4 to 51.7	-4.3 to 3.1
Hip to Waist Ratio	N	101	101	101	95	95	95
	Mean (SE)	1.0 (0.01)	1.0 (0.01)	-0.0 (0.01)	1.0 (0.01)	1.0 (0.01)	-0.0 (0.01)
	Median	1.0	1.0	-0.0	1.0	1.1	0.0
	Range	0.9 to 1.2	0.9 to 1.2	-0.2 to 0.1	0.7 to 1.2	0.8 to 1.2	-0.2 to 0.2
Hip Circum (cm)	N	101	101	101	95	95	95
	Mean (SE)	111.5 (1.06)	109.8 (1.09)	-1.7 (0.50)	112.0 (1.56)	111.6 (1.42)	-0.4 (0.54)
	Median	109.2	106.7	0.0	110.0	109.2	0.0
	Range	86.4 to 139.7	82.6 to 139.7	-22.9 to 8.9	66.0 to 170.2	71.1 to 165.1	-15.2 to 10.4
Waist Circum (cm)	N	101	101	101	95	95	95
	Mean (SE)	109.1 (1.36)	108.0 (1.36)	-1.1 (0.58)	109.0 (1.38)	107.5 (1.39)	-1.5 (0.50)
	Median	109.2	106.7	0.0	106.7	106.7	-1.3
	Range	78.7 to 137.2	81.3 to 142.2	-17.8 to 12.7	86.0 to 148.0	84.0 to 152.0	-12.7 to 15.9

Grip Strength							
Grip Strength (Right Hand)	N	101	101	101	94	94	94
	Mean (SE)	43.3 (0.85)	42.2 (0.88)	-1.1 (0.65)	43.5 (1.15)	43.3 (1.07)	-0.1 (0.84)
	Median	42.7	41.3	-1.0	42.7	41.3	-0.7
	Range	22.0 to 69.7	23.0 to 64.7	-18.0 to 14.7	6.7 to 65.0	17.7 to 66.0	-17.3 to 42.0
Grip Strength (Left Hand)	N	101	101	101	95	95	95
	Mean (SE)	41.5 (0.92)	40.3 (0.91)	-1.2 (0.67)	42.7 (1.03)	41.8 (1.08)	-0.9 (0.63)
	Median	42.0	40.3	-0.7	42.0	40.7	-1.0
	Range	16.7 to 64.7	7.0 to 62.7	-22.7 to 16.0	6.0 to 72.3	17.3 to 80.7	-16.3 to 30.7

<u>Reviewer's Comment</u>: It is not possible to discern a clear effect of TU on these body parameters.

18.0 Efficacy Conclusions

18.1 Summary of Pharmacokinetics of T

(b) (4)

For both treatment groups, the Sponsor believed that the following correlations between T concentrations and clinical outcomes were observed:

• T concentrations were not correlated with changes in mood states.

• T concentrations were weakly correlated with changes in psychosexual outcomes. Modest improvements from baseline noted in subject psychosexual functioning were observed to be slightly higher (better) in those patients with higher T exposure than those subjects with lower T exposure.

• T concentrations were weakly correlated with changes in erectile functioning outcomes. Again, modest improvements from baseline noted in subject erectile function were observed to be somewhat higher (better) in those subjects with higher T exposure than in those subjects with lower T exposure.

• T concentrations were weakly inversely correlated with decreases (improvements) from baseline in the patient global assessments. Subjects with higher T exposure tended to have more satisfaction with the treatment than those with lower T exposure.

• Changes in hip to waist ratios and in grip strength outcomes demonstrated no meaningful correlations with T exposure.

18.2 Summary of Other Secondary Efficacy Outcomes

Average changes from pre-treatment to on-treatment in both hematocrit and hemoglobin as they related to changes in T concentrations over time were as expected for a TRT. Erythropoiesis outcomes demonstrated that, for both treatment groups:

• Average values of hemoglobin and hematocrit increased slightly from pre-treatment to Week 36 as average T concentrations increased; however, the average increases in these erythropoietic markers were small in magnitude and well within the normal range.

• Changes in hemoglobin or hematocrit were not apparent at the Week 12 time point, but rather were seen only by the Week 36 time point, suggesting that more than 12 weeks of treatment with TU 1000 mg or TU 750 mg was required to manifest the small average increases in these parameters.

Hemoglobin and hematocrit demonstrated low variability across treatments and visits, and thus were relatively stable during the treatment period.

Lipid changes were marked by:

• Reductions in average triglycerides as average T concentrations increased, noted for both treatment groups but slightly greater for the TU 1000 mg arm. Over the course of the 48 weeks of treatment, patients in the TU 1000 mg group experienced an average reduction in triglycerides of 40 mg/dL.

• Minor reductions in average total cholesterol and HDL were noted for both treatment groups. Over the course of the 48 weeks of treatment, patients in the TU 1000 mg group experienced an average reduction in total cholesterol of 12 mg/dL and an average reduction in HDL of 2 mg/dL.

No meaningful changes in average LDL were observed in either treatment group.

• For both treatment groups, average Free T concentrations closely paralleled T concentrations and tended to remain within or above the normal range, with concentrations of Free T in the TU 1000 mg arm higher than those in the TU 750 mg arm at most time points post-1st and 4th injection. Mean ratios of Free T:T remained relatively constant throughout the 1st and 4th injection intervals.

• For both treatment groups, average DHT concentrations closely paralleled T concentrations and tended to remain within the lower end of the normal range, with concentrations of DHT in the TU 1000 mg arm higher than those in the TU 750 mg arm at most time points post-1st and 4th injection. Mean ratios of DHT:T remained relatively constant throughout the 1st and 4th injection intervals, and of note, the DHT:T ratio was no different between the TU 750 mg arm and the TU 1000 mg arm.

• For both treatment groups, average E2 concentrations closely paralleled T concentrations and tended to remain within the middle of the normal range, with concentrations of E2 in the TU 1000 mg arm higher than those in the TU 750 mg arm at most time points post 4th injection.

Mean ratios of E2:T remained relatively constant throughout the 1st and 4th injection intervals. The average on-treatment ratios remained similar to the average pre-treatment ratios.

• For both treatment groups, average SHBG concentrations remained constant and tended to remain within the middle of the normal range. Mean ratios of SHBG:T tended to drop immediately following the injection (at the Day 4 time point); this was due to changes in T concentrations (and not changes in SHBG concentrations).

Concentration values of DHTU were below the limit of quantification for the majority of samples collected; for those concentrations that were quantifiable, the values remained low and demonstrated little variability. Average concentration values of serum TU are shown in Appendix A Figure 11. Esterification of testosterone with undecanoic acid increases the lipophilicity of the steroid. When administered intramuscularly as an oily formulation, a gradual release of the ester from the depot into the systemic circulation is achieved. The rate-limiting step is the release of the intact ester from the injection depot into the circulation, and this in turn is determined by the chain length of the fatty acid and the nature of the formulation. The ester is rapidly cleaved by nonspecific esterases to liberate free testosterone.

Outcomes from the assessments of psychosexual function and erectile function are summarized by the Sponsor as follows:

• Following treatment with TU, higher scores (ie, improvements) were observed in the PSDQ sexual desire and performance outcomes through the 4th injection interval for both treatment groups. Subjects reported more positive moods and fewer negative moods following treatment with TU.

• Following treatment with TU, higher scores (i.e., improvements) were observed in the IIEF outcomes through the 4th injection interval for both treatment groups.

Reviewer's Comment: Lacking a placebo control, it is not possible to assess the independent effect of TU on these subjective clinical parameters.

Outcomes for the subject assessment of satisfaction are summarized as follows:

• As collected via the M-PGA, both treatment groups had a majority of subjects with improvements in confidence/self esteem, moods/behavior, satisfaction with performance, feeling of well-being, and satisfaction with the treatment.

Reviewer's Comment: Again, lacking a placebo control, it is not possible to assess the independent effect of TU on these subjective clinical parameters.

• Over 93% of subjects in the TU 1000 mg arm expressed satisfaction with treatment with TU, compared to 86% of subjects in the TU 750 mg arm.

o In this study population of hypogonadal men (80% of whom had used prior TRT before entering this study), satisfaction with treatment with TU was very high.

There were no notable changes in body composition measures. Average weight, BMI, and the hip to waist ratios remained essentially unchanged during the study. Further, no change was observed in average grip strength for either the left or right hand.

19.0 Overall Efficacy Conclusions

[redacted] (b) (4)

After [redacted] (b) (4) the Sponsor's submission of data for Part C (the 750mg Loading Regimen), the Sponsor decided [redacted] (b) (4) to seek approval only of the 750mg Loading regimen.

20.0 Safety Evaluation

Average safety follow-up in Part A was over 300 days (i.e., over 43 weeks) for both treatment groups, with the majority of subjects completing all 5 injections (and thus completing the 48 week treatment period). The average duration of exposure to Stage 1 study medication is summarized in Appendix A Table 20, while the number of patients by duration of exposure categorized (e.g., less than 24 weeks, 24 to 48 weeks, etc.) is summarized in Appendix A Table 21.

Appendix A Table 20. Duration of Exposure (Days) to Stage 1 Study Medication and Safety Follow- up Duration (Days) – Total Patient Sample

	TU 750 (N=120)	TU 1000 (N=117)
Number of patients with exposure information	120	117
Duration of Exposure to Study Medication (Days)[1]		
Mean (standard error)	378.0 (8.81)	376.5 (8.50)
Median	418.0	418.0
Range (minimum to maximum)	84.0 to 438.0	84.0 to 440.0
Duration of Safety Follow-up for this Study Report (Days)[2]		
Mean (standard error)	308.6 (6.52)	306.6 (6.20)
Median	334.0	334.0
Range (minimum to maximum)	0.0 to 354.0	0.0 to 348.0

Appendix A Table 21. Number of Hypogonadal Men Treated with TU by Duration of Safety Follow-up--Total Subject Sample

Duration[1] of Exposure (Weeks)	Number (%) of Patients	
	TU 750 mg (N=120)	TU 1000 mg (N=117)
0 ≤ Duration ≤ 12 weeks	4 (3.4)	1 (0.9)
12 < Duration ≤ 24 weeks	5 (4.2)	11 (9.4)
24 < Duration ≤ 36 weeks	7 (5.9)	6 (5.1)
36 < Duration ≤ 48 weeks	91 (77.1)	92 (78.6)
> 48 weeks	11 (9.3)	7 (6.0)

20.1 AEs

20.2 All TEAEs

Appendix A Table 22 summarizes TEAEs reported in at least 2 % of subjects in both treatment groups irrespective of relationship to study medication, by preferred term in decreasing order based on incidence rates in the TU 1000 group.

Appendix A Table 22. Incidence of All TEAEs Regardless of Relationship, Reported in at Least 2.0% of Patients in Either Treatment Group by Preferred Term in Decreasing Frequency in TU 1000 mg arm – Total Patient Sample

MedDRA Preferred term	Number of patients (%)	
	TU 750 (N=120)	TU 1000 (N=117)
Total patients with at least 1 TEAE	70 (58.3)	73 (62.4)
Upper respiratory tract infection	5 (4.2)	5 (4.3)
Diarrhoea	2 (1.7)	5 (4.3)
Pain in extremity	2 (1.7)	4 (3.4)
Nasopharyngitis	5 (4.2)	4 (3.4)
Hypertension	3 (2.5)	4 (3.4)
Sinusitis	3 (2.5)	4 (3.4)
Insomnia	3 (2.5)	4 (3.4)
Headache	2 (1.7)	4 (3.4)
Depression	2 (1.7)	4 (3.4)
Weight increased	3 (2.5)	4 (3.4)
Procedural pain	0 (0.0)	3 (2.6)
Arthralgia	2 (1.7)	3 (2.6)
Musculoskeletal pain	1 (0.8)	3 (2.6)
Urinary tract infection	3 (2.5)	3 (2.6)
Rash	1 (0.8)	3 (2.6)
Pain	0 (0.0)	3 (2.6)
Foot fracture	0 (0.0)	3 (2.6)
Muscle strain	0 (0.0)	3 (2.6)
Anxiety	0 (0.0)	3 (2.6)
Nasal congestion	0 (0.0)	3 (2.6)
Abdominal pain	0 (0.0)	3 (2.6)
Constipation	0 (0.0)	3 (2.6)
Vomiting	1 (0.8)	3 (2.6)
Gout	0 (0.0)	3 (2.6)
Benign prostatic hyperplasia	2 (1.7)	3 (2.6)
Cough	1 (0.8)	3 (2.6)
Fatigue	7 (5.8)	2 (1.7)
Bronchitis	5 (4.2)	2 (1.7)
Back pain	4 (3.3)	2 (1.7)
Nausea	3 (2.5)	2 (1.7)
Prostatic specific antigen increased	4 (3.3)	1 (0.9)
Hypercholesterolaemia	3 (2.5)	1 (0.9)

20.3 Summary of TEAEs of Interest

TEAEs of interest were experienced by 24 (20.0%) of subjects treated with TU 750 mg and 30 (25.6%) of subjects treated with TU 1000 mg. Most of these events are described in more detail in the appropriate sections of this report. No TEAE of any particular type was reported in more than 4 patients in either treatment group. Appendix A Table 23 summarizes the TEAEs of interest.

Appendix A Table 23. Incidence of TEAEs of Interest Regardless of Relationship, by Preferred Term-Total Patient Sample

Event Class	MedDRA System Organ Class	MedDRA Preferred term	Number of patients (%)	
			TU 750 (N=120)	TU 1000 (N=117)
Total Patients With At Least One TEAE of Interest			**24 (20.0)**	**30 (25.6)**
Endocrine Disorder	Investigations	Oestradiol increased	0 (0.0)	2 (1.7)
		Glycosylated haemoglobin increased	0 (0.0)	1 (0.9)
	Metabolism and nutrition disorders	Diabetes mellitus	1 (0.8)	1 (0.9)
Tolerability of Injection	General disorders and administration site conditions	Injection site erythema	0 (0.0)	1 (0.9)
		Injection site irritation	0 (0.0)	1 (0.9)
		Injection site pruritus	1 (0.8)	1 (0.9)
		Injection site pain	2 (1.7)	2 (1.7)
		Injection site reaction	0 (0.0)	1 (0.9)
Adverse Lipid Profiles	Investigations	Blood triglycerides increased	1 (0.8)	2 (1.7)
		Blood triglycerides abnormal	0 (0.0)	1 (0.9)
		Blood cholesterol increased	0 (0.0)	2 (1.7)
		High density lipoprotein decreased	1 (0.8)	0 (0.0)
	Metabolism and Nutritional disorders	Hypercholesterolaemia	3 (2.5)	1 (0.9)
		Hyperlipidemia	1 (0.8)	1 (0.9)
Erythropoiesis	Investigations	Haematocrit increased	0 (0.0)	1 (0.9)
		Haemoglobin increased	0 (0.0)	1 (0.9)
		Red blood cell count increased	0 (0.0)	1 (0.9)
	Blood and lymphatic system disorders	Polycythaemia	1 (0.8)	1 (0.9)
Aggression or depression	Psychiatric disorders	Depression	2 (1.7)	4 (3.4)
Urinary Symptoms	Renal and urinary disorders	Pollakiuria	0 (0.0)	2 (1.7)
		Urinary hesitation	0 (0.0)	1 (0.9)
		Urinary retention	1 (0.8)	2 (1.7)
		Urine flow decreased	1 (0.8)	2 (1.7)
		Nocturia	0 (0.0)	1 (0.9)
		Dysuria	1 (0.8)	2 (1.7)
	Infections and infestations	Urinary tract infection	3 (2.5)	3 (2.6)
Prostate health	Investigations	Prostatic specific antigen increased	4 (3.3)	1 (0.9)
		Prostate examination abnormal	2 (1.7)	1 (0.9)
	Reproductive system and breast disorders	Benign prostatic hyperplasia	2 (1.7)	3 (2.6)
		Prostatic intraepithelial neoplasia	1 (0.8)	2 (1.7)
		Prostatitis	0 (0.0)	2 (1.7)
		Prostatic disorder	1 (0.8)	0 (0.0)
Liver Abnormalities	Neoplasms benign, malignant and unspecified	Hepatic neoplasm malignant	0 (0.0)	1 (0.9)
	Investigations	Aspartate aminotransferase increased	1 (0.8)	0 (0.0)
Cerebrovascular events	Nervous system disorders	Cerebrovascular accident	0 (0.0)	1 (0.9)

20.4 Deaths, Other SAEs, and Other Significant Adverse Events

20.4.1 Deaths

There was 1 patient who died during this study. A 54 year old Caucasian male who received 2 injections of TU 750 mg, died of injuries sustained after being stabbed. The subjects died 165 days following his first injection; the death was considered unrelated to study treatment.

20.4.2 Other Serious Adverse Events

Serious AEs (SAEs) were defined as those events that led to death, were immediately life-threatening, resulted in a persistent or significant disability or incapacity, required or prolonged hospitalization, involved congenital anomaly, or required intervention to prevent one of the prior conditions from occurring.

Eight (6.7%) subjects in the TU 750 group and 10 (8.5%) subjects in the TU 1000 group experienced at least one treatment-emergent SAE during the treatment period. Only 2 SAEs were observed in more than 1 subject; Atrial fibrillation was reported in 2 subjects in the TU 750 mg group, while knee arthroplasty was reported in 2 subjects in the TU 1000 mg group.

20.4.3 Other Significant Adverse Events

AEs were defined as "other significant events" if they met 1 or more of the following criteria: led to discontinuation of study medication, led to temporary interruption of study medication, or required dose reduction of study medication. Appendix A Table 24 summarizes TEAEs that met 1 or more of the criteria as "other significant events" and led to discontinuation.

Table 24. Incidence of TEAEs Regardless of Relationship, Leading to Discontinuation of Study Medication, by Preferred Term, in Decreasing Frequency – Total Subject Sample

MedDRA Preferred term	Number of patients (%)	
	TU 750 (N=120)	TU 1000 (N=117)
Total patients with at least 1 TEAE	70 (58.3)	73 (62.4)
Total patients with at least 1 TEAE Leading to Discontinuation of Study Medication	6 (5.0)	4 (3.4)
Oestradiol increased	0 (0.0)	1 (0.9)
Injury	1 (0.8)	0 (0.0)
Heat exhaustion	1 (0.8)	0 (0.0)
Red blood cell count increased	0 (0.0)	1 (0.9)
Back pain	1 (0.8)	0 (0.0)
Pain in extremity	1 (0.8)	0 (0.0)
Hepatic neoplasm malignant	0 (0.0)	1 (0.9)
Prostatic intraepithelial neoplasia	1 (0.8)	0 (0.0)
Prostatic specific antigen increased	1 (0.8)	0 (0.0)
Testicular atrophy	1 (0.8)	0 (0.0)
Nasal congestion	0 (0.0)	1 (0.9)
Skin ulcer	0 (0.0)	1 (0.9)

21.0 Clinical Laboratory Evaluations

The analysis of average changes from pre-treatment to endpoint is summarized as follows:

• With the exception of changes in erythropoiesis, hormones, and a few other outcomes, the mean and median changes from baseline to endpoint were generally small in magnitude and similar between the treatment groups for most laboratory parameters.

• Liver function tests (e.g., alkaline phosphatase, ALT, and AST) demonstrated slight average decreases from pre-treatment to endpoint; these reductions in these enzymes were judged to not be clinically meaningful.

• Blood urea nitrogen (BUN) and calcium decreased from pre-treatment in both treatment groups; the average decreases were similar between the treatment groups. Sodium, potassium, and phosphorus did not demonstrate meaningful changes in average values from pre-treatment in either treatment group.

• The most notable changes from pre-treatment to endpoint were the decreases in average FSH and LH. Average FSH and LH each decreased approximately 60% from pre-treatment to the endpoint in both treatment arms. The TU 1000 mg arm had a slightly higher pre-treatment mean LH, and thus the slightly larger (but likely not clinically relevant) decrease to the endpoint is possibly a result of the higher pre-treatment mean, as compared to the TU 750 mg arm.

Appendix A Table 25 provides a summary of average changes from pre-treatment to endpoint for most laboratory parameters.

Appendix A Table 25. Laboratory Changes from Pre-Treatment to Endpoint Hematology, Chemistry, and Lipids)—Total Subject Sample

Laboratory Parameter	TU 750 (N=120)			TU 1000 (N=117)		
	Pre-Treatment	Endpoint	Change	Pre-Treatment	Endpoint	Change
Hematology						
WBC (10^3/uL) N	119	119	119	114	114	114
Mean (SE)	6.7 (0.16)	6.8 (0.18)	0.01(0.14)	6.5 (0.15)	6.8 (0.18)	0.3 (0.15)
Median	6.4	6.5	-0.0	6.4	6.5	0.3
Range	2.3, 14.9	2.6, 15.7	-4.2, 7.6	2.9, 11.7	3.6, 15.4	-5.1, 8.6
Lymphocytes (%) N	119	119	119	114	114	114
Mean (SE)	30.2 (0.73)	29.5 (0.73)	-0.7 (0.56)	29.7 (0.66)	29.2 (0.66)	-0.5 (0.60)
Median	29.7	28.4	-1.2	28.6	28.8	-0.1
Range	12.5, 54.2	11.2, 53.8	-16.9, 19.4	9.8, 53.9	17.3, 50.4	-18.6, 19.0
Monocytes (%) N	119	119	119	114	114	114
Mean (SE)	6.0 (0.14)	6.2 (0.17)	0.2 (0.18)	6.2 (0.16)	6.3 (0.15)	0.0 (0.16)
Median	5.8	6.1	0.1	6.1	6.2	0.2
Range	1.0, 12.2	0.0, 15.0	-7.0, 8.5	2.7, 11.5	3.0, 10.9	-6.8, 4.0
Basophils (%) N	119	119	119	114	114	114
Mean (SE)	0.9 (0.04)	0.9 (0.04)	0.0 (0.05)	0.8 (0.04)	0.9 (0.06)	0.1 (0.07)
Median	0.8	0.8	0.0	0.8	0.8	0.0
Range	0.0, 2.5	0.0, 3.0	-1.3, 2.1	0.0, 2.6	0.0, 3.0	-1.9, 2.5
Eosinophils (%) N	119	119	119	114	114	114
Mean (SE)	2.6 (0.14)	3.0 (0.18)	0.4 (0.15)	2.6 (0.13)	2.9 (0.16)	0.2 (0.15)
Median	2.2	2.7	0.2	2.5	2.5	0.2
Range	0.3, 9.4	0.0, 13.2	-6.4, 9.9	0.4, 7.0	0.0, 8.5	-4.4, 5.1
Neutrophils (%) N	119	119	119	114	114	114
Mean (SE)	60.3 (0.74)	60.4 (0.78)	0.1 (0.65)	60.6 (0.73)	60.6 (0.72)	0.0 (0.71)
Median	60.2	61.4	0.7	60.8	60.6	-0.4
Range	37.4, 81.7	36.9, 77.4	-25.4, 16.4	39.5, 82.2	39.3, 76.4	-27.4, 20.6
RBC (10^6/uL) N	119	119	119	114	114	114
Mean (SE)	5.2 (0.04)	5.1 (0.04)	-0.1 (0.03)	5.2 (0.04)	5.2 (0.04)	-0.0 (0.04)
Median	5.2	5.2	-0.1	5.3	5.2	0.0
Range	4.0, 6.3	3.9, 5.9	-1.0, 0.8	4.1, 6.5	3.9, 6.6	-0.9, 1.0
Hematocrit (%) N	119	119	119	114	114	114
Mean (SE)	45.0 (0.36)	45.1 (0.36)	0.1 (0.32)	44.8 (0.34)	45.9 (0.36)	1.0 (0.34)
Median	45.0	45.0	0.0	45.0	46.0	1.0
Range	28.0, 56.0	30.0, 55.0	-15.0, 11.0	35.0, 52.0	34.0, 61.0	-7.0, 12.0
Hemoglobin (g/dL) N	119	119	119	114	114	114
Mean (SE)	15.0 (0.12)	15.3 (0.12)	0.3 (0.11)	14.9 (0.13)	15.5 (0.13)	0.6 (0.11)
Median	15.0	15.5	0.3	15.0	15.5	0.5
Range	9.9, 17.8	10.4, 18.3	-3.4, 4.0	11.2, 18.2	11.2, 18.9	-3.0, 4.0
Platelet Count (10^3/uL) N	117	117	117	114	114	114
Mean (SE)	240.8 (5.34)	240.2 (5.59)	-0.6 (3.43)	244.3 (5.33)	241.5 (5.59)	-2.9 (2.97)
Median	234.0	232.0	-1.0	239.5	232.0	-3.5
Range	122.0, 392.0	114.0, 384.0	-94.0, 164.0	120.0, 416.0	138.0, 463.0	-80.0, 89.0
PTT Value (sec) N	115	115	115	112	112	112
Mean (SE)	23.8 (0.29)	24.9 (0.27)	1.1 (0.27)	24.0 (0.37)	24.8 (0.34)	0.8 (0.39)
Median	23.1	24.6	1.1	23.4	24.4	1.0
Range	18.4, 42.7	20.0, 36.6	-16.2, 10.1	18.5, 54.5	17.8, 48.4	-31.1, 20.1
INR Value N	115	115	115	112	112	112
Mean (SE)	1.0 (0.01)	1.1 (0.01)	0.0 (0.02)	1.1 (0.01)	1.1 (0.01)	-0.0 (0.01)
Median	1.0	1.1	0.0	1.0	1.0	0.0
Range	0.8, 2.1	0.8, 1.9	-1.0, 1.0	0.8, 1.7	0.8, 1.6	-0.8, 0.3

Serum Chemistry						
Total Protein (g/dL) N	119	119	119	114	114	114
Mean (SE)	7.3 (0.04)	7.3 (0.04)	0.0 (0.03)	7.3 (0.04)	7.3 (0.04)	0.0 (0.03)
Median	7.2	7.3	0.0	7.3	7.3	0.0
Range	6.0, 8.3	6.2, 8.1	-0.8, 1.2	6.2, 8.5	6.4, 8.3	-1.0, 0.8
Albumin (g/dL) N	119	119	119	114	114	114
Mean (SE)	4.3 (0.03)	4.2 (0.03)	-0.1 (0.02)	4.3 (0.03)	4.2 (0.03)	-0.1 (0.02)
Median	4.2	4.1	-0.1	4.3	4.2	-0.1
Range	3.5, 5.5	3.6, 5.3	-0.9, 0.8	3.4, 4.8	3.5, 4.9	-0.6, 0.7
Creatinine (mg/dL) N	119	119	119	114	114	114
Mean (SE)	1.0 (0.02)	1.1 (0.02)	0.1 (0.01)	1.0 (0.02)	1.1 (0.02)	0.1 (0.01)
Median	1.0	1.1	0.1	1.0	1.0	0.1
Range	0.6, 1.6	0.6, 1.7	-0.2, 0.8	0.7, 1.6	0.7, 1.9	-0.3, 0.5
Urea Nitrogen (BUN) (mg/dL) N	119	119	119	114	114	114
Mean (SE)	17.5 (0.42)	16.9 (0.42)	-0.6 (0.32)	19.4 (0.52)	17.5 (0.42)	-1.9 (0.35)
Median	17.0	16.0	-1.0	19.0	17.0	-2.0
Range	7.0, 31.0	7.0, 30.0	-8.0, 7.0	7.0, 43.0	9.0, 34.0	-13.0, 9.0
Uric Acid (mg/dL) N	119	119	119	114	114	114
Mean (SE)	6.5 (0.12)	6.3 (0.13)	-0.2 (0.10)	6.9 (0.14)	6.5 (0.15)	-0.4 (0.11)
Median	6.4	6.2	-0.2	6.7	6.2	-0.4
Range	3.3, 10.1	3.7, 10.7	-3.3, 4.6	3.9, 12.8	3.9, 16.4	-4.1, 3.6
Direct Bilirubin (mg/dL) N	119	119	119	114	114	114
Mean (SE)	0.1 (0.01)	0.1 (0.01)	0.0 (0.01)	0.1 (0.01)	0.2 (0.01)	0.0 (0.01)
Median	0.1	0.1	0.0	0.1	0.1	0.0
Range	0.1, 0.3	0.1, 0.4	-0.2, 0.1	0.1, 0.3	0.1, 0.4	-0.1, 0.2
Total Bilirubin (mg/dL) N	119	119	119	114	114	114
Mean (SE)	0.6 (0.05)	0.6 (0.05)	0.1 (0.02)	0.6 (0.02)	0.6 (0.02)	0.1 (0.02)
Median	0.5	0.5	0.0	0.5	0.6	0.1
Range	0.2, 5.5	0.2, 6.2	-0.5, 0.7	0.2, 1.3	0.2, 1.8	-0.6, 0.9
Alkaline Phosphatase (U/L) N	119	119	119	114	114	114
Mean (SE)	72.4 (1.92)	69.8 (1.77)	-2.6 (0.86)	73.9 (1.88)	71.1 (1.76)	-2.8(0.97)
Median	68.0	67.0	-2.0	73.0	68.5	-2.0
Range	27.0, 140.0	25.0, 124.0	-38.0, 19.0	25.0, 143.0	23.0, 126.0	-39.0, 33.0
SGPT (ALT) (U/L) N	119	119	119	114	114	114
Mean (SE)	32.0 (1.25)	31.1 (1.31)	-0.9 (0.98)	30.0 (1.13)	28.4 (1.00)	-1.6 (1.06)
Median	30.0	27.0	-1.0	27.0	26.0	0.5
Range	11.0, 87.0	13.0, 95.0	-48.0, 34.0	8.0, 84.0	11.0, 66.0	-56.0, 30.0
SGOT (AST) (U/L) N	119	119	119	114	114	114
Mean (SE)	26.8 (0.74)	25.6 (0.86)	-1.2 (0.68)	26.6 (1.17)	24.5 (0.88)	-2.2 (1.22)
Median	25.0	23.0	-1.0	24.5	23.0	-1.0
Range	15.0, 62.0	13.0, 81.0	-27.0, 39.0	16.0, 139.0	13.0, 103.0	-110.0, 56.0
Creatine Phosphokinase (U/L) N	119	119	119	114	114	114
Mean (SE)	172.8 (10.92)	184.8 (17.90)	12.0 (16.71)	191.5 (34.35)	170.3 (12.84)	-21.2 (33.86)
Median	136.0	139.0	0.0	123.0	139.0	-1.5
Range	44.0, 715.0	40.0, 1944.0	-374.0, 1633.0	28.0, 3922.0	26.0, 930.0	-3686.0, 566.0
Fasting Glucose (mg/dL) N	96	96	96	106	106	106
Mean (SE)	105.8 (3.00)	110.2 (3.39)	4.4 (2.20)	104.1 (2.16)	109.0 (2.82)	4.9 (2.20)
Median	97.5	102.0	4.0	100.0	101.0	3.0
Range	71.0, 260.0	48.0, 264.0	-92.0, 81.0	74.0, 212.0	79.0, 243.0	-58.0, 135.0
Calcium (mg/dL) N	119	119	119	114	114	114
Mean (SE)	9.8 (0.04)	9.7 (0.03)	-0.1 (0.04)	9.8 (0.03)	9.7 (0.03)	-0.1 (0.04)
Median	9.8	9.7	-0.1	9.8	9.7	-0.1
Range	8.9, 11.4	9.0, 10.6	-1.1, 1.2	9.1, 11.0	8.8, 10.4	-1.7, 0.9
Phosphorus (mg/dL) N	119	119	119	114	114	114
Mean (SE)	3.4 (0.05)	3.2 (0.06)	-0.2 (0.06)	3.5 (0.05)	3.3 (0.05)	-0.2 (0.06)
Median	3.4	3.2	-0.1	3.5	3.3	-0.1
Range	1.8, 5.6	1.6, 5.1	-2.2, 1.4	2.2, 5.6	2.3, 4.5	-2.0, 1.1

Sodium (mEq/L) N	119	119	119	114	114	114
Mean (SE)	140.6 (0.24)	140.4 (0.24)	-0.2 (0.24)	140.5 (0.24)	140.7 (0.21)	0.2 (0.23)
Median	140.0	140.0	0.0	140.0	140.0	0.0
Range	133.0, 151.0	133.0, 152.0	-8.0, 7.0	134.0, 153.0	136.0, 150.0	-7.0, 7.0
Potassium (mEq/L) N	119	119	119	114	114	114
Mean (SE)	4.3 (0.04)	4.3 (0.03)	0.0 (0.04)	4.3 (0.04)	4.3 (0.04)	0.1 (0.03)
Median	4.2	4.3	0.0	4.3	4.3	0.0
Range	3.0, 5.4	3.4, 5.6	-0.9, 1.3	3.3, 5.5	3.2, 5.7	-0.9, 1.2
Chloride (mEq/L) N	119	119	119	114	114	114
Mean (SE)	102.9 (0.23)	102.6 (0.22)	-0.3 (0.23)	102.3 (0.27)	102.2 (0.24)	-0.1 (0.27)
Median	103.0	102.0	0.0	103.0	102.0	0.0
Range	99.0, 112.0	96.0, 112.0	-11.0, 7.0	94.0, 110.0	93.0, 111.0	-7.0, 9.0
Bicarbonate (mEq/L) N	119	119	119	114	114	114
Mean (SE)	26.2 (0.23)	25.8 (0.24)	-0.3 (0.25)	26.3 (0.24)	26.1 (0.26)	-0.2 (0.23)
Median	26.2	26.3	-0.4	26.4	25.8	-0.4
Range	18.2, 34.1	18.8, 32.8	-7.6, 6.9	18.3, 32.0	19.6, 33.7	-6.4, 7.7
FSH (mIU/dL) N	119	119	119	114	114	114
Mean (SE)	9.4 (1.11)	3.6 (0.67)	-5.8 (0.78)	9.9 (1.27)	2.9 (0.85)	-7.0 (0.72)
Median	6.0	1.0	-3.0	6.0	1.0	-5.0
Range	1.0, 71.0	1.0, 66.0	-62.0, 3.0	1.0, 113.0	1.0, 92.0	-41.0, 2.0
LH (mIU/dL)	119	119	119	114	114	114
Mean (SE)	5.7 (0.57)	2.1 (0.41)	-3.5 (0.44)	6.4 (0.89)	1.6 (0.31)	-4.7 (0.66)
Median	4.0	1.0	-2.0	4.0	1.0	-2.5
Range	1.0, 34.0	1.0, 44.0	-29.0, 10.0	1.0, 82.0	1.0, 34.0	-48.0, 2.0
Lipids[1]						
Triglycerides (mg/dL) N	98	98	98	107	107	107
Mean (SE)	204.6 (13.17)	193.3 (16.64)	-11.4 (12.59)	192.9 (15.17)	169.6 (11.74)	-23.2 (15.67)
Median	170.0	155.5	-9.0	165.0	146.0	-12.0
Range	47.0, 776.0	50.0, 1391.0	-396.0, 615.0	49.0, 1333.0	47.0, 1044.0	-1158.0, 639.0
Total Cholesterol (mg/dL) N	98	98	98	107	107	107
Mean (SE)	190.5 (4.17)	187.1 (4.22)	-3.4 (3.32)	190.1 (3.62)	181.4 (3.78)	-8.7 (3.34)
Median	191.0	187.5	-2.5	193.0	180.0	-11.0
Range	100.0, 327.0	91.0, 345.0	-107.0, 94.0	106.0, 281.0	103.0, 328.0	-112.0, 101.0
HDL (mg/dL) N	98	98	98	107	107	107
Mean (SE)	44.3 (1.07)	41.4 (1.08)	-2.9 (0.85)	44.9 (0.94)	43.1 (0.95)	-1.7 (0.70)
Median	44.0	40.0	-2.0	43.0	42.0	-1.0
Range	25.0, 71.0	21.0, 86.0	-48.0, 15.0	30.0, 75.0	29.0, 77.0	-35.0, 34.0
LDL (mg/dL) N	89	89	89	106	106	106
Mean (SE)	105.9 (3.57)	108.5 (3.40)	2.6 (2.89)	109.1 (3.11)	105.9 (3.37)	-3.2 (2.81)
Median	104.0	110.0	3.0	109.5	104.0	-2.0
Range	40.0, 200.0	43.0, 206.0	-81.0, 90.0	27.0, 197.0	33.0, 228.0	-79.0, 85.0

21.1 Summary of Laboratory Outcomes

The analysis of these data reveals that changes from pre-treatment to endpoint in laboratory parameters were similar between the treatment groups, both with respect to their average effects (or lack of effects) on the parameters as well as on the incidence of subjects with values judged to be potentially clinically significant. The changes in lipids, erythropoiesis, and other parameters over the treatment period were consistent with those changes that have been reported for other testosterone replacement medications.

The outcomes from the analysis of laboratory data reveal that treatment with TU 750 mg or with TU 1000 mg, given every 12 weeks, resulted in expected changes in parameters known to be affected by testosterone replacement, and in no clinically relevant changes in parameters thought to be generally unaffected by testosterone replacement.

22.0 Vital Signs, Physical Findings, and Other Observations Related to Safety

Hypertension was reported as an adverse event in several patients (n=7). The use of testosterone sometimes increases blood pressure by either slightly increasing blood electrolytes or by increasing extracellular fluid volume. The small changes in blood pressure noted in this study could be related to fluid retention in some subjects.

22.1 ECG Data

Descriptive statistics for ECG changes are provided in Appendix A Table 26.

Appendix A Table 26. Changes from Pre-Treatment to Endpoint in ECG Parameters – Total Subject Sample

Vital Sign Parameter	TU 750 (N=120)			TU 1000 (N=117)		
	Pre-Treatment	Endpoint	Change	Pre-Treatment	Endpoint	Change
PR Interval (msec) N	109	109	109	103	103	103
Mean (SE)	165.7 (2.30)	166.0 (2.22)	0.3 (1.10)	166.2 (2.85)	165.9 (2.69)	-0.3 (2.09)
Median	164.0	164.0	0.0	162.0	162.0	-1.0
Range	110.0 to 252.0	128.0 to 256.0	-50.0 to 50.0	82.0 to 284.0	118.0 to 256.0	-90.0 to 76.0
QRS Interval (msec) N	111	111	111	103	103	103
Mean (SE)	92.3 (2.10)	95.3 (1.31)	3.0 (1.77)	94.0 (1.86)	97.1 (1.60)	3.0 (1.56)
Median	94.0	96.0	0.0	96.0	94.0	0.0
Range	6.0 to 174.0	33.0 to 160.0	-75.0 to 95.0	21.0 to 166.0	60.0 to 164.0	-22.0 to 99.0
QTcF (msec) N	111	111	111	103	103	103
Mean (SE)	405.9 (2.03)	403.6 (1.94)	-2.3 (1.96)	408.4 (2.29)	403.1 (2.71)	-5.4 (2.39)
Median	406.2	402.1	-4.2	404.7	401.9	-5.5
Range	336.9 to 490.4	344.7 to 490.4	-48.1 to 91.1	338.8 to 477.3	242.1 to 485.6	-155.2 to 48.1
Heart Rate (bpm) N	111	111	111	103	103	103
Mean (SE)	67.5 (1.01)	68.2 (0.98)	0.7 (0.92)	65.6 (1.00)	67.7 (1.02)	2.1 (0.92)
Median	67.0	66.0	2.0	66.0	66.0	3.0
Range	47.0 to 108.0	45.0 to 95.0	-39.0 to 29.0	41.0 to 92.0	44.0 to 97.0	-23.0 to 31.0

Reviewer's Comment: There were no obvious treatment-related changes from baseline in ECG parameters.

23.0 Prostate Health

23.1 PSA

Appendix A Table 27 provides the number (%) of subjects with PSA > 4 ng/mL at any time during study.

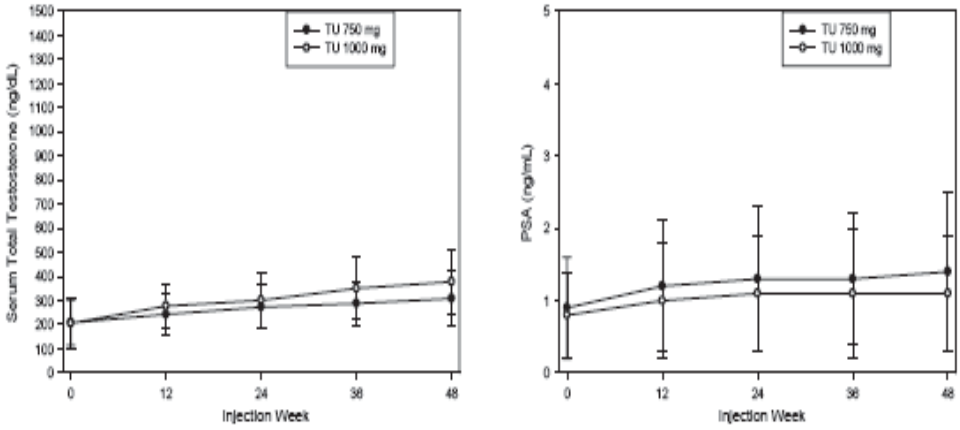
Appendix A Table 27. Number (%) of Patients with PSA Value Above 4 ng/mL by Visit, Endpoint and At Any Time—Total Subject Sample

Time (Visit)	Relation to normal range	Number (%) of Patients	
		TU 750 (N=120)	TU 1000 (N=117)
Screening	Within 0 to 4 ng/mL	120 (100.0)	116 (100.0)
	Above 4 ng/mL	0 (0.0)	0 (0.0)
Baseline (1st Injection Visit)	Within 0 to 4 ng/mL	116 (100.0)	116 (100.0)
	Above 4 ng/mL	0 (0.0)	0 (0.0)
Week 12 (2nd Injection Visit)	Within 0 to 4 ng/mL	109 (97.3)	114 (100.0)
	Above 4 ng/mL	3 (2.7)	0 (0.0)
Week 24 (3rd Injection Visit)	Within 0 to 4 ng/mL	99 (96.1)	104 (100.0)
	Above 4 ng/mL	4 (3.9)	0 (0.0)
Week 36 (4th Injection Visit)	Within 0 to 4 ng/mL	99 (97.1)	95 (99.0)
	Above 4 ng/mL	3 (2.9)	1 (1.0)
Endpoint - Week 48 (5th Injection Visit) or Early Discontinuation	Within 0 to 4 ng/mL	112 (94.1)	111 (97.4)
	Above 4 ng/mL	7 (5.9)	3 (2.6)
Any Time[1]	Within 0 to 4 ng/mL	110 (92.4)	110 (96.5)
	Above 4 ng/mL	9 (7.6)	4 (3.5)

Reviewer's Comment*: The number of patients with serum PSA > 4ng/mL appears to increase with duration of treatment.*

Appendix A Figure 12 provides a plot of by-treatment mean (SD) PSA values over time from the Screening visit through the Injection 5 visit, and the corresponding mean (standard deviation) T concentrations at the same time points. These data are presented for the PK Population (as these were the patients who had T concentrations through the 4th injection interval). This figure demonstrates that while T concentrations rose to within the normal range during the course of the study, average PSA values did not increase by more than 0.5 ng/mL from pre-treatment to the end of the 48 week treatment period. Treatment with other TRT preparations has been reported to increase PSA by approximately 0.5 ng/mL, and this study demonstrated a similar average rise in serum PSA.

Appendix A Figure 12. Mean (SD) serum PSA values over time from the Screening Visit through the Injection 5 Visit, and the corresponding mean (SD) serum T concentrations at the same time points



Appendix A Table 28 presents a list of TEAE's related to prostate health.

Appendix A Table 28. TEAE's related to prostate health in Part A

MedDRA System Organ Class	MedDRA Preferred term	Number of patients (%)	
		TU 750 (N=120)	TU 1000 (N=117)
Investigations	Prostatic specific antigen increased	4 (3.3)	1 (0.9)
	Prostate examination abnormal	2 (1.7)	1 (0.9)
Reproductive system and breast disorders	Benign prostatic hyperplasia	2 (1.7)	3 (2.6)
	Prostatic intraepithelial neoplasia	1 (0.8)	2 (1.7)
	Prostatitis	0 (0.0)	2 (1.7)
	Prostatic disorder	1 (0.8)	0 (0.0)

Appendix A Table 29 presents a listing of subjects with prostate health related outcomes of interest.

Appendix A Table 29. Prostate health related outcomes of interest.

Patient Number	Treatment Group (mg TU)	Age (years)	Prior TRT use	Screening Prostate Volume (via TRUS in cm^3)	Relevant Past Medical History/ Baseline DRE Assessment	TU Exposure (# inj)	Lab normal range for PSA (ng/mL)	PSA values of interest (ng/mL)	Biopsy findings/ Summary
Completed Stage 1									
011-1026	750	65	Yes	39	Enlarged prostate	5 Yes	<=5.10	BL 3.32 Inj 3 4.78 Inj 3 repeat 3.85 Inj 4 4.57 Inj 4 repeat 4.23 Inj 5 5.53 Inj 5 repeat 6.25	On-treatment biopsy performed pre-inj 5 which was negative (no findings). The investigator determined that an additional biopsy following inj 5 (despite PSA values > 4) was not medically indicated given the recent neg biopsy.
014-4195	750	69	Yes	46	Normal DRE	5 Yes	<=7.00	BL 1.23 Inj 5 4.48 Inj 5 repeat 2.5	Repeat PSA value < 4, so no biopsy required or conducted.
020-4165	750	65	Yes	75	BPH/Normal DRE	5 Yes	<=5.10	BL 2.62 Inj 2 4.19 Inj 2 repeat 3.94 Inj 5 4.12 Inj 5 repeat 3.72	Both repeat PSA values < 4, so no biopsy required or conducted.
046-4028	1000	53	Yes	22	Prostatitis/ Normal DRE	5 Yes	<=3.70	BL 2.53 Inj 5 4.02 Inj 5 repeat 4.69	Following PSA elevation at inj 5, Investigator treated with oral Cipro 500 mg, twice daily, for 20 days then repeated the PSA which was relatively unchanged following the full course of antibiotics. On-treatment biopsy performed pre-inj 6 which showed HG PIN.

Patient Number	Treatment Group (mg TU)	Age (years)	Prior TRT use	Screening Prostate Volume (via TRUS in cm^3)	Relevant Past Medical History/ Baseline DRE Assessment	TU Exposure (# inj) / Completed Stage 1	Lab normal range for PSA (ng/mL)	PSA values of interest (ng/mL)	Biopsy findings/ Summary
050-4022	750	56	Yes	16	Normal DRE	5 Yes	<=3.70	BL 2.94 Inj 3 4.21 Inj 4 4.24 Inj 4 repeat 4.26 Inj 5 3.98	On-treatment biopsy performed pre-inj 5 which showed NCS acute and chronic inflammation with some glandular atrophy and no evidence of malignancy.
065-4066	750	73	Yes	44	BPH/ Normal DRE	5 Yes	<=7.00	BL 2.34 Inj 3 4.02 Inj 3 repeat 4.42 Inj 4 4.17 Inj 4 repeats 4.48, 4.03 & 3.87 Inj 5 4.02	On-treatment biopsy performed pre-inj 4 which was negative (no findings). Inj 4 PSA was drawn just prior to the biopsy so the PSA was repeated three times. The investigator determined that an additional biopsy prior to inj 5 was not medically indicated given the recent neg biopsy and stable PSAs.
069-4184	750	41	Yes	37	Normal DRE	5 Yes	<=2.70	BL 0.42 Inj 3 4.09 Inj 3 repeat 2.81	Repeat PSA value < 4, so no biopsy required or conducted.
073-4052	1000	52	Yes	21	Normal DRE	5 Yes	<=3.70	No PSA values > 4	DRE prior to inj 5 was hard, so Investigator requested biopsy which showed HG PIN. Investigator did not discontinue patient and PSA remains < 4 to date.
078-4158	1000	60	No prior TRT	2	Normal DRE	5 Yes	<=5.10	BL 2.28 Inj 4 4.58 Inj 4 repeats 4.09 & 3.35 Inj 5 3.53	On-treatment biopsy performed pre-inj 5 that revealed new HG PIN but no evidence of malignancy. Investigator did not discontinue patient and PSA remains < 4 to date.
078-4164	1000	64	No prior TRT	22	BPH/ Normal DRE	2 No	<=5.10	BL 1.52 ET/EOS 6.83 ET/EOS repeat 2.22	Repeat PSA value < 4, so no biopsy required or conducted. Patient discontinued study on an unrelated AE

Thirteen (13) patients experienced at least one on-treatment PSA > 4 ng/mL and one patient, 073-4052, never exceeded a PSA > 4 ng/mL but did have an on-treatment biopsy. Of the 13 patients with PSAs > 4 ng/mL, four were randomized to the 1000 mg TU arm. Nine patients had a prostate biopsy and none demonstrated evidence of prostate carcinoma, four showed a high-grade prostatic intraepithelial neoplasia and five were negative or showed benign inflammation.

The Sponsor's summary of prostate health in this study is as follows:

• Approximately 5% of the 237 patients treated in this study had at least one on-treatment PSA concentration over 4 ng/mL.

o A higher percentage of patients in the low-dose arm (TU 750 mg) had at least one elevated PSA (as compared to the TU 1000 mg arm). The clinical relevance of this is unknown.

o There were 6 patients with a pre-treatment PSA between 3 ng/mL and 4 ng/mL; 3 (50%) of these patients had at least one on-treatment PSA over 4 ng/mL.

• Rigorous tracking of PSA was performed in this study, with an average of 4 on-treatment PSA assessments performed per patient in this study (a PSA sample was collected once every 12 weeks while the patients were on-treatment). The incidence of elevated PSA concentrations may have been artificially inflated by the frequency of PSA testing.

• Average PSA increased with the TU 1000 mg dose by a median of 0.2 ng/mL during the 48-week treatment period).

• There were no prostate cancers reported in this 48 week study. There were a number of AEs related to the prostate reported in both treatment groups (PSA increased, prostate examination abnormal, benign prostatic hyperplasia, prostatic intraepithelial neoplasia, prostatitis, and prostate disorder).

• The incidence of on-treatment visit-wise DRE findings were similar to the incidence observed pre-treatment.

o A higher percentage of patients in the low-dose arm (TU 750 mg) had at least one DRE finding as compared to the TU 1000 mg arm.

The Sponsor believes that the prostate health outcomes in this study were considered to be "clinically consistent with those expected in a population of hypogonadal men receiving testosterone replacement".

Reviewer's comment: The average increase in serum PSA is considered to be potentially clinically relevant. All rises in serum PSA into the abnormal range in individual patients are also potentially relevant. Clinical adverse events such as BPH and prostatitis are clearly clinically relevant. Taken together, the reviewer believes that this information reflects potential prostate-related risk of androgen replacement therapy, although much larger studies would be necessary to properly define such risks.

24.0 Changes in Mood States (POMS)

Changes from pre-treatment to the 5th injection visit indicated that subjects in both groups demonstrated reductions (improvements) in their Total Mood Disturbance scores; similar reductions (improvements) in all the subscales were also noted, except Vigor, in which increases (improvements) were noted for both treatment groups. The pre-treatment difference between the groups were reflected in the magnitudes of the shifts; the subjects in the TU 750 mg arm, who tended to have worse pre-treatment mood disturbances, tended to have slightly better (larger magnitude) improvements from pre-treatment than subjects in the TU 1000 mg arm. However, subjects in the TU 1000 mg arm still demonstrated numerically similar mood disturbance scores at the end of the 48 week treatment period than the TU 750 mg arm.

Appendix A Table 30 presents summary statistics of the POMS for the PK population, pre-treatment to 5^{th} injection.

Appendix A Table 30. Summary statistics of the POMS for the PK population, pre-treatment to 5th injection

POMS Parameter	TU 750 (N=102)			TU 1000 (N=97)		
	Pre-Treatment	5th Injection Visit	Change	Pre-Treatment	5th Injection Visit	Change
Total Mood Disturbance N	100	100	100	95	95	95
Mean (SE)	34.0 (3.37)	14.1 (2.60)	-19.8 (2.82)	28.2 (3.05)	14.6 (2.89)	-13.6 (2.98)
Median	27.0	10.0	-13.0	25.0	7.0	-13.0
Range	-20.0 to 115.0	-24.0 to 90.0	-106.0 to 49.0	-19.0 to 133.0	-24.0 to 100.0	-85.0 to 94.0
Subscales						
Tension-anxiety N	100	100	100	95	95	95
Mean (SE)	10.4 (0.57)	7.5 (0.44)	-2.9 (0.51)	9.8 (0.56)	7.8 (0.51)	-2.0 (0.50)
Median	8.5	7.0	-3.0	8.0	7.0	-2.0
Range	2.0 to 26.0	2.0 to 23.0	-17.0 to 15.0	2.0 to 24.0	0.0 to 25.0	-16.0 to 11.0
Depression-dejection N	100	100	100	95	95	95
Mean (SE)	10.2 (1.02)	5.8 (0.70)	-4.3 (0.83)	9.0 (0.92)	6.4 (0.88)	-2.5 (0.94)
Median	7.0	4.0	-2.0	6.0	3.0	-2.0
Range	0.0 to 39.0	0.0 to 28.0	-31.0 to 10.0	0.0 to 46.0	0.0 to 35.0	-33.0 to 25.0
Anger-hostility N	100	100	100	95	95	95
Mean (SE)	9.0 (0.87)	5.6 (0.66)	-3.4 (0.73)	7.8 (0.79)	5.9 (0.73)	-1.9 (0.90)
Median	6.0	3.5	-1.5	5.0	3.0	-1.0
Range	0.0 to 37.0	0.0 to 25.0	-32.0 to 11.0	0.0 to 33.0	0.0 to 31.0	-23.0 to 29.0
Vigor-activity N	100	100	100	95	95	95
Mean (SE)	14.8 (0.59)	17.5 (0.64)	2.6 (0.61)	16.2 (0.61)	18.7 (0.67)	2.5 (0.58)
Median	14.0	18.0	2.0	16.0	20.0	2.0
Range	0.0 to 32.0	1.0 to 32.0	-13.0 to 18.0	2.0 to 31.0	1.0 to 32.0	-10.0 to 16.0
Fatigue-inertia N	100	100	100	95	95	95
Mean (SE)	11.9 (0.70)	6.8 (0.56)	-5.1 (0.62)	10.8 (0.65)	7.1 (0.56)	-3.7 (0.63)
Median	12.0	6.0	-4.0	10.0	6.0	-3.0
Range	0.0 to 27.0	0.0 to 21.0	-19.0 to 14.0	0.0 to 26.0	0.0 to 21.0	-20.0 to 12.0
Confusion-bewilderment N	100	100	100	95	95	95
Mean (SE)	7.4 (0.39)	5.9 (0.32)	-1.5 (0.32)	7.0 (0.37)	6.1 (0.34)	-0.9 (0.39)
Median	6.0	5.0	-1.0	6.0	5.0	-1.0
Range	0.0 to 18.0	0.0 to 15.0	-11.0 to 6.0	2.0 to 16.0	1.0 to 17.0	-11.0 to 13.0

Reviewer's Comment: Sponsor believes that the POMS data supports an improvement in mood related to TRT. Lacking a placebo control, it is not possible to draw conclusions from this data. Also, it should be noted that several patients reported depression as a clinical AE.

25.0 Urological Health

The treatment groups were similar with respect to their average pre-treatment AUA total and subscales scores. Both groups averaged approximately 6.1 (out of a maximum of 35) on the AUA total symptom score (AUA-SS) at baseline, indicated a low level of BPH symptomatology in the treatment group. At Day 21, during the 4th injection interval, the AUA Total Score increased by an average of 0.1 and 0.6 (out of a maximum of 35) for TU 750 mg and TU 1000 mg, respectively, although median changes for both treatments were 0. No individual subscale increased by an average of more than 0.2 points (on the 5-point scale for each item); median changes for all subscales were 0 (zero) in both treatment groups.

Appendix A Table 31 presents summary statistics of the AUA for the Day 21 time point during the 4th injection interval.

Appendix A Table 31. Summary statistics for the AUA-SS at Day 21 during the 4th injection interval.

AUA Parameter	TU 750 (N=102)			TU 1000 (N=97)		
	Baseline	Day 21 of 4th Injection Interval	Change	Baseline	Day 21 of 4th Injection Interval	Change
Overall Total N	98	98	98	93	93	93
Mean (SE)	6.1 (0.42)	6.2 (0.60)	0.1 (0.42)	6.2 (0.44)	6.7 (0.57)	0.6 (0.44)
Median	5.0	4.0	0.0	6.0	6.0	0.0
Range	0.0 to 17.0	0.0 to 28.0	-13.0 to 15.0	0.0 to 14.0	0.0 to 27.0	-8.0 to 16.0
Subscales						
Incomplete Emptying N	98	98	98	93	93	93
Mean (SE)	0.8 (0.10)	0.7 (0.10)	-0.1 (0.08)	0.9 (0.12)	0.9 (0.12)	-0.0 (0.13)
Median	0.5	0.0	0.0	1.0	0.0	0.0
Range	0.0 to 4.0	0.0 to 4.0	-2.0 to 2.0	0.0 to 5.0	0.0 to 4.0	-5.0 to 3.0
Frequency N	98	98	98	93	93	93
Mean (SE)	1.2 (0.10)	1.4 (0.14)	0.2 (0.10)	1.3 (0.11)	1.4 (0.11)	0.1 (0.10)
Median	1.0	1.0	0.0	1.0	1.0	0.0
Range	0.0 to 4.0	0.0 to 5.0	-3.0 to 3.0	0.0 to 4.0	0.0 to 4.0	-3.0 to 3.0
Intermittency N	98	98	98	93	93	93
Mean (SE)	0.5 (0.08)	0.6 (0.09)	0.0 (0.07)	0.6 (0.08)	0.7 (0.11)	0.1 (0.08)
Median	0.0	0.0	0.0	0.0	0.0	0.0
Range	0.0 to 3.0	0.0 to 5.0	-2.0 to 3.0	0.0 to 3.0	0.0 to 4.0	-2.0 to 3.0
Urgency N	98	98	98	93	93	93
Mean (SE)	0.7 (0.10)	0.9 (0.13)	0.2 (0.11)	0.8 (0.10)	0.8 (0.12)	0.1 (0.11)
Median	0.0	0.0	0.0	0.0	0.0	0.0
Range	0.0 to 4.0	0.0 to 5.0	-2.0 to 4.0	0.0 to 4.0	0.0 to 5.0	-3.0 to 3.0
Weak stream N	98	98	98	93	93	93
Mean (SE)	0.9 (0.12)	0.9 (0.12)	-0.0 (0.10)	0.8 (0.12)	1.0 (0.14)	0.1 (0.11)
Median	1.0	0.0	0.0	0.0	0.0	0.0
Range	0.0 to 5.0	0.0 to 5.0	-5.0 to 3.0	0.0 to 5.0	0.0 to 5.0	-3.0 to 3.0
Straining N	98	98	98	93	93	93
Mean (SE)	0.4 (0.08)	0.4 (0.09)	-0.1 (0.09)	0.4 (0.08)	0.6 (0.10)	0.2 (0.09)
Median	0.0	0.0	0.0	0.0	0.0	0.0
Range	0.0 to 5.0	0.0 to 5.0	-5.0 to 4.0	0.0 to 5.0	0.0 to 4.0	-2.0 to 4.0
Nocturia N	98	98	98	93	93	93
Mean (SE)	1.5 (0.10)	1.5 (0.12)	-0.0 (0.12)	1.4 (0.10)	1.3 (0.12)	-0.1 (0.11)
Median	1.0	1.0	0.0	1.0	1.0	0.0
Range	0.0 to 5.0	0.0 to 5.0	-3.0 to 4.0	0.0 to 5.0	0.0 to 5.0	-3.0 to 5.0
Urinary Condition	98	98	98	93	93	93
Mean (SE)	1.7 (0.14)	1.5 (0.14)	-0.2 (0.09)	1.6 (0.14)	1.5 (0.13)	-0.1 (0.10)
Median	1.0	1.0	0.0	1.0	1.0	0.0
Range	0.0 to 5.0	0.0 to 5.0	-2.0 to 3.0	0.0 to 5.0	0.0 to 4.0	-2.0 to 3.0

Reviewer's Comment: The minor average increases in AUA-SS may not be clinically relevant when viewed alone, but they may reflect a clinically relevant androgen effect in that some individual patients reported clinical urological adverse events such as urinary hesitancy, urinary retention, nocturia, etc.

26.0 Local Tolerability

The majority of subjects did not report pain, tenderness, erythema or swelling following any of their injections, but some subjects did report pain and/or tenderness at the site when prompted on the questionnaire. The majority of subjects responses on the questionnaire for each symptom were either 'none' or 'mild'; there were very few reports of any symptom reported as having of moderate or worse severity. Only one subject reported severe pain following one of his injections (with no report of tenderness, redness or swelling). Importantly, there was very little erythema or swelling of the injection site reported in either treatment group. Further, the treatment groups were generally similar with respect to the local tolerability outcomes, providing evidence that the 3 mL and 4 mL injections were both well-tolerated.

Appendix A Table 32 presents a tabulation of the within-patient worst (most severe) level of each local (injection site) tolerability symptom (e.g., pain, tenderness, etc) as captured on the local tolerance questionnaire during Stage 1 (i.e., across all 5 injections).

Appendix A Table 32. Within-patient worst (most severe) level of each local (injection site) tolerability symptom as captured on the local tolerance questionnaire during Stage 1 (across all 5 injections)

Tolerability Symptom	Severity (Worst at Any Time)	Number (%) of Patients	
		TU 750 (N=120)	TU 1000 (N=117)
Pain	None	66 (55.0)	58 (49.6)
	Mild	51 (42.5)	51 (43.6)
	Moderate	3 (2.5)	7 (6.0)
	Severe	0 (0.0)	1 (0.9)
	Life Threatening	0 (0.0)	0 (0.0)
Tenderness	None	68 (56.7)	65 (55.6)
	Mild	45 (37.5)	45 (38.5)
	Moderate	7 (5.8)	6 (5.1)
	Severe	0 (0.0)	1 (0.9)
	Life Threatening	0 (0.0)	0 (0.0)
Erythema/Redness	None	106 (88.3)	96 (82.1)
	Mild	14 (11.7)	19 (16.2)
	Moderate	0 (0.0)	2 (1.7)
	Severe	0 (0.0)	0 (0.0)
	Life Threatening	0 (0.0)	0 (0.0)
Swelling	None	109 (90.8)	109 (93.2)
	Mild	11 (9.2)	6 (5.1)
	Moderate	0 (0.0)	2 (1.7)
	Severe	0 (0.0)	0 (0.0)
	Life Threatening	0 (0.0)	0 (0.0)

This clinical study included injection of over 500 TU 750 mg injections and over 500 TU 1000 mg injections (thus, over 1000 injections of TU were given to subjects in this study); a total of 7 of 237 (3%) of subjects reported an TEAE related to injection tolerability, providing evidence that the injections were well-tolerated by the patient population. The treatment groups were generally similar with respect to the incidence of TEAEs associated with local tolerability, providing additional evidence that the 3 mL and 4 mL injections were similarly well-tolerated.

Appendix A Table 33 presents a list of the incidence rate of these TEAEs related to local tolerability.

Appendix A Table 33. Incidence rate of TEAEs related to local tolerability.

MedDRA System Organ Class	MedDRA Preferred term	Number of patients (%)	
		TU 750 (N=120)	TU 1000 (N=117)
Total patients with at least 1 TEAE Associated with Local Tolerability		2 (1.7)	5 (4.3)
General disorders and administration site conditions	Injection site erythema	0 (0.0)	1 (0.9)
	Injection site irritation	0 (0.0)	1 (0.9)
	Injection site pruritus	1 (0.8)	1 (0.9)
	Injection site pain	2 (1.7)	2 (1.7)
	Injection site reaction	0 (0.0)	1 (0.9)

<u>Reviewer's Comment</u>: There were no reports of post-injection "cough reactions" in this study and no reports of allergic reaction.

Overall Safety Conclusions, Part A

Treatment with TU 750 and with TU 1000 mg, given every 12 weeks, resulted in a low overall incidence rate of TEAEs in all system organ classes; there were, as expected, a few reports of AEs related to prostate health, mood, erythropoiesis, and local tolerability at the injection site. There were a few subjects in each treatment group who discontinued from study treatment due to AEs, some of which were judged to be at least possibly related to study treatment. There were some subjects who experienced SAEs (none of which were judged to be at least possibly related to study treatment by the investigator). The number of subjects experiencing serious events or events requiring discontinuation of study medication was few in each treatment arm. There were no reports of post-injection "cough reactions" in this study and no reports of allergic reaction.

Changes in laboratory parameters were similar between the treatment groups, both with respect to their average effects (or lack of effects) on the parameters as well as on the incidence of subjects with values judged to be potentially clinically significant. The changes in lipids, erythropoiesis, serum PSA, and other parameters were consistent with those changes that have been reported for other testosterone replacement medications.

Prostate health was rigorously tracked during this clinical study. There was an average increase from baseline in serum PSA of 0.5 ng/mL. There were subjects in both treatment groups with elevated PSAs, abnormal DREs, and adverse events reported that were associated with the prostate. The incidence of these events was relatively low in both treatment arms.

Vital sign, ECG and other safety outcomes were generally unremarkable. Some subjects did report hypertension as an adverse event. Some subjects also reported discomfort associated with the injection, most of which was mild.

Average safety follow-up was over 300 days (ie, over 43 weeks) for both treatment groups, with the majority of subjects completing all 5 injections. The overall safety and tolerability profile of treatment with TU 750 mg and TU 1000 mg given every 12 weeks as demonstrated in this study was reasonable.

Overall Conclusions, Part A

The data from this study provide evidence that both the TU 750 mg and TU 1000 mg dose (given every 12 weeks) were generally safe and well-tolerated. In this study, there were no "cough reactions" and no allergic reactions. The safety data reflect the known potential risks of androgen replacement therapy. (b) (4)

F. Study IP157-001, Part C

1.0 Introduction

This clinical study report for Study IP157-001 Part C assessed the safety and efficacy of treatment with Nebido 750 mg, given with a 4-week loading injection and every 10 weeks thereafter, in hypogonadal men. TU is a long-acting depot formulation of testosterone undecanoate in castor oil and benzyl benzoate solution intended as replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous testosterone. The dosage form is an oily solution of 250 mg/mL TU, with 4 mL (b) (4) intended for intramuscular injection. An injection of 3 mL yields 750 mg TU.

There was 1 treatment regimen studied:

• 3 mL of 250 mg/mL TU (ie, TU 750 mg) given intramuscularly (IM) with a 4-week loading injection and every 10 weeks thereafter

This treatment will be referred to as the TU 750 mg LOADING regimen throughout this report.

1.1 Dose Selection

The TU 750 mg LOADING regimen selected for Part C of the IP157-001 Study was expected, based on modeling and simulations using data from earlier clinical studies, to provide steady state Cmax values that would not exceed 2500 ng/dL for any patient, would not exceed 1800 ng/dL in more than 5% of patients, and would not exceed 1500 ng/dL in more than 15% of patients. Further, the dosing regimen selected was expected to provide steady state Cavg values within the normal range (300-1000 ng/dL) for at least 75% of patients (with a lower bound for the 95% confidence interval about the proportion being no lower than 65%). Finally, the regimen was expected to attain steady state earlier than the dosing regimens studied in Study IP157-001 Part A.

2.0 Study Objectives

The primary objective of Part C of this study is to evaluate the pharmacokinetics of testosterone undecanoate 750 mg given at baseline, TU 750 mg given 4 weeks later and then every 10 weeks thereafter (i.e., the TU 750 mg LOADING regimen), via measurements of serum total testosterone concentrations in up to approximately 130 hypogonadal men. The measurement of serum testosterone for the Part C primary objective was to be performed during the 3rd injection dosing interval (ie, after the 3rd injection).

Secondary objectives included:

• To evaluate the pharmacokinetics of TU 750 mg LOADING via multiple measurements of serum total testosterone

• To compare serum levels of Free T, DHT, E2, and SHBG to simultaneous levels of serum total testosterone over the 3rd injection interval.

• To evaluate safety in all patients via treatment with TU 750 mg LOADING through up to 9 injections in hypogonadal men.

Safety assessment included:

• Serum levels of prostate-specific antigen (PSA, by enzyme-linked immunoassay [EIA])

• Prostate assessment via digital rectal exam (DRE)

• AUA Symptom Score (only collected pre-treatment and during Stage 2)

• Local Tolerability at Injection Site

• Adverse Events

• Standard clinical laboratory parameters

• Sex hormones, including measurement of serum free testosterone, SHBG, DHT and estradiol.

• LH and FSH with clinical laboratory parameters

• Vital Signs

• ECG and Physical examinations (only collected pre-treatment and during Stage 2)

Additional clinical assessments included:

• Male Patient Global Assessment (M-PGA)

• Profile of Mood States (POMS) (only collected pre-treatment and during Stage 2)

2.1 Overall Study Design

Up to 130 patients were to be enrolled. All patients were to undergo intensive pharmacokinetic (IPK) assessments during the 3rd injection interval.

• Screening: Approximately 1-5 week screening period (washout from select prior testosterone replacement therapies may have extended this period for some patients)

• Baseline: Final pre-study measurements were captured and patients were enrolled.

• Stage 1: The first 3 injection intervals (through the 4th injection visit). This included the first injection at the Baseline visit. The end of Stage 1 was the 4th injection visit. This Stage 1 analysis and report includes only data through the 4th injection visit, and is the primary analysis for this Part of the study, submitted in support of this new dosing regimen for approval in the NDA.

• Stage 2: (Long-term safety extension): The study will continue following the 4th injection visit, with 5 additional injections (at 10-week intervals) during an extended treatment phase. The Stage 2 analysis will include all patients and all data.

The primary analysis for Part C was to be performed following the completion of the post-3rd injection IPK collections.

Patients were to have sampling for PK assessment at the 4th injection and were to continue to have trough samples (prior to each injection) captured thereafter (ie, during the extension portion of the study) at each 10-week dosing interval visit through the remainder of the study. Additional IPK was to be collected for all patients post-injection 4 (to be reported in the Part C Stage 2 clinical study report).

The total exposure for individual patients will be up to 9 injections (approximately 20 months). Long-term safety will be assessed through 9 injections up to approximately 20 months (the "Stage 2" analysis).

2.2 Intensive PK Collection

The PK sampling schedule reflected the loading dose followed by a 10-week dosing interval of TU. Sampling for PK was to be performed as follows:

• After the 3rd injection was given, PK draws were planned at Day 0 (pre-3rd 4, 7, 11, 14, 21, 28, 42, 56, and 70 (pre-4th injection), where the 4th injection visit defined as the end of the injection interval.

These 3rd injection interval data were to be used to determine primary pharmacokinetic (based on the thresholds of approvability for Cavg and Cmax) and to be included in the Stage 1 analysis, as appropriate.

2.2.1 Trough Pharmacokinetic Collection

Trough assessments (immediately prior to each injection) were to be performed at every injection visit until the end of the study, and at the last visit for each patient.

2.2.2. Hormone Concentration Analysis for Pharmacokinetic Determination

All hormone concentrations were to be analyzed centrally by a sponsor-designated laboratory using validated methods. Collection and transfer procedures were be provided in a separate laboratory manual.

2.2.3 Replacement of Drop Outs

Subjects who dropped out during the study were not replaced. The sample size for the primary analysis (Stage 1 assessments) took into account an expected dropout rate of approximately of subjects per year.

2.2.4 Extension Phase Safety Updates

During the Stage 2 extension phase of the study, statistical safety updates may be performed to assess the long-term safety of treatment. These brief assessments may include tabulation of safety outcomes, serum PK concentrations collected (primarily at trough), PSA and other prostate markers and clinical outcomes.

2.2.5 Inclusion and Exclusion Criteria

These criteria were essentially the same as in the Part A protocol.

2.2.6 Subject Discontinuation

If a subject was discontinued from the study prematurely, the Investigator was to select a reason for discontinuation on the End of Study Phase Status eCRF. In addition, every effort was to be made to complete the assessments listed under the End of Study visit.

Subjects withdrawn from the study were generally considered evaluable for statistical assessments, but may have been excluded from some assessments (eg, PK) if insufficient data was present to warrant inclusion in the analysis.

The study protocols and amendments listed the following reason for why a subject may have been removed from the study:

• Adverse Event: If a subject experienced an adverse event that the subject finds unacceptable or that, in the judgment of the Principal Investigator, Indevus Pharmaceuticals, Inc., or the Medical Monitor presents an unacceptable consequence or risk to the subject, the subject may be discontinued from further participation in the study.

• Administrative Discontinuation: After consultation with the Sponsor or Medical Monitor, a subject may be discontinued from the study for failure to comply with protocol requirements. All instances of noncompliance must be documented in the eCRF.

• Refusal of Treatment: If for any reason the subject refuses treatment during the study, the subject shall be discontinued from the study and the reasons for refusal documented on the eCRF. Reasonable efforts shall be made to monitor the patient for adverse events following such discontinuation. Such efforts shall be documented on the eCRF.

2.2.7 Early Discontinuation Criteria

In the event a subject experienced any of the following or a significant change in status as judged by the investigator was detected, the evaluation should have been repeated on a separate day and, if confirmed, the patient should have been terminated from the study.

1. Hemoglobin > 21.0 gm/dL

2. Uncontrolled hypertension, defined as blood pressure with systolic blood pressure ≥ 160 and diastolic blood pressure ≥ 95

3. PSA > 4 ng/mL and ≤ 10 ng/mL, unless prostate cancer is ruled out by new biopsy

4. PSA > 10 ng/mL.

A schedule of protocol events and PK samplings can be seen in Appendix B Tables 1 and 2.

Appendix B Table 1. Schedule of protocol events in Part C

	Injection Number and Week											
	Screening Phase		1	2	3	4	5	6	7	8	9	EOS
	Days -35 to -1	Post-Washout	Baseline Day 0	4	14	24	34	44	54	64	74	84[4]
Informed Consent	X											
Eligibility	X		X[1]									
Medical History (includes height)	X		X[1]									
Physical Exam	X											X
Digital Rectal Examination, PSA	X		X	X	X	X	X	X	X	X	X	X
Vital Signs (includes pulse, blood pressure, weight, temperature)	X		X			X						X
12 Lead ECG	X											X
Hematology, Coagulation, Chemistry (includes lipids), Urinalysis, FSH, LH	X		X			X						X
Prostate Volume (via TRUS)[2]	X											
Pharmacokinetic Sampling (T, DHT, FREE T, SHBG, E2)	X only if Washout NOT Required	X if Washout Required	X	X	X	X	X	X	X	X	X	X
Adverse Events			X	X	X	X	X	X	X	X	X	X
Prior/Concomitant Medications	X		X	X	X	X	X	X	X	X	X	X
Injection (includes drug accountability)			X (750 mg)	X (750 mg)	X (750 mg)	X (750 mg)	X (750 mg)	X (750 mg)	X (750 mg)	X (750 mg)	X (750 mg)	
Local tolerability assessment[3]			X	X	X	X	X	X	X	X	X	X
Profile of Mood States			X									X
AUA Symptom Score	X		X									X
Male Patient Global Assessment				X	X	X						X

1 Medical History and Eligibility pages were updated at Baseline visit as appropriate.
2 TRUS may be repeated during the study at the investigator's discretion.
3 Injection site was assessed by investigator if, at any time, the patient indicates a tolerability issue with the injection site.
4 Patients who discontinued prematurely from the study and who did not complete all of the treatment injections were to be administered assessments as listed under Week 84 or End of Study (EOS) Visit

Appendix B Table 2.
Schedule of PK Samplings in Part C

Intensive PK Collection Time Points (All time points collected Post-Injection 3 and GRAY shaded region time points collected Post-Injection 4)										
	Day									
Assessments	0[a]	4	7	11	14	21	28	42	56	70[b]
Serum Total Testosterone	X	X	X	X	X	X	X	X	X	X
DHT	X	X	X	X	X	X	X	X	X	X
Estradiol	X	X	X	X	X	X	X	X	X	X
Free T (measured)	X	X	X	X	X	X	X	X	X	X
SHBG	X	X	X	X	X	X	X	X	X	X
Male Patient Global Assessment						X				

a Day 0 and Day 70 assessments are also described in Table 9. The assessments are not different nor intended to be duplicative.
b Day 70 of Injection Period 3 is the same as Day 0 of Injection Period 4

2.2.7 Primary Efficacy Variable (s)

The primary hypothesis in this study was based on the 7550 mg Loading dose arm, and was:

• Ho: Testosterone Undecanoate 750 mg given at baseline, week 4 and every 10 weeks thereafter during the 3rd injection interval does not provide adequate testosterone replacement in hypogonadal men

• Ha: Testosterone Undecanoate 750 mg given at baseline, week 4 and every 10 weeks thereafter during the 3rd injection interval does provide adequate testosterone replacement in hypogonadal men

In order to reject the primary pharmacokinetic null hypothesis in favor of the alternative hypothesis, the lower bound of the two-sided 95% confidence interval about the defined primary efficacy variable must be no lower than 65%, and the point estimate for the primary efficacy variable must be at least 75%.

According to the statistical plan, where p=observed proportion, the following 2 criteria must be met in order to reject the null hypothesis Ho in favor of the alternative hypothesis Ha:

- $\rho * 100 \geq 75\%$, and;
- $\left(\rho \pm 1.96 * \sqrt{\frac{\rho(1-\rho)}{n}}\right) * 100 \geq 65\%$

Given the large sample size, the normal approximation to the binomial was to be assumed when deriving the confidence interval.

Subjects for whom it was confirmed that they had taken concomitant testosterone replacement or other androgens during this study were excluded from the pharmacokinetic analysis for the primary and secondary efficacy assessments, as well as the assessment of Cmax data against the decision criteria.

The primary efficacy variable upon which the null hypothesis was to be tested is “the proportion of subjects responding to treatment post protocol-defined 3rd injection interval”.

A subject was to be defined as a responder if his average concentration of T (Cavg) fell within the normal range of 300 to 1000 ng/dL, where Cavg was to be derived as the AUC of the dose interval divided by the duration of the dosing interval.

• A subject was to be considered a responder if his Cavg was in the interval [300,1000] ng/dL.

• A subject was to be considered NOT a responder if his Cavg was either < 300 ng/dL or > 1000 ng/dL.

The time point for assessment of the primary efficacy outcome was the post-3rd injection period (Weeks 14 - 24).

The safety parameters collected during this study included adverse events, clinical laboratory tests, vital signs, physical examinations, assessment of prostate health (including digital rectal examinations, prostate specific antigen measurement), injection site tolerability, and 12-lead ECGs.

2.2.8 Secondary Efficacy Variables

Secondary efficacy was further assessment of T and its association with other outcomes, and included:

• additional serum T pharmacokinetic assessments

o The number (and percent) of subjects with serum T concentration values outside the normal range (below 300 ng/dL or above 1000 ng/dL), both separately for high/low values, and pooled (high and/or low values), for each time point following the 3rd injection.

o The number (%) of subjects for whom the serum T concentration values were within the normal range for each time point following the 3rd injection.

o "Clinical Success". This was defined based on Cavg and Ctrough concentrations during the 3rd injection interval. Subjects were classified as a 'Clinical Success' if both their Cavg and Ctrough values fell within the normal range of 300 to 1000 ng/dL.

• Steady state assessment of serum T concentrations during the injection interval

• Serum T Cmax outcomes compared to the approvability threshold criteria

• Additional exploratory assessments

o Correlation assessments of serum T concentrations with clinical outcome (M-PGA) changes from pre-treatment to the 3rd injection interval.

The clinical outcomes would be correlated with select serum T PK parameters (eg, Cmax, Cavg, and CTrough) obtained from the 3rd injection interval.

o Changes from pre-treatment in body measurement characteristics (including weight and BMI) were assessed for correlation (Pearson coefficients) with serum T concentration PK parameters (Cmax, Cavg, and CTrough) obtained from the 3rd injection interval.

Plots of the average changes in values for body measurement parameters over time for the entire Stage 1 period would be provided.

o The impact of serum T concentrations on erythropoiesis assessed via plots of the time course of hemoglobin and hematocrit versus serum T concentrations for the Stage 1 period.

o The impact of serum T concentrations on lipid markers (HDL, LDL, total cholesterol) assessed via plots of their time course versus serum T concentrations for the Stage 1 period.

o Exploration of factors that may be predictive of serum T Cmax or Cavg during the 3rd Injection interval, such as:

.. Age

.. Baseline (pre-1st injection) serum T

.. Baseline BMI and weight

.. Prior TRT use

.. Other variables as warranted

• Other hormone serum concentration assessments over time and their association with changes in T concentrations (including Free T, DHT, SHBG, E2 and their ratios to T over time)

2.2.9 Clinical Efficacy

Clinical efficacy included the assessment of clinical markers of TRT, including:

• Body Composition (weight, BMI)

• Male Patient Global Assessment

3.0 Statistical Methods.

Consistent with the primary objectives of the study, the primary analysis was the Stage 1 assessment of T pharmacokinetics during the 3rd injection interval. The Stage 1 analysis included all subjects and all data (including baseline characteristics, pharmacokinetic assessment of 3rd injection interval, and safety data) through the 4th injection visit for each subject . (Note that Stage 2 analyses will be based on data collected the day following the 4th injection visit, and through the last study assessment for each subject.) Other secondary objectives, including long-term assessment of safety during the extension portion of the clinical trial, will be assessed at regular intervals during the course of the study and summarized in a final report at the end of the extension study.

3.1 Sample Size

The sample size was based on the primary efficacy outcome parameter, the proportion of subjects responding to treatment during the 3rd injection interval as measured by Cavg [i.e., the proportion of subjects with a Cavg value falling within the normal reference range for T (300 – 1000 ng/dL)].

When the sample size is 73, a two-sided 95% confidence interval using the large sample normal approximation to the binomial will extend 0.10 from the observed proportion, based on an assumed expected proportion of 0.75. Thus, assuming a response rate of 75% or greater, the lower bound of the 95% confidence interval will fall no lower than 65%.

This study includes a long-term safety component of up to 1-year duration, in order to allow for adequate assessment of safety outcomes. Assuming 10% subject dropout in the first year, up to approximately 130 subjects were anticipated to be enrolled in this study in order to provide for up to approximately 100 subjects completing the intensive 3rd injection interval PK assessments.

4.0 Safety Assessments

Safety data was to be captured as described in the study protocol schedule of events.

All safety data collected and captured in the eCRF were to be included in data listings sorted by domain, subject and time point, or as appropriate. Mean changes from baseline (pre-treatment) to on-treatment were generally be tabulated by protocol-specified time points, while the

incidence of shifts from baseline of values from the pre-determined potentially clinically significant ranges (with individual values categorized as low, normal or high based on those ranges) were presented for endpoint/final values. For those subjects missing a baseline value for a particular parameter, the screening value was used as the pre-treatment value for that parameter.

For purposes of safety assessment, the 'endpoint' and 'final' value are both defined as the last observed value for a subject during the Stage 1 treatment period (up to and including the 4th Injection visit). This value represented the point at which the patient has had the longest exposure to TU during Stage 1.

Generally, safety assessments were to be performed using the Total Patient Sample. Additional analyses were to be performed using the PK Population or other subgroups of subjects . Potentially clinically significant ranges were defined in the SAP (Section 16.1.9) for clinical laboratory parameters, vital signs and ECG outcomes.

4.1 AE's

Adverse events were to be classified using the MedDRA coding dictionary Version 9.1. Tabulations included an overall incidence of at least one adverse event, incidence within body system, and incidence by preferred term. Each patient only contributed once (i.e., first occurrence) to each of the incidence rates, regardless of the number of occurrences.

Events occurring prior to the first injection were to be reported in the medical history section of the eCRF. The incidence of adverse events for the Stage 1 analysis was presented as follows:

• The incidence of treatment-emergent adverse events was tabulated for the Stage 1 Treatment Phase. Treatment-emergent was defined as any adverse event with an onset date greater than or equal to the study medication first injection date. If the patient went into Stage 2, events that started after the completion of the Stage 1 period (i.e., AE start date is after the 4th injection visit date) were not included in the Stage 1 analysis, but will be included in the Stage 2 analysis.

Patients with serious adverse events (including deaths) and patients who discontinued due to adverse events were listed. Patients who had other significant serious adverse events deemed to be of special interest because of clinical importance were also listed. Patient narratives are included in this Stage 1 clinical study report for these patients.

Reviewer's Comment*: Based upon the separation of this study into two stages, this report (for Stage 1) includes safety data (including AEs) only up to the 4th injection date. Therefore, the bulk of safety data for this study will appear in the report for Stage 2 – which includes the fourth injection interval and an additional 5 injections thereafter. This serves to limit the safety conclusions from the Stage 1 study report.*

4.2. Serum levels of prostate-specific antigen (PSA)

PSA levels in serum were to be determined by the Central laboratory. Blood samples were to be collected at Screening, Baseline, and on-treatment as noted in the schedules of events (see Section 9.6). Generally, the last pre-treatment value prior to the injection was used in the analysis for assessment of changes over time.

Descriptive statistics at baseline (pre-treatment), endpoint, and change from pre-treatment were calculated for the patients who had both pre-treatment and on-treatment serum PSA evaluations. Shifts from pre-treatment to endpoint were examined. Other assessments of PSA may have been performed in an exploratory manner.

When applicable, PSA samples were to be obtained prior to digital rectal examinations being performed.

4.3. Prostate Volume

Transrectal ultrasonography (TRUS) of the prostate was to be performed during screening (prior to randomization) to determine the volume of the organ and - if necessary - to clarify abnormal findings of palpation if present. These data were to be listed.

4.4. Clinical Laboratory Tests

Clinical laboratory tests were to be performed as noted in the schedule of events in the study protocol. Parameters were to include:

• CLINICAL CHEMISTRY - Total protein, albumin, serum creatinine, blood urea nitrogen (BUN), uric acid, bilirubin (total & direct), alkaline phosphatase, alanine aminotransferase (ALT, SGPT), aspartate aminotransferase (AST, SGOT), creatine phosphokinase (CPK), glucose, calcium, phosphorus, sodium, potassium, chloride, bicarbonate, follicle stimulating hormone (FSH), and luteinizing hormone (LH)

• LIPID PANEL - Triglycerides, total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL). Best attempts were to be made to collect FASTING LIPIDs, where the fast was to have begun at least 8 hours prior to lipid assessment.

• HEMATOLOGY - White blood cell (WBC) count, differential white cell count (lymphocytes, monocytes, basophils, eosinophils, neutrophils), red blood cell (RBC) count, hematocrit, hemoglobin, platelet count, PT, PTT and INR

o Notably, the methods for assessment of coagulation parameters were changed by the central laboratory part-way through the study, and thus reference ranges were changed for these parameters. Outcomes for coagulation parameters should be interpreted with this laboratory change in mind.

• URINALYSIS - Color, specific gravity, pH, glucose, ketones, blood, protein, nitrates, leukocyte esterase, RBC, WBC.

These data were to be analyzed as follows:

• Descriptive statistics at pre-treatment, on-treatment, and change from pre-treatment were to be calculated for the patients who had both pre-treatment and on-treatment evaluations. These values were assessed at each protocol-specified time point.

• Shifts from pre-treatment to the last (endpoint) value were to be tabulated.

• The number of patients with potentially clinically significant values at pre-treatment and at the last (endpoint) value were to be tabulated

o Special attention was to be given to markers of erythropoiesis (eg, hematocrit, hemoglobin) and serum lipids.

Other assessments of laboratory outcomes were to be performed if the data warranted. Assessments of laboratory outcomes were o be performed using the Total Patient Sample; however, some assessments were also to be performed for the PK Population or other subgroups.

4.5 Vital Signs

Vital signs were to be measured as noted in the schedule of events in the study protocol. These data were to be analyzed as follows.

• Descriptive statistics at pre-treatment, on-treatment, and change from pre-treatment were to be calculated for the patients who had both pre-treatment and on-treatment evaluations . These values were to be assessed at each protocol-specified time point.

• Shifts from pre-treatment to the last (endpoint) value were be tabulated.

• The number of subjects with potentially clinically significant values at pre-treatment and at the last (endpoint) value was to be tabulated.

4.6 ECG's

ECGs were to be performed as noted in the schedule of events in the study protocol. ECGs were not performed during the on-treatment portion of Stage 1 of Part C, and thus assessment of these outcomes was not performed for Stage 1 (except some for subjects who discontinued prematurely from Stage 1). For Stage 2, these data will be analyzed as follows.

• Descriptive statistics at pre-treatment, on-treatment, and change from pre-treatment were to be calculated for the subjects who had both Screening and on-treatment evaluations. These values were to be assessed at each protocol-specified time point.

• Shifts from pre-treatment to the last (endpoint) value were to be tabulated.

• The number of subjects with potentially clinically significant values at pre-treatment and at the last (endpoint) value was to be tabulated.

4.7 Digital Rectal Examinations

DREs were to be conducted at screening, baseline, and on-treatment as noted in the schedule of events. Descriptive statistics at baseline (pre-treatment), on-treatment, and change from pre-treatment were to be calculated for the patients who had both pre-treatment and on-treatment evaluations.

4.8 AUA Symptom Score

The AUA Symptom Score was assessed as noted in the schedule of events in the study protocol. The AUA was not performed during the on-treatment portion of Stage 1 of Part C.

The AUA Symptom Score is a self-reported 7 item validated instrument. The score is the sum of questions 1 to 7. The lowest score is 0 and the maximum total score is 35 with higher scores indicating more bothersome urinary symptoms. Seven response domains include incomplete emptying, frequency, intermittency, urgency, weak stream, straining, and nocturia. Changes in these assessments over time (from baseline) were tabulated only for patients who discontinued prematurely from Stage 1. If, for a particular subject, there were approximately 30% or more missing items, the score was set to missing for that subject.

4.9 Local Tolerability

Local tolerability was assessed as per the schedule of events. These data were to be tabulated by response category. Note that clinically significant finding(s) as judged by the investigator were to be recorded as Adverse Events; thus, tolerability symptoms reported on the questionnaire are not considered to be AEs unless assessed by the investigator as such.

4.10 Physical Examinations

Physical examinations were to be performed at screening and on-treatment as noted in the schedule of events. Physical examinations were not performed during the on-treatment portion of Stage 1 of Part C. Descriptive statistics were to be calculated for subjects who had both Baseline and on treatment evaluations, where appropriate. On-treatment statistics were tabulated only for subjects who discontinued prematurely from Stage 1.

4.11 Body Measurements

Body measurements (height/weight) were to be performed at baseline and on-treatment. Descriptive statistics for weight and BMI were to be calculated for subjects who had both baseline and on treatment evaluations. Mean changes over time (from baseline) were to be tabulated.

4.12 Profile of Mood States (POMS)

During Stage 1 of Part C, the POMS was performed only at pre-treatment.

4.13 Psychosexual Daily Questionnaire

The Psychosexual Daily Questionnaires (PSDQ) was not performed for Part C.

4.14 International Index of Erectile Function (IIEF)

The International Index of Erectile Function (IIEF) was not performed for Part C.

4.15 Male Patient Global Assessment

Patient global self-evaluation of change in hypogonadal symptoms and overall well-being were to be assessed using the Male- Patient Global Assessment (M-PGA) questionnaire starting on treatment at Week 4 and as noted in Schedule of Events. The M-PGA is a 5-item self-report questionnaire designed to assess patient perception of change from pre-treatment or baseline in their hypogonadal symptoms including confidence/self-esteem, sexual performance, moods/behavior, overall feeling of well-being, and satisfaction with the study treatment.

M-PGA responses were to be tabulated by original responses and by a collapsed set of categories. For the first 4 questions, the proportion of subjects with improvement (eg, 'Very Much Improved', 'Much Improved', or 'Minimally Improved') were collapsed into a single category, while the proportion of the corresponding group with worsening ('Very Much Worse', 'Much Worse', or 'Minimally Worse') was collapsed into a second category. 'No Change' responses were the third category. Similar categories were derived for the Patient Satisfaction question. Note that the patient satisfaction with study treatment was measured and tabulated by the response to the question: "Please, rate your satisfaction with the study treatment according to the following scale:

- (1 = very much satisfied to 7 = very much dissatisfied)."

Note that the algorithm for collapsing the categories differs from that originally specified in the protocol (where only the 2 'best' categories were to be collapsed, versus all other responses); however, because that algorithm was collapsing subjects who had either minimally improved or who had no change into the category 'worsening', the revised algorithm (as used in this study report) was introduced in the SAP prior to database lock.

4.16 T Pharmacokinetic Assessment

The purpose of the PK sampling was to assess serum T concentrations resulting from treatment with TU, specifically:

• To characterize the T pharmacokinetics from the TU 750 mg LOADING regimen during the 3rd injection interval (Weeks 14 through 24 of treatment) in subjects with hypogonadism.

For all subjects, serum T was to be measured at all injection visits (pre-injection, ie, trough) during the course of the study and at the last study visit. IPK monitoring was to be performed in all subjects after the 3rd injection, and was to include the following time points: Day 0 (pre-3rd injection), Day 4, 7, 11, 14, 21, 28, 42, 56, and the end of the injection interval at Day 70 (pre-4th injection), ie, at the 4th injection visit.

4.16.1 Pharmacokinetic Assessments during the 3rd Injection Interval

A complete description of the pharmacokinetics of T during the 3rd injection interval was to be performed. In addition, the number (and percent) of subjects with concentration values outside the normal range were to be tabulated, both separately for high/low values, and pooled (high and/or low values). For those subjects who had concentration values outside the normal range, the duration of time (in days) that the values were outside the range was to be tabulated, both

separately for high/low values, and pooled (high and/or low values). [Note that the analysis of the duration of time was not performed, but rather a review of the individual patient concentration-time profiles was performed to assess the approximate time T concentrations were outside the normal range.]

The number (%) of subjects for whom the concentration values were within the normal ranges at all time points measured during the injection interval was to be tabulated.

Individual concentration-time plots of each subject were to be presented, with upper and lower normal range reference lines, to demonstrate whether testosterone levels fell within these normal ranges during the course of treatment for each subject, and if the levels did fall outside the range, at what time points this occurred. Mean concentration plots were to be constructed in a similar manner.

Other parameters were to be derived, and may have included the area under the 10-week time-concentration curve [AUC(0-10 weeks)], Ctrough at the end of the dosing interval, Tmax, and t½ (half-life). Other pharmacokinetic determinations may also have been performed. These parameters and methods for derivation and analysis can be found in the SAP.

4.17 Other Hormone Assessments

Select hormones were assessed during all scheduled time-points that T was measured. Hormone data, including free testosterone, DHT, estradiol and SHBG were presented using concentration-time plots. Ratios of DHT:T and E2:T were presented over the dosing interval.

5.0 Study Subjects

5.1 Subject Disposition

Appendix B Tables 3 and 4 summarize the subject accounting and the reasons for screening failures.

Appendix B Table 3. Summary of subject accounting

	Number of patients
	TU 750 mg LOADING
Screened	354
Enrolled[1]	130
Completing 4th Injection Visit N (% Based on Enrolled Patients)	116 (89.2)
Premature Discontinuation N (% Based on Enrolled Patients)	14 (10.8)

Appendix B Table 4. Summary of reasons for screening failure

Reason for Screen Failure	Number (%) of Patients
Total Number Patients Screen Failure	224
Screening testosterone ≥ 300 ng/dL	146 (65.2)
Study enrollment completed	21 (9.4)
Liver function tests exceeding 1.5 times upper limit of normal	10 (4.5)
AUA Symptom Score ≥ 15)	7 (3.1)
Other reasons[1]	40 (17.9)

6.0 Efficacy Evaluation

6.1 Demographics and Other Baseline Characteristics

Appendix B Table 5 summarizes the characteristics of the Total Patient Sample.

Appendix B Table 5. Demographic characteristics of the Total Patient Sample

Characteristic	TU 750 mg LOADING (N=130)
Age (in years)	
Mean ± SE	54.2 ± 0.90
Median (range)	55.0 (24.0, 75.0)
Age Categories, N (%)	
< 30	1 (0.8)
30 - <40	10 (7.7)
40 - <50	30 (23.1)
50 - <60	50 (38.5)
60 - <70	33 (25.4)
70 - <80	6 (4.6)
≥ 80	0 (0.0)
Gender, N (%)	
Male	130 (100.0)
Race, N (%)	
White	97 (74.6)
Black	16 (12.3)
Hispanic	14 (10.8)
Asian	0 (0.0)
Other	3 (2.3)
Height (in cm)	
Mean ± SE	177.8 ± 0.65
Weight (in kg)	
Mean ± SE	101.2 ± 1.58
BMI (kg/m^2)[1]	
Mean ± SE	32.0 ± 0.48
Screening Inclusion Serum Total Testosterone (ng/dL)	
Mean ± SE	214.7 ± 6.01
Median (range)	236.1 (24.3, 298.8)

6.2 Prior T Replacement Therapy

A summary of prior TRT is seen in Appendix B Table 6

Appendix B Table 6. Summary of prior use of TRT

Prior Testosterone Replacement Therapy	Number (%) of patients TU 750 mg LOADING (N=130)
At least one prior testosterone replacement therapy	**81 (62.3)**
Androgel	36 (27.7)
Depo-Testosterone	21 (16.2)
Testim	22 (16.9)
Androderm	8 (6.2)
Testosterone Enanthate (generic or Delatestryl)	4 (3.1)
Testosterone Cypionate (generic)	6 (4.6)
Striant Buccal	1 (0.8)
Other	3 (2.3)

7.0 Efficacy Results

Appendix B Table 7 provides the point estimate for the number (%) of subjects meeting the Cavg threshold, and the 95% CI about the point estimate. TU 750 mg LOADING met the Cavg threshold criteria, with 110 (94.0%) patients meeting the Cavg threshold criteria [95% CI = (89.6, 98.4)]. Thus, the null hypothesis is rejected in favor of the alternative, ie, it is concluded that the TU 750 mg LOADING regimen does provide adequate testosterone replacement in hypogonadal men. Of note, serum trough deteminations have shown that the primary assesment of efficacy was conducted at steady-state in this study (see Appendix D).

Appendix B Table 7. Point estimate for the number (%) of subjects meeting the Cavg threshold, and the 95% CI about the point estimate

	Number (%) of Patients and 95% CI	
	TU 750 mg LOADING (N=117)	
Outcome	**N (%)**	**95% CI**
C_{avg} within [300,1000] ng/dL	110 (94.0)	(89.6, 98.4)
C_{avg} NOT within [300,1000] ng/dL	7 (6.0)	

7.1 PK of Serum T at Steady-State

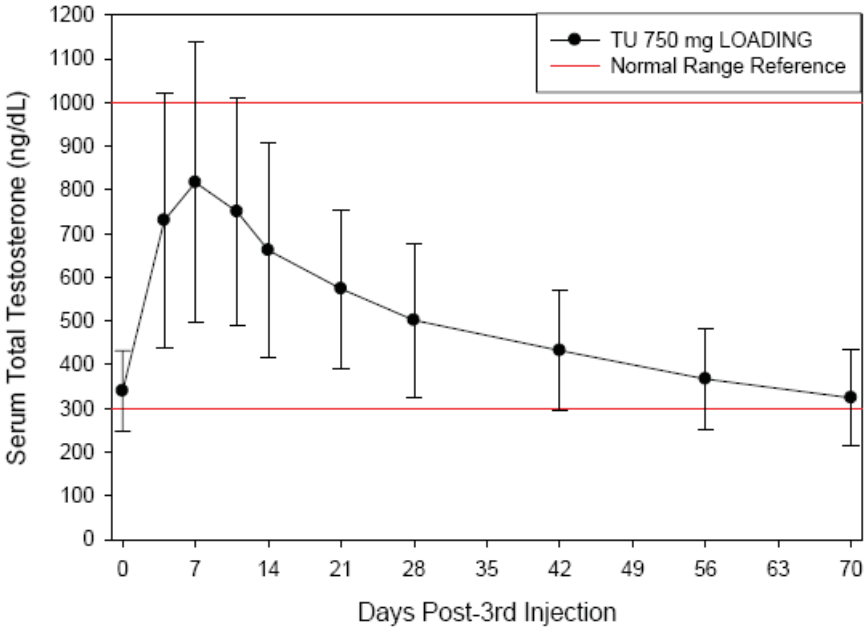
Prior to the 3rd injection, subjects had an average T concentration equal to 339.5 ng/dL. Average T concentrations rose quickly after injection, with median Tmax on Day 7 (generally, Tmax was observed on Days 4, 7 or 11 for most subjects). Average T concentrations gradually lowered over the next 10 weeks of the treatment interval, with the Ctrough concentrations (at Day 70, or Week 10) averaging 323.8 ng/dL. Average T concentrations remained within the normal range for the entire 10 week dosing interval. Variability in concentrations tended to be highest during the earlier time points in the dosing interval (around Tmax), however, the coefficient of variation (CV%) was maintained between 30% and 45% across all time points, demonstrating that variability was generally proportional to the mean during the dosing interval.

Appendix B Table 8 and Appendix B Figure 1 provide summaries of the 3rd injection T concentration-time profile.

Appendix B Table 8. Summary of the 3rd injection T concentration-time profile.

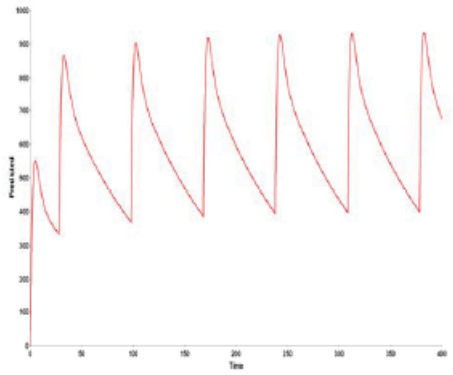
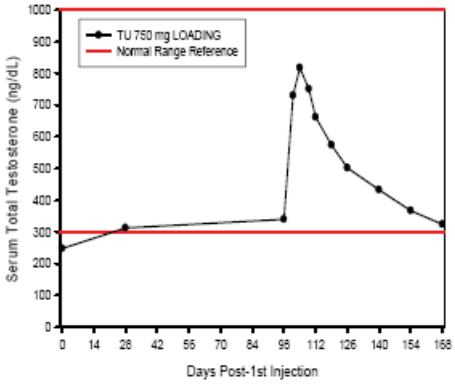
Treatment Group	Days Post-Injection	Number Patients	Mean	Standard Deviation	Minimum	Median	Maximum	CV%	Geometric Mean
TU 750 mg LOADING	0 (Pre-Injection)	117	339.5	122.69	141.4	303.0	754.1	36.1	319.8
	4	111	730.1	325.36	304.6	656.4	1715.0	44.6	662.9
	7	111	816.9	352.15	276.4	737.6	1758.5	43.1	747.5
	11	107	750.1	280.64	245.6	740.9	1757.0	37.4	697.9
	14	114	661.6	237.55	230.9	610.8	1352.3	35.9	619.2
	21	115	573.5	197.15	182.7	558.6	1350.4	34.4	541.3
	28	111	501.6	149.92	190.9	481.4	947.0	29.9	479.5
	42	109	432.3	152.16	171.3	399.8	1161.2	35.2	409.5
	56	115	367.0	120.67	144.5	349.8	780.8	32.9	348.7
	70[1]	116	323.8	99.51	138.2	317.2	611.1	30.7	309.2

Appendix B Figure 1. Serun T concentration-time profile for the 3rd injection interval



According to the Sponsor, the pre-study modeling and simulations of the PK profile for the TU 750 mg LOADING regimen predicted the actual observed pharmacokinetic profile. A comparison between the modeled and observed concentrations at the injection (trough) time points (ie, Weeks 4, 14, and 24) as well as the IPK time points during the 3rd injection interval reveals that the modeled outcomes corresponded well with the observed outcomes (see Appendix B Figure 2). Of particular note, the sponsor stated that the means at the trough time points (Days 0, 28, 98, and 168) and at Tmax (Day 7, corresponding to Day 105 of the 3rd injection interval) for the concentration-time profile were almost identical between the modeled profile and the actual profile observed.

Appendix B Figure 2. Comparison of the modeled outcomes to the observed outcomes

a priori Predicted Mean T Concentrations (Model-Based Simulation)	Actual Observed Mean T Concentrations (N=117)
	

Treatment with TU 750 mg demonstrated an average T concentration over the 70 day treatment interval that was within the normal range for T (ie, 300 to 1000 ng/dL): average C_{avg} was 494.9 ng/dL. Average C_{max} was 890.6 ng/dL, and average C_{Trough} was maintained within the normal range at steady state at 323.5 ng/dL. Median T_{max} was 7 days following the 3rd injection.

Appendix B Table 9 presents a summary of the PK parameters during the 3rd injection interval. The variability of the PK parameters was generally low; the coefficients of variation for all key PK parameters were ≤ 40 %.

Appendix B Table 9. Summary of the PK parameters during the 3rd injection interval

TU Dose	Pharmacokinetic Parameter	Number Patients	Mean	Standard Deviation	Minimum	Median	Maximum	CV (%)	Geometric Mean
TU 750 mg LOADING	$AUC_{(0-70)}$ (days*ng/dl)	117	34645.6	9902.45	13755.1	33342.2	70016.9	28.6	33263.6
	C_{Trough} (Day 70)	117	323.5	99.11	138.2	316.9	611.1	30.6	309.0
	C_{max} (ng/dL)	117	890.6	345.11	311.0	813.6	1758.5	38.8	826.8
	Dose-normalized C_{max}(ng/dL)[1]	117	1.2	0.46	0.4	1.1	2.3	38.8	1.1
	T_{Last} (days)	117	70.0	0.00	70.0	70.0	70.0	0.0	70.0
	T_{max} (days)	117	10.0	7.11	4.0	7.0	42.0	71.1	8.4
	Dose-normalized $AUC_{(0-70)}$ (days*ng/dl)[1]	117	46.2	13.20	18.3	44.5	93.4	28.6	44.4
	$C_{avg, 0-70}$ (ng/dL)[2]	117	494.9	141.46	196.5	476.3	1000.2	28.6	475.2

8.0 Secondary Efficacy Results

Secondary assessments of T pharmacokinetics included:

• The number (and percent) of subjects with T concentration values outside the normal range (below 300 ng/dL or above 1000 ng/dL), both separately for high/low values, and pooled (high and/or low values), for each time point following the 3rd injection.

• The number (%) of subjects for whom the T concentration values were within the normal range for each time point following the 3rd injection.

• "Clinical Success". This was defined based on Cavg and Ctrough concentrations during the 3rd injection interval. Subjects were classified as a 'Clinical Success' if both their Cavg and CTrough values fell within the normal range of 300 to 1000 ng/dL.

Appendix B Table 10 provides a summary of select secondary PK outcome results.

Appendix B Table 10. Summary of select secondary PK outcome results

Secondary Outcome Parameter	TU 750 mg LOADING (N=117)
Number Patients with C_{avg} < 300, 300 - 1000, > 1000 ng/dL	
<300 ng/dL	6 (5.1)
300 to 1000 ng/dL	110 (94.0)
>1000 ng/dL	1 (0.9)
Number Patients with C_{avg} ≥ 300 ng/dL	
<300 ng/dL	6 (5.1)
≥300 ng/dL	111 (94.9)
Number Patients with at least one serum total testosterone below 300 ng/dL	
At least one concentration < 300 ng/dL	61 (52.1)
No concentration < 300 ng/dL	56 (47.9)
Number Patients with C_{max} ≤1500, > 1500 - < 1800, 1800 - <2500, ≥ 2500 ng/dL	
≤ 1500 ng/dL	108 (92.3)
> 1500 - < 1800 ng/dL	9 (7.7)
1800 - <2500 ng/dL	0 (0.0)
≥ 2500 ng/dL	0 (0.0)
Number Patients with at least one serum total testosterone > 1000 ng/dL	
At least one T concentration > 1000 ng/dL	35 (29.9)
No T concentration > 1000 ng/dL	82 (70.1)

Appendix B Table 11 presents the number (and percent) of subjects with T concentration values outside the normal range (below 300 ng/dL or above 1000 ng/dL, or either) for each time point during the 3rd injection interval.

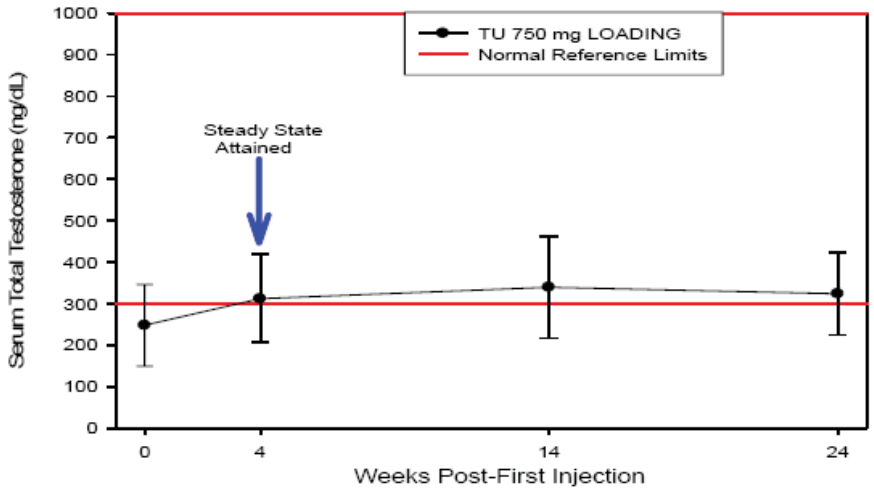
Table 11. Number (%) of subjects with serum T concentration values outside the normal range for each time point during the 3rd injection interval

	Number (%) of Patients									
	Days Post-3rd Injection									
Treatment/Outcome	0	4	7	11	14	21	28	42	56	70
TU 750 mg LOADING										
< 300 ng/dL	53 (45.3)	0 (0.0)	2 (1.8)	2 (1.9)	4 (3.5)	3 (2.6)	6 (5.4)	20 (18.3)	38 (33.0)	52 (44.8)
300 to 1000 ng/dL	64 (54.7)	90 (81.1)	80 (72.1)	86 (80.4)	99 (86.8)	109 (94.8)	105 (94.6)	88 (80.7)	77 (67.0)	64 (55.2)
> 1000 ng/dL	0 (0.0)	21 (18.9)	29 (26.1)	19 (17.8)	11 (9.6)	3 (2.6)	0 (0.0)	1 (0.9)	0 (0.0)	0 (0.0)
< 300 or > 1000 ng/dL	53 (45.3)	21 (18.9)	31 (27.9)	21 (19.6)	15 (13.2)	6 (5.2)	6 (5.4)	21 (19.3)	38 (33.0)	52 (44.8)

8.1 Steady-State Assessment of Serum T During the 3rd Injection Interval

Appendix B Figure 3 provides a presentation of the mean serum T concentrations at each trough time point, i.e., at baseline, Week 4 (Trough 1), Week 14 (Trough 2), and Week 24. As demonstrated in this plot, the trough serum T concentrations reached a plateau by the 2nd injection interval, and thus the treatment can be considered to have reached steady state by the 4th week of treatment.

Figure 3. Mean serum T concentrations at each trough time point



8.2 Cmax Outcomes Compared to the Approvability Thresholds

A secondary hypothesis in this study was related to the Cmax values at steady state. The following was tested:

• Ho: 750 mg TU given at baseline, TU 750 mg given 4 weeks later, and then every 10 weeks thereafter during the 3rd injection interval does result in excessively high serum total testosterone values in hypogonadal men

• Ha: 750 mg TU given at baseline, TU 750 mg given 4 weeks later, and then every 10 weeks thereafter during the 3rd injection interval does not result in excessively high serum total testosterone values in hypogonadal men

Each subject was compared to the criteria listed in Appendix b Table 29, and categorized as either meeting the criteria for success, or not meeting the criteria for success. In order to reject this secondary objective null hypothesis in favor of the alternative hypothesis, all three criteria for success as defined must have been met.

Appendix B Table 12 provides a summary of the comparison of serum T concentrations to the Cmax approvability thresholds. The comparison indicates that treatment with TU 750 mg with a 4-week loading injection and every 10 weeks thereafter does not result in excessively high T concentrations. No subject in the PK population exceeded either the 2500 ng/dL or 1800 ng/dL threshold, while only 9 (of 117, 7.7%) subjects exceeded the 1500 ng/dL threshold.

Based on these assessments of maximum concentrations at steady state, treatment did not provide excessive TRT that resulted in violations of the thresholds.

Appendix B Table 12. Comparison of serum T concentrations to the Cmax approvability thresholds

	Number of Patients Exceeding/Number of Patients Assessed (Percent of Patients Exceeding)
C_{max} Outcome	TU 750 mg LOADING (N=117)
> 1500 ng/dL[1]	9 of 117 (7.7%)
≥ 1800 ng/dL and < 2500 ng/dL	0 of 117 (0%)
≥ 2500 ng/dL	0 of 117 (0%)
Did Dose Meet Threshold Limits?	Yes

8.3 Correlation Assessments of T with Clinical Outcome Measures

The intent of this analysis was to assess whether any changes in clinical outcomes were related to serum T concentrations.

Clinical outcome measures included in this assessment were the M-PGA (patient global assessment). The following outcomes were observed:

• According to the Sponsor, serum T concentrations weakly inversely correlated with changes in the patient global assessments at both Day 0 and Day 21 of the 3rd injection interval; i.e., greater improvements were noted in patient global satisfaction for subjects with higher T exposure than for subjects with lower T exposure. The strength of the linear correlation was weak, with the Pearson correlation coefficients generally between 0 and 0.2.

8.4 Body Measurements and T

The intent of this analysis was to assess whether higher T concentrations result in larger changes in body measurements. Generally, according to the Sponsor, serum T concentrations were weakly inversely correlated with changes from pre-treatment weight and BMI during this study.

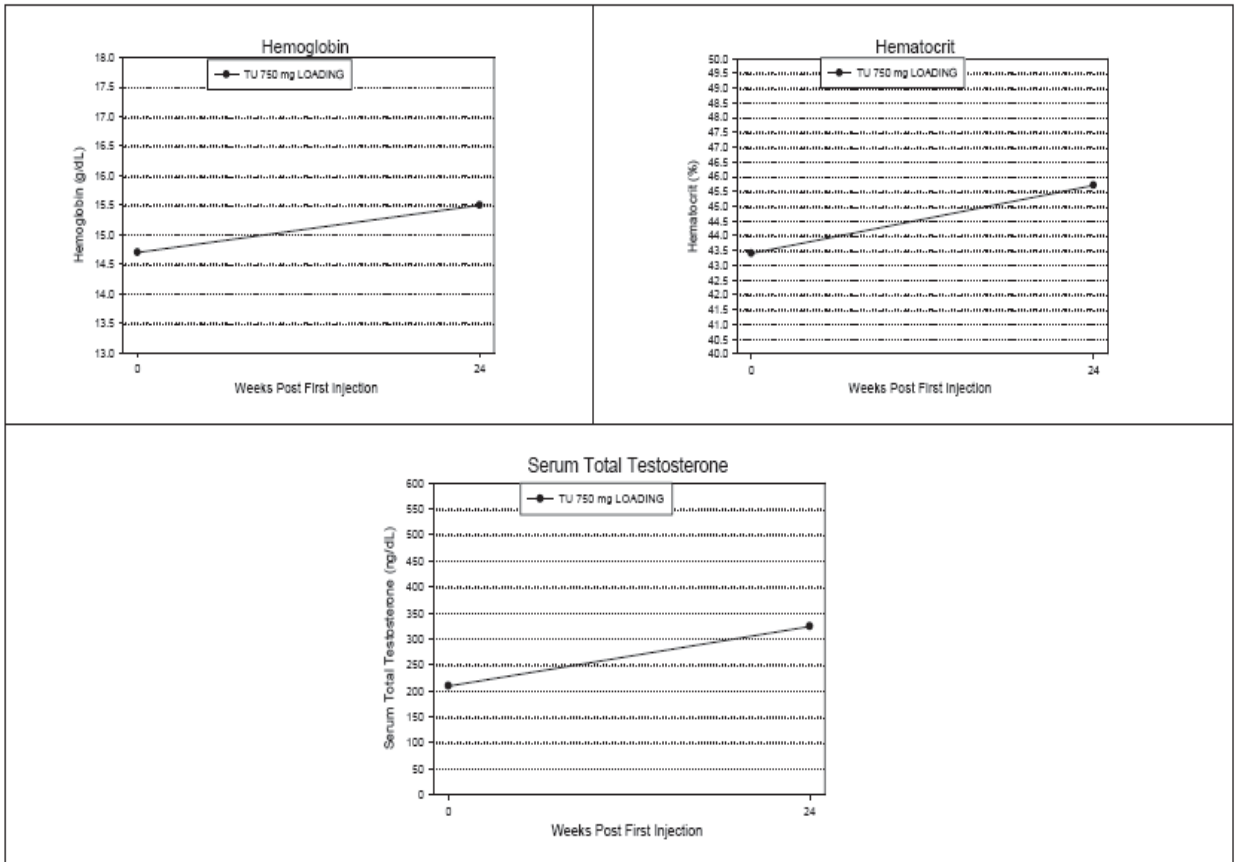
8.5 Erythropoiesis Laboratory Parameters and T

Analysis of erythropoiesis outcomes (hemoglobin and hematocrit) was performed to assess the association between serum T concentrations and these parameters.

These data demonstrated that average values of hemoglobin and hematocrit increased slightly from pre-treatment to Week 24 as average T concentrations increased; however, the average increases in these erythropoietic markers were small in magnitude, with average values remaining well within the normal range. These outcomes were generally consistent with those outcomes observed in Part A of Study IP157-001.

Appendix B Figure 4 presents plots of the average hemoglobin and hematocrit values over time (as measured at each time point). The corresponding average T concentrations at these time points are plotted for reference.

Figure 4. Plots of the average hemoglobin and hematocrit values at each timepoint



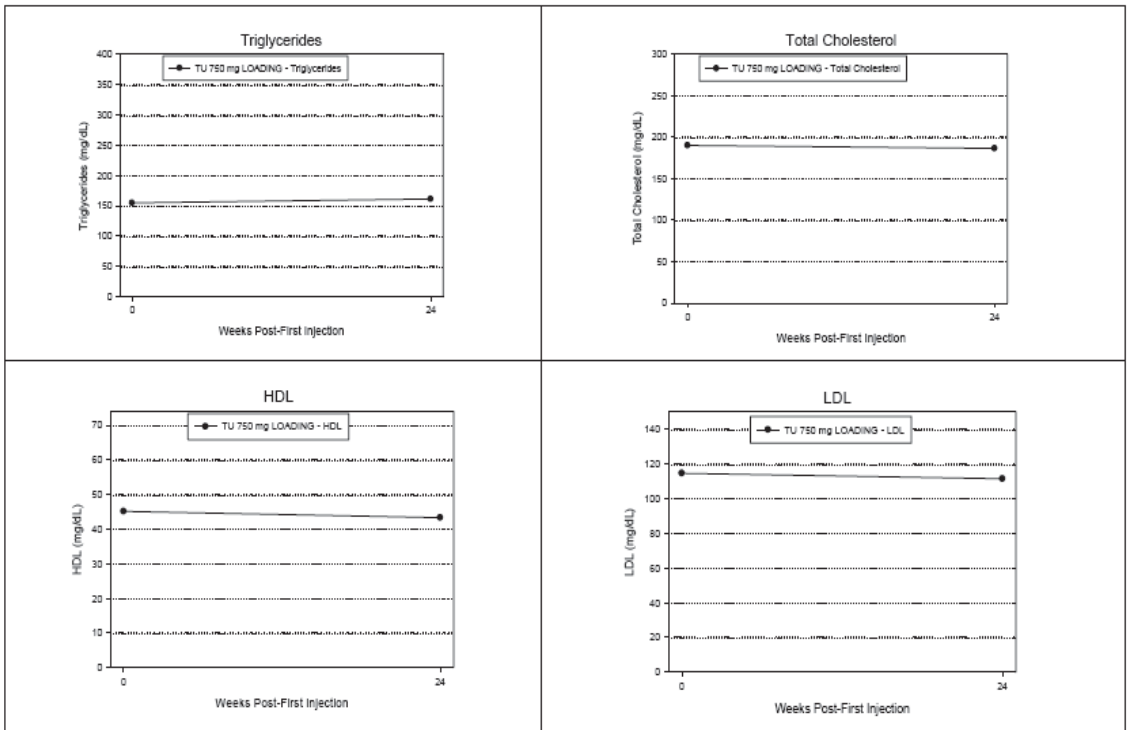
8.6 Serum Lipid Laboratory Parameters and serum T

Analysis of lipid outcomes was performed to assess the association between serum T concentrations and serum lipid values. Because the fasting status (whether a subject has fasted prior to the laboratory sample being drawn) impacts lipid outcomes, the outcomes for lipid parameters reported in this section include only data reported under fasting conditions (per the protocol, fasting was to be 12 hours prior to sample collection). Only fasting subjects in the PK Population were considered for this analysis of the lipids.

Slight reductions in total cholesterol, HDL, and LDL were noted; however, these reductions less than those observed in Part A of Study IP157-001 (possibly relating to the fact that Part C Stage 1 was shorter in duration than Stage 1 for Part A.)

Appendix B Figure 5 presents the average serum lipids for PK Population subjects who reported fasting prior to sample collection for the PK Population subjects. Injection visits are denoted by the number of weeks post-first injection.

Figure 5. Average serum lipids for PK Population subjects who reported fasting prior to sample collection



8.7 Other Factors Associated with T Exposure

Factors that may have been predictive of T exposure, as measured by PK parameters Cmax and Cavg during the 3rd Injection interval, were investigated. Included in this assessment were variables for age, pre-treatment or pre-dose T concentration, baseline BMI (or baseline weight), prior TRT use, and race.

This exploratory analysis revealed that, consistent with finding in Part A of Study IP157-001, the pre-injection T concentration, the pre-treatment body mass index (BMI) of the patient, and the pre-treatment body weight of the patient were each predictive of T exposure.

Subjects with a higher pre-dose T (ie, their Day 0 T concentration collected on the day of the 3rd injection) tended to have a higher Cmax and Cavg during the 3rd injection interval compared to subjects with a lower pre-dose T.

To demonstrate the association between pre-injection T and post-injection T, subgroups were defined (in an a priori manner for Part C) by their pre-3rd injection T concentrations using the following baseline classifications;

• T < 300 ng/dL

• T between 300 and 450 ng/dL

• T > 450 ng/dL.

Subjects in the lowest T subgroup had approximately 50% less exposure to T than subjects in the highest T subgroup.

The pre-treatment BMI and weight were both univariately predictive of these PK parameters. The univariate association between BMI (and weight) and exposure was characterized by lower average Cmax and Cavg values as average BMI (and weight) increased. Subjects in the highest BMI subgroup had approximately 20% less exposure to T than subjects in the lowest BMI subgroup. These findings were generally consistent with those observed in Part A of Study IP157-001.

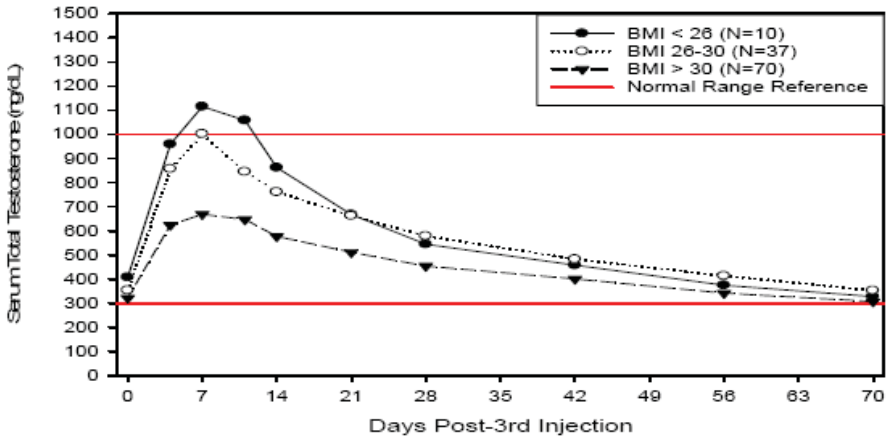
Appendix B Table 13 provides a summary of the average Cmax and Cavg values by the pre-defined BMI subgroups.

Appendix B Table 13. Summary of average Cmax and Cavg values by the pre-defined BMI subgroups.

	TU 750 mg LOADING (N=117)		
	<26 kg/m^2 (N=10)	26-30 kg/m^2 (N=37)	>30 kg/m^2 (N=70)
	Mean (SD)	Mean (SD)	Mean (SD)
C_{max} (ng/dL)	1233.8 (339.57)	1061.5 (394.43)	751.2 (277.14)
C_{avg} (ng/dL)	578.8 (100.86)	566.7 (154.60)	445.0 (116.33)

Appendix B Figure 6 provides the average concentration-time profiles for T by BMI group.

Appendix B Figure 6. Average concentration-time profiles for T by BMI group



8.8 Other Hormones and T

Appendix B Table 14 presents units and the general normal ranges used for testosterone and for other hormones assessed in this study.

Table 14. Units and the general normal ranges used for serum testosterone and for other hormones

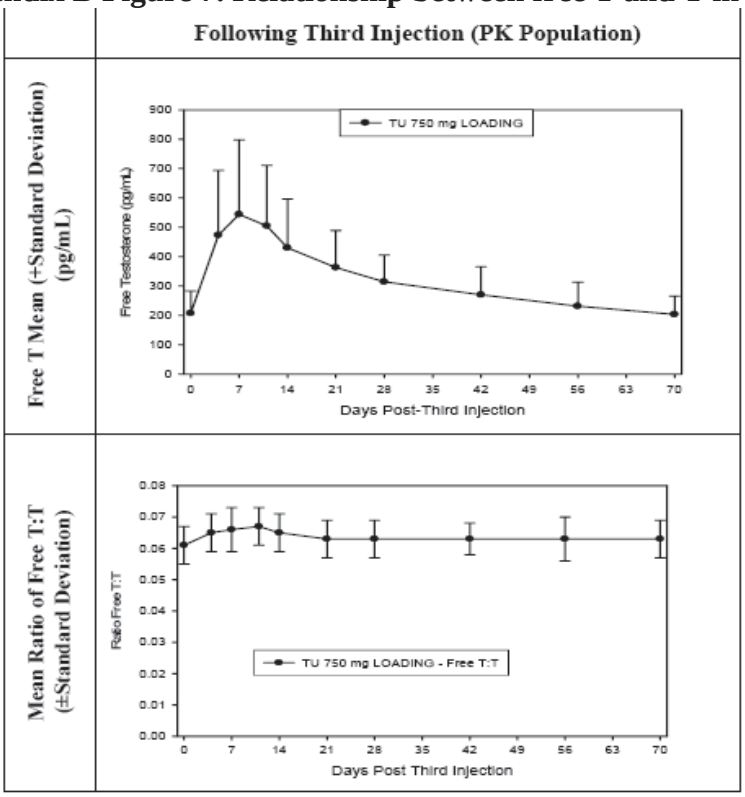
Analyte	Reported Units from Central Lab	Conversion	Reporting Units for Clinical Study Report	Normal Range	Source of Normal Range[1]
Total Testosterone (T)	ng/dL	N/A	ng/dL	300 to 1000 ng/dL	Sponsor
Free Testosterone (Free T)	ng/dL	$(ng/dL) \times 10 = pg/mL$	pg/mL	50 to 210 pg/mL (equivalent: 5.0 to 21.0 ng/dL)	Central Laboratory
Dihydrotestosterone (DHT)	ng/dL	$(ng/dL) \times 10 = pg/mL$	pg/mL	300 to 850 pg/mL (equivalent: 30 to 85 ng/dL)	Sponsor
Estradiol (E2)	pg/mL	N/A	pg/mL	0 to 35 pg/mL (equivalent to 0.0 to 3.5 ng/dL)	Central Laboratory
Sex Hormone Binding Globulin (SHBG)	nmol/L	N/A	nmol/L	13.0 to 71.0 nmol/L	Central Laboratory
Free T:T Ratio (using ng/dL units for both analytes)	N/A	N/A	N/A	0.03 to 0.06	Sponsor
DHT:T Ratio (using ng/dL units for both analytes)	N/A	N/A	N/A	0.047 to 0.250	Sponsor
E2:T Ratio (using ng/dL units for both analytes)	N/A	N/A	N/A	0.002 to 0.02	Sponsor
SHBG:T Ratio (using units reported from central lab)	N/A	N/A	N/A	0.02 to 0.40	Sponsor

N/A=Not applicable.

[1] Note that the central laboratory did not provide normal ranges for T, DHT, or any of the ratios in this table. The normal ranges provided for T, DHT and the ratio were determined by the Sponsor based a review of numerous literature and other clinical laboratory ranges, and thus should be viewed as generally representing the ranges seen in healthy subjects in the general population, but do not be necessarily represent expected normal ranges from the central laboratory in this study. Thus, hormone concentration values in this study that are either within or outside these ranges should be viewed with this understanding regarding the ranges provided.

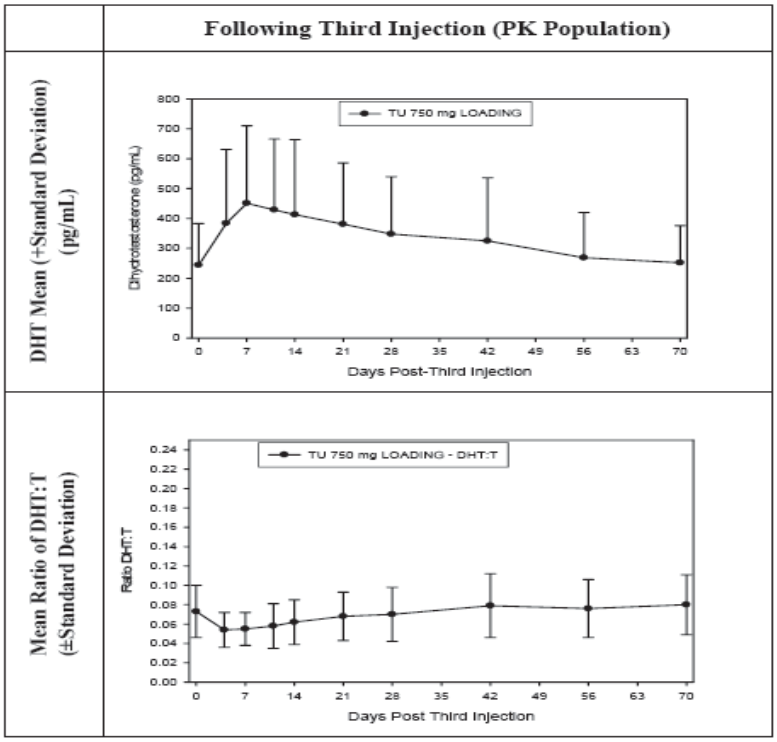
Appendix B Figure 7 demonstrates the relationship between free T and T in Part C Stage 1.

Appendix B Figure 7. Relationship between free T and T in Part C Stage 1



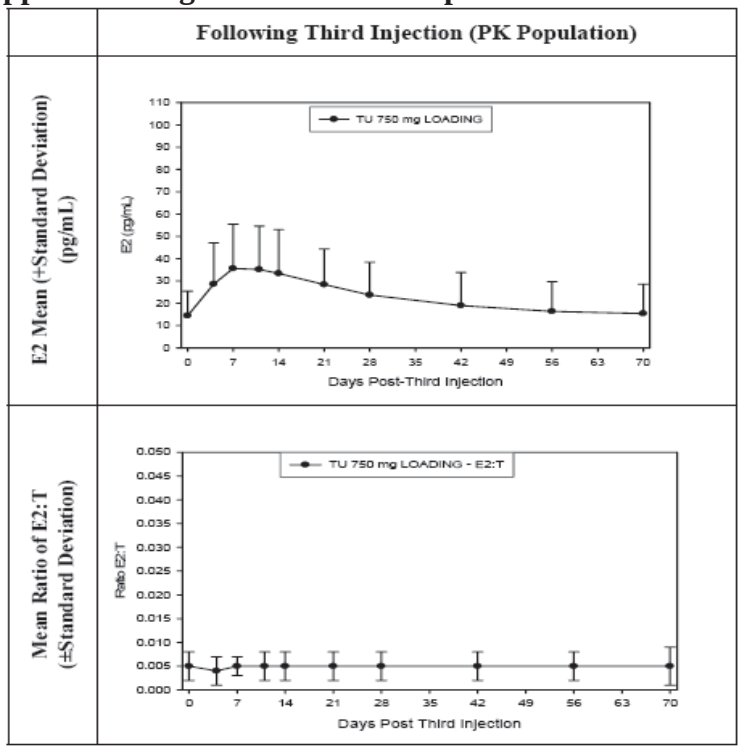
Appendix B Figure 8 demonstrates the relationship between DHT and T in Part C Stage 1.

Appendix B Figure 8. Relationship between DHT and T in Part C Stage 1



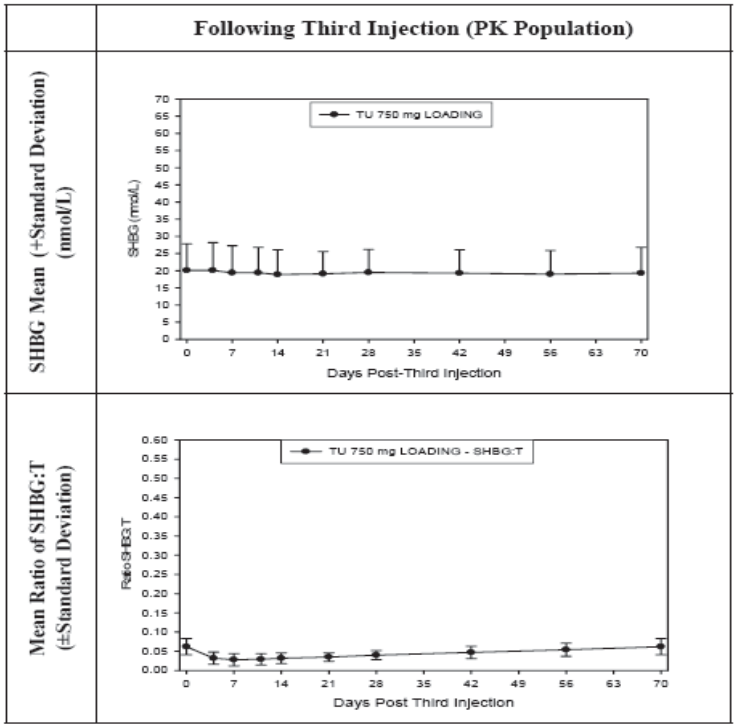
Appendix B Figure 9 demonstrates the relationship between E2 and T in Part C Stage 1.

Appendix B Figure 9. Relationship between E2 and T in Part C Stage 1



Appendix B Figure 10 demonstrates the relationship between SHBG and T in Part C Stage 1.

Appendix B Figure 10. Relationship between SHBG and T in Part C Stage 1



9.0 Clinical Efficacy Results

Clinical efficacy included the assessment of clinical markers of TRT and the assessment of body measurements, as follows:

• Male Patient Global Assessment (M-PGA)

• Weight

• BMI

No inferential testing was performed in this section; all statements regarding improvements or worsening were generally based on the numerical direction and magnitude of the change. Analyses in this section were performed using the PK Population on the 3rd injection interval outcomes

For the M-PGA, lower scores are better. Outcomes from these analyses are summarized by sponsor as follows:

• Following treatment with TU 750 mg, over 70% of patients reported improvement for each item on the M-PGA. The improvements were observed as early as Week 4 and these improvements increased from the first injection interval to the end of the treatment period.

o At Day 21 of the 3rd injection interval, at least 80% of patients demonstrated improvements in each of the M-PGA items.

Reviewer's Comment: Lacking a placebo control, it is not possible to determine the independent effect of TU on improvements in clinical symptoms.

o Notably, over 92% of patients expressed satisfaction with treatment with TU. Thus, in this study population of hypogonadal men (62% of whom had used prior TRT before entering this study), satisfaction with treatment with TU was very high.

Appendix B Table 15 presents outcomes for the M-PGA for the 3rd injection interval (Day 0 and Day 21).

Appendix B Table 15. Outcomes for the M-PGA for the 3rd injection interval

M-PGA Item	Change from Pre-Treatment	TU 750 mg LOADING (N=117)	
		Day 0	Day 21
		N (%)	N (%)
Confidence/Self-Esteem	Improved	77 (65.8)	94 (82.5)
	No Change	39 (33.3)	20 (17.5)
	Worsened	1 (0.9)	0 (0.0)
Sexual Performance	Improved	91 (77.8)	91 (79.8)
	No Change	25 (21.4)	20 (17.5)
	Worsened	1 (0.9)	3 (2.6)
Moods/Behavior	Improved	80 (68.4)	93 (81.6)
	No Change	34 (29.1)	21 (18.4)
	Worsened	3 (2.6)	0 (0.0)
Overall Feeling of Well-Being	Improved	83 (70.9)	94 (82.5)
	No Change	32 (27.4)	20 (17.5)
	Worsened	2 (1.7)	0 (0.0)
Satisfaction with Study Treatment	Satisfied	100 (85.5)	105 (92.1)
	No Opinion	15 (12.8)	9 (7.9)
	Dissatisfied	2 (1.7)	0 (0.0)

There were no notable changes from pre-treatment to the injection (Week 24) in body composition measures, including BMI.

Appendix B Table 16 provides a summary of the pre-treatment, Week 24, and change from pre-treatment to Week 24 values for BMI.

Appendix B Table 16. Summary of the pre-treatment, Week 24, and change from pre-treatment to Week 24 values for BMI

		TU 750 mg LOADING (N=117)		
	Statistic	Pre-Treatment	Week 24	Change
Body Measurements				
BMI (kg/m^2)	N	116	116	116
	Mean (SE)	32.0 (0.49)	32.0 (0.51)	0.0 (0.09)
	Median	31.1	31.0	0.0
	Range	24.1, 50.6	24.3, 52.5	-2.2, 3.4

10.0 Efficacy Conclusions

10.1 Summary of PK

Treatment with TU 750 mg LOADING was found to provide adequate TRT (as measured by Cavg) while not providing excessive TRT (as measured by Cmax). The treatment demonstrated a Cavg within the normal range and a Cmax profile that did not exceed the approvability thresholds provided. Thus, the primary objectives of this study were met, i.e., treatment with TU 750 mg LOADING provided adequate TRT in hypogonadal men.

• Subjects treated with TU 750 mg maintained average T concentrations within the normal range for the entire treatment period (i.e., through Week 24).

• No subjects treated experienced a T concentration above 1800 ng/dL. Less than 8% of subjects experienced a T concentration above 1500 ng/dL; for those subjects who did, the duration of time above this threshold was brief (3 to 7 days), with T concentrations returning to the normal range shortly thereafter.

• Steady-state was reached by the 2nd injection (Week 4). Thus, the loading injection was effective in allowing subjects to reach a steady state condition quickly.

• The univariate association between BMI (and weight) and exposure was marked by lower average Cmax and Cavg values as average BMI (and weight) increased. The strength of this association was n was sufficient to allow for an overall population-based conclusion that subjects with higher BMI (and weight) tended to have slightly lower PK exposure at steady-state.

The following correlations between T concentrations and clinical outcomes were observed:

• With the caveat that the study lacked a placebo control, T concentrations were weakly inversely correlated with decreases (improvements) in the patient global assessments. Subjects with higher T exposure tended to have more satisfaction with the treatment than subjects with lower T exposure. T concentrations were also weakly inversely correlated with changes from pre-treatment in weight and BMI. Thus, decreases in body weight and BMI from pre-treatment to the 3rd injection interval tended to be modestly greater (ie, more weight loss, lower BMI) in those subjects with higher T exposure than in those subjects with lower T exposure.

10.2 Summary of Secondary Efficacy Outcomes

Secondary efficacy objectives included the assessment of clinical markers related to changes in T concentrations, ie, changes in body weight and subject satisfaction with the treatment. Objectives also included the study of changes in clinical laboratory parameters as related to changes in T, specifically outcomes related to erythropoiesis, lipids, and hormones. The Sponsor's conclusions were as follows:

• Average values of hemoglobin and hematocrit increased slightly from pre-treatment to Week 24 as average T concentrations increased; however, the average increases in these erythropoietic markers were small in magnitude and well within the normal range.

• Slight changes from pre-treatment in hemoglobin or hematocrit were seen at the Week 24 time point.

Hemoglobin and hematocrit demonstrated low variability across treatments and visits, and thus were relatively stable during the treatment period.

Serum lipid changes were as expected, with minor changes in the parameters from pre-treatment to the Week 24 time point.

Average changes from pre-treatment to on-treatment in other hormones as they related to changes in serum T concentrations over time were as expected for a TRT. Hormone outcomes were marked by:

• Average Free T concentrations closely paralleled T concentrations and tended to remain within or above the normal range. Mean ratios of Free T:T remained relatively constant throughout.

• Average DHT concentrations closely paralleled T concentrations and tended to remain within the lower end of the normal range. Mean ratios of DHT:T remained relatively constant.

• Average E2 concentrations closely paralleled T concentrations and tended to remain within the middle of the normal range. Mean ratios of E2:T remained relatively constant. The average on-treatment ratios remained similar to the average pre-treatment ratios.

Average SHBG concentrations remained constant (in the middle of the normal range). Mean ratios of SHBG:T tended to drop immediately following the injection (at the Day 4 time point); this was due to changes in T concentrations (and not changes in SHBG concentrations).

Outcomes from the patient assessment of satisfaction are summarized as follows:

• As collected via the M-PGA, the majority of subjects had improvements in confidence/self esteem, moods/behavior, satisfaction with performance, feeling of well-being, and were satisfied with the treatment.

Reviewer's Comment: Lacking a placebo control, it is not possible to determine the independent contribution of TU to this effect.

• Over 92% of subjects expressed satisfaction with treatment with TU.

o In this study population of hypogonadal men (62% of whom had used prior TRT before entering this study), satisfaction with treatment with TU was very high.

There were no notable changes in body weight or BMI in this study.

10.3 Overall Efficacy Conclusions

The TU 750 mg LOADING regimen (TU 750 mg given with a 4-week loading injection and every 10 weeks thereafter) was found to provide adequate TRT (as measured by T Cavg) while not providing excessive TRT (as measured by Cmax). The dosing regimen demonstrated a Cavg within the normal range and a Cmax profile that did not exceed the approvability thresholds provided. Thus, the primary objectives of this study were met. The reviewer concurs with these Sponsor conclusions.

11.0 SAFETY EVALUATION

11.1 Extent of Exposure

Average safety follow-up was over 160 days (i.e., 23 weeks), with the majority of subjects completing all 4 injections (and thus completing the 24 week treatment period). The average duration of exposure to Stage 1 study medication is summarized in Appendix B Table 17, while

the number of subjects by duration of exposure categorized (e.g., less than 12 weeks, 12 to 24 weeks, etc.) is summarized in Appendix B Table 18.

Appendix B Table 17. Average duration of exposure to Stage 1 study medication

	TU 750 mg LOADING (N=130)
Number of patients with exposure information	130
Duration of Exposure to Study Medication (Days)[1]	
Mean (standard error)	226.1 (3.27)
Median	238.0
Range (minimum to maximum)	70 to 248
Duration of Safety Follow-up for this Study Report (Days)[2]	
Mean (standard error)	160.6 (2.41)
Median	168.0
Range (minimum to maximum)	16 to 178

Appendix B Table 18. Number of subjects by duration of exposure

Duration[1] of Exposure (Weeks)	Number (%) of Patients
	TU 750 mg LOADING (N=130)
0 < Duration ≤ 12 weeks	4 (3.1)
12 < Duration ≤ 24 weeks	112 (86.2)
24 < Duration ≤ 36 weeks	14 (10.8)
36 < Duration ≤ 48 weeks	0 (0.0)
> 48 weeks	0 (0.0)

11.2 All TEAE's

Approximately 59 % of subjects experienced at least one AE during the study, with acne and fatigue being the AEs reported with the highest incidence; each was reported in 6 (4.6%) patients. Cough, injection site pain, nasopharyngitis, and pharyngolaryngeal pain were each reported in 4 (3.1%) patients. The types of events reported tended to be of a minor (and non-serious) nature.

There was one post-injection "coughing fit" event that immediately followed an injection with TU.

Subject 050-7006 was a 53-year old white male who was diagnosed with primary hypogonadism in August 2006. [The subject had been briefly treated with a transdermal TRT (Androgel) but discontinued that treatment due to lack of efficacy.] He received his 3rd injection on Day 98, and immediately experienced a mild and non-serious "coughing fit lasting ~10 minutes following [the] injection". The investigator reported the cough was non-productive and that the subject experienced no wheezing or difficulty breathing; no intervention was given, and the subject recovered prior to leaving the office. The subject received his 1st, 2nd, and 4th injections with no associated cough event; further, the patient has continued into Stage 2 where he is still receiving treatment with TU 750 mg every 10 weeks, with no further cough events having been reported. During treatment the subject has demonstrated T concentrations generally within the eugonadal range; his Cmax was 1067 ng/dL during the 3rd injection interval.

There were no other coughs associated with the IM injection of TU during the office visit.

No AE was reported with an incidence higher than 6 subjects, and thus the overall incidence of individual AEs was relatively low in this 24 week study.

Appendix B Table 19 summarizes TEAEs reported in at least 2.0% of subjects, irrespective of relationship to study medication, by preferred term in decreasing order based on incidence rate.

Appendix B Table 19. TEAEs reported in at least 2.0% of subjects

MedDRA Preferred term	Number of patients (%) TU 750 mg LOADING (N=130)
Total patients with at least 1 TEAE	70 (53.8)
Acne	6 (4.6)
Fatigue	6 (4.6)
Cough	4 (3.1)
Injection Site Pain	4 (3.1)
Nasopharyngitis	4 (3.1)
Pharyngolaryngeal Pain	4 (3.1)
Arthralgia	3 (2.3)
Insomnia	3 (2.3)
Prostatitis	3 (2.3)
Sinusitis	3 (2.3)

11.3 Summary of TEAE's of Interest

Special attention was given to TEAEs of interest, specifically TEAEs related to the following classifications: • endocrine disorders • injection related tolerability • adverse lipid profiles • erythropoiesis (adverse hematopoietic profiles/ polycythemia) • aggression or depression • urinary symptoms • prostate health • liver abnormalities • sleep apnea syndrome • cerebrovascular events • skin events

Appendix B Table 20 summarizes the TEAE's of interest.

Appendix B Table 20. TEAE's of interest

Event Class	MedDRA System Organ Class	MedDRA Preferred term	Number of patients (%) TU 750 mg LOADING (N=130)
Total Patients With At Least One TEAE of Interest			28 (21.5)
Tolerability of Injection	General disorders and administration site conditions	Injection site irritation	2 (1.5)
		Injection site pain	4 (3.1)
		Injection site rash	2 (1.5)
Adverse Lipid Profiles	Investigations	Blood triglycerides increased	1 (0.8)
	Metabolism and Nutritional disorders	Hyperlipidemia	1 (0.8)
Erythropoiesis	Investigations	Haematocrit increased	1 (0.8)
		Haemoglobin increased	2 (1.5)
		Estradiol increased	2 (1.5)
Aggression or depression	Psychiatric disorders	Mood swings	2 (1.5)
		Aggression	2 (1.5)
Urinary Symptoms	Renal and urinary disorders	Urine flow decreased	1 (0.8)
		Nocturia	1 (0.8)
Prostate health	Investigations	Prostatic specific antigen increased	2 (1.5)
		Prostate examination abnormal	1 (0.8)
	Reproductive system and breast disorders	Prostatic intraepithelial neoplasia	1 (0.8)
		Prostatitis	3 (2.3)
		Paraesthesia of genital male	1 (0.8)
Skin	Skin and subcutaneous tissue disorders	Acne	6 (4.6)

11.4 Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

11.4.1 Deaths

No subject died during this study.

11.4.2 Other SAE's

Eight (6.2%) subjects experienced at least one treatment-emergent SAE during the treatment period. No SAE was observed in more than 1 subject. Appendix B Table 21 presents a summary of the incidence of treatment-emergent SAEs that occurred in this study.

Appendix B Table 21. Incidence of treatment-emergent SAEs

MedDRA Preferred term	Number of patients (%) TU 750 mg LOADING (N=130)
Total patients with at least 1 TEAE	70 (53.8)
Total patients with at least 1 Treatment-emergent SAE	8 (6.2)
Colitis ischaemic	1 (0.8)
Deep vein thrombosis	1 (0.8)
Faecaloma	1 (0.8)
Intervertebral disc protrusion	1 (0.8)
Myocardial infarction	1 (0.8)
Prostatitis	1 (0.8)
Spinal column stenosis	1 (0.8)
Urinary tract infection	1 (0.8)
Wrist fracture	1 (0.8)

11.4.3 Adverse Events Leading to Discontinuation

There was no event resulting in discontinuation that was reported in more than one subject during this study. Appendix B Table 22 summarizes TEAEs that led to discontinuation.

Appendix B Table 22. TEAEs that led to discontinuation

MedDRA Preferred term	Number of patients (%) TU 750 mg LOADING (N=130)
Total patients with at least 1 TEAE	70 (53.8)
Total patients with at least 1 TEAE Leading to Discontinuation of Study Medication	5 (3.8)
Acne	1 (0.8)
Mood swings	1 (0.8)
Myocardial infarction	1 (0.8)
Estradiol increased	1 (0.8)
Deep vein thrombosis	1 (0.8)

11.5 Clinical Laboratory Evaluation

The analysis of average changes from pre-treatment to endpoint is summarized as follows (note that these outcomes were similar to those observed in Part A of Study IP157-001):

• With the exception of changes in erythropoiesis, hormones, and a few other outcomes, the mean and median changes from baseline to endpoint were generally small in magnitude for most laboratory parameters.

• Liver function tests (e.g., alkaline phosphatase, ALT) demonstrated slight average decreases from pre-treatment to endpoint; these reductions in these enzymes were judged to not be clinically meaningful.

• Blood urea nitrogen (BUN) decreased from pre-treatment. Calcium, sodium, potassium, and phosphorus did not demonstrate meaningful changes in average values from pre-treatment.

• The most notable changes from pre-treatment to endpoint were the decreases in average FSH and LH. Average FSH and LH each decreased approximately 65% to 70% from pre-treatment to the endpoint.

Appendix B Table 23 provides a summary of the average changes from pre-treatment to endpoint (i.e., the last laboratory value collected during Stage 1) for most laboratory parameters.

Appendix B Table 23. Summary of the average changes from pre-treatment to endpoint for most laboratory parameters

Laboratory Parameter	TU 750 mg LOADING (N=130)		
	Pre-Treatment	Endpoint	Change
WBC (10^3/uL) N	121	121	121
Mean (SE)	6.5 (0.14)	6.8 (0.17)	0.3 (0.14)
Median	6.2	6.5	0.2
Range	3.4, 10.7	2.5, 13.0	-3.4, 6.3
Lymphocytes (%) N	121	121	121
Mean (SE)	30.6 (0.66)	29.2 (0.68)	-1.4 (0.55)
Median	30.2	29.0	-1.2
Range	10.3, 51.2	7.8, 50.7	-28.9, 14.5
Monocytes (%) N	121	121	121
Mean (SE)	6.3 (0.16)	6.4 (0.16)	0.0 (0.18)
Median	6.2	6.0	0.2
Range	2.1, 14.0	2.0, 13.9	-7.4, 5.8
Basophils (%) N	121	121	121
Mean (SE)	0.8 (0.04)	0.9 (0.05)	0.1 (0.05)
Median	0.7	0.8	0.0
Range	0.0, 2.4	0.0, 4.0	-2.0, 3.0
Eosinophils (%) N	121	121	121
Mean (SE)	2.6 (0.12)	2.6 (0.15)	0.0 (0.14)
Median	2.2	2.1	-0.1
Range	0.0, 7.8	0.0, 8.8	-4.0, 5.5
Neutrophils (%) N	121	121	121
Mean (SE)	59.7 (0.69)	60.9 (0.75)	1.2 (0.64)
Median	59.7	60.7	1.3
Range	41.3, 86.1	42.1, 89.1	-18.1, 29.2
RBC (10^6/uL) N	121	121	121

Mean (SE)	4.9 (0.04)	5.3 (0.05)	0.3 (0.03)
Median	4.9	5.3	0.3
Range	3.4, 6.2	3.9, 6.9	-0.5, 1.2
Hematocrit (%) N	121	121	121
Mean (SE)	43.3 (0.32)	45.7 (0.35)	2.4 (0.30)
Median	43.0	46.0	2.0
Range	31.0, 52.0	37.0, 55.0	-6.0, 12.0
Hemoglobin (g/dL) N	121	121	121
Mean (SE)	14.6 (0.11)	15.5 (0.13)	0.9 (0.09)
Median	14.7	15.5	0.8
Range	10.2, 17.2	10.9, 18.4	-2.0, 3.6
Platelet Count (10^3/uL) N	115	115	115
Mean (SE)	244.4 (5.51)	245.1 (5.95)	0.8 (3.22)
Median	239.0	237.0	-2.0
Range	141.0, 509.0	133.0, 418.0	-91.0, 124.0
PT Value (sec) N	122	122	122
Mean (SE)	11.9 (0.05)	11.0 (0.29)	-0.9 (0.29)
Median	11.8	10.4	-1.4
Range	10.4, 13.9	9.5, 38.9	-3.3, 27.7
PTT Value (sec) N	121	121	121
Mean (SE)	24.3 (0.25)	25.2 (0.30)	0.9 (0.26)
Median	24.0	24.8	0.5
Range	19.4, 42.3	19.3, 41.8	-4.6, 19.0
INR Value N	122	122	122
Mean (SE)	1.0 (0.01)	1.0 (0.03)	0.0 (0.03)
Median	1.0	1.0	-0.0
Range	0.08, 1.4	0.9, 3.9	-0.4, 3.0

Laboratory Parameter	**TU 750 mg LOADING (N=130)**		
	Pre-Treatment	**Endpoint**	**Change**
Serum Chemistry			
Total Protein (g/dL) N	125	125	125
Mean (SE)	7.2 (0.03)	7.3 (0.04)	0.1 (0.03)
Median	7.1	7.2	0.0
Range	6.5, 8.3	6.4, 8.3	-1.0, 0.9
Albumin (g/dL) N	125	125	125
Mean (SE)	4.2 (0.02)	4.2 (0.03)	0.0 (0.02)
Median	4.2	4.2	0.0
Range	3.6, 5.0	3.2, 5.1	-0.7, 0.8
Creatinine (mg/dL) N	125	125	125
Mean (SE)	1.0 (0.02)	1.1 (0.03)	0.1 (0.02)
Median	1.0	1.0	0.0
Range	0.7, 2.4	0.7, 4.0	-0.2, 2.9
Urea Nitrogen (BUN) (mg/dL) N	125	125	125
Mean (SE)	18.0 (0.50)	17.7 (0.50)	-0.3 (0.38)
Median	17.0	17.0	-1.0
Range	9.0, 52.0	8.0, 48.0	-12.0, 19.0
Uric Acid (mg/dL) N	125	125	125
Mean (SE)	6.1 (0.11)	6.4 (0.11)	0.2 (0.08)
Median	6.1	6.3	0.1
Range	2.9, 10.1	3.6, 10.0	-2.0, 3.0
Direct Bilirubin (mg/dL) N	124	124	124
Mean (SE)	0.1 (0.00)	0.1 (0.01)	0.0 (0.01)
Median	0.1	0.1	0.0
Range	0.1, 0.3	0.1, 0.4	-0.1, 0.3
Total Bilirubin (mg/dL) N	125	125	125
Mean (SE)	0.5 (0.02)	0.6 (0.03)	0.1 (0.02)
Median	0.5	0.5	0.1

Range	0.2, 1.3	0.2, 2.3	-0.5, 1.4
Alkaline Phosphatase (U/L) N	125	125	125
Mean (SE)	73.2 (1.77)	72.0 (1.74)	-1.2 (1.04)
Median	73.0	70.0	-2.0
Range	35.0, 150.0	34.0, 130.0	-33.0, 40.0
SGPT (ALT) (U/L) N	124	124	124
Mean (SE)	29.8 (1.04)	28.2 (1.09)	-1.5 (1.08)
Median	28.0	26.0	-2.0
Range	11.0, 62.0	10.0, 100.0	-35.0, 81.0
SGOT (AST) (U/L) N	124	124	124
Mean (SE)	24.8 (0.71)	25.0 (0.70)	0.2 (0.62)
Median	24.0	23.0	0.0
Range	11.0, 63.0	9.0, 55.0	-34.0, 24.0
Creatine Phosphokinase (U/L) N	125	125	125
Mean (SE)	192.7 (16.39)	190.5 (10.21)	-2.2 (16.19)
Median	155.0	167.0	0.0
Range	46.0, 1896.0	34.0, 672.0	-1701.0, 420.0
Fasting Glucose (mg/dL) N	71	71	71
Mean (SE)	102.3 (2.60)	108.6 (2.78)	6.4 (2.25)
Median	98.0	103.0	3.0
Range	58.0, 203.0	73.0, 209.0	-68.0, 95.0
Calcium (mg/dL) N	125	125	125
Mean (SE)	9.6 (0.03)	9.6 (0.03)	-0.0 (0.03)
Median	9.6	9.6	0.0
Range	8.8, 10.8	8.7, 11.1	-0.8, 1.1
Phosphorus (mg/dL) N	125	125	125
Mean (SE)	3.4 (0.05)	3.3 (0.05)	-0.1 (0.05)

Laboratory Parameter	**TU 750 mg LOADING (N=130)**		
	Pre-Treatment	**Endpoint**	**Change**
Median	3.4	3.3	-0.1
Range	1.8, 4.5	1.6, 4.8	-2.0, 1.6
Sodium (mEq/L) N	125	125	125
Mean (SE)	140.7 (0.19)	140.3 (0.23)	-0.3 (0.23)
Median	141.0	140.0	0.0
Range	131.0, 146.0	134.0, 150.0	-7.0, 7.0
Potassium (mEq/L) N	124	124	124
Mean (SE)	4.3 (0.03)	4.3 (0.03)	0.0 (0.03)
Median	4.3	4.3	0.0
Range	3.5, 5.4	3.5, 5.6	-1.3, 1.0
Chloride (mEq/L) N	125	125	125
Mean (SE)	102.9 (0.21)	102.3 (0.24)	-0.6 (0.23)
Median	103.0	102.0	-1.0
Range	91.0, 109.0	96.0, 111.0	-8.0, 5.0
Bicarbonate (mEq/L) N	125	125	125
Mean (SE)	24.6 (0.22)	26.2 (0.27)	1.6 (0.27)
Median	24.7	26.0	1.6
Range	18.6, 30.4	18.4, 32.4	-5.3, 10.1
FSH (mIU/dL) N	124	124	124
Mean (SE)	7.3 (0.59)	2.0 (0.23)	-5.3 (0.52)
Median	6.0	1.0	-4.0
Range	1.0, 51.0	1.0, 18.0	-50.0, 0.0
LH (mIU/dL)	124	124	124
Mean (SE)	4.8 (0.36)	1.6 (0.21)	-3.1 (0.28)
Median	4.0	1.0	-2.0
Range	1.0, 27.0	1.0, 19.0	-26.0, 0.0
Lipids[1]			
Triglycerides (mg/dL) N	71	71	71

Mean (SE)	153.6 (10.90)	159.9 (11.58)	6.3 (10.99)
Median	125.0	126.0	4.0
Range	54.0, 488.0	48.0, 575.0	-334.0, 381.0
Total Cholesterol (mg/dL) N	71	71	71
Mean (SE)	190.2 (4.88)	186.7 (3.95)	-3.5 (3.33)
Median	187.0	183.0	-2.0
Range	116.0, 348.0	120.0, 248.0	-130.0, 66.0
HDL (mg/dL) N	71	71	71
Mean (SE)	45.3 (1.23)	43.2 (1.06)	-2.1 (0.76)
Median	44.0	44.0	-2.0
Range	24.0, 86.0	21.0, 67.0	-19.0, 18.0
LDL (mg/dL) N	69	69	69
Mean (SE)	115.1 (4.05)	112.1 (3.44)	-3.1 (2.74)
Median	110.0	113.0	-4.0
Range	44.0, 246.0	54.0, 166.0	-103.0, 61.0

11.5 Summary of Laboratory Outcomes

Serum and urine samples for assessment of hematology, coagulation, serum chemistry, LH, FSH, PSA, and urinalysis parameters were collected pre-treatment and on-treatment time points. The analysis of these data included the assessment of average changes over time, the identification of individual values of potential clinical significance, and the recording of some laboratory values as adverse events.

The analysis of these data reveals the changes in lipids, erythropoiesis, and other parameters over the treatment period that were consistent with those changes that have been reported for other testosterone replacement medications.

12.0 Vital Signs, Physical Findings, and Other Observations Related to Safety

This section includes outcomes for vital signs, physical examination, ECG, prostate health, mood states, and local tolerability.

12.1 Vital Signs

Vital signs, including supine blood pressure and pulse rate, were to have been measured at screening and on-treatment as per the schedule of events. There were no clinically meaningful changes in average blood pressure or pulse from pre-treatment to endpoint; average (median) systolic BP increased approximately 0.4 (0.0) mmHg, while average (median) diastolic BP increased approximately 0.8 (0.0) mmHg. No clinically relevant changes in pulse rate were noted.

12.2 ECG Data

Descriptive statistics and analysis of shifts from baseline were not applicable for Stage 1 of this study.

13.0 Prostate Health

13.1 PSA

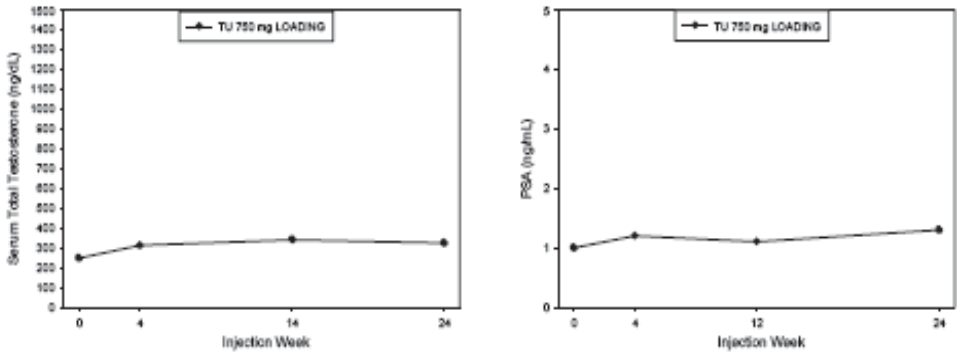
Appendix B Table 24 provides the number (%) of subjects who had serum PSA value > 4ng/mL at any time during study.

Appendix B Table 24. Number (%) of subjects who had PSA value > 4ng/mL at any time during study.

Time (Visit)	Relation to normal range	Number (%) of Patients
		TU 750 mg LOADING (N=130)
Screening	Within 0 to 4 ng/mL	128 (99.2)
	Above 4 ng/mL	1 (0.8)
Baseline (1st Injection Visit)	Within 0 to 4 ng/mL	126 (98.4)
	Above 4 ng/mL	2 (1.6)
Week 4 (2nd Injection Visit)	Within 0 to 4 ng/mL	122 (99.2)
	Above 4 ng/mL	1 (0.8)
Week 14 (3rd Injection Visit)	Within 0 to 4 ng/mL	118 (98.3)
	Above 4 ng/mL	2 (1.7)
Endpoint - Week 24 (4th Injection Visit) or Early Discontinuation	Within 0 to 4 ng/mL	119 (96.7)
	Above 4 ng/mL	4 (3.3)
Any Time[1]	Within 0 to 4 ng/mL	124 (96.1)
	Above 4 ng/mL	5 (3.9)

Appendix B Figure 11 provides a plot of by-treatment mean PSA values over time, from the Screening Visit through the 4th injection visit, and the corresponding mean T concentrations at the same time points. These data are presented for the PK Population. This figure demonstrates that average PSA values increased by no more than 0.3 ng/mL from pre-treatment to the end of the 24 week treatment period. Treatment with other TRT preparations has been reported to increase PSA by approximately 0.5 ng/mL per year, and this study demonstrated similar PSA increases. Note that Part A demonstrated similar outcomes for the TU dosing regimens studied in that part of Study IP157-001.

Appendix B Figure 11. Plots of by-treatment mean PSA values over time, from the Screening Visit through the 4th injection visit, and the corresponding mean T concentrations at the same time points



Appendix B Table 25 presents a list of the incidence rates of TEAE's related to prostate health.

Appendix B Table 25. Incidence rates of TEAE's related to prostate health.

MedDRA System Organ Class	MedDRA Preferred term	Number of patients (%)
		TU 750 mg LOADING (N=130)
Investigations	Prostatic specific antigen increased	2 (1.5)
	Prostate examination abnormal	1 (0.8)
Reproductive system and breast disorders	Benign prostatic hyperplasia	0 (0.0)
	Prostatic intraepithelial neoplasia	1 (0.8)
	Prostatitis	3 (2.3)
	Prostate induration	0 (0.0)
	Prostatic disorder	0 (0.0)
Neoplasms benign, malignant and unspecified	Prostate cancer	0 (0.0)

13.2 Prostate Health Narratives

A brief narrative was written for any subject with a prostate-health related outcome of interest, generally defined as any subject with a PSA > 4 ng/mL at any time, or subjects that underwent a biopsy of the prostate for any reason.

Appendix B Table 26 provides a list of subjects with prostate health related outcomes of interest, their demographic characteristics, a brief description of the biopsy or PSA outcome, and information related to the outcome.

Appendix B Table 26. List of subjects with prostate health related outcomes of interest

Patient ID	Age (years)	Prior TRT Use?	Screen Prostate Volume (cc)	Relevant Prostate Medical History and Baseline DRE	Exposure Stage 1 (# TU injections received)	Biopsy findings/ summary	PSA Normal Range and Values of Interest (ng/mL) [retest value, where applicable]					
							Normal Range	Screen	Baseline	2nd inj	3rd inj	4th Inj ET
002-7119	73	no	40	ED, BPH, baseline elevated PSA. Normal DRE.	1	Declined biopsy following consecutive PSA levels > 4 and discontinued due to an SAE of MI	<=7.00	3.79	4.01 [5.21]	n/a	n/a	n/a
014-7104	60	yes	42	Prostatitis in 2005, ED, '5 lymph nodes right groin' in 1970. Normal DRE.	4	One PSA elevation > 4 (indicated as CS per PI) but was < 4 upon repeat assessment and no biopsy was performed or required per protocol	<=5.10	1.06	1.3	1.38	1.3	4.72 [3.77]
021-7118	53	yes	24	Mildly elevated PSA from 2/2007. Normal DRE.	2	Performed on (b) (6) prior to enrollment (due to PMH of mildly elevated PSAs). Repeated on 30-AUG-2007 following 2nd injection; both bx were benign. Pt discontinued for mood swings	<=3.70	3.97	3.57	3.43	n/a	3.31
031-7093	64	no	34	ED. Normal DRE.	4	Performed on (b) (6) following consecutive PSA levels > 4; bx was benign. SAE of prostatitis reported.	<=5.10	1.06	1.15	1.59	4.52 [5.46]	4.99 [3.66]
040-7024	68	no	63	ED, BPH. Abnormal DRE, prostate enlargement	4	One PSA elevation > 4 (indicated as NCS per PI) but was < 4 upon repeat assessment and no biopsy was performed or required per protocol	<=5.10	3.23	3.23	3.31	4.01 [3.58]	3.27
044-7097	44	yes	29	None. Normal DRE.	1	Performed on (b) (6) showing focal glandular hyperplasia; patient discontinued (due to baseline PSA) and bx findings but PI considers all PSA and bx results NCS.	<=2.70	1.22	3.89 [3.92]	n/a	n/a	2.46
063-7043	62	no	42	ED, BPH, baseline elevated PSA. Normal DRE.	4	Patient enrolled in violation of protocol eligibility requirements (elevated PSA); repeat PSA at screen was < 4. (b) (6) (b) (6) biopsy demonstrated high grade prostatic intraepithelial neoplasia (PIN) but was negative for malignancy. Pt completed study.	<=5.10	4.04 [3.84]	4.16 [4.15]	7.8 [3.89]	3.55	4.35 [4.64]
082-7089	49	no	19	None. Normal DRE.	4	One PSA elevation > 4 (indicated as NCS per PI) but was < 4 upon repeat assessment and no biopsy was performed or required per protocol	<=2.70	0.89	0.91	1.1	1.14	5.95 [2.82]

ED = erectile dysfunction, BPH = benign prostatic hyperplasia, BX = prostate biopsy, CS = clinically significant, NCS = not clinically significant, DRE = digital rectal examination, PMH = past medical history, TRT = testosterone replacement therapy, SAE = serious adverse event, MI = myocardial infarction, PI = principle investigator, PSA=prostate specific antigen.

13.3 Summary of Prostate Health Outcomes

The Sponsor providedaA summary of prostate health in this study, as follows:

• There were 5 (3.9%) subjects with at least one post-baseline PSA value over 4 ng/mL during this study. However, 2 of these subjects had a baseline (pre-1st injection) PSA of 4.2 ng/mL. Therefore, there were 3 (2.3%) subjects who had a new-onset PSA value over 4 ng/mL.

• Subjects with a higher pre-treatment PSA were more likely to exceed the 4 ng/mL threshold during the study than those subjects with a lower pre-treatment PSA. Notably, there were 7 subjects with pre-treatment PSA concentrations between 3 and 4 ng/mL. Of these 7 subjects, 2 (33.3%) exceeded the 4 ng/mL PSA threshold at some time in this study. Subjects who had a pre-treatment PSA < 3 ng/mL rarely exceeded the 4 ng/mL threshold while under treatment with TU.

• Average PSA values did not increase by more than 0.3 ng/mL from pre-treatment to the end of the 24 week treatment period. Treatment with other TRT preparations has been reported to increase PSA by approximately 0.5 ng/mL per year, and this study demonstrated similar increases in serum PSA.

• Average PSA velocity was = 0.3 ng/mL over the 24-week treatment period, and there were a few individual subjects in this study with a PSA velocity that exceeded 2 ng/mL.

• A review of TEAEs was performed to identify any events related to prostate health. Events included prostatitis, benign prostatic hyperplasia, PSA elevations and other events associated with prostate health. The most commonly reported AE associated with prostate health was prostatitis, reported for 3 (2.3%) patients. PSA increased was reported by 2 (1.5%) subjects.

• The incidence of abnormal prostate findings varied from visit to visit. The Screening Visit had the highest incidence of abnormal prostate findings, with 17 (13.1%) subjects having an abnormal outcome on the screening DRE. Of these 17 subjects with abnormal findings, 16 (94.1%) subjects had an enlarged prostate at the screening visit. The incidence of on-treatment abnormal prostates was generally the same across the on-treatment weeks.

• 11 (8.5%) subjects had, at any given time post-1st injection, an abnormal prostate finding based on their DRE; most of these 11 subjects had an enlarged prostate as their abnormality.

Reviewer's Comment: The new-onset serum PSA changes in this short-term study is notable, as are the few reports of enlarged prostate and prostatitis. Determining the actual risk of TU to prostate health would require much larger studies.

14.0 Changes in Mood (POMS)

Appendix B Table 27 presents a list of the incidence rate of the TEAE's related to mood.

Appendix B Table 27. Incidence rate of the TEAE's related to mood

MedDRA System Organ Class	MedDRA Preferred term	Number of patients (%)
		TU 750 mg LOADING (N=130)
Psychiatric disorders	Anger	0 (0.0)
	Depression	0 (0.0)
	Mood swings	2 (1.5)
	Aggression	2 (1.5)
	Anxiety	1 (0.8)
General disorders and administration site conditions	Irritability	2 (1.5)

Reviewer's Comment: there were several reports of mood-related AEs in this short-term study (e.g., mood swings, aggression, irritability, etc)

15.0 Urologic Health

Appendix B Table 28 presents a list of the incidence rate of TEAE's related to urinary symptoms.

Appendix B Table 28. Incidence rate of TEAE's related to urinary symptoms.

MedDRA System Organ Class	MedDRA Preferred term	Number of patients (%)
		TU 750 mg LOADING (N=130)
At least one Urinary Symptom Event		**2 (1.5)**
Renal and urinary disorders	Pollakiuria	0 (0.0)
	Urinary hesitation	0 (0.0)
	Urinary retention	0 (0.0)
	Urine flow decreased	1 (0.8)
	Nocturia	1 (0.8)

16.0 Local Tolerability

Appendix B Table 29 presents a tabulation of the within-patient worst (most severe) level of each local (injection site) tolerability symptom as captured on the local tolerance questionnaire during Stage 1 (i.e., across all 4 injections).

Appendix B Table 29. Within-patient worst (most severe) level of each local (injection site) tolerability symptom as captured on the local tolerance questionnaire during Stage 1

Tolerability Symptom	Severity (Worst at Any Time)	Number (%) of Patients
		TU 750 mg LOADING (N=130)
Pain	None	71 (54.6)
	Mild	57 (43.8)
	Moderate	2 (1.5)
	Severe	0 (0.0)
	Life Threatening	0 (0.0)
Tenderness	None	74 (56.9)
	Mild	51 (39.2)
	Moderate	5 (3.8)
	Severe	0 (0.0)
	Life Threatening	0 (0.0)
Erythema/Redness	None	109 (83.8)
	Mild	20 (15.4)
	Moderate	1 (0.8)
	Severe	0 (0.0)
	Life Threatening	0 (0.0)
Swelling	None	122 (93.8)
	Mild	7 (5.4)
	Moderate	1 (0.8)
	Severe	0 (0.0)
	Life Threatening	0 (0.0)

Appendix B Table 30 presents a list of the incidence rate of TEAE's related to local tolerability.

Appendix B Table 30. Incidence rate of TEAE's related to local tolerability

MedDRA System Organ Class	MedDRA Preferred term	Number of patients (%)
		TU 750 mg LOADING (N=130)
Total patients with at least 1 TEAE Associated with Local Tolerability		7 (5.4)
General disorders and administration site conditions	Injection site erythema	0 (0.0)
	Injection site irritation	2 (1.5)
	Injection site pruritus	0 (0.0)
	Injection site pain	4 (3.1)
	Injection site rash	2 (1.5)
	Injection site reaction	0 (0.0)

17.0 Overall Safety Conclusions, Part C

Average safety follow-up was over 160 days (i.e., 23 weeks), with the majority of subjects completing all 4 injections (and thus completing the 24 week treatment period). In general, and with a major caveat concerning the occurrence of post-marketing adverse events of post-injection "coughing fits" and allergic reactions (including one coughing fit even in this short-term and fairly small study), the safety of treatment with TU 750 mg given with a 4-week loading injection and every 10 weeks thereafter was reasonable in this Part C Stage 1 study. The Sponsor's summary of key safety conclusions for this study follows:

17.1 Adverse Events

Approximately 54 % of subjects experienced at least one AE during the study; acne and fatigue were the AEs reported with the highest incidence, each in 6 (4.6%) subjects. Cough, injection site pain, nasopharyngitis, and pharyngolaryngeal pain were each reported in 4 (3.1%) subjects. Thus, the types of events reported tended to be of a minor (and non-serious) nature. No AE was reported with an incidence higher than 6 subjects. General disorders and administration site

conditions, infections and infestations, and respiratory, thoracic and mediastinal disorders were the 3 system organ classes reported with the highest incidence.

There was one cough event that immediately followed an injection with TU. Subject 050-7006, a 53-year old white male who was diagnosed with primary hypogonadism in August 2006 [and who had previously discontinued treatment with transdermal TRT (Androgel) due to lack of efficacy], received his 3rd injection on Day 98. The subject experienced a mild and non-serious "coughing fit lasting ~10 minutes following [the] injection". The investigator reported the cough was non-productive, and that the subject experienced no wheezing or difficulty breathing. No intervention was given, and the subject recovered prior to leaving the office. The subject received his 1st, 2nd, and 4th injections with no associated cough event. The subject continued into Stage 2 where he is still receiving treatment with TU 750 mg every 10 weeks, and no further cough events have been reported.

Approximately 23.8% of subjects experienced at least one TEAE that was judged to be at least possibly related to study medication. In summary:

• The events reported as at least possibly related were generally consistent with those expected for a population treated with a TRT. Hemoglobin increased, mood swings, and irritability have been reported to be sometimes related to TRT.

• The only hormone parameter with an associated TEAE was estradiol, in which an increase was reported in 2 (1.5%) subjects.

There were no deaths in this study. Eight (6.2%) subjects experienced at least one treatment-emergent SAE during the treatment period. No SAE was observed in more than 1 subject. There were 5 (3.8%) subjects who experienced TEAEs that led to discontinuation from the study medication (and from the study). Four AEs that resulted in discontinuation from the study were judged by the investigator as at least possibly related to study medication: a deep vein thrombosis, estradiol increase, mood swings, and acne. There were no subjects who had their study medication temporarily interrupted due to AEs.

Reviewer Comment: It is of interest that one coughing event occurred in this study where 117 total patients received no more than 4 injections each (<500 total injections). The Sponsor has previously stated that the incidence of coughing fits is 1 in 10-15,000 injections.

17.2 Clinical Laboratory

The outcomes from the analysis of laboratory data reveal that treatment with TU 750 mg LOADING resulted in expected changes in parameters known to be affected by testosterone replacement. These data are generally consistent with those observed in Part A.

17.3 Vital signs, Prostate health, Mood states, and Tolerability.

There were no clinically meaningful changes in average blood pressure or pulse from pre-treatment to endpoint; average (median) systolic BP increased approximately 0.4 (0.0) mmHg, average (median) diastolic BP increased approximately 0.8 mmHg. No clinically changes in pulse rate were noted.

The Sponsor's summary of prostate health in this study is as follows:

• There were 5 (3.9%) subjects with at least one post-baseline PSA value over 4 ng/mL during this study. However, 2 of these subjects had a baseline (pre-1st injection) PSA of 4.2 ng/mL. Thus, there were 3 (3.2%) subjects who had a new-onset PSA value over 4 ng/mL.

• Subjects with a higher pre-treatment PSA were more likely to exceed the 4 ng/mL threshold during the study than those subjects with a lower pre-treatment PSA. Notably, there were 7subjects with pre-treatment PSA concentrations between 3 and 4 ng/mL. Of these 7 subjects , 2 (33.3%) exceeded the 4 ng/mL PSA threshold at some time in this study. Subjects who had a pre-treatment PSA < 3 ng/mL rarely exceeded the 4 ng/mL threshold while under treatment with TU.

• Average PSA values increased by no more than 0.3 ng/mL from pre-treatment to the end of the 24 week treatment period. Treatment with other TRT preparations has been reported to increase PSA by approximately 0.5 ng/mL per year, and this study showed a similar increase.

• Average PSA velocity was ≤ 0.3 ng/mL over the 24-week treatment period, and a few individual subjects in this study with a PSA velocity that exceeded 2 ng/mL.

• A review of TEAEs was performed to identify any events related to prostate health. Events included prostatitis, benign prostatic hyperplasia, PSA elevations and other events associated with prostate health. The most commonly reported AE associated was reported by 2 (1.5%) subjects. Note that some of the prostate health-related events were judged by the investigator to be at least possibly related to study treatment.

• 11 (8.5%) subjects had, at any given time post-1st injection, an abnormal prostate finding based on their DRE; most of these 11 subjects had an enlarged prostate as their abnormality.

Prostate health outcomes in this study were considered to be clinically consistent with those expected in a population of hypogonadal men receiving testosterone replacement. It is notable that average serum PSA increased and some individual serum PSA values were clinically relevantly increased in this short-term study.

17.4 Overall Safety Conclusions, Part C

Treatment with TU 750 mg LOADING resulted in safety outcomes consistent with those expected for a TRT provided to men with primary or secondary hypogonadism. Treatment resulted in a low overall incidence rate of TEAEs in all system organ classes, with some reports of expected TEAEs. Changes in laboratory parameters were generally minor and not clinically meaningful, while changes in lipids, erythropoiesis, and hormone parameters were consistent with those changes that have been reported for other testosterone replacement medications. Prostate health was carefully monitored, and no unexpected incidence rates of any untoward event were observed. PSA concentrations increased slightly, as expected. No clinically meaningful changes in vital sign or other safety outcomes were noted, and the injections were well-tolerated. Average safety follow-up was over 160 days, with the vast majority of subjects completing all 4 injections. Given this extended duration of treatment and safety follow-up, the safety and tolerability profile of treatment with TU 750 mg LOADING has been demonstrated.

18.0 Overall Conclusions

The data collected during this 24-week clinical study show that the treatment regimen met FDA thresholds for average and maximum T concentrations, and that treatment resulted in the attainment of steady state by the 4th week of treatment. This study demonstrated that, compared to the dosing regimens used in Part A, the Part C regimen may provide better replacement of testosterone.

Based on the preponderance of evidence, the TU 750 mg dose given with a 4-week injection and every 10 weeks thereafter may be the best treatment option for the general population of men with primary or secondary hypogonadism.

With the exception of a single post-injection coughing fit event in this study, consistent with those reported in the post-marketing period in Europe, the overall safety profile of the TU 750 Loading Regimen was consistent with TRT. The occurrence of an average increase in serum PSA and a few individual clinically relevant increases in serum PSA in this short-term study is also notable.

C. "120 Day Safety Update", Study IP157-001 Part A Stage 2 and Part B Stage 1

1. Background

This 120-Day Safety Update presents exposure and adverse event (AE) data from 327 subjects with primary or secondary hypogonadism treated with testosterone undecanoate (TU). Subjects were enrolled into Study IP157-001 in order to assess the safety and efficacy of treatment with TU. The study included 3 distinct enrollment periods (referred to as Parts A, B, and C), with each period designed to test a specific dosing regimen.

This update includes data from Part A Stage 2 and Part B Stage 1 only.

• Part A included assessment of 2 dosing regimens:

o TU 1000 mg given every 12 weeks

o TU 750 mg given every 12 weeks.

• Part B included assessment of 2 dosing regimens:

o An initial injection of TU 1000 mg, followed 8 weeks later with a loading injection of TU 1000 mg and then TU 1000 mg given every 12 weeks thereafter

o An initial injection of TU 1000 mg, followed 8 weeks later with a loading injection of TU 750 mg and then TU 750 mg given every 10 weeks thereafter

• Part C included assessment of a single dosing regimen:

o An initial injection of TU 750 mg, followed 4 weeks later with a loading injection and then TU 750 mg given every 10 weeks thereafter

Data from Parts A and B are included in this update; data from Part C Stage 1 was submitted in NDA amendment 3 on January 2, 2008.

Reviewer's Comment: The safety data from Part C Stage 2 was not submitted with this Update nor as an amendment. The safety data derived from Part C Stage 2 is considered important safety extension data and should be submitted for our review at some point.

Subjects continuing in Part A were eligible to have up to 156 weeks of exposure to either TU 1000 mg or TU 750 mg given every 12 weeks; actual exposure through this Safety Update includes information on patients with up to approximately 72 weeks exposure. Subjects continuing in Part B have had at least 28 to 32 weeks of exposure to TU 1000 mg and/or TU 750 mg (as given with the prescribed dosing regimens for Part B). This Safety Update reflects data from Part A Stage 2 recorded in the clinical database as of October 12, 2007.

• The incidence of AEs in this summary was tabulated for Part A Stage 2, and is comprised of AEs that began on or after the start of Stage 2 (i.e., after the 5th injection visit).

• Part A exposure data in this summary has been derived using data from both Stage 1 and Stage 2; however, only subjects who continued into Stage 2 are included in the exposure analysis.

Part B data were collected during Part B, Stage 1; this Safety Update reflects data from Part B Stage 1 recorded in the clinical database as of November 28, 2007. Part B Stage 1 has been completed and subjects are continuing treatment in Stage 2.

The incidence of adverse events (AEs) and the duration of exposure to study medication comprise the core data reported in this Safety Update. Specifically:

• For Part A, the incidence of AEs is comprised of AEs that began on or after the start of Stage 2 (ie, after the 5th injection visit). For Part B, the incidence of AEs is comprised of AEs that began on or after the start of Stage 1 through the 4th injection visit.

• For Part A, exposure data in this summary has been derived using data from both Stage 1 and Stage 2; however, only subjects who continued into Stage 2 are included in the exposure analysis. For Part B, exposure data in this summary has been derived using data through the completion of Stage 1.

2.0 Exposure

Average safety follow-up was over 420 days for both treatment groups. The average duration of exposure of study medication in Part A Stage 2 is summarized in Appendix C Table 1, while the number of patients by duration of exposure in Part A Stage 2 is summarized in Appendix C Table 2.

Appendix C Table 1. Average duration of exposure to study medication in Part A Stage 2

	TU 750 (N=99)	TU 1000 (N=94)
Number of patients with exposure information	99	94
Duration of Exposure to Study Medication (Days)[1]		
Mean (standard error)	520.0 (3.98)	519.0 (4.18)
Median	504	504
Range (minimum to maximum)	416 to 592	416 to 592
Duration of Safety Follow-up for this Study Report (Days)[2]		
Mean (standard error)	436.0 (3.98)	435.0 (4.18)
Median	420	420
Range (minimum to maximum)	332 to 508	332 to 508

[1]Duration of Exposure to Study Medication was calculated as the time from the first injection to the last injection, plus 84 days (12 weeks). Thus, patients who received 7 injections were exposed to TU for 84 weeks.
[2]Duration of Safety Follow-up for this Study Report was calculated as the time from the first injection to their last visit (thus far) during Stage 2; for most patients, this was the 6th injection visit.

Appendix C Table 2. Number of patients by duration of exposure in Part A Stage 2

Duration[1] of Exposure (Weeks)	Number (%) of Patients	
	TU 750 mg (N=99)	TU 1000 mg (N=94)
36 ≤ Duration ≤ 48 weeks	3 (3.0)	4 (4.3)
48 < Duration ≤ 60 weeks	59 (59.6)	54 (57.4)
60 < Duration ≤ 72 weeks	36 (36.4)	34 (36.2)
72 < Duration ≤ 84 weeks	1 (1.0)	2 (2.1)

[1]Duration of exposure (safety follow-up) was calculated as days from first injection to day of last visit during Stage 2. A window of 3 days was added to the duration of exposure classifications. For example, patients followed for 87 days (84 days plus 3 days) would be classified as having had a duration of exposure ≤ 12 weeks.

Appendix C Table 3 provides a summary of the number of patients by treatment group and total cumulative exposure for Part A Stage 2 as of October 12, 2007.

Appendix C Table 3. Number of patients by treatment group and total cumulative exposure for Part A Stage 2 as of October 12, 2007

Treatment	Number of Injections Administered	Total exposure per Patient (mg of TU)	Number (%) of Patients
TU 750 mg (N=99)	5	3750	3 (3.0)
	6	4500	74 (74.7)
	7	5250	22 (22.2)
TU 1000 mg (N=94)	5	5000	4 (4.3)
	6	6000	69 (73.4)
	7	7000	21 (22.3)

3.0 Demographics

Subjects included in this update for Part A Stage 2 reflect similar characteristics as those randomized into Part A Stage 1.

4.0 AE's

4.1 Part A, Stage 2

Events reported here are new-onset TEAE's from Part A Stage 2. "Carry-over" AEs that first occurred in the Stage 1 phase are not reported here as those events have been previously reported in the clinical study report for the Stage 1 phase.

Treatment-emergent AEs (TEAEs) are presented in this section irrespective of the investigator's causal assessment of the relationship to study medication. Following the "all TEAE" section, the TEAEs assessed by the investigator as at least possibly related to study medication (ie, possibly-, probably-, and definitely-related TEAEs) are presented.

Appendix C Table 4 summarizes the TEAE's reported in at least 2 subjects in either group irrespective of relationship to study medication in Part A Stage 2, by preferred term in decreasing order based on incidence rates in the TU 1000 mg group.

Appendix C Table 4. TEAE's reported in at least 2 subjects in either group irrespective of relationship to study medication in Part A Stage 2

MedDRA Preferred term	Number of patients (%)	
	TU 750 (N=99)	TU 1000 (N=94)
Total patients with at least 1 TEAE	28 (28.3)	22 (23.4)
Arthralgia	0 (0.0)	2 (2.1)
Back pain	0 (0.0)	2 (2.1)
Sinusitis	0 (0.0)	2 (2.1)
PSA Increased	2 (2.0)	1 (1.1)
Hypercholesterolaemia	2 (2.0)	1 (1.1)
Hypertension	2 (2.0)	0 (0.0)

Appendix C Table 5 provides a summary of the incidence of all system organ classes with at least 2 subjects experiencing at least one AE in either treatment group in Part A Stage 2, irrespective of relationship to study medication, by system organ class in decreasing order based on incidence rates in the TU 1000 mg group.

Appendix C Table 5. Incidence of all system organ classes with at least 2 subjects experiencing at least one AE in either treatment group in Part A Stage 2, irrespective of relationship to study medication, by system organ class

MedDRA System Organ Class	Number of patients (%)	
	TU 750 (N=99)	TU 1000 (N=94)
Total patients with at least 1 TEAE	28 (28.3)	22 (23.4)
Musculoskeletal and connective tissue disorders	0 (0.0)	5 (5.3)
Infections and infestations	4 (4.0)	5 (5.3)
Reproductive system and breast disorders	6 (6.1)	3 (3.2)
Psychiatric disorders	0 (0.0)	3 (3.2)
Renal and urinary disorders	1 (1.0)	2 (2.1)
General disorders and administrative site conditions	2 (2.0)	2 (2.1)
Investigations	5 (5.0)	2 (2.1)
Metabolism and nutrition disorders	3 (3.0)	2 (2.1)
Injury, poisoning and procedural complications	1 (1.0)	2 (2.1)
Nervous system disorders	4 (4.0)	2 (2.1)
Skin and subcutaneous tissue disorders	2 (2.0)	1 (1.1)
Gastrointestinal Disorders	3 (3.0)	1 (1.1)
Vascular disorders	2 (2.0)	0 (0.0)
Cardiac Disorders	4 (4.0)	0 (0.0)
Eye disorders	4 (4.0)	0 (0.0)

4.2 Part B

Appendix C Table 6 summarizes TEAEs reported in at least 2.0% of subjects in the TU 1000 mg LOADING group in Part B, irrespective of relationship to study medication, by preferred term in decreasing order based on incidence rates in the TU 1000 group.

Appendix C Table 6. TEAEs reported in at least 2.0% of subjects in the TU 1000 mg LOADING group in Part B, irrespective of relationship to study medication, by preferred term

MedDRA Preferred term	Number of patients (%)	
	TU 1000 to 750 mg LOADING (N=22)	TU 1000 mg LOADING (N=112)
Total patients with at least 1 TEAE	9 (40.9)	62 (55.4)
Fatigue	1 (4.5)	7 (6.3)
Libido decreased	1 (4.5)	5 (4.5)
Injection site pain	0 (0.0)	4 (3.6)
Nasopharyngitis	1 (4.5)	4 (3.6)
Nephrolithiasis	0 (0.0)	4 (3.6)
Diarrhoea	0 (0.0)	3 (2.7)
Prostatic specific antigen increased	0 (0.0)	3 (2.7)
Adjustment disorder with mixed anxiety and depressed mood	0 (0.0)	3 (2.7)
Dizziness	0 (0.0)	3 (2.7)

Appendix C Table 7 provides a summary of the incidence of all system organ class TAEs in at least 5.0% of subjects in the TU 1000 mg LOADING group in Part B, irrespective of relationship to study by system organ class in decreasing order based on incidence rates in the TU 1000 mg LOADING group.

Appendix C Table 7. Incidence of all system organ class TAEs reported in at least 5.0% of subjects in the TU 1000 mg LOADING group in Part B, irrespective of relationship to study, by system organ class

MedDRA System Organ Class	Number of patients (%)	
	TU 1000 to 750 mg LOADING (N=22)	TU 1000 mg LOADING (N=112)
Total patients with at least 1 TEAE	9 (40.9)	62 (55.4)
Infections and infestations	4 (18.2)	21 (18.8)
General disorders and administration site conditions	2 (9.1)	14 (12.5)
Investigations	0 (0.0)	13 (11.6)
Reproductive system and breast disorders	2 (9.1)	12 (10.7)
Gastrointestinal disorders	1 (4.5)	10 (8.9)
Musculoskeletal and connective tissue disorders	2 (9.1)	10 (8.9)
Psychiatric disorders	1 (4.5)	10 (8.9)
Nervous system disorders	0 (0.0)	9 (8.0)
Renal and urinary disorders	0 (0.0)	7 (6.3)
Injury, poisoning and procedural complications	1 (4.5)	6 (5.4)

4.3 At Least Possibly Related TEAE's

4.3.1 Part A, Stage 2

Appendix C Table 8 summarizes the incidence of TEAEs judged by the investigator as being at least possibly related to study treatment, sorted by descending frequency in the TU 1000 mg LOADING arm.

Appendix C Table 8. Incidence of TEAEs judged by the investigator as being at least possibly related to study treatment in Part A Stage 2

MedDRA Preferred term	Number of patients (%)	
	TU 750 (N=99)	TU 1000 (N=94)
Total patients with at least 1 TEAE	28 (28.3)	22 (23.4)
Total patients with at least 1 at least possibly related TEAE	6 (6.1)	3 (3.2)
Injection site pain	1 (1.0)	1 (1.1)
Testicular disorder	1 (1.0)	1 (1.1)
PSA increased	2 (2.0)	1 (1.1)
Injection site odema	1 (1.0)	0 (0.0)
Injection site pruritis	1 (1.0)	0 (0.0)
Neoplasm prostate	1 (1.0)	0 (0.0)

4.3.2. Part B

Appendix C Table 9 summarizes the incidence of TEAEs reported in at least 1.0% of subjects in the TU 1000 mg LOADING arm in Part B and judged by the investigator as being at least possibly related to study treatment, sorted by descending frequency in the TU 1000 mg LOADING arm.

Appendix C Table 9. Incidence of TEAEs reported in at least 1.0% of subjects in the TU 1000 mg LOADING arm in Part B and judged by the investigator as being at least possibly related to study treatment

	Number of patients (%)	
	TU 1000 to 750 mg LOADING (N=22)	TU 1000 mg LOADING (N=112)
Total patients with at least 1 TEAE	9 (40.9)	62 (55.4)
Total patients with at least 1 at least possibly related TEAE	1 (4.5)	24 (21.4)
Fatigue	1 (4.5)	6 (5.4)
Libido decreased	1 (4.5)	5 (4.5)
Injection site pain	0 (0.0)	4 (3.6)
PSA Increased	0 (0.0)	3 (2.7)
Adjustment disorder with mixed anxiety and depressed mood	0 (0.0)	3 (2.7)
Irritability	0 (0.0)	2 (1.8)
Blood testosterone free increased	0 (0.0)	2 (1.8)
Blood testosterone increased	0 (0.0)	2 (1.8)
Disturbance in attention	0 (0.0)	2 (1.8)

4.4 AE's of Interest

The following were selected as AEs of interest for an injectable TRT product: • endocrine disorders • injection related tolerability • adverse lipid profiles • erythropoiesis (adverse hematopoietic profiles/polycythemia) • aggression or depression • urinary symptoms • prostate health • liver abnormalities • sleep apnea syndrome• cerebrovascular events • skin disorders (eg, acne) • ear and labyrinth disorders.

4.4.1 Part A, Stage 2

Appendix C Table 10 summarizes the TEAE's of interest in Part A Stage 2.

Appendix C Table 10. TEAE's of interest in Part A Stage 2

Event Class	MedDRA System Organ Class	MedDRA Preferred term	Number of patients (%)	
			TU 750 (N=99)	TU 1000 (N=94)
Total Patients With At Least One TEAE of Interest			**16 (16.2)**	**10 (10.6)**
Endocrine Disorder	Metabolism and nutrition disorders	Diabetes mellitus	1 (1.0)	0 (0.0)
Tolerability of Injection	General disorders and administration site conditions	Injection site pain	1 (1.0)	1 (1.1)
		Injection site oedema	1 (1.0)	0 (0.0)
		Injection site pruritus	1 (1.0)	0 (0.0)
Adverse Lipid Profiles	Investigations	Blood triglycerides increased	1 (1.0)	1 (1.1)
	Metabolism and Nutritional disorders	Hypercholesterolaemia	2 (2.0)	1 (1.1)
Aggression or depression	Psychiatric disorders	Depression	0 (0.0)	1 (1.1)
		Insomnia	0 (0.0)	1 (1.1)
Urinary Symptoms	Renal and urinary disorders	Pollakiuria	1 (1.0)	0 (0.0)
		Renal Failure	0 (0.0)	1 (1.1)
		Dysuria	1 (1.0)	1 (1.1)
Prostate health	Investigations	Prostatic specific antigen increased	2 (2.0)	1 (1.1)
		Prostate examination abnormal	0 (0.0)	1 (1.1)
	Reproductive system and breast disorders	Prostatic intraepithelial neoplasia	0 (0.0)	1 (1.1)
		Testicular atrophy	0 (0.0)	1 (1.1)
		Testicular disorder	1 (1.0)	1 (1.1)
		Ejaculation disorder	1 (1.0)	0 (0.0)
		Neoplasm prostate	1 (1.0)	0 (0.0)
		Prostatic atrophy	1 (1.0)	0 (0.0)
		Testicular pain	1 (1.0)	0 (0.0)
Liver Abnormalities	Neoplasms benign, malignant and unspecified	Bladder Cancer	1 (1.0)	0 (0.0)
Cerebrovascular events	Nervous system disorders	Cerebrovascular accident	1 (1.0)	0 (0.0)
Skin	Skin and Subcutaneous tissue disorders	Acne	1 (1.0)	0 (0.0)
		Rash	1 (1.0)	0 (0.0)
Sleep apnea	Respiratory, thoracic and mediastinal disorders	Sleep apnoea syndrome	1 (1.0)	0 (0.0)
Ear and labyrinth disorders	Ear and labyrinth disorders	Tinnitus	0 (0.0)	1 (1.1)

4.4.2 Part B

Appendix C Table 11 summarizes the TEAE's of interest in Part B.

Appendix C Table 11. TEAE's of interest in Part B

Event Class	MedDRA System Organ Class	MedDRA Preferred term	Number of patients (%)	
			TU 1000 to 750 mg LOADING (N=22)	TU 1000 mg LOADING (N=112)
Total Patients With At Least One TEAE of Interest			**2 (9.1)**	**21 (18.8)**
Endocrine disorder	Metabolism and nutrition disorders	Diabetes mellitus	0 (0.0)	1 (0.9)
Tolerability of Injection	General disorders and administration site conditions	Injection site erythema	0 (0.0)	1 (0.9)
		Injection site irritation	0 (0.0)	1 (0.9)
		Injection site pruritus	0 (0.0)	1 (0.9)
		Injection site pain	0 (0.0)	4 (3.6)
		Irritability	0 (0.0)	2 (1.8)
Erythropoietic	Investigations	Haemoglobin increased	0 (0.0)	1 (0.9)
Aggression or depression	Psychiatric disorders	Depression	1 (4.5)	1 (0.9)
		Anger	0 (0.0)	1 (0.9)
		Mood swings	0 (0.0)	1 (0.9)
Urinary Symptoms	Renal and urinary disorders	Pollakiuria	0 (0.0)	1 (0.9)
		Urine flow decreased	0 (0.0)	1 (0.9)
Prostate health	Investigations	Prostatic specific antigen increased	0 (0.0)	3 (2.7)
		Prostate examination abnormal	0 (0.0)	2 (1.8)
	Reproductive system and breast disorders	Benign prostatic hyperplasia	0 (0.0)	1 (0.9)
		Prostate induration	0 (0.0)	1 (0.9)
		Prostatitis	1 (4.5)	2 (1.8)
		Testicular pain	0 (0.0)	1 (0.9)
	Neoplasms benign, malignant and unspecified	Prostate cancer	0 (0.0)	2 (1.8)
Skin	Skin and subcutaneous tissue disorders	Acne	0 (0.0)	1 (0.9)

4.5 SAE's

4.5.1. Part A, Stage 2

Appendix C Table 12 presents a summary of treatment-emergent SAE's in Part A Stage 2.

Appendix Table 12. Treatment-emergent SAE's in Part A Stage 2

MedDRA Preferred term	Number of patients (%)	
	TU 750 (N=99)	TU 1000 (N=94)
Total patients with at least 1 TEAE	28 (28.3)	22 (23.4)
Total patients with at least 1 Treatment-emergent SAE	3 (3.0)	2 (2.1)
Coronary artery disease	1 (1.0)	0 (0.0)
Arthritis infective	0 (0.0)	1 (1.1)
Spinal column stenosis	0 (0.0)	1 (1.1)
Bladder cancer	1 (1.0)	0 (0.0)
Cerebrovascular accident	1 (1.0)	0 (0.0)

4.5.2 Part B

Appendix C Table 13 presents a summary of the incidence of treatment-emergent SAE's in Part B.

Appendix C Table 13. Incidence of treatment-emergent SAE's in Part B

MedDRA Preferred term	Number of patients (%)	
	TU 1000 to 750 mg LOADING (N=22)	TU 1000 mg LOADING (N=112)
Total patients with at least 1 TEAE	9 (40.9)	62 (55.4)
Total patients with at least 1 Treatment-emergent SAE	1 (4.5)	6 (5.4)
Prostate cancer	0 (0.0)	2 (1.8)
Pneumonia	0 (0.0)	1 (0.9)
Accidental overdose	0 (0.0)	1 (0.9)
Cervical spinal stenosis	0 (0.0)	1 (0.9)
Lung neoplasm malignant	0 (0.0)	1 (0.9)
Metastases to bone	0 (0.0)	1 (0.9)
Convulsion	0 (0.0)	1 (0.9)
Hip arthroplasty	0 (0.0)	1 (0.9)
Colon cancer	1 (4.5)	0 (0.0)

4.6. Adverse Events Resulting in Premature Discontinuation from Study

4.6.1. Part A Stage 2

There were 2 (2.0%) subjects in the TU 750 mg arm and 2 (2.1%) subjects in the TU 1000 mg arm in Part A Stage 2 who experienced TEAEs that led to discontinuation from the study medication (and from the study).

Appendix C Table 14 summarizes TEAE's that led to discontinuation.

Appendix C Table 14. TEAE's that led to discontinuation in Part A Stage 1

MedDRA Preferred term	Number of patients (%)	
	TU 750 (N=99)	TU 1000 (N=94)
Total patients with at least 1 TEAE	28 (28.3)	22 (23.4)
Total patients with at least 1 TEAE Leading to Discontinuation of Study Medication	2 (2.0)	2 (2.1)
Arthritis infective	0 (0.0)	1 (1.1)
Prostatic specific antigen increased	1 (1.0)	1 (1.1)
Prostatic intraepithelial neoplasia	0 (0.0)	1 (1.1)
Sleep apnoea syndrome	1 (1.0)	0 (0.0)

4.6.1 Part B

Appendix C Table 15 summarizes TEAE's that led to discontinuation in Part B.

Appendix C Table 15. TEAE's that led to discontinuation in Part B

MedDRA Preferred term	Number of patients (%)	
	TU 1000 to 750 mg LOADING (N=22)	TU 1000 mg LOADING (N=112)
Total patients with at least 1 TEAE	9 (40.9)	62 (55.4)
Total patients with at least 1 TEAE Leading to Discontinuation of Study Medication	1 (4.5)	7 (6.3)
Prostate cancer	0 (0.0)	2 (1.8)
Blood testosterone free increased	0 (0.0)	1 (0.9)
Blood testosterone increased	0 (0.0)	1 (0.9)
Haemoglobin increased	0 (0.0)	1 (0.9)
Lung neoplasm malignant	0 (0.0)	1 (0.9)
Bipolar disorders	0 (0.0)	1 (0.9)
Dyspnoea	0 (0.0)	1 (0.9)
Prostate specific antigen increased	0 (0.0)	1 (0.9)
Colon cancer	1 (4.5)	0 (0.0)

4.7 Deaths

4.7.1 Part A, Stage 2

No subject died during Stage 2.

4.7.2 Part B,

There was 1 subject who died during this study. Subject 001-6020, a 75 year old Caucasian male received 1 injection of TU 1000 mg (in the TU 1000 mg LOADING regimen), and then died of a malignant lung neoplasm 54 days following his first injection; the death was considered unrelated to study treatment.

4.8 Summary of AE's

4.8.1 Part A, Stage 2

As of October 12, 2007, 28 (28.3%) subjects in the TU 750 mg arm experienced at least one TEAE during Stage 2, while 22 (23.4%) subjects in the TU 1000 mg arm experienced at least one TEAE during Stage 2. No type of AE was reported in more than 2 subjects in either arm during Stage 2. There were no reports of adverse events related to either hormone laboratory outcomes or hematocrit/hemoglobin laboratory outcomes during Stage 2. There was one report of a prostate cancer (prostate neoplasm) in the TU 750 mg arm.

There were few adverse events reported to be at least possibly related to study treatment; 3 (3.2%) subjects in the TU 1000 mg arm and 6 (6.1%) subjects in the TU 750 mg arm had at least one TEAE that was judged to be at least possibly related to study medication. PSA increase was reported in 2 subjects in the TU 750 mg arm and 1 subject in the TU 1000 mg arm; each of these events was judged as at least possibly related to study medication. No other adverse event was reported as being at least possibly related to study treatment in more than 1 subject in either treatment group during Stage 2.

There were 3 (3.0%) subjects in the TU 750 group and 2 (2.1%) subjects in the TU 1000 group who experienced at least one treatment-emergent SAE during Stage 2 treatment period. No individual type of SAE was observed in more than 1subject, and no SAE was judged by the investigator to be at least possibly related to study medication.

There were 2 (2.0%) subjects in the TU 750 mg arm and 2 (2.1%) subjects in the TU 1000 mg arm who experienced TEAEs that led to discontinuation from the study medication (and from study). Those TEAEs that resulted in discontinuation from the study were, for each of these 4subjects: infective arthritis; sleep apnea syndrome; and prostatic intraepithelial neoplasia and PSA increase.

There were no subjects who had their study medication temporarily interrupted due to an event, and no subject died during Part A Stage 2.

There were 2 subjects who discontinued from the study due to prostate health-related events, specifically a PSA > 4 ng/mL but = 10 ng/mL.

4.8.1 Part B

This section describes the safety outcomes for the TU 1000 mg Loading regimen as in Part B.

Average safety follow-up was over 215 days (i.e., over 30 weeks), with the majority of subjects completing all 4 injections.

Approximately 55.4% of subjects in the TU 1000 mg LOADING group experienced at least one AE during the study. Fatigue and libido decrease were the AEs reported with the highest incidence in the TU 1000 mg LOADING arm. No event was reported with an incidence higher than 7 subjects.

The proportion of patients experiencing at least one TEAE was similar across the subgroups assessed, with no notable trends observed. Importantly, no clinically meaningful difference in the incidence of any type of individual TEAE was noted across subgroups.

Approximately 21% of subjects in the TU 1000 mg LOADING arm experienced at least one TEAE that was judged to be at least possibly related to study medication.

• The events reported as at least possibly related were generally consistent with those expected for a population treated with a TRT. The most commonly reported at least possibly related TEAEs were: fatigue, libido decreased, and injection site pain. Other events reported in 3 (2.7%) subjects included PSA increased, and adjustment disorder with mixed anxiety and depressed mood.

• Blood testosterone increased and blood testosterone free increased were each reported in 2 (1.8%) subjects in the TU 1000 mg LOADING arm. There were no other hormone parameters with an associated TEAE that were judged to be at least possibly related to study treatment.

• At least possibly related increased hemoglobin was reported in 1 subject in the TU 1000 mg LOADING arm.

There was 1 subject who died in Part B, Stage 1. Subject 001-6020, a 75 year old Caucasian male received 1 injection of TU 1000 mg (in the TU 1000 mg LOADING regimen), and then died of a malignant lung neoplasm 54 days following his first injection; the death was considered unrelated to study treatment.

Six (5.4%) subjects in the TU 1000 mg LOADING arm and 1 (4.5%) subject in the TU 1000 to 750 mg LOADING arm experienced at least one treatment-emergent SAE during the treatment period regardless of relationship to study drug. Only 1 SAE was observed in more than 1subject; prostate cancer was reported in 2 subjects in the TU 1000 mg LOADING group.

5. 120-Safety Update: Brief Statement of Conclusion

The safety data compiled for this 120 day NDA safety update are consistent with those reported during the original NDA filing of Stage 1 of Parts A and C.

According to the data submitted in this Safety Update, there were no unexpected events observed during the Part A Stage 2 or Part B Stage 1 treatment periods. While this 120-Day Safety Update did contain 4 additional cases of acute post-injection “cough reactions/allergic reactions” derived from the spontaneously reported postmarketing period in Europe, there were no such reports of post-injection “coughing fits” in these extension trials.

There were no dose-related trends in any safety outcomes measured, and the overall safety profile observed in Part A Stage 2 and Part B Stage 1 revealed no new trends or significant safety information when compared to that of the original NDA

D. Addendum. Part C, Steady–State Assessment

1.0 Background

The initial review of the study report for IP57-001 Part C noted that an additional trough measurement after the 5th injection visit would enable a more rigorous assessment of whether steady-state was indeed achieved by the 3rd injection visit using the 750 mg Loading Dose regimen. This addendum describes our analysis of the requested information.

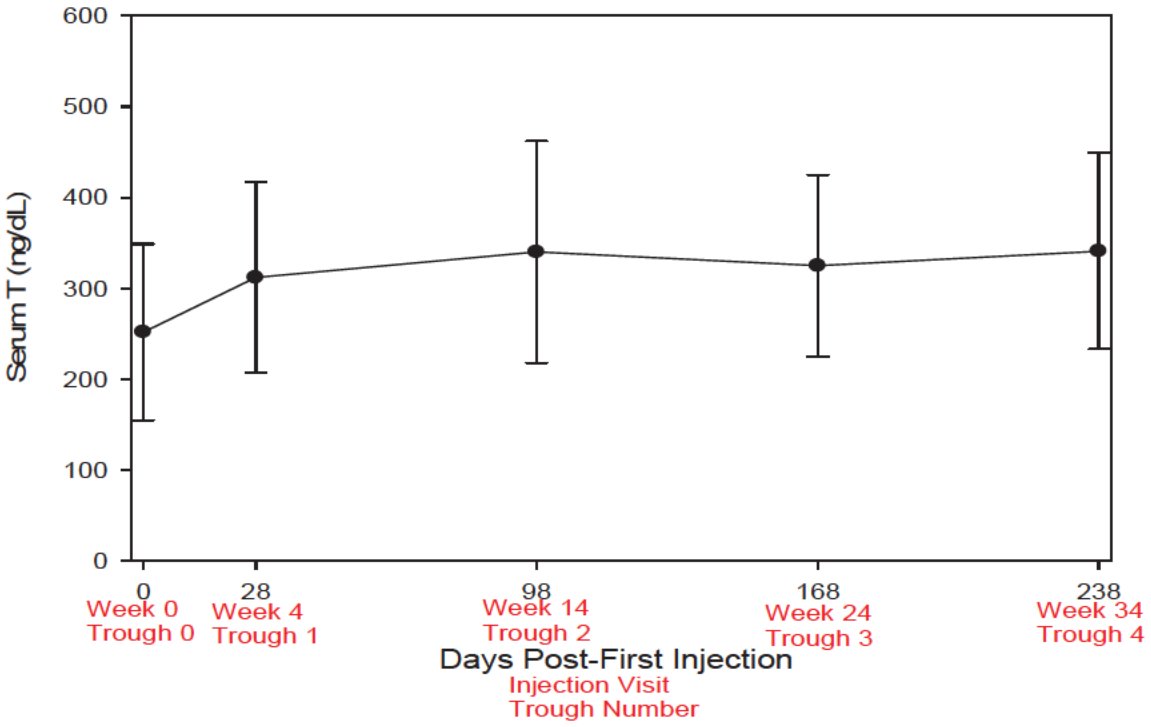
2.0 Patient Population

There were 117 subjects included in this Steady-State PK Population (SS PK Population). Of these, 105 had a 5th injection.

3.0 Steady-State Outcomes

Appendix D Figure 1 provides the serum total testosterone group-mean trough concentrations (from the 1st through 5th injections) resulting from treatment with the TU 750 mg LOADING regimen. The average concentrations at Weeks 14, 24, and 34 (Days 98, 168, and 238) were similar. In addition, variability at the trough time points was similar across the 5 injection visits. The serum sampling was performed prior to the injections, and the X-axis in this figure is reported as days (and weeks) from the 1st injection.

Appendix D Figure 1. Serum total testosterone group-mean trough concentrations (from the 1st through 5th injections) resulting from treatment with the TU 750 mg LOADING regimen



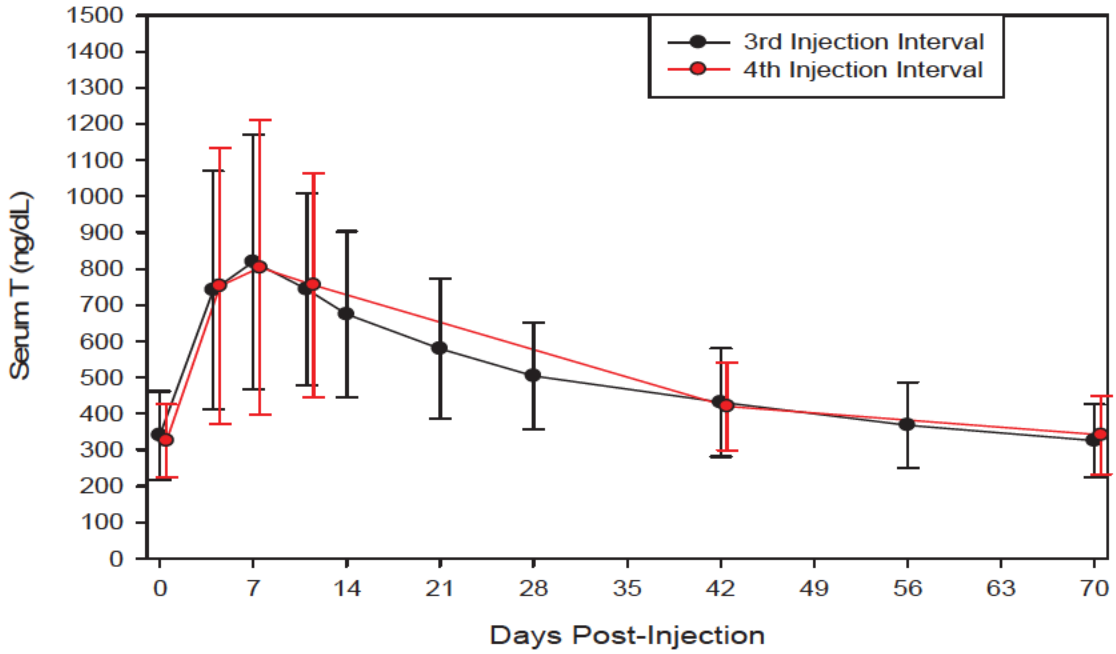
Appendix D Table 1 provides descriptive statistics for the data presented in Appendix D Figure 1. The average T concentrations at the 3rd and 5th injection visits were 340 ng/dL and 341 ng/dL, respectively.

Appendix D Table 1. Descriptive statistics for the data presented in Appendix D Figure 1

	Serum Total Testosterone (ng/dL) (N=105)		
Time	**Mean**	**Standard Deviation**	**Range**
Week 0/Injection 1	251.3	96.79	0 to 538
Week 4/Injection 2	312.2	104.85	133 to 706
Week 14/Injection 3	340.1	122.17	141 to 754
Week 24/Injection 4	325.0	99.64	107 to 611
Week 34/Injection 5	340.9	108.09	148 to 634

Appendix D Figure 2 provides a comparison of the T group-mean IPK concentration-time profiles resulting from the 3rd and the 4th injections of TU 750 mg LOADING. The average T concentrations at each of the time points measured were similar between the 2 injection intervals. Variability of the T concentrations at each time point was also similar between the 2 injection intervals

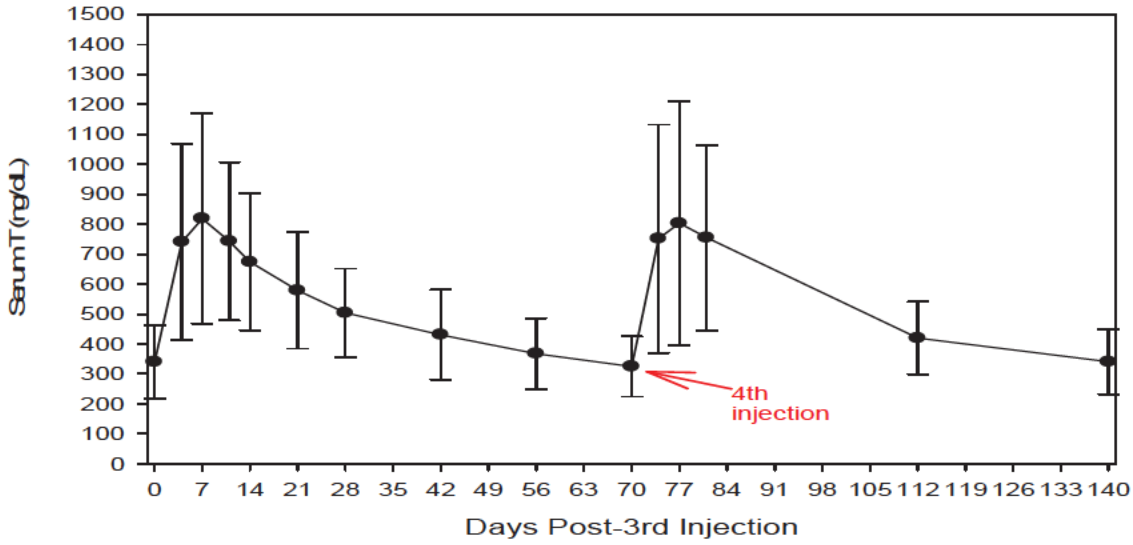
Appendix D **Figure 2. Comparison of the T group-mean IPK concentration-time profiles resulting from the 3rd and the 4th injections of TU 750 mg LOADING**



The conclusion from each method of assessment of steady state was that steady state had been achieved by the 3rd injection, i.e. Week 14/Day 98. Thus, treatment with TU 750 mg LOADING resulted in attainment of steady state by Week 14 of treatment (ie, by the 3rd injection visit), and the intensive sampling for PK outcomes (eg, C_{max} and C_{avg} outcomes per the approvability thresholds) for Part C Stage 1 was performed at steady state and can be extrapolated as representing PK outcomes under extended dosing beyond 3 injections.

Appendix D Figure 3 presents the same average concentration data but in a linear fashion. This figure provides support that steady-state was attained by the 3rd injection; visual inspection of both the mean values and the standard deviations at each time point measured reveals that 3rd injection concentrations were mirrored by the 4th injection concentrations.

Appendix D Figure 3. Average serum T concentration-time curves for 3rd and 4th injection intervals, presented in a linear fashion



The formal steady-state testing (using Helmert Contrast methodology) resulted in no statistically significant difference between the average of the troughs for the 4th and 5th injection visits when compared to the trough for the 3rd injection visit (p-value=0.7180). Based on the sequential testing methodology as described by Helmert, steady-state was attained by the 3rd injection visit.

4. Conclusions

The conclusion from each method of assessment of steady-state was that steady-state had been achieved by the 3rd injection, (Week 14/Day 98). Treatment with TU 750 mg LOADING resulted in attainment of steady-state by Week 14 of treatment, and the intensive sampling for PK outcomes (eg, C_{max} and C_{avg} outcomes per the approvability thresholds) for Part C Stage 1 was performed at steady-state and can be extrapolated as representing PK outcomes under extended dosing beyond 3 injections.

E. Post-Marketing Data

1.0 CIOMS Reports Since NDA Filing

In the 120-Safet Update, the new events reported in controlled extension studies were generally consistent with those in previous PSURs and were as would be expected in a population of males undergoing testosterone replacement treatment for hypogonadism. PSURs were also submitted reflecting the post-marketing safety experience in Europe. Most adverse events in those PSURs were consistent with those expected for an injectable TRT product. However, four new events suspected of possibly being a pulmonary oil microembolism (or hypersensitivity type events) were reported since the NDA filing (case numbers DE-2007-023890, DE- 2007-030464, AT-2007-035468, and ZA-2007-035469). These were additive to the 6 reported in the original NDA and the 2 reported in clinical trials (n= approximately 600 in trials).

The new initial CIOMS reports as received since June 30, 2007 are summarized in Appendix D Table 1 for the period between June 30, 2007 and October 12, 2007.

Appendix D Table 1. New initial CIOMS reports as received since June 30, 2007 (included in the 120-Day Safety Update)

Case Number	Event Term(s) Verbatim	Onset Date	Relatedness to Nebido	Initial Report	Follow-up Report(s)
DE-2007-023890	Anaphylactic reaction	(b) (6)	possible	4-Jul-2007	13-Jul-2007, 11-Sep-2007
CO-2007-025007	Cardiac failure	unk	possible/unlikely	13-Jul-2007	18-Jul-2007
BR-2007-028116	Retinal detachment	unk-Jun-2007	none	1-Aug-2007	7-Sep-2007
AU-2007-029476	Lymphoedema	8-Aug-2007	none	14-Aug-2007	
DE-2007-030464	Dyspnea, cough, laryngospasm	(b) (6)	possible	20-Aug-2007	
RU-2007-031850	PSA level increased	26-Jun-2007	unclassifiable	28-Aug-2007	3-Sep-2007
AT-2007-035468	Anaphylactic reaction, retching, throat irritation	13-Jun-2007	possible	25-Sep-2007	
ID-2007-032962	Tooth disorder	13-Aug-2007	none	7-Sep-2007	
ZA-2007-035469	Bronchospasm	(b) (4)	certain/unclassifiable	24-Sep-2007	
The lymphoedema and the tooth disorder were considered serious events; no other event was considered serious.					

On February 12, 2008, in response to the Division's request to provide all known cases of post-injection "cough reaction", Sponsor submitted narrative and case reports of patients who experienced immediate post-injection reactions "suspect of POME" in the post-marketing experience between April, 2004 and January, 2007. These reactions, characterized by symptoms including cough, dyspnea, and respiratory distress, were reported in **66 cases**, 28 of which were reported as serious or life-threatening, 12 required emergency medical care, and 6 required hospitalization. Twenty-four of these cases, selected based upon their medical significance, are presented in the Integrated Summary of Safety (ISS) and are not repeated here.

In most cases, these reactions were transient and attributed to POME. However, in over 20 cases, the event was coded as "medically serious" or required medical intervention to prevent serious outcome. In some reported POME cases, the event was described as life-threatening. In the opinion of the Clinical review team, additional cases were life-threatening.

In addition, and importantly, our consultant from the Division of Pulmonary and Allergy products concluded that 2 of these events met diagnostic criteria for anaphylaxis, another case was consistent with urticaria and angioedema, and in an additional case, anaphylaxis could not be excluded (describing a total of 4 possible cases of serious allergic reaction).

An additional CIOMS report submitted by Sponsor on February 29, 2008 involved a 38 year old hypogonadal male who experienced a mild allergic reaction following his first Nebido injection, and 6 months later was given his second injection in hospital where he developed a severe life-threatening allergic reaction (severe throat swelling).

2.0 Post-Marketing Conclusions

The nature of the post-marketing events reported with Nebido pose concerns of risk/benefit which, to date, remain unresolved.

Reviewer's Comments: ***Based on the review of the available safety data and the opinions of our Pulmonary/Allergy consultants, severe and life-threatening reactions associated with the use of Nebido mandate further assessment of these risks in order to eliminate or substantially reduce them.***

F. Division of Pulmonary and Allergy Drug Products (DPAP) Consultation

In their initial consultation, DPAP concluded (in agreement with Sponsor) that most of the reported cases of post-injection respiratory AE's were consistent with POME. However, two cases met recently proposed diagnostic criteria for anaphylaxis.

DPAP provided the following initial recommendations for consideration if the product were to be approved:

1. It would be appropriate to note in the product label that it should be administered only in a practitioner's office.
2. It would be also be appropriate to consider a labeling recommendation that there be a waiting period after injection.
3. The sponsor should attempt to provide as much detail as possible in any post-marketing reports suggestive of anaphylaxis. Follow-up requests for additional medical information may be necessary to provide the additional detail necessary to interpret the adverse event.
4. It would be reasonable for the sponsor to provide expedited reporting of all events that are suggestive of POME or anaphylaxis.

The Sponsor responded to a Clinical discipline-specific review letter with additional information about the postmarketing POME/allergy cases. A second consultation was requested from DPAP and they concluded the following:

At least 2 cases of anaphylaxis had been reported for TU. Medically serious cases of POME had been reported too. These posed a significant safety concern to the consultant. DPAP maintained that the decision to approve the product would be a risk versus benefit decision, and should be made in light of the degree of efficacy, the seriousness of the indication, the availability of alternative products for that indication, and the extent of the safety data.

DPAP suggested that it would be appropriate for Sponsor to characterize the frequency of these POME/POME-like events (b) (4) DPAP recommended that these studies be conducted prior to approval. The product is currently approved and marketed in Europe; DPAP was of the opinion that it would be reasonable and appropriate to conduct these studies abroad prior to considering the product for approval in the United States.

DPAP also recommended that consideration be given to advising the Sponsor to characterize the nature of the anaphylaxis events. DPAP stated that establishing the mechanism of these allergic reactions could help to make a decision on the approvability of the drug more scientific and rational. DPAP also recommended that the Division consider asking the Sponsor to develop an in vitro test for specific IgE and IgG antibody to the drug, both active and excipient ingredients, and to evaluate the presence of antibodies in patients who have had anaphylaxis events associated with the drug, those who have been exposed to the drug but who have not had anaphylaxis, as well as unexposed controls. In addition, the Sponsor should develop a skin testing procedure to the product and its excipients to evaluate the same populations to be studied with in vitro testing.

Reviewer's Comment: The reviewer is in broad agreement with the recommendations of the DPAP consultant.

G – Review of 10 June 2008 Clinical Amendment

1.0 Background

On June 10, 2008, the Sponsor submitted data from 3 clinical studies that included 1451 subjects treated with a total of 7246 injections of Nebido. These new data are derived from: 1) a completed clinical trial studying TU for suppression male spermatogenesis 2) a large ongoing observational safety study being conducted in Germany, and 3) a completed observational safety study conducted in several European countries and Australia.

2.0 Brief Review of the Submitted Information

The clinical studies are summarized by Sponsor as follows:

· **Study NE0601** is an on-going clinical trial to assess the tolerability and treatment outcomes associated with 1 year of treatment with Nebido 1000 mg every 10-14 weeks. This ad hoc interim analysis was based on incomplete data from 284 subjects treated with a total of 1129 injections as of June 3, 2008. There were no POME events reported to date in this study. There were 4 adverse events (AE's) leading to discontinuation; lymphedema, severe tooth problem, skin rash around injection site, and "allergic reaction". The CRF related to the "allergic reaction" noted that 7 days following the injection, Keflex was prescribed for "infected injection site" and Telfast (antihistamine) was prescribed for "injection site reaction". Sponsor notes that this event, "while reported as an allergic reaction, was local reaction limited to the injection site".

> *Reviewer's Comments: This reviewer notes that the reported "allergic reaction" does not represent the type of post-injection reaction that is of concern to the Division. The submitted data are very scanty and incomplete (less than 10 pages), making a reasonable assessment impossible.*

· **Study 42306** was a completed 8-month fertility study (progestagen implant plus Nebido 750 mg or 1000 mg) in which 297 healthy volunteers were treated with Nebido for a total of 1114 injections. There were no reported POME or allergic reactions.

> *Reviewer's Comments: The population in this study is significantly different from hypogonadal males, which may change the nature and incidence of reported AE's. The absence of reported post-injection reactions conflicts with the previous experience in the prior NDA submissions.*

· The **NIS study** is an ongoing post-marketing study that enrolled 870 subjects receiving a total of 5003 injections of Nebido 1000 mg. There were no reported POME or allergic reactions.

> *Reviewer's Comments: The report of this 870 patient study comprises 6 pages and very scant information in the form of summary results. The reported incidence AE's in this study are lower than seen in any of the trials submitted in the original NDA. This inconsistency requires some reconciliation that would be facilitated by access to the complete data rather than the brief and incomplete date submitted here in only 6 pages.*

3.0 Reviewer's Conclusion in regard to the June 10 Amendment

In this reviewer's opinion, the Sponsor continues to ignore the fact that a significant number of the reported post-injection reactions (POME and/or hypersensitivity) were regarded as "severe" and/or "life-threatening", some of which were long-lasting, and some required urgent treatment and/or hospitalization. The fact that no deaths were reported was fortuitous.

The submission of this additional material by Sponsor is of some interest but not persuasive, due to its incomplete nature. It does not allay the reviewer's concern regarding risk/benefit for this product.

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/s/

Harry Handelsman
6/16/2008 01:22:28 PM
MEDICAL OFFICER

Mark S. Hirsch
6/16/2008 01:29:47 PM
MEDICAL OFFICER
I concur.

DIVISION OF PULMONARY AND ALLERGY DRUG PRODUCTS
MEDICAL OFFICER CONSULTATION

Date:	5/27/08
To:	Eufrecina Deguia, Project Manager Division of Reproductive and Urologic Products
From:	Charles E. Lee, M.D., Medical Team Leader Division of Pulmonary and Allergy Products, HFD-570
Through:	Badrul A. Chowdhury, M.D., Ph.D., Director Division of Pulmonary and Allergy Products, HFD-570
Subject:	Medical Officer Consultation addendum regarding respiratory adverse events occurring with Nebido (testosterone undecanoate) for intramuscular injection

General Information

NDA/IND#:	NDA 22-219
Sponsor:	Indevus Pharmaceuticals, Inc.
Drug Product:	Nebido (testosterone undecanoate) for intramuscular injection
Request From:	John Kim, Project Manager Division of Reproductive and Urologic Products
Date of Request:	5/19/08
Date Received:	5/18/08
Materials Reviewed:	Consultation request Sponsor summary of allergic reactions and adverse event reports Expert medical opinions from sponsor's consultants Sponsor submission 5/9/08 and sponsor E-mail messages of 5/22/08 and 5/23/08

1. BACKGROUND

The Division of Reproductive and Urologic Products (DRUP) is reviewing an NDA for Nebido® (testosterone undecanoate) for IM injection (NDA 22-219, N-000, 8/24/07). The sponsor is Indevus Pharmaceuticals, Inc. Adverse events characterized by sudden onset of cough, dyspnea, and respiratory distress occurring shortly after injection were noted in clinical trials and postmarketing spontaneous adverse event reports from Europe.

DPAP recently completed a consultation regarding these respiratory adverse events. Of 66 cases submitted by the sponsor, DPAP concluded that two met recently proposed diagnostic criteria for anaphylaxis. [1, 2] Most of the remaining cases were consistent with pulmonary oil microembolism (POME), a short-lasting reaction due to the direct vascular or lymphovascular delivery of oil-based preparations.

DPAP noted that the decision to approve the product will be a risk versus benefit decision, and should be made in light of the degree of efficacy, the seriousness of the indication, the availability of alternative products for that indication, and the extent of the safety data. DPAP also provided the following recommendations for DRUP's consideration if the product were to be approved:

1. It would be appropriate to note in the product label that it should be administered only in a practitioner's office.
2. Most of these adverse events occurred immediately after injection. It would be also be appropriate to consider a labeling recommendation that there be a waiting period after injection.
3. The sponsor should attempt to provide as much detail as possible in any postmarketing reports suggestive of anaphylaxis. Follow-up requests for additional medical information may be necessary to provide the additional detail necessary to interpret the adverse event.
4. It would be reasonable for the sponsor to provide expedited reporting of all events that are suggestive of POME or anaphylaxis.

Subsequent to the previous consultation, the sponsor submitted additional information. The sponsor pointed out that the two cases identified by DPAP as meeting clinical criteria for anaphylaxis and two that were less defined could also have been due to POME. The sponsor states that with proper labeling and communication, the prescriber and patient can be adequately alerted and prepared for PME reactions and the possibility of hypersensitivity. The sponsor proposed to note POME and hypersensitivity reactions in the product label, provide educational and outreach tools to promote proper injection technique, (b) (4)

DPAP comments on the recently submitted information follows.

[1] Sampson HA, et. al. J Allergy Clin Immunol. 115(3):584-591, 2005.
[2] Sampson HA, et. al. J Allergy Clin Immunol. 117(2):391-397, 2006.

2. DPAP COMMENTS

1. DPAP disagrees that the two postmarketing cases identified as meeting clinical criteria for anaphylaxis could have been due to POME.

   Case GB-2007-023826 had respiratory distress, throat tightness, and a raised rash on the abdomen and chest. As noted previously, the case meets recently proposed diagnostic criteria for anaphylaxis. It is difficult to attribute the rash, whose onset was concurrent with the respiratory symptoms, to be due to use of testosterone patches and gels in the past.

   Case ZA-3007-035469 had bronchospasm and a drop in blood pressure. This presentation is more consistent with anaphylaxis than POME. Additional information recently submitted noted the presence of tachycardia, an oxygen saturation of 94% at the onset of the event, and treatment of the bronchospasm with nebulized epinephrine. The additional information submitted by the sponsor adds additional support to anaphylaxis as the most likely interpretation of this event.

   It should be noted that the sponsor states that the events in question are not inconsistent with a possible allergic or hypersensitivity reaction.

2. The sponsor notes that two other postmarketing cases reviewed and noted in the previous DPAP consult are less well defined and that one of the two cases followed improper intravenous administration of the product.

   Case GB-2006-006197 experienced coughing and tightness in the throat and the medical assessment at the time of the event was “acute anaphylactic reaction.” DPAP previously noted that anaphylaxis could not be excluded. DPAP maintains that anaphylaxis cannot be excluded, particularly in light of the assessment of the practitioner treating the event.

   Case SE-2006-022330 experienced cutaneous itching, angioedema, ocular swelling, and itching of the throat. DPAP concluded that the case did not meet clinical criteria for anaphylaxis and that the case was consistent with acute urticaria and angioedema. DPAP concurs, as the sponsor points out, that the patient did not have urticaria, but maintains that the patient had manifestations of acute angioedema and cutaneous and mucosal itching.

3. DPAP points out that the seriousness of these findings is not less if there are only two cases of anaphylaxis instead of four cases. The important thing is that postmarketing cases of anaphylaxis have been reported. The sponsor has been concerned enough about these events to propose conducting postmarketing studies to further define the character and frequency of these events.

4. DPAP maintains that the decision to approve the product will be a risk versus benefit decision, and should be made in light of the degree of efficacy, the seriousness of the

indication, the availability of alternative products for that indication, and the extent of the safety data.

At recent internal meetings regarding this product, DRUP has indicated that there are a number of alternative testosterone products in various formulations that are available. In addition, DRUP has noted that neither POME nor anaphylaxis is considered to be part of the safety profile for these alternative products. IgE-mediated sensitivity to castor bean allergen in castor bean extract and castor wax extract has been reported in patients with occupational hypersensitivity to castor beans.[3] Anaphylaxis has also been reported with use of polyethoxylated castor oil (Cremophor EL) when used as a solubilizing vehicle for various drugs. [4, 5]

Given this background, it would be appropriate to characterize the frequency of these events (b) (4) we would recommend that these studies be conducted prior to approval. The product is currently approved and marketed in Europe; it would be reasonable and appropriate to conduct these studies abroad prior to considering the product for approval in the United States.

Given the unclear mechanism of these reactions, we also recommend that consideration be given to advising the sponsor to characterize the nature of the anaphylaxis events. Establishing the mechanism of these allergic reactions can help to make a decision on the approvability of the drug more scientific and rational. We also recommend that DRUP consider asking the sponsor to develop an in vitro test for specific IgE and IgG antibody to the drug, both active and excipient ingredients, and to evaluate the presence of antibodies in patients who have had anaphylaxis events associated with the drug, those who have been exposed to the drug but who have not had anaphylaxis, as well as unexposed controls. In addition, the sponsor should develop a skin testing procedure to the product and its excipients to evaluate the same populations to be studied with in vitro testing.

[3] Final report on the safety assessment of Ricinus communis seed oil. Int J Toxicol; 26(1):31-77, 2007.
[4] Riegert-Johnson DL, Volcheck GW. Ann Allergy Asthma Immunol; 89(4):400-406, 2002.
[5] Kuiper RA, et. al. Ann Pharmacother; 34(7-8):858-861, 2000.

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/s/

Charles Lee
5/28/2008 11:45:24 AM
MEDICAL OFFICER

Badrul Chowdhury
5/28/2008 11:58:05 AM
MEDICAL OFFICER
I concur

DIVISION OF PULMONARY AND ALLERGY DRUG PRODUCTS
MEDICAL OFFICER CONSULTATION

Date:	4/14/08
To:	John Kim, Project Manager Division of Reproductive and Urologic Products
From:	Charles E. Lee, M.D., Medical Team Leader Division of Pulmonary and Allergy Products, HFD-570
Through:	Badrul A. Chowdhury, M.D., Ph.D., Director Division of Pulmonary and Allergy Products, HFD-570
Subject:	Medical Officer Consultation regarding respiratory adverse events occurring with Nebido (testosterone undecanoate) for intramuscular injection

General Information

NDA/IND#:	NDA 22-219
Sponsor:	Indevus Pharmaceuticals, Inc.
Drug Product:	Nebido (testosterone undecanoate) for intramuscular injection
Request From:	John Kim, Project Manager Division of Reproductive and Urologic Products
Date of Request:	2/29/08
Date Received:	2/29/08
Materials Reviewed:	Consultation request Sponsor summary of allergic reactions and adverse event reports Expert medical opinions from sponsor's consultants References

1. BACKGROUND

The Division of Reproductive and Urologic products is reviewing an NDA for Nebido® (testosterone undecanoate) for IM injection (NDA 22-219, N-000, 8/24/07). The sponsor is Indevus Pharmaceuticals, Inc. The product contains testosterone undecanoate in castor oil and benzyl benzoate and is administered as an intramuscular injection for testosterone replacement in hypogonadal adult men with conditions associated with deficiency of endogenous testosterone. The injection contains 250 mg/mL and the proposed regimen is an initial dose of 750 mg repeated at 1 month, then every 10 weeks thereafter. The product is marketed in Europe since 2004 and the sponsor reports that more than (b) (4) ampoules have been distributed. Adverse events characterized by sudden onset of cough, dyspnea, and respiratory distress occurring shortly after injection were noted in clinical trials and postmarketing spontaneous adverse event reports from Europe. In the total clinical trial population of approximately 600 subjects (4,000 injections), there were 2 post-injection reactions reported. In the post-marketing experience since April 2004, a total of 66 cases were reported and the sponsor provided narratives and adverse event reports for these 66 cases on February 12, 2008. Among these 66 cases, 28 were categorized as serious adverse events and 6 required hospitalization. Twelve required emergency medical care and were treated with epinephrine, antihistamines, steroids, and/or oxygen. Some of the cases were reported as episodes of anaphylaxis. DRUP notes that hydrogenated and polyoxyethylated forms of castor oil in the drugs Prograf and Sandimmune have been cited in drug labeling as the etiology for anaphylaxis. DRUP also notes that castor oil has been reported to enhance histamine release.

The sponsor attributes all these immediate post-injection reactions to pulmonary oil microembolism (POME) and recommends that care should be taken to slowly inject the product, being sure to follow precautions for intramuscular injection, such as aspiration of the syringe to check for penetration of a vessel. The sponsor states that the volume of castor oil may play a role in the incidence of reactions, and that (b) (4) 3 mL (750 mg) might mitigate the problem.

DRUP asked DPAP to assess the 66 postmarketing adverse event reports occurring with Nebido and requested DPAP to address the following questions:

1. Are all of the reactions attributable to pulmonary oil microembolism (POME) or are some of them allergic reactions?

2. Do you agree with the sponsor's assertion that careful and slow intramuscular injection, as well as the lower volume per injection (3 mL), is adequate to mitigate these reactions?

2. DPAP RESPONSES

POME is a short-lasting reaction due to the direct vascular or lymphovascular delivery of oil-based preparations. It is characterized desire to cough, cough, dyspnea, and/or respiratory distress shortly after intramuscular injection of oil-based preparations. As the sponsor notes, these reactions have been noted to occur with other oil-based testosterone

preparations (testosterone enanthate), an unapproved anabolic steroid used by body builders (trenbolone acetate), paraffin oil, and radiocontrast media used for lymphangiography and hysterosalpingography. The reaction is thought to be due to lymphovascular microembolization of oil to the lung, with possible transient acute pulmonary hypertension from mechanical vascular occlusion.

Anaphylaxis is a clinical syndrome characterized by acute onset of an illness with involvement of skin, mucosal tissue, and respiratory and/or cardiovascular systems. Clinical criteria for the diagnosis of anaphylaxis have recently been proposed. [1, 2]

Anaphylaxis is highly likely when any one of the following 3 criteria are fulfilled:

1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (e.g., generalized hives, pruritus or flushing, swollen lips-tongue-uvula), and at least one of the following:
    a. Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
    b. Reduced BP or associated symptoms of end-organ dysfunction (e.g., hypotonia [collapse], syncope, incontinence)
2. Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):
    a. Involvement of the skin-mucosal tissue (e.g., generalized hives, itch-flush, swollen lips-tongue-uvula)
    b. Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
    c. Reduced BP or associated symptoms (e.g., hypotonia [collapse], syncope, incontinence)
    d. Persistent gastrointestinal symptoms (e.g., crampy abdominal pain, vomiting)
3. Reduced BP after exposure to known allergen for that patient (minutes to several hours):
    a. Infants and children: low systolic BP (age specific) or greater than 30% decrease in systolic BP
    b. Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that person's baseline

DPAP responses to DRUP's questions follow below.

Are all of the reactions attributable to pulmonary oil microembolism (POME) or are some of them allergic reactions?

DPAP response:

Of the 66 cases submitted by the sponsor, two meet diagnostic criteria for anaphylaxis. Unfortunately, these postmarketing adverse event case reports are not entirely conclusive because they lack detail.

[1] Sampson HA, et. al. J Allergy Clin Immunol. 115(3):584-591, 2005.
[2] Sampson HA, et. al. J Allergy Clin Immunol. 117(2):391-397, 2006.

Ultimately, the decision to approve the product will be a risk versus benefit decision, and should be made in light of the degree of efficacy, the seriousness of the indication, the availability of alternative products for that indication, and the extent of the safety data.

The following are recommendations for your consideration if the product is to be approved.

1. *It would be appropriate to note in the product label that it should be administered only in a practitioner's office.*

2. *Most of these adverse events occurred immediately after injection. It would be also be appropriate to consider a labeling recommendation that there be a waiting period after injection.*

3. *The sponsor should attempt to provide as much detail as possible in any postmarketing reports suggestive of anaphylaxis. Follow-up requests for additional medical information may be necessary to provide the additional detail necessary to interpret the adverse event.*

4. *It would be reasonable for the sponsor to provide expedited reporting of all events that are suggestive of POME or anaphylaxis.*

Do you agree with the sponsor's assertion that careful and slow intramuscular injection, as well as the lower volume per injection (3 mL), is adequate to mitigate these reactions?

DPAP response:
The information provided suggests that POME may be less likely when oil-based products are injected carefully and slowly and when smaller volumes are injected. Rate or volume of intramuscular injection would not be expected to influence the rate of anaphylaxis due to either IgE-mediated or non-IgE mediated mechanisms.

3. DPAP CASE REVIEWS

The sponsor's adverse event reports were reviewed. The amount of information in most of these reports is scanty, as with most postmarketing adverse event reports, and complicates their interpretation. Of the 66 cases, 51 clearly did not meet clinical criteria for the diagnosis of anaphylaxis. The majority of these 51 cases were consistent with POME. There were 15 adverse event reports that warranted additional scrutiny. Narratives for these cases and DPAP reviewer comments follow below.

Nonserious Cases

Nonserious Case 17:

DE-2006-002815: Immediately after receiving his second injection of Nebido, this 15 year old patient with Kallman syndrome experienced extremely severe urge to cough, mild dyspnea, tachycardia, retrosternal pain, and redness of his eyes lasting 10-15 minutes. The events were considered non-serious. Blood pressure was normal. The reporting physician suspected a Type I allergic reaction and treated the patient with an antihistamine and an anti-inflammatory steroid. The patient recovered.

DPAP comments:

This case is more suggestive of POME than anaphylaxis. Ocular redness may come in response to severe coughing. No pruritus was noted, there are no cutaneous signs or symptoms, and there is no other mucosal involvement. Although treatment for anaphylaxis was given, the patient's response could also be due to the self-limited course of POME.

Nonserious Case 25

DK-2005-009832: Three minutes after receiving his first Nebido injection, the patient experienced non-serious, severe arthralgia in the knee and foot, intense cough, chest pain, burning feeling in most parts of the body, and pruritus in the palate. The symptoms resolved within 20 minutes. The physician considered the symptoms short-lasting and constituting only minor problems.

DPAP comments:

This case is more suggestive of POME than anaphylaxis. Anaphylaxis is not typically associated with a sensation of burning or arthralgia. It appears that the patient did not receive any treatment for the reaction and the symptoms resolved within 20 minutes.

Nonserious Case 32

NO-2007-008557: The patient experienced non-serious "hypersensitivity reaction" manifested by dry cough, itching, and a tingling sensation. The time course in relation to the injection was not reported. The patient recovered without treatment.

DPAP comments:

There is very little information in this report. Respiratory involvement appears to be limited to cough. The extent and location of the itching is not noted. Anaphylaxis is not typically associated with a "tingling" sensation. Recovery without treatment would suggest that this event is not anaphylaxis.

Nonserious Case 36

SE-2007-002541: The patient experienced non-serious warmth over his chest and head, coughing, and redness of his face. The proximity of the events to the Nebido injection was not stated, but it is assumed that the events began immediately after the injection.

DPAP comments:
This case is more suggestive of POME than anaphylaxis. Flushing of the face may be seen as a result of a coughing fit. There is no mention of other respiratory symptoms and no mention of pruritus.

Serious Cases
Serious Case 2
200711270BNE: The patient received the injection in the GP's office "given quickly" and the patient collapsed and began coughing and was short of breath. He also experienced a burning sensation in his mouth and chest. He was hospitalized for two days. He subsequently received Nebido in the clinic, without any reaction.

DPAP comments:
This case is more suggestive of POME than anaphylaxis, although anaphylaxis cannot be entirely excluded. It is clear from the report that the initial symptom was coughing, which occurred immediately after the injection. There is no report of cutaneous or mucosal itching. Acute pulmonary hypertension could result in cardiovascular collapse, as experienced by this patient. Although the patient was hospitalized, there is no note of the treatment that he received.

Serious Case 5
AT-2007-035468: On his approximately seventh injection of Nebido, which was given slowly, the patient experienced what was termed "anaphylactic reaction", manifested by gag-irritation and a tickle in the throat, beginning 30 seconds after the injection (serious, medically important). He received cetirizine 10 mg orally. The patient recovered within 15 minutes of the injection. For the next Nebido injection, three months later, the volume was divided in half and administered as 2 mL in left and right gluteal muscles. No symptoms occurred.

DPAP comments:
This case does not meet criteria for diagnosis of anaphylaxis. Recovery within 15 minutes after treatment with an oral antihistamine is not suggestive of anaphylaxis.

Serious Case 7
BR-2007-005496: Immediately upon his first dose of Nebido in a drugstore in Brazil, a patient was reported to experience "anaphylactic shock" manifested as breathlessness (presumed to be glottal edema) and malaise. The events were considered serious (medically important). The reporter stated the breathlessness became worse 30 minutes after the injection and the malaise lasted three days. The patient received corticosteroids and apparently received oxygen ("he was lying down and was ventilated in the drug store"). The reporter stated that there was no need for hospitalization. The patient recovered.

DPAP comments:
A lack of information complicates this case, which does not meet the diagnostic criteria for anaphylaxis. The report notes that there were symptoms of glottis edema but does not describe those symptoms and it is unclear if the symptoms were stridor or just a sensation of throat swelling. There are no other symptoms or signs noted other than breathlessness. It would be unlikely for glottis edema from anaphylaxis to persist for three days. The patient did not require hospitalization.

Serious Case 10
DE-2004-037302: A 38 year old female-to-male transsexual patient experienced "allergic reaction" during the injection, manifested by hyperventilating followed by pronounced redness of the face. There was no urticaria and blood pressure (132/102 mmHg) and heart rate were considered normal. After these manifestations, the patient experienced malaise and shivers. He received a corticosteroid and an antihistamine. Blood pressure increased to 172/109 and heart rate rose to 90 bpm. The patient remained in the office for one hour and 40 minutes and then left in "a relatively recovered state." The next day, the patient had feelings of heat in his thigh and upper arms, malaise and felt feverish, but had no symptoms or urticaria. The patient recovered.

DPAP comments:
This case does not meet diagnostic criteria for anaphylaxis. Hyperventilation, malaise, and shivers are not characteristic of anaphylaxis.

Serious Case 15
DE-2005-009283: On receiving his first dose of Nebido (correct technique was verified) the patient experienced an event of suspected fat embolization (serious, medically important), manifested by non-serious cough immediately after the injection, flushing, sweating, trembling, dizziness, feeling of unrest, and increase in blood pressure up to 150/95 mmHg. The symptoms lasted longer than 20 minutes. The patient had previously tolerated injections of testosterone enanthate (ground-oil as the oily vehicle) and had a history of hypotensive blood pressure. The patient was seen in the ER and held in the hospital for observation until that evening. Laboratory tests demonstrated no abnormalities. While in the doctor's office, the patient received supportive treatment with cortisone and ranitidine and in the hospital received an antihistamine. The patient recovered. The reporter considered the reaction to be suggestive of fat embolism, but difficult to distinguish from a hypersensitivity reaction.

DPAP comments:
This case is more suggestive of POME than anaphylaxis. Flushing may come in response to severe coughing. No pruritus is noted and there are no cutaneous signs other than sweating, which is not characteristic of anaphylaxis. Although treatment for anaphylaxis was given, the patient's response could also be due to the self-limited course of POME.

Serious Case 16
DE-2006-003298: Three minutes after receiving his fourth Nebido injection, the patient experienced "idiosyncratic drug reaction" manifested by 1-2 minutes of apnea (serious, medically important) and other symptoms lasting 10-20 minutes including cough, dyspnea, hot flush, and paresthesia in the mouth/head area. No treatment was given, and the patient recovered. The patient had a history of atopy (hay fever and an allergy to wine, and mild allergy to sesame), but no allergy to castor bean. IgE testing was negative.

DPAP comments:
Recover within 20 minutes without treatment is not suggestive of anaphylaxis. Paresthesia is not characteristic of anaphylaxis. It is unclear what is meant by IgE testing being negative. A total IgE level is not helpful in diagnosing anaphylaxis. A test for specific IgE to a constituent of castor oil is not likely to be standardized or validated, if that the type of IgE testing that the reporter is referring to.

Serious Case 19
DE-2007-023890: This complicated case involves a patient who, on his first injection of Nebido, experienced a multitude of symptoms including dizziness, tingling in the abdominal area, sensation of weakness, pressure in the head, numbness in the fingers and toes, a hot, hard, and painful injection site, and also complained that everything went black. Anaphylactic reaction was suspected initially, but later considered doubtful due to negative extensive allergy testing for all components of Nebido, and IgE was normal. Instead, POME was suspected, and a psychosomatic reaction was not ruled out. There was no dyspnea, bronchospasm, angioedema, or urticaria, and blood pressure was normal. The events were considered serious (medically important), and the patient was treated in the ER with an antihistamine, a corticosteroid, ranitidine, and an infusion of electrolyte solution E153. The patient recovered. The patient's history included resection of a pituitary tumor eight years earlier and chronic treatment with cortisone and testosterone depot as replacement therapies.

DPAP comments:
This reaction is not suggestive of anaphylaxis. Numbness of fingers and toes, dizziness, and tingling are more suggestive of a vasovagal reaction. Cardiac and pulmonary examinations were negative, according to the report. A total IgE level is not helpful in diagnosing anaphylaxis. Testing of constituents of the drug product is not helpful unless the testing is validated, standardized, and conducted with appropriate controls.

Serious Case 21
GB-2006-006197: On his second injection of Nebido, the patient was reported to experience an "acute anaphylactic reaction," manifested by a coughing fit and tightness in the throat. There was no wheezing and no cardiovascular compromise. The patient received treatment with an antihistamine and epinephrine. The patient was hospitalized and the event of acute anaphylactic reaction was considered life threatening. After treatment, the patient was recovering.

DPAP comments:
This event was described as starting first with coughing during injection with progressive difficulty breathing. Sweating was also present according to the adverse event report and at one point the patient was reported to be near respiratory arrest. The pulse was reported to be 48. The patient was taken to the hospital, however it is not known if he was admitted and there is no information about the treatment given at the hospital. Anaphylaxis cannot be excluded in this case. That said, tachycardia is more likely with anaphylaxis than bradycardia.

Serious Case 23
GB-2007-023826: The patient had been receiving Nebido injections for two years when, on his next Nebido injection, he began to experience coughing about 30 seconds into the injection. It was reported that it required a fair amount of pressure and took two minutes to administer the full injection in this reportedly needle-phobic patient. Needle size was not reported. The coughing began to be accompanied by urge to cough, respiratory distress, tightening of the throat, closing of the airways, and inspiratory wheeze. The patient was also noted to have a rash on his abdomen, raised blotches on his chest (which quickly cleared), and an itchy scalp. The physician interpreted the above symptoms to reflect "anaphylaxis" and "anaphylactic shock" (considered life threatening), and the patient was treated with an antihistamine and adrenaline. Following administration of antihistamine and adrenaline in the general practitioner's office, the patient was taken to the ER where T wave inversion on ECG was observed. Troponin level was negative, and there was no chest pain. He was observed in the CCU, and then the patient recovered and was discharged the same day as the Nebido injection. A follow-up report indicates that the T wave inversion was likely due to the adrenaline that had been administered. The patient had a history of skin rashes to topical testosterone products and was receiving chronic injections of growth hormone administered subcutaneously in the abdomen. Follow-up information also indicates that the physician would hesitate to call the reaction "anaphylaxis" as the reaction was not severe, and there was no objective evidence of anaphylaxis, but stated that the prompt administration of adrenaline may have prevented this.

DPAP comments:
This case meets diagnostic criteria for anaphylaxis. Respiratory compromise, cutaneous itching, and a raised erythematous rash that is suggestive of urticaria were present.

Serious Case 27
SE-2006-022330: The patient received his first dose of Nebido, but it was given intravenously, and he then experienced angioedema and pruritus (serious, medically important), as well as slight nausea, malaise, swelling around the eyes, and itching of the throat. The patient was treated with an antihistamine and an injection of hydrocortisone. He was discharged home after a few hours of observation.

DPAP comments:
This case is characterized by cutaneous and mucosal findings. There was no respiratory or cardiovascular involvement. The diagnostic criteria for anaphylaxis were not met. The case is consistent with acute urticaria and angioedema.

Serious Case 28
ZA-2007-035469: The mother of the patient reported that within a minute of receiving an injection of Nebido, her 29 year old son experienced an "allergic reaction" manifested by bronchospasm (considered life threatening). In follow-up information it was reported that his blood pressure dropped, and he collapsed. It was reported that he recovered from the bronchospasm. The case has not been medically confirmed.

DPAP comments:
This case meets the diagnostic criteria for anaphylaxis. Bronchospasm with hypotension with circulatory collapse were present. Unfortunately, there is little information on this case and there is no information on other symptoms or signs or on the emergency medical care that the patient received.

The sponsor provided opinions from three medical experts. The were (b) (4) a pulmonary and critical care medical specialist, (b) (4) a professor of musculoskeletal radiology, and (b) (4) a professor of internal medicine. Each concluded that the adverse events in question are likely to be related to POME and not likely to be due to anaphylaxis.

DPAP comments:
DPAP agrees that most of the adverse events are due to POME. Two cases meet diagnostic criteria for anaphylaxis, however, despite the limited information in the reports.

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/s/

Charles Lee
4/21/2008 12:56:55 PM
MEDICAL OFFICER

Badrul Chowdhury
4/21/2008 02:28:42 PM
MEDICAL OFFICER
I concur

Medical Officer's Memorandum
NDA Filing Review

Date Submitted: August 24, 2007
Date Received: August 26, 2007
Draft Memo Completed September 10, 2007
Revisions Completed October 10, 2007

Drug Product: Testosterone undecanoate IM injection (Nebido)
Dose: 750 mg (b) (4)
Sponsor: Indevus Pharmaceuticals, Inc.
Indication: Adult male hypogonadism

I. Summary:

Objective:

This review of the submitted data for safety, efficacy, and dosing recommendations is conducted to fulfill the regulatory requirement that a NDA be reviewed to determine its suitability for filing under 21 CFR 314. This memorandum will also serve as a basis for identifying potential review issues discovered during the filing review period to be communicated to sponsor as required by CDER manual MaPP 6010.x.

Conclusion:

Review of the clinical sections of the NDA submission did not identify any deficiencies that would constitute the basis for a Refuse-to File action. In the opinion of this reviewer, the information and data in the submitted application is adequate to permit a substantive clinical review.

II. Filing Review:

Drug Product:

Testosterone undecanoate is an ester of natural testosterone which is normally synthesized in males in the testes and in small amounts in the adrenal cortex. Until recently, when other routes of administration of testosterone (T) have become available for hormonal therapy (i.e, pellet implants, transdermal and buccal), testosterone esters in an oily depot as an ethanate or cypionate had been the most frequently used form of androgen replacement therapy (ART). Commonly prescribed doses of 200-250 mg of T administered every 2 weeks yielded supra-physiologic T levels for 2-3 days followed by a steady decline to sub-physiological levels by the time of the next scheduled dose. These fluctuations in T levels were often reflected by an increased frequency of reported adverse events (AE's). The advantages of an injectable form of ART include dose adjustability, absent skin irritation, and relatively low cost. The convenience of using longer acting T-esters is offset by precluding the rapid withdrawal of T in the advent of serious AE's. The initial use of an oral T-undecanoate, which partially avoided the first-pass effect of the liver, was associated with large fluctuations in serum T levels.

Currently, the use of an IM preparation of T-undecanoate (Nebido) administered every 6 weeks, has demonstrated a favorable PK profile and was first marketed in Finland in 2003, is currently approved for marketing in 72 countries, and is actively marketed in 36 countries.

This NDA submission includes data from a pivotal Phase 3 study report involving 110 subjects randomized into each of 2 treatment dose arms, and including assessment of data through the 5th injection.

Review Method:
This review is based on criteria proposed in FDA guidance for filing, reflecting FDA's interpretation of 21 CFR 314.101 (d)(3);

- Omission or incomplete submission of a required section of the NDA under 21 CFR 314.50.
- Failure to include evidence of effectiveness compatible with statutes and regulations.
- Omission of critical data, information or analyses necessary for evaluation of safety and effectiveness, or failure to provide adequate directions for product use.

Filing Review Results:

1. **Does the submission have omissions or incomplete presentations of required sections as listed in Table 1 on Page 5.**
   Answer: No. The NDA contains all the critical sections in sufficient detail to conduct an adequate review.

2. **Does the NDA clearly fail to include evidence of effectiveness compatible with the statute and regulations?**
   Answer: No. The sponsor has provided data from a single multi-center (69 sites) randomized, open-label, PK and long-term safety study of Nebido administered (IM 750 or 1000 mg) to hypogonadal men every12 weeks for up to13 injections
   The study appears to be adequate.

   The primary study objective is to evaluate the PK over the 12 week interval following the 4th injection.

   The secondary objectives are:
   · Evaluate the PK over the 12 week intervals following the first 3 injections in 20 subjects per treatment arm.
   · Compare serum levels of T, DHT, and SHBG to simultaneous levels of serum total T.
   · Evaluate the long-term safety in all subjects for up to 48 weeks.
   · Collect additional clinical measures (e.g.-BMI, body measurements, sexual activity, patient reported satisfaction).

3. Does the NDA omit critical data, information or analyses needed to evaluate safety and effectiveness or fail to provide adequate directions for product use?

Answer: No.

III. Summary of the Pivotal Study

Study # IP157-001 was a Phase-3, multi-center, randomized, study of PK and safety of of Nebido administered (IM 750 or 1000 mg) to hypogonadal men every 12 weeks for up to13 injections.

Objectives.

The primary study objective is to evaluate the PK over the 12 week interval following the 4th injection.

The secondary objectives are:

- Evaluate the PK over the 12 week intervals following the first 3 injections in 20 subjects per treatment arm.
- Compare serum levels of T, DHT, and SHBG to simultaneous levels of serum total T.
- Evaluate the long-term safety in all subjects for up to 48 weeks.
- Collect additional clinical measures (e.g.-BMI, body measurements, sexual activity, patient reported satisfaction).

Trial Design and Procedures.

Approximately 110 subjects were randomized into each of the two treatment dose arms, with stratification by screening serum T levels as T < 150 ng/dL, T ≥ 150 ng/dL and < 250 ng/dL and; T ≥ ng/dL and 300 ng/dL. Subjects were randomized between the 750 mg and 1000 mg administered every 12 weeks for up to 13 injections (3 years). This, Stage 1 of the study, included up to 48 weeks of treatment. Stage 2 included the remaining 8 injections and follow-up, and that was reported in a separate clinical study report.

The first 40 subjects underwent intensive PK assessments during the 1st and 4th injection intervals, while the remaining 180 subjects underwent PK assessments only during the 4th injection interval. Specifically:

1) In the first 20 subjects in each study arm after the 1st injection, at Day 0 (pre-injection), and at Day 4, 7,11,14, 21, 28, 42, 56, 70, and at the end of the 1st injection interval at Day 84, and;
2) In up to 110 subjects in each treatment arm after the 4th injection, at Day 0 (pre-injection), 4, 7, 11, 14, 21, 28, 42, 56, 70, and Day 84 of the 4th injection interval.

Demographics:

There were no significant differences in baseline characteristics in the 2 arms.
Age ranged from 1 subject less than 30 to 5 subjects ≥ 80; age 30-39 (4-8 %), age 40-49 (19-24 %), age 50-59 (31-40 %), age 60-69 (23-34 %), age 70-79 (3-8 %).
Race; White (84-91 %), Black (7-9%), Hispanic (3 % in each arm), Asian (0 and 2 %) and other (0 and 3 %).

Efficacy Considerations:

Hypothesis to be assessed for each treatment group were; does Nebido given every 12 weeks during the 4th injection interval provide adequate T replacement in hypogonadal men without resulting in excessively high serum total T levels.

Efficacy Results:

(b) (4)

[redacted]

Safety Considerations:

Measured free T, LH, FSH, SHBG, DHT, E2, PSA, AUA symptom score, DRE, clinical laboratory data, PE, vital signs, ECG, and AE monitoring.

Safety Results:

The average safety follow-up for both groups was over 300 days. There was a low overall incidence of TEAE's, and those reported in at least 1 % of subjects are seen in Table 1. Safety outcomes were generally the same for both groups.

Across all clinical studies there were 41 (13.6%) subjects in the 1000 mg group and 8 (6.7%) in the 750 mg group who experienced at least 1 SAE. Two SAEs were judged by the investigator as being possibly related to study drug (BPH in the 1000 mg arm, and injection-related cough/dyspnea in the 1000 mg arm.

Three deaths occurred during treatment with Nebido, none of which were judged by the investigator as being related to study treatment. One death was from complications of a stabbing wound (homicide). The second death was from injuries related to a motorcycle accident. The third death was from pneumonia secondary to thrombocytopenic sepsis in a 59 year old male with preexisting idiopathic thrombocytopenia who had been receiving 1000 mg of study drug every 12 weeks for 19 months.

In total, there were only 18 subjects (4.2 %) who discontinued due to an AE with either dose. The majority of events leading to discontinuation were judged by the investigator as being unrelated to study drug. Only 1 subject in the 750 mg arm and 4 subjects in the 1000 mg arm discontinued due to an AE judged by the investigator to be at least possibly related to study drug. These events included estradiol increase, red cell count increase, breast pain, and prostatitis.

Table: **TEAE's of Interest by MedDRA Prefered Terms**:

Table 1.

	Number of Patients (%)	
	Nebido 750 mg N = 120	**Nebido** 1000 mg N = 117
MedDRA Preferred Term		
Subjects with at least 1 TEAE	70 (58.3)	73 (62.4)
Subjects with at least 1 possibly related TEAE	22 (18.3)	25 (21.4)
Injection site pain	2 (1.7)	2 (1.7)
Estradiol increase	0	2 (1.7)
Cholesterol increase from baseline	0	2 (1.7)
BPH	1 (0.8)	2 (1.7)
Fatigue	3 (2.5)	1 (0.9)
Insomnia	3 (2.5)	1 (0.9)
Libido decrease	2 (1.7)	1 (0.9)
PSA increase	4 (3.3)	0
Hypercholesterolemia	2 (1.7)	0

Reviewer's Comments:

The study design for this pivotal trial was appropriate for both dose and indication. The reported clinical AE's were those expected for this class of drugs, and were generally safe and well tolerated.

Recommended Regulatory Action

1. This NDA is considered filable from a clinical perspective.
2. Sponsor should model testosterone C_{max} for doses beyond the 4th injection. C_{max} values outside of normal range for both the 750 mg and 1000 mg doses will be a review issue.
3. Sponsor should be made aware that the data for Nebido 750 mg will also be reviewed during this review cycle.

Harry Handelsman, DO
Medical Officer
Division of Reproductive and Urologic Products

Suresh Kaul, MD, MPH
Acting Medical Team Leader

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Suresh Kaul
10/25/2007 09:50:33 AM
MEDICAL OFFICER