CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Memo

Date	February 28, 2013
From	Mark S. Hirsch, M.D.
Subject	Cross-Discipline Team Leader Memo
NDA/BLA #	22-219
Applicant	Endo Pharmaceuticals
Date of Submission	August 29, 2013
PDUFA Goal Date	February 28, 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:	***Approval***

1. Executive Summary

1.1 Brief 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.

Multiple preparations of testosterone have been approved by the Agency for replacement therapy in hypogonadal men. Each preparation has its 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 13-26 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. The AVEED 750 mg Loading regimen (the to-be-marketed regimen) was shown to provide an acceptable level of testosterone replacement. Results of secondary efficacy endpoints correlated with the primary endpoints.

In regard to safety, the adverse reactions associated with intramuscular testosterone undecanoate are consistent with those of all testosterone replacement therapies, except for the rare occurrence of severe post-injection reactions. These events were reported to occur either during or soon after the injection. The manifestations of the post-injection reactions have included: cough, urge to cough, dyspnea, flushing, throat-related symptoms (such as tickling in the throat or sensation of throat tightening), dizziness, and in rare cases, urticaria, syncope,

difficulty breathing, and instability in vital signs. 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.

The exact mechanism for these reactions 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.

Since the signs and symptoms overlap, it is often not possible to differentiate serious POME from anaphylaxis. Some of the patients who were experiencing a severe post-injection reaction received treatment as if they were experiencing an anaphylactic reaction, including treatment with epinephrine, steroids, antihistamines, and oxygen.

In 19 clinical trials of intramuscular testosterone, at various doses and dose regimens, in approximately 3600 subjects, there were 9 reported events of POME and 2 reports of anaphylaxis. This translates to an overall POME incidence rate of 4.6 cases per 10,000 injections, or 21.3 cases per 10,000 person-years; and an overall anaphylaxis incidence rate of 0.9 cases per 10,000 injections, or 4.7 cases per 10,000 person-years. In approximately 8 years of postmarketing experience with intramuscular testosterone undecanoate outside the United States, mostly at a dose of 1000 mg (4 mL) per injection, we identified 137 cases of severe POME or anaphylaxis. An additional 19 months of postmarketing experience showed no apparent change in the severity or frequency of reports. Although some of the events have been reported as serious, with hospitalization or emergency room visits, no case has led to death or permanent disability.

While there have also been rare reports of severe POME and anaphylaxis for testosterone enanthate and testosterone cypionate injections, the totality of reports in FDA's voluntary adverse event reporting system (FAERS) is 33 cases over a 44 year period for all approved T injections combined.

Based on the occurrence of rare but serious POME and anaphylaxis events for intramuscular testosterone enanthate, we required the Sponsor to submit a comprehensive Risk Evaluation and Mitigation Strategy (REMS) with Elements to Assure Safe Use (ETASU). We also required the product labeling to include a Boxed Warning as well as a restricted new indication. In order to receive the product, health care providers will need to be specially certified. Product will only be distributed to certified heath care settings and certified health care providers. Health care providers will be trained in proper administration of the product. Health care providers will attest to their awareness of the risk of serious POME and anaphylaxis, their ability to manage the rare potential severe post-injection event, and their willingness to keep the patient under observation in the health care facility for 30 minutes. Patients will be thoroughly informed of the potential risk of serious POME and anaphylaxis. The Sponsor will manage this program on a continuous basis and will conduct periodic assessments to assure its effective functioning. The Sponsor will be vigilant to reports of

serious POME and anaphylaxis, will investigate them thoroughly, and will report them promptly.

I am convinced that the new Risk Evaluation and Mitigation Strategy (REMS) with Elements to Assure Safe Use (ETASU) mitigates the potential adverse consequences of the rare serious POME and anaphylaxis reactions such that the benefit of Aveed now outweighs its potential risks in the restricted target population. I recommend that this application be **Approved**.

1.2 Sources of Clinical Data

1.2.1 Clinical Trial Data

The clinical trials of testosterone undecanoate injection consisted of a single U.S. Phase 3 Hypogonadism study (Study IP157-001), six European Phase 1, Phase 2 and Phase 3 Hyypogonadism studies, 6 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=447)

- 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
- 303923, Italy, 4-6 doses, n=40

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

1.2.2 Postmarketing Safety Update Reports

Additional clinical data for this application come from voluntarily submitted adverse event reports from 9.5 years of worldwide postmarketing experience with testosterone undecanoate injection outside of the United States.

The original NDA and three Complete Responses have included a total of eleven (11) Bayer/Schering Periodic Safety Update Reports (PSURs) from approximately 9 years of worldwide postmarketing use (specifically from November 25, 2003 through November 24, 2012), as well as an Addendum covering the period until May 24, 2013. Bayer-Schering is the Sponsor of TU outside the US.

1.2.3 Risk Evaluation and Mitigation Strategy (REMS)

The current submission contains an extensive REMS, which includes Elements to Assure Safe Use (ETASU) and a number of documents related to the structure and functioning of the Aveed REMS Program, including: the REMS Document, REMS Supporting Document, Health Care Provider Enrollment Form, Health Care Setting Enrollment Form, Health Care Provider Education Program, Health Care Setting Education Program, Health Care Provider Webpage, Patient Counseling Tool and Aveed REMS Program Introduction Piece.

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 clinical trial patients in the original NDA, such events were reported in 66 patients in the postmarketing period outside of the United States. In the Approvable letter, the Sponsor was asked to submit additional

information to further assess and to mitigate the risk of these 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 ***Chemistry*** deficiency came from Drug Master File (DMF) # (b) (4) The DMF 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 DMF deficiencies must be satisfactorily resolved prior to application 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 submission, 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 proposed an incidence of 0% in clinical trials. The Division identified several other cases that may have reflected POME or anaphylaxis, although the data for those cases was too sparse to allow for definitive conclusions. The Division further 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 events.

In addition, the Sponsor submitted a Risk Evaluation and Mitigation Strategy (REMS). The proposed 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, as well as a risk management plan, the Division remained uncomfortable with the occurrence of severe post-injection reactions.

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

Therefore, on December 2, 2009, the application received a **Complete Response** 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. In addition, 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.

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 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. At that time, the Division recommended that the Sponsor submit another CR and the application would likely be discussed at an Advisory Committee Meeting.

On November 29, 2012, the **second Complete Response** was submitted. The submission contained additional information intended to better quantify the rate of serious POME and anaphylaxis cases as well as a revised REMS. On April 18, 2013, an AC Meeting was held to discuss the application. The AC was split as to the safety of the product (9 yes; 9 no) but was fairly unanimous (17:1) that the proposed risk mitigation strategy and product labeling needed improvement. Therefore, on May 29, 2013, the application again received a Complete Response action based upon inadequate risk mitigation. The Complete Response letter outlined in detail a REMS with ETASU that would be appropriate to ensure safe use of Aveed and also informed the Sponsor of the need for a restricted indication.

On August 29, 2013, the third Complete Response was submitted.

2.3 PRIMARY MEDICAL REVIEWER'S RECOMMENDATION FOR APPROVABILITY

The primary reviewer, Guodong Fang, stated in his final review dated February 21, 2014:

> *"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.*

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

"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."

CDTL Comment: I concur with Dr. Fang's overall conclusion and recommendation.

3. CMC/Device

For this cycle, in their final review, dated February 3, 2014, the CMC review team (Yichun Sun and Moo Jhong Rhee) concluded that the NDA is not recommended for Approval until the Office of Compliance makes an overall Acceptable recommendation. The CMC review team required the outcomes of an ongoing inspection of the drug substance manufacturing site (b) (4)

On February 24, 2014, the Office of Compliance entered an overall Acceptable recommendation to the EES system.

On February 25, 2014, in a final review, the CMC review team noted that the Office of Compliance provided an overall "Acceptable" recommendation. Therefore, the application is now recommended for Approval from the ONDQA perspective.

Otherwise, the CMC review team notes that the for this re-submission, the two DMFs ((b) (4) and (b) (4)) were adequate as of August 5, 2013, and there have been no further amendments for the DMFs, and therefore the two DMFs are still deemed adequate. In addition, the submitted information on labels and labeling are satisfactory.

4. Nonclinical Pharmacology/Toxicology

For this review cycle, in their final review, dated October 15, 2013, the nonclinical review team (Eric Andreason and Lynnda Reid) concluded that the Sponsor's nonclinical program, references from the literature, and general knowledge of testosterone provided reasonable assurance of the safety of testosterone undecanoate (TU) in hypogonadal men. In their review, the nonclinical review team provided recommendations for labeling. The current re-submission contained no new nonclinical information.

Previously, the nonclinical reviewers noted that the Sponsor had conducted a local toxicity that demonstrated only non-specific tissue injury at the site of injection.

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 appears to have played a role in at least one case of severe post-injection reactions reported in the postmarketing period outside the United States. In that 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.

5. Clinical Pharmacology/Biopharmaceutics

For this review cycle, in their final review, dated February 20, 2014, the Clinical Pharmacology review team (Hyunjin Kim and Myong-Jin Kim) found the application acceptable for approval provided that an agreement was reached on all outstanding labeling issues. All labeling issues have been resolved through labeling discussions with Sponsor. There were no new clinical pharmacology data submitted in this resubmission.

In regard to prior Clinical Pharmacology review issues:

Excessive testosterone exposure was noted in a single patient who weighed <65 kg. This led to a potential concern that the increased exposure may be demonstrated in patients with lower body weight/lower body mass index. To resolve this issue, the ClinPharm review team considered several options for labeling, including a possible new Warning/Precaution. Ultimately, it was decided to create a new section within Section 12.3 (Pharmacokinetics) entitled "*Effect of Body Weight and Body Mass Index (BMI)*". This new section describes in detail the effect of body weight on exposure.

Testosterone undecanoate (TU) concentrations were observed in the blood in patients administered Aveed. 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, Section 12.3 (Pharmacokinetics) describes the maximum TU concentrations observed in patients on Day 4 after dosing as well as the almost undetectable TU concentrations observed on Day 42 after dosing.

6. Clinical Microbiology

On April 29, 2009, the Clinical Microbiology review team (Vinayak Pawar and David Hussong) recommended approval of the NDA. Upon review of amendment 9-11 to DMF

(b) (4) (referred for the drug product), 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. For this review cycle, there was no new Micro information and no new Micro review.

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), which is the to-be-marketed dose regimen, 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 IP157-001.

(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. However, data from Study IP157-001 Part A was used as the source of first-dose PK 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 cm^3 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 3rd injection interval. This is the currently acceptable primary efficacy endpoint for the proposed indication.

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 Sponsor's 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 C_{avg} 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, $\leq$ 1500 ng/dL in $\geq$ 85% of patients, 1800 – 2500 ng/dL in $\leq$ 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

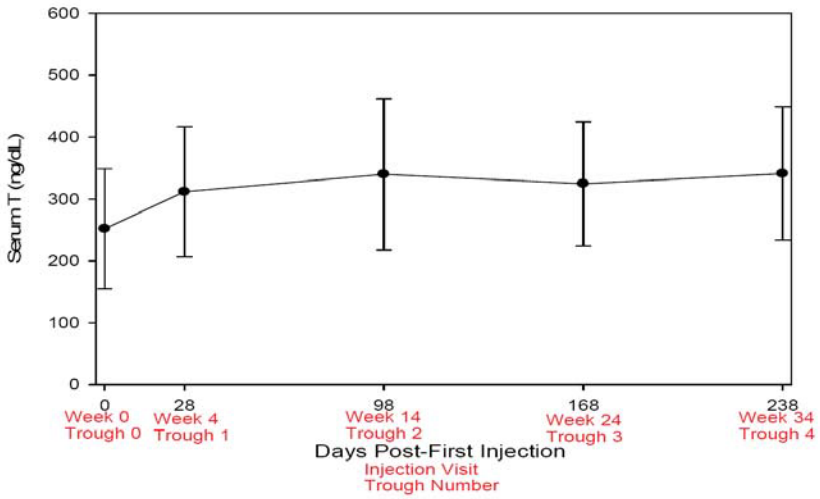
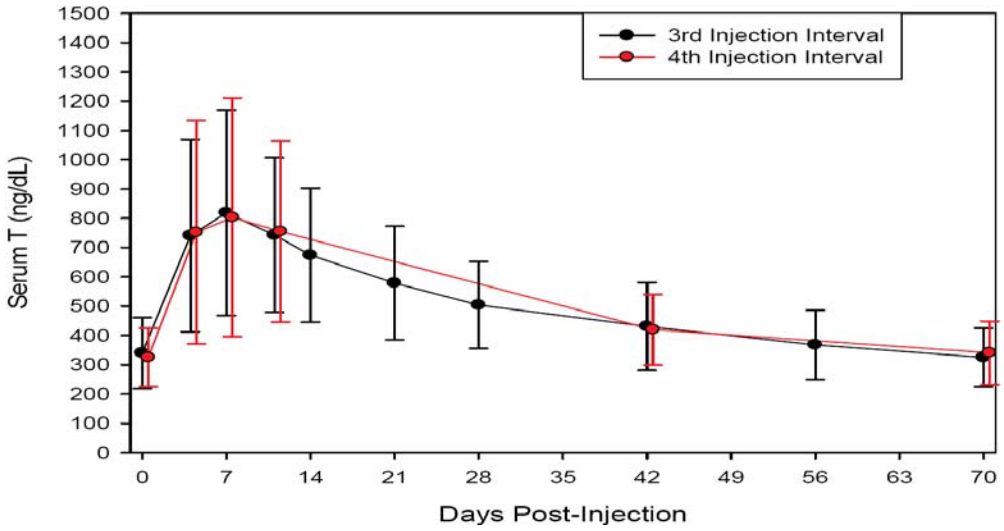


Figure 2: Comparison of serum total T concentrations between the 3rd and 4th injection intervals – Steady state PK population, Study IP157-001 Part C



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

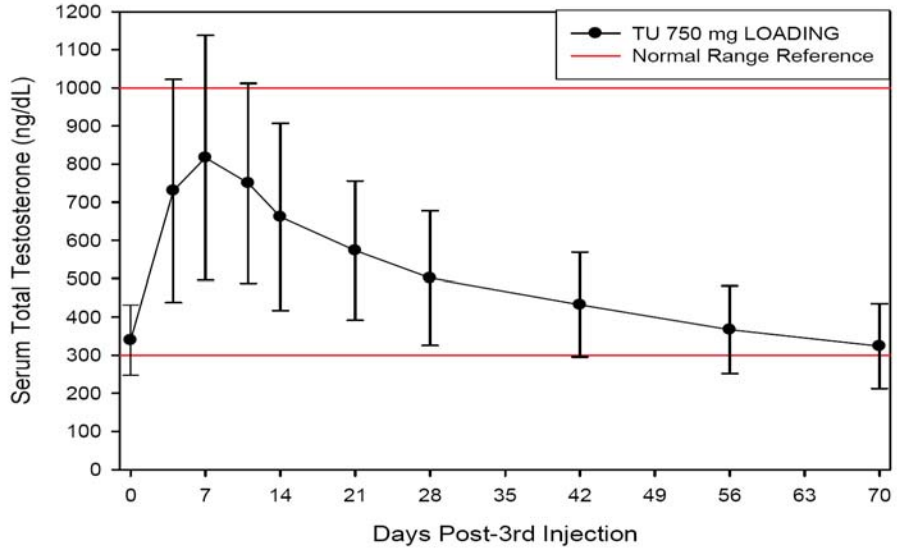
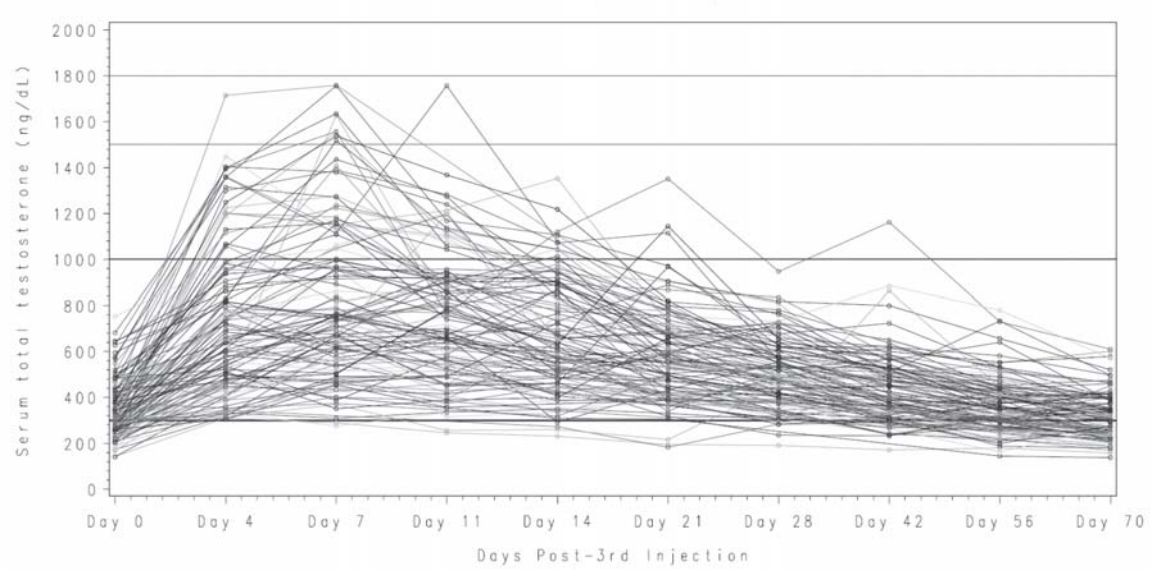


Figure 4: Composite of individual serum total T concentration following the 3rd injection of the TU 750 mg LOADING regimen – PK population, Study IP157-001 Part C



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} ≥ 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

For this cycle, in his final review dated February 4, 2014, the Biometrics Team Leader (Mahboob Sobhan) stated that no new efficacy data was submitted in this resubmission. Therefore, no statistical input was necessary.

In prior reviews, the Biometrics Team Leader (Mahboob Sobhan) had the following conclusions:

> For the review of the original NDA submission (review dated June 24, 2008): "*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.*"
>
> For the first Complete Response submission (review dated July 21, 2009): "*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.*"
>
> For the second Complete Response: No new statistical analyses were conducted as part of the review of the 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

This Safety Introduction provides an overview of the contents and safety findings from the original NDA and each of the three subsequent Complete Response submissions.

Contents and Safety Findings From the Original NDA

The original NDA submission contained safety data from 6 studies, as follows:

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 to-be-marketed dosage 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 more recent 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 urge to cough with dyspnea, and a coughing fit, 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-type 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 clinical 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 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), 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.

The Sponsor detected no additional cases amongst the 2125 additional 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 potential 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).

In summary, whether the clinical trials show 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 for the first Complete Response.

Contents and Safety Findings from the Second Complete Response

In the second Complete Response, the Sponsor provided safety data from one additional study, bringing the total to 18 clinical studies. 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. FDA and Endo had agreed in advance on terms to be used in this search. According to the analysis conducted 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 identified a total of 268 post-injection reaction cases, including 223 cases of POME and 45 cases of anaphylaxis. In compliance with FDA's request, the Sponsor included individual CIOMS reports in the second CR submission for all postmarketing adverse events of potential interest (e.g., POME and anaphylaxis).

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.

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

1. In regard to the incidence of post-injection reactions in clinical trials, in an analysis of all cases adjudicated as POME or anaphylaxis among 3,556 subjects in 18 clinical trials,
   a. 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. Thus, for both doses combined, there were 9 POME cases among 3556 subjects, which translates to 4.6 cases per 10,000 injections, or 21.3 cases per 10,000 person-years.

   b. 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. Thus, for both doses combined, the rate of anaphylaxis is 0.9 cases per 10,000 injections, or 4.7 cases per 10,000 person-years.

2. In regard to the postmarketing Safety Updates,

a. FDA reviewed case narratives for 330 potential cases of anaphylaxis for the entire postmarketing experience for testosterone undecanoate. From these, we identified a total of 53 and 76 cases of anaphylaxis, using strict and less restrictive anaphylaxis identification criteria, respectively.

b. FDA reviewed case narratives for 533 potential cases of POME. We identified a total of 170-191 cases of POME cases (the range is due to overlap with anaphylaxis cases identified using strict or less strict anaphylaxis identification criteria and thus, greater or fewer POME cases are tallied). Of these, we adjudicated 55-76 cases as severe POME.

Based on this safety information, as well as the advice provided to FDA by a joint meeting of the Reproductive Health and Risk Management Advisory Committees on April 18, 2013, DBRUP issued another CR action, this time requiring submission of a Risk Evaluation and Mitigation Strategy (REMS) focused on mitigating the risks associated with serious POME and anaphylaxis.

Contents and Safety Findings from the Third Complete Response

In this third Complete Response, the Sponsor submitted a detailed and extensive Risk Evaluation and Mitigation Strategy (REMS) including Elements to Assure Safe Use (ETASU). The REMS would assure that Aveed was only administered by certified prescribers who were aware of the risks of serious POME and anaphylaxis, who would share that risk information with potential patients, and who would observe the patients in the healthcare setting for at least 30 minutes after each injection.

In regard to new safety information, the third Complete Response included one, small, postmarketing clinical study conducted in 2004 in which 40 subjects were administered intramuscular TU and the progestin noresthisterone enanthate for the purposes of investigating this combination as a potential male contraceptive. In addition, the submission also included a Safety Update for another 19 months of worldwide postmarketing experience with intramuscular testosterone undecanoate.

The safety information in this submission did not yield any qualitatively new information. The data is discussed in more detail in the sections that follow.

> *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 described in Section 8.1.3 (Postmarketing Safety Findings).*

8.1.1 Deaths and Serious Adverse Events

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

Two subjects died in Study IP157 Part C. Subject 050-7010 was a 52 year old with a history of diabetes mellitus, hypertension and cardiovascular disease who experienced cardiac arrest 65 days after his 6th dose of study drug. The investigator considered the relationship to drug as "remotely possible". Subject 078-7012 was a 45 year old male with a history of hypertension and erectile dysfunction who experienced a myocardial infarction approximately 41 days after his 4th dose of study drug. The investigator considered the relationship to study drug as "definitely not related".

In the original NDA, a total of 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.

In the original NDA, 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 the adverse events leading to discontinuation, all but myocardial infarction were judged by the investigator to be at least possibly related to study drug.

In the second Complete Response, the Sponsor updated the safety results from Study IP157-001 Parts C, including Part C2 (an additional 40 subjects). With continued dosing out to 9 injections of TU, a total of 22 subjects (14%) reported an SAE. The only SAEs, irrespective of the investigator's assessment of causality, reported by more than 1 subject were prostate cancer (in 3 subjects), spinal column stenosis (in 3 subjects), intervertebral disc disorder (in 2 subjects), and myocardial infarction (in 2 subjects). In addition, with up to 9 doses administered, a total of 16 subjects (10.5%) discontinued treatment due to AEs, irrespective of the investigator's assessment of causality. The only AEs leading to study discontinuation reported by more than 1 subject were: prostate cancer (in 3 subjects); and hematocrit increased, mood swings, anxiety, and myocardial infarction (in 2 subjects each).

Thus, the SAEs and AEs leading to discontinuation in Part C were qualitatively consistent between the original NDA and the second Complete Response, despite a longer duration of dosing.

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 were two deaths reported in the Part A study. Subject 070-4006 died as a result of a homicide (by stabbing during an altercation). Subject 078-4162 was a 68 year old male with a history of COPD, hypertension, coronary artery disease status-post triple coronary artery bypass graft surgery, hyperlipidemia, erectile dysfunction, and left bundle branch block who died due to a cerebrovascular accident 71 days after his 8th dose of study medication. The investigator consider the event to be "definitely not related" to study medication.

In the original NDA, 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.

In the original NDA, 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.

In the second Complete Response, the Sponsor updated the safety results from Study IP157-001 Part A, including both Stages 1 and 2. With continued dosing out to 13 injections of TU, a total of 37 subjects (15%) in both the 750 mg and 1000 mg dose groups reported an SAE. In the pooled Part A study population (750 mg and 1000 mg), the only SAEs reported by more than two patients were: coronary artery disease (in 4 patients, 1.7%); and atrial fibrillation, CVA, and prostatitis (in 3 patients each, 1.3%). In the 750 mg dose group only, only one SAE was reported by more than 1 subject: atrial fibrillation (in 2 subjects, 1.7%). In addition, with

up to 13 doses administered, in the pooled Part A study population (750 mg and 1000 mg), a total of 22 subjects (9.3%) discontinued treatment due to AEs. The only AEs leading to study discontinuation reported by more than 1 subject were: increased PSA (in 5 subjects, 4.1%); prostatic intraepithelial neoplasia (in 3 subjects, 2.5%), and increased hemoglobin (in 2 subjects, 1.7%). In the 750 mg dose group only, only one SAE was reported by more than 1 subject: atrial fibrillation (in 2 subjects, 1.7%).

Thus, the SAEs and AEs leading to discontinuation in Part A were qualitatively consistent between the original NDA and the second Complete Response, despite a longer duration of dosing.

8.1.2 Other Adverse Events

Overall Adverse Events

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

In the Original NDA

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

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.

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%).

In the Complete Response (with treatment out to 9 doses):

The incidences of commonly reported adverse events in Part C, reported by >5% of subjects, with treatment out to 9 doses, without regard to attributed causality, included: acne (6.1%), fatigue (7.7%), injection site pain (5.4%), insomnia (6.9%), PSA increased (7.7%), prostatitis (7.7%), nasopharyngitis (5.4%), sinusitis (6.9%), arthralgia (6.1%), and back pain (5.4%).

The incidences of overall adverse events in Part C as judged by the investigator to be at least possibly related to treatment, with treatment out to 9 doses, reported by at least 2% of subjects (n=130), included: acne (6.1%), injection site pain (5.4%), PSA increased (5.4%), fatigue (4.6%), estradiol increased (3%), irritability (2.3%), hematocrit increased (2.3%), hemoglobin increased (2.3%), insomnia (2.3%), and mood swings (2.3%).

Thus, the quality and general incidence of overall adverse events in Part C were consistent between the original NDA and the second Complete Response.

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

In the Original NDA

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)

In the Complete Response (with treatment out to 13 doses):

In Part A, for the combined 750mg and 100 mg dose groups, the most commonly reported adverse events (>5% in either dose group – with overall incidences shown in parenthesis next to the AE term), regardless of the investigator's judgment on causality, were: fatigue (6.3%), bronchitis (4.2%), upper respiratory tract infection (6.8%), nasopharyngitis (5.5%), back pain (5.5%), PSA increased (5.5%), urinary tract infection (4.6%), hypertension (7.6%), sinusitis (7.2%), insomnia (5.1%), nausea (3.8%), diarrhea (3.8%), pain in extremity (4.6%), headache (4.2%), depression (4.2%), injection site pain (4.6%), arthralgia (4.2%), musculoskeletal pain (4.2%), anxiety (3.0%), constipation (3.0%), prostatitis (5.1%), dysuria (3.4%), erectile dysfunction (3.8%), and sleep apnea syndrome (3.8%).

Thus, the quality and general incidence of overall adverse events in Part A were consistent between the original NDA and the second Complete Response.

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

In the Original NDA, "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)

In the second Complete Response, the adverse events of interest were anaphylaxis, POME and injection site reactions. No case of anaphylaxis and 1 case of POME was reported in Part C. Injection site pain was reported by 7 subjects (5.4%). Injection site erythema was reported by

2 subjects (1.5%) and injection site pruritis, injection site swelling, and peripheral edema were reported by 1 subject each.

In the original NDA, "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)

In the second Complete Response, the adverse events of interest were anaphylaxis, POME and injection site reactions. No case of anaphylaxis and no case of POME was reported in Part A. Injection site pain was reported by 11 subjects overall (4.6%). Injection site swelling was reported by 3 subjects (2.6%).

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 conducted outside the US (Study 306605), 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 this postmarketing information is important to an understanding of the potential risks 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 results were pooled with the results from the U.S. Study IP157-001, along with the results from the 5 European Hypogonadism studies, the total number of trials and clinical trial subjects available for analysis is 18 trials and 3,556 subjects, respectively.

As part of the review of the March 2009, first Complete Response, the Clinical review team assessed all of these studies (except for Study 14853, which was submitted as part of the second 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 review of the second Complete Response, 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 second 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. For both doses combined, there were 9 total adjudicated cases of POME, which translates to an incidence rate for POME of 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 both doses combined, there were 2 total cases of anaphylaxis, which translates to an incidence rate for anaphylaxis of 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.

There are no additional data in the third Complete Response that contribute meaningfully to the FDA's prior analysis of the incidences POME and anaphylaxis.

8.1.3.2 Post-Injection Reactions from Voluntary Reports

The 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, 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 rare cases, syncope, apnea, and cardiovascular collapse have been reported, however, there have been no reported deaths. 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, may act as 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. DPARP 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 second Complete Response. 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 all 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, 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 conducting 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 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 final Safety Update to the second Complete Response.

   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 as the first assessment, 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 that intramuscular testosterone undecanoate has been associated with infrequent reports of severe post-injection reaction, which reflect both serious POME and anaphylaxis. There has been no reported case of death or permanent disability. However, the serious POME and anaphylaxis events have shown some severe signs and symptoms including severe cough, dyspnea, throat-related symptoms, and in rare cases, syncope, respiratory distress and instability in vital signs. Patients have been treated as if for

anaphylaxis. Some patients were hospitalized or were transported to the emergency department. Severe post-injection reactions are acute events that occur during or soon after injection. 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 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)

In my opinion, the Risk Evaluation and Mitigation Strategy (REMS) with Elements to Assure Safe Use (ETASU) is appropriately constructed and well-focused on the major potential risk for this product; that is, the potential for rare events of serious POME and anaphylaxis. I agree with Dr. Fang that the REMS serves to assure safe use by bringing the main safety concern under control.

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" also 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, including testosterone injections. 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 increase the number of adverse events. It was also noted that the Agency was persuasive in communicating their concerns.

The AC members did note that if the drug product was approved by the Agency, the FDA should consider including a Black Box warning as part of the labeling and a detailed patient package insert while continuing to monitor for safety and follow up as appropriate.

For Question #2, all but one member voted "No". There was a general consensus to strengthen the REMS proposal from the Sponsor (which was 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. The FDA might consider placing limitations on the health care sites where the product 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.

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 the health care provider and patient education is assessed on a periodic basis to assure it is effective.

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 and the REMS materials was requested and completed by OPDP.

In his final consult report for labeling, dated February 12, 2014, Trung-Hieu (Brian) Tran provided comments and recommendation on various sections of the Package Insert (PI). Comments on the Medication Guide were provided under separate cover. Each of the OPDP comments on the PI and Medication Guide were considered by 1) the Clinical review team, 2) the discipline relevant to the appropriate section, and 3) the DBRUP management. The team, including OPDP, discussed all aspects of labeling at a series of internal labeling meetings. Where the team agreed that action was indicated, (e.g., in Section 12.1, *Mechanism of Action*), the OPDP comment was acted upon and resolved through labeling discussions with Sponsor.

In his final consult report for REMS documents, dated February 19, 2014, Trung-Hieu (Brian) Tran provided comments and recommendations on the various REMS-related documents. Each of the OPDP comments on the REMS-related materials were considered by 1) the Clinical review team, 2) the Division of Risk Management (DRISK), and 3) the DBRUP management. The team, including OPDP, discussed all aspects of the REMS documents at a series of internal meetings. Where the team agreed that action was indicated, (e.g., (b) (4)), the OPDP comment was acted upon and resolved through discussions with 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)

For this review cycle, DEPI was not asked to provide consultation.

In the previous review cycle, Cynthia Kornegay and Rita Ouellet-Hellstrom of DEPI provided consultative support. 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. Details of this DEPI consult are provided in other sections of this memo, and will not be repeated here.

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

For this review cycle, DPV was not asked to provide consultation.

In the previous review cycle, Teresa Rubio and Adrienne Rothstein of DPV provided consultative support. 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)

For this review cycle, DRISK provided extensive consultative support on the proposed Risk Evaluation and Mitigation Strategy (REMS) with Elements to Assure Safe Use (ETASU). Suzanne Robttom, Mary Willy, Cynthia LaCivita and Claudia Manzo of DRISK provided 4 reviews of REMS-related documents (on January 31, 2014, February 5, 2014, February 11, 2014 and February 22, 2014). The REMS-related documents and items for FDA review are listed in this section, along with some of the DRISK comments.

The REMS-related documents included:

- REMS Document
- REMS Supporting Document
- Health Care Provider Enrollment Form
- Health Care Setting Enrollment Form
- Health Care Provider Education Program
- Health Care Setting Education Program
- Health Care Provider Webpage
- Patient Counseling Tool
- Aveed REMS Program Introduction Piece

DRISK concluded that the proposed REMS, in principle, was consistent with the REMS outlined in the Division's, May 29, 2013, CR action letter. However, DRISK had a significant number of recommendations for revisions and improvements to the Aveed REMS Program, including:

- The Sponsor was asked to clarify how they will ensure that Aveed is not shipped until they know that the prescriber and HCP setting are certified.
- The Sponsor was asked to create a single, patient-directed educational piece focused on the risks of serious POME and anaphylaxis (e.g., the Patient Counseling Tool).
- The Sponsor was instructed to delete the Medication Guide from the REMS. It will be a part of labeling.

- The Sponsor was instructed to remove all proposed elements of the Communication Plan and replace them with a single REMS Program Introduction Piece.
- The Sponsor was instructed to make a large number of revisions (b) (4) for clarity and brevity.
- The Sponsor was asked to submit a REMS Program website.
- The Sponsor was told to update the REMS Supporting document to be consistent with all revisions to the REMS document and other REMS-related forms.

DRISK also provided significant input on the Sponsor's proposed REMS Assessment Plan.

Finally, DRISK engaged in iterative communications with DBRUP and Sponsor until all issues on REMS-related documents and other items were resolved.

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

For this review cycle, DMEPA provided consultation on the container/carton and Package Insert labeling from the medications errors perspective; as well as on the tradename.

In their final review dated February 11, 2014, Justine Harris and Lisa Khosla stated that the container and carton labeling had been revised appropriately and was acceptable.

Also, in a final review dated February 11, 2014, Justine Harris and Lisa Khosla provided recommendation for edits to Section 2 (Dosage and Administration) of the Package Insert. DMEPA's recommendations for the PI were conveyed to Sponsor and all were accepted.

Lastly, in a final review dated February 14, 2014, Justine Harris and Lisa Khosla stated that in a review dated March 14, 2013 (OSE Review #2013-2995), DMEPA found the proposed tradename, Aveed, acceptable. In that review, DMEPA stated that the proprietary name must be re-reviewed within 90 days of the anticipated approval date. DMEPA no longer re-reviews proprietary names within 90 days of approval, unless there is a change in the product characteristics. Since there has been no change to the characteristics of Aveed, the proposed tradename remains acceptable, with no objections from DMEPA.

Office of Medical Policy / Division of Medical Policy Programs (DMPP)

In their final review dated February 4, 2014, Trung-Hieu (Brian) Tran, Shawna Hutchins and Melissa Hulett provided recommendations for edits to the proposed Medication Guide. These recommendations were intended to

- improve consistency between the PI and the MedGuide,
- improve readability and reduce redundancy,
- ensure that MedGuide meets the criteria in FDA's Guidance on Consumner Medication Information
- remove promotional language.

DMPP's recommendations were conveyed to the Sponsor and all DMPP-related issues in the MedGuide were resolved through iterative labeling correspondences with Sponsor.

Study Endpoints and Labeling Development Team (SEALD)

In their final review, dated February 10, 2014, Abimbola Adebowale and Eric Brodsky provide 5 recommendations for revision to the label so that it is in compliance with labeling regulations. These 5 items were revised accordingly.

Office of Compliance

For this review cycle, Office of Compliance issued an Acceptable recommendation in EES on January 24, 2014.

Controlled Substances Staff (CSS)

DBRUP requested a consult from CSS to verify the scheduling status of Aveed (Schedule III of the Controlled Substances Act) and to assess the labeling as it applies to Section 9, Abuse and Dependence.

For this review cycle, Alicja Lerner and Michael Klein provided three consult reports, including an original consult (final dated January 24, 2014), and two Addenda (finals dated February 4, 2014 and February 18, 2014).

In their original consult, CSS provided recommendations for extensive changes to Section 9 (Drug Abuse and Dependence). CSS's second consult provided only one change (addition of one word, "*homicides*") to their original recommendation. Subsequent to receiving these two consult reports, DBRUP arranged an internal meeting with CSS and other relevant review disciplines, including DEPI and DPV, to discuss a path forward for the CSS recommendations. It was decided by the team, including CSS, that the proposed labeling changes require additional review and consideration by DBRUP and by OSE before they could be enacted for Aveed or for the drug class. Therefore, in their third and final consult report, CSS stated that "*…CSS's recommended labeling changes will not be instituted at this time. CSS will collaborate with OND and OSE on the assessment of the evidence outside the review of Aveed*

application, and final regulatory decision(s) will most likely apply to all testosterone products, including Aveed."

Division of Pulmonary, Allergy and Rheumatology Products (DPARP)

For this review cycle, DPARP was not asked to provide consultation.

However, DPARP provided consultative support to DBRUP on each of the previous 3 review cycles in regard to the events of post-injection pulmonary oil microembolism (POME) and anaphylaxis.

Rather than describing each DPARP consultation, this section provides information only from the most recent DPARP consultation. The reader may refer to previous CDTL memos for a summary of DPARP's two prior consults.

For the third review cycle (of the second Complete Response), and as part of FDA's preparation for the April 18, 2013, Advisory Committee meeting, DPARP was again asked to adjudicate potential cases of POME and anaphylaxis in the postmarketing period.

As discussed earlier in this memo (Section 8.1.3.2), and as documented in their final consult dated March 22, 2013, 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 used were less restrictive (NAIAID/FAAN criteria #1 *or* #2), then DPARP identified a total of 68 cases. Additional anaphylaxis cases were identified in the Sponsor's final Safety Update to the second Complete Response, 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 Safety Update to the second Complete Response.

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 in intensity.

- The severity of the POME episodes are due, at least in part, to decreased cardiac output as a result of acute pulmonary hypertension (due to oil microembolism) resulting in dyspnea, dizziness and rarely, collapse.
- It is likely that POME also results in pulmonary inflammatory changes with a similar pathology to that observed in patients and in animal 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, as well as during the review of the second and third Complete Responses.

During this review cycle, the Sponsor and FDA worked collaboratively to generate a label that accurately described the efficacy and safety results for Aveed and that would allow for safe and effective use of Aveed. The highlights of the label include: a Boxed Warning for serious POME and anaphylaxis and a restricted Indication. The Warning describes the existence of the Aveed REMS program, the potential for serious POME and anaphylaxis, and the need to observe the patient in the healthcare setting for 30 minutes after each injection. The restricted indication is intended to narrow the target population to patients in whom the benefits of Aveed (effective testosterone replacement using the 10-week dosing interval) outweigh the potential risks of serious POME and anaphylaxis.

13. Recommendations/Risk Benefit Assessment

13.1 Recommended Regulatory Action

I recommend that the NDA be approved at this time. I am convinced that the new Risk Evaluation and Mitigation Strategy (REMS) with Elements to Assure Safe Use (ETASU) mitigates the potential adverse consequences of the rare serious POME and anaphylaxis reactions such that the benefit of Aveed now outweighs its potential risks in the restricted target population. In order to receive the product, health care providers will need to be specially certified. Product will only come from certified distributors. Health care providers will be trained in proper administration of the product. Health care providers will attest to their awareness of the risk of serious POME and anaphylaxis, their ability to manage the rare potential severe post-injection event, and their willingness to keep the patient under observation in the health care facility for 30 minutes. Patients will be thoroughly informed of the potential risk of serious POME and anaphylaxis.

13.2 Risk Benefit Assessment

Aveed confers the expected benefit for a testosterone replacement therapy (TRT), with the need for fewer injections per year compared to other injectable TRT products. In a subgroup of patients, especially those who currently receive bimonthly IM injections, Aveed offers an option to meet their testosterone replacement needs with 6 or 7 injections per year.

The risks of Aveed include the usual androgen-related side effects plus the potential for rare serious POME and anaphylaxis reactions after the injection. In 19 clinical trials of intramuscular testosterone, at various doses and dose regimens, in approximately 3600 subjects, there were 9 reported events of POME and 2 of anaphylaxis. In approximately 8 years of postmarketing experience with intramuscular testosterone undecanoate outside the United States, mostly at a dose of 1000 mg (4 mL) per injection, we identified 137 cases of severe POME or anaphylaxis. In an additional 19 months of postmarketing experience, the information on POME and anaphylaxis remains qualitatively the same with no apparent increase in reporting rates for these events. Although some of the events have been reported as serious, with hospitalization or emergency room visit in some cases, no case has led to death or permanent disability.

With the new comprehensive Risk Evaluation and Mitigation Strategy (REMS) with Elements to Assure Safe Use (ETASU) in place to mitigate the potential adverse consequences of the rare serious POME and anaphylaxis reactions, and an awareness by the provider and the patient of the potential serious risks, I am persuaded that the benefit of Aveed outweighs its potential risks in the restricted target population.

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

The postmarketing risk management activities for Aveed are extensive. The approved REMS-related documents will include:

- REMS Document
- REMS Supporting Document
- Health Care Provider Enrollment Form
- Health Care Setting Enrollment Form
- Health Care Provider Education Program
- Health Care Setting Education Program
- Health Care Provider Webpage
- Patient Counseling Tool
- Aveed REMS Program Introduction Piece

The REMS with ETASU will assure safe use by enforcing a restricted distribution of the product only to certified prescribers who are aware of the product risks, who are trained to administer the product properly, who will inform the patient of these risks, and who will observe the patient for 30 minutes in the healthcare setting in order to manage the

consequences of a serious POME or anaphylactic reaction, in the unlikely event of such an occurrence.

In conjunction with our colleagues in DRISK, I conclude that the proposed REMS is consistent with the REMS requested by FDA in our May 29, 2013, CR action letter.

13.4 Recommendation for other Postmarketing Study Commitments

In addition to the comprehensive REMS with ETASU, we recommend that Sponsor conduct "enhanced" pharmacovigilance, such that cases of serious POME or anaphylaxis are reported to FDA within 15 days, are followed up thoroughly by Sponsor using a pre-defined and comprehensive inquiry methodology, and are reported in detail in quarterly summary safety update reports.

13.5 Recommended Comments to Applicant

None

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
02/28/2014

CHRISTINE P NGUYEN
02/28/2014
I concur with Dr. Hirsch's overall recommendation of approval.