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APPLICATION NUMBER:

022219Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY ADDENDUM

NDA 022219	Submission Date(s): 8/24/2007, 12/20/2007, 2/8/2008, 4/2/2008, 11/29/2012, 8/29/2013, and 2/24/2014
Brand Name	AVEED
Generic Name	Testosterone undecanoate
Reviewer	Hyunjin Kim, Pharm.D., M.S.
Team Leader	Myong-Jin Kim, Pharm.D.
OCP Division	Division of Clinical Pharmacology 3
OND Division	Division of Bone, Reproductive and Urologic Products (DBRUP)
Sponsor	Endo Pharmaceuticals
Relevant IND	072297
Submission Type	Resubmission
Formulation and Strength	Intramuscular injection solution, 250 mg/mL
Indication	Testosterone replacement therapy

The original Clinical Pharmacology review of NDA 022219 (DARRTS, 2/20/2014) stated that the clinical pharmacology information submitted in NDA 022219 was acceptable provided that agreement is reached between the sponsor and the Division regarding the language in the package insert. The agreement on language in the package insert was reached on 2/24/2014. The final agreed upon label is included in section 1.3 of this review.

1.1 Recommendation

The Division of Clinical Pharmacology 3, Office of Clinical Pharmacology finds NDA 022219 acceptable from a Clinical Pharmacology perspective.

1.2 Phase IV Commitments

None

1.3 Final agreed upon label

The final agreed upon label is attached.

13 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page.

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/s/

HYUNJIN KIM
02/26/2014

MYONG JIN KIM
02/26/2014

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA 022219	Submission Date(s): 8/24/2007, 12/20/2007, 2/8/2008, 4/2/2008, 11/29/2012, and 8/29/2013
Brand Name	AVEED
Generic Name	Testosterone undecanoate
Reviewer	Hyunjin Kim, Pharm.D., M.S.
Team Leader	Myong-Jin Kim, Pharm.D.
OCP Division	Division of Clinical Pharmacology 3
OND Division	Division of Bone, Reproductive and Urologic Products (DBRUP)
Sponsor	Endo Pharmaceuticals
Relevant IND	072297
Submission Type	Resubmission
Formulation and Strength	Intramuscular injection solution, 250 mg/mL
Indication	Testosterone replacement therapy

1 Executive Summary

This is a resubmission (4th cycle) for testosterone undecanoate (TU), which is an ester prodrug of testosterone (T), with the proposed indication of T replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous T. The proposed dose in this application is 750 mg TU at start of therapy, 4 weeks later, and then every 10 weeks administered intramuscularly (IM) in the buttock.

The original NDA was submitted on 8/24/2007 and it was considered acceptable from a Clinical Pharmacology perspective (Clinical Pharmacology review, DARRTS, dated 5/5/2008). However, the NDA was not approved based on the safety and chemistry, manufacturing, and controls (CMC) issues (refer to the Approvable Letter dated 06/27/2008).

On 03/02/2009, the sponsor submitted a resubmission to provide a response to the Approvable letter. No new clinical pharmacology data were submitted at that time. The NDA was acceptable from a Clinical Pharmacology perspective (Clinical Pharmacology review, DARRTS, dated 7/2/2009). On 12/02/2009, the Complete Response (CR) letter was issued for the 2nd cycle resubmission for safety reasons (mainly immediate post injection adverse reactions).

Another resubmission (3rd) was submitted on 1/29/2012 to address the deficiencies listed in the CR letter dated 12/02/209. In the 3rd cycle resubmission, the sponsor submitted Clinical Pharmacology studies (IP157-001 Part C (part of this study was submitted and reviewed previously during the 1st cycle) and Part C2) and study results from Part A, Part

B and Part D, which primarily focused on the safety evaluation. The 3rd cycle resubmission was considered acceptable from a Clinical Pharmacology perspective (Clinical Pharmacology review, DARRTS, dated 5/24/2013). The CR letter was issued for the 3rd cycle resubmission on 5/29/2013 because the sponsor's proposed risk evaluation and mitigation strategy (REMS) did not adequately address the risk associated with the use of AVEED.

The 4th cycle resubmission (current review cycle) was submitted on 8/29/2013 with safety data and revised REMS. There were no new clinical pharmacology data submitted during the 4th cycle resubmission.

1.1 Recommendation

The Division of Clinical Pharmacology 3, Office of Clinical Pharmacology finds the Clinical Pharmacology information submitted in NDA 022219 acceptable provided that an agreement is reached between the sponsor and the Division regarding the language in the package insert.

1.2 Phase IV Commitments

None.

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

/s/

HYUNJIN KIM
02/20/2014

MYONG JIN KIM
02/20/2014

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA: 22219	Submission Date(s): 11/29/2012
Submission Type;	Resubmission
Brand Name	AVEED
Generic Name	Testosterone undecanoate
Reviewers	Dilara Jappar, Ph.D.
Team Leader	CAPT E. Dennis Bashaw, Pharm.D
OCP Division	Division of Clinical Pharmacology 3
OND Division	Division of Gastroenterology and Inborn Errors Products (DGIEP)
Sponsor	Endo Pharmaceuticals
Relevant IND(s)	72,297
Formulation; Strength(s)	Intramuscular injection solution, 250 mg/mL
Proposed Indication	Testosterone replacement therapy
Proposed Dosing Regiment	3 mL (750 mg) is to be injected intramuscularly at initiation, at 4 weeks, and every 10 weeks thereafter
PDUFA Goal Date:	05/29/2013

Table of Contents

1 Executive Summary

This is a resubmission (3rd cycle) for Testosterone undecanoate (TU), which is an ester prodrug of testosterone (T), with the proposed indication of Testosterone (T) replacement therapy in males for conditions associated with a deficiency or absence of endogenous testosterone. Currently, there are various testosterone replacement products on the market with different formulations. The proposed dose in this application is 750 mg TU at start of therapy, 4 weeks later, and then every 10 weeks administered intramuscularly (IM) in the buttock.

The original NDA 22-219 was submitted on 8/28/2007 and it was considered acceptable from a clinical pharmacology perspective (Clinical Pharmacology review, dated 5/5/2008). There were safety and chemistry, manufacturing, and controls (CMC) issues that prevented the approval of NDA 22-219 during the original review cycle. An Approvable Letter was issued on 6/27/2008 listing Clinical and CMC deficiencies. There was no Clinical Pharmacology deficiency listed in the Approvable letter. The sponsor submitted a resubmission on 3/2/2009 to provide a response to the Approvable letter.
No new clinical pharmacology data were submitted in that 2nd cycle submission. Clinical Pharmacology review during the 2nd cycle primarily focused on the labeling recommendation regarding the safety of administering the current TU product in patients with body weight below 65 kg. The sponsor was issued a Complete Response (CR) letter for this 2nd submission on 12/02/2009 for safety reason.

Another resubmission (3rd) was submitted on 11/29/2012 to address CR letter dated 12/02/209. In this resubmission, the sponsor had submitted the following pivotal clinical pharmacology studies that evaluated the dose that is being sought in this application:

- IP157-001 Part C- to evaluate the PK up to 9 injections (part of this study up to 5 injections was submitted and reviewed previously during the 1st cycle)
- IP157-001 Part C2- to evaluate the C_{max}

In addition to those above studies, the sponsor had also submitted study results from Part A, Part B and Part D, which primarily focused on the safety evaluation. These 3 studies had different dosing regimen or different route of administration than the dose being sought in the application.

An Advisory committee meeting is scheduled for 04/18/2013.

1.1 Recommendation

The application is acceptable from the clinical pharmacology perspective provided that a mutual agreement is reached on the labeling languages.

1.2 Summary of Clinical Pharmacology and Biopharmaceutics Findings

During the 1st cycle, the sponsor had submitted part of two phase 3 safety and efficacy studies, Study IP157-001 Part C and Study IP157-001 Part A, to support the NDA. The study report for Study IP157-001 Part C had data up to 5 injections and study report for Study IP157-001 Part A had data up to 7 injections. There was a full clinical pharmacology review during the 1st cycle and application was found to be acceptable from clinical pharmacology standpoint. Please refer to the Clinical Pharmacology Review by Dr. Doanh Tran dated 05/05/2008 for further details of the review. During the 2nd submission, the sponsor did not submit any new clinical pharmacology data. The review primarily focused on the labeling recommendation regarding the safety of administering the current TU product in patients with body weight below 65 kg. Please refer to Clinical Pharmacology review by Dr. Doanh Tran dated 07/10/2009.

In this resubmission, the sponsor submitted the study report for Study IP157-001 Part C with data up to 9 injections and study report for Study IP157-001 Part C2. Both of theses studies had evaluated the dose that is being sought in this application, IM injection of 750 mg TU at start of therapy, 4 weeks later, and then every 10 weeks thereafter. This clinical pharmacology review will primarily focus on the newly submitted clinical pharmacology data.

In Study IP157-001 Part C, the sponsor had evaluated the full pharmacokinetics of serum total testosterone (including C_{avg} and C_{max}) following the 3rd and 4th injections and trough concentrations up to 9 injections (data up to 5 injections were submitted and reviewed previously during the 1st review cycle). In Study IP157-001 Part C2, the sponsor had evaluated the full pharmacokinetics of serum total testosterone (focusing on the C_{max}) following the 2nd injection and trough concentrations up to 6 injections. The steady state was considered to be reached by the 3rd injection. Please refer to Clinical Pharmacology Review by Dr. Doanh Tran dated 05/05/2008 for detailed discussion of steady state assessment. Therefore, data from the 3rd injection interval was used as the primary PK and efficacy assessment.

$\underline{C_{avg}}$:
Following the 3rd and 4th injections, the serum total testosterone had very similar PK profiles with the mean C_{avg} of 494.9 ± 141.5 ng/dL and 514.3 ± 163.11 ng/dL, respectively. Please refer to Clinical Pharmacology Review by Dr. Doanh Tran dated 05/05/2008 for detailed discussion. Following the 2nd injections, the mean C_{avg} was 449.6 ± 157.01 ng/dL. The mean serum testosterone concentrations were within the normal range of 300 – 1000 ng/dL throughout the 2nd, 3rd and 4th injection dosing intervals.

The mean tough concentration (immediately prior to injection) of serum testosterone levels up to 9 injections ranged from 307.8 to 389.8 ng/dL after the 1st injection and were within the normal range (300 to 1000 ng/dL).

$\underline{C_{max}}$:
The PK parameter C_{max} was assessed following the 2nd, 3rd and 4th injections and was used as a measure to decide whether the administered dose of TU resulted in excessively high serum testosterone level in man with hypogonadism. Following all injections,

greater than 85% of patients had C_{max} value ≤1500 ng/dL. No patients following 2nd and 3rd injection and 4 (3.8%) patients following 4th injection had C_{max} value between 1800 and 2500 ng/dL; No patient had a C_{max} value >2500 ng/dL following any of the injections when TU 750 mg given intramuscularly at baseline, at 4 weeks, then at 10-week intervals thereafter.

2 Question Based Review

2.1 List the Pharmacology and Biopharmaceutics studies and the clinical studies with PK and/or PD information submitted in the NDA

The sponsor had submitted total of 5 clinical pharmacology studies in this submission. Of these, two studies, IP157-001 Part C and Study IP157-001 Part C2, that used dose that is being sought, 750 mg TU at start of treatment, at 4 weeks, and every 10 weeks thereafter, were considered to be pivotal studies in this submission. The first study, IP157-001 Part C, evaluated the PK of testosterone up to 9 injections (part of this study up to 5 injections was submitted and reviewed during the 1st cycle) and the second study, Study IP157-001 Part C2, evaluated the C_{max} of testosterone following the 2nd injection. Other 3 studies, IP157-001 Part A, IP157-001 Part B, and IP157-001 Part D had evaluated different dosing regimen or different route of administration than the one being sought in this application.

Table 1. List of Clinical Pharmacology Studies

Study Identifier Type of Study	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
IP157-001 Part A Phase 3	5.3.5.1	Primary objective was to evaluate the PK of TU 750 and 1000 mg IM Q12wk via multiple measurements of serum total T, over the 12-wk interval following the 4th injection	Open-label, 2-arm, randomized, multicenter PK and long-term safety study Assessment of both a 750 and 1000 mg dose with fixed intervals of 12 wk between each injection	TU 750 or 1000 mg IM Q12wk	S: 692 E: 237 TPS: 237	Hypogonadal males (aged ≥18 y)	Subjects received up to 13 injections (144 wk)	Study complete; full CSR prepared for Part A, Stage 1 (previously submitted), abbreviated CSR for Part A (and a subset of patients from Part A who crossed over into Part D)

IP157-001 Part B Phase 3	5.3.5.1	Primary objective was to evaluate the PK of TU 1000 mg IM, given at baseline, at 8 wk, and Q12wk thereafter via multiple measurements of serum total T, over the 12-wk interval following the 3rd injection	Open-label, 2-arm randomized, multicenter PK and long-term safety	TU 1000 mg IM dose at baseline and wk 8 followed by: a 750-mg dose with 10-wk intervals or 1000 mg dose with 12-wk intervals thereafter	TPS:134	Hypogonadal males (aged ≥18 y)	Subjects in the 1000 mg group received up to 8 injections (80 wk) Subjects in the 750 mg group received up to 10 injections (88 wk)	Study complete; abbreviated CSR prepared
IP157-001 Parts C Phase 3	5.3.5.1	To evaluate the PK of T from TU 750 mg IM at baseline, at 4 wk, and then Q10wk thereafter	Open-label, single-arm, multiple-dose, multicenter study	TU 750 mg IM at baseline, at wk 4, and then Q10wk thereafter	S: 354 E: 130 TPS: 130 PKP: 117 SSPK: 104 LTPKP: 98	Hypogonadal males (aged ≥18 y)	Up to 9 injections (84 wk)	Study complete; full CSRs prepared
IP157-001 Parts C2 Phase 3	5.3.5.1	To evaluate the C_{max} of TU 750 mg IM at baseline, at 4 wk, and then every 10 wk thereafter	Open-label, single-arm, multiple-dose, multicenter study (Part C2 functioned as a second cohort to Part C)	TU 750 mg IM at baseline, at wk 4, and then Q10wk thereafter	S: 38 E: 23 TPS: 23 PKP:23	Hypogonadal males (aged ≥18 y)	Up to 6 injections (44 wk)	Study complete; full CSRs prepared
IP157-001 Parts D Phase 3	5.3.5.1 (see study status)	To compare the PK of T from 2 routes of TU administration (IM vs SC) in subsets of patients from Parts A and C	Open-label, single-arm, multiple-dose, multicenter study (subjects from Parts A and C were crossed over into Part D to receive subcutaneous injections)	TU 750 or 1000 mg SC Q10wk, starting the 8th injection after crossing over into Part D from Parts A and C (if subjects could not tolerate the SC route, they could return back to the IM route)	TPS: 22 (crossed from Part A) TPS: 21 (crossed from Part C)	Hypogonadal males (aged ≥18 y)	Up to 2 SC injections (20 wk)	Study complete; included in Part A abbreviated CSR and Part C full CSR

2.2 General Attributes

Please refer to the Clinical Pharmacology Review by Dr. Doanh Tran dated 05/05/2008

2.3 General Clinical Pharmacology

2.3.1 What are the design features of the clinical pharmacology and biopharmaceutics studies and the clinical studies used to support dosing or claims?

Please refer to Study IP157-001 Part C and Part C2 in Table 1.

2.3.2 What are the preset primary and secondary endpoints for the phase 3 study?

The primary efficacy endpoint is C_{avg} being within the normal range of 300 – 1000 ng/dL to show TU 750 mg given intramuscularly at baseline, at 4 weeks, and then every 10 weeks thereafter does provide adequate testosterone replacement in hypogonadal men. C_{avg} was calculated as $AUC_{0\text{-}tau}$/tau where tau is the dosing interval.

The secondary endpoint was on C_{max} (based on the criteria in table 2) to support that the administered dose of TU does not result in excessively high serum testosterone level in hypogonadal men.

Table 2. Decision Criteria for C_{max}

Serum Total Testosterone Maximum Concentration (C_{max}) Observed During the 3rd Injection Interval	**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

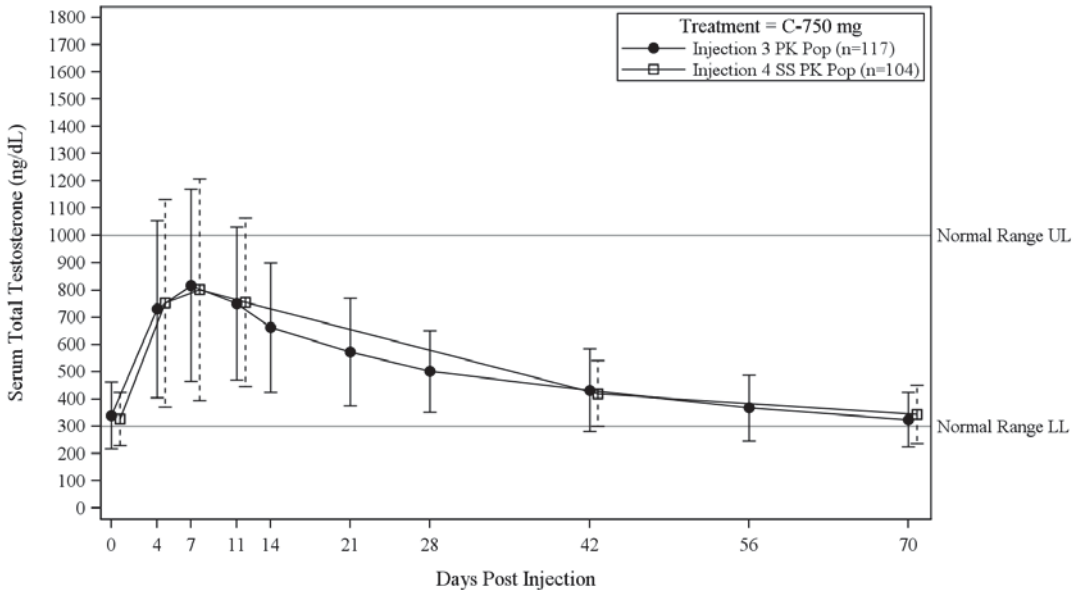
All 3 criteria must be met in order to reject the null hypothesis in favor of the alternative hypothesis.

2.3.3 Does IM administration of TU 750 mg at baseline, at 4 weeks, and then every 10 weeks thereafter provide adequate testosterone replacement in hypogonadal men at steady state?

Yes, IM administration of TU 750 mg at baseline, at 4 weeks, and then every 10 weeks thereafter does provide adequate testosterone replace in hypogonadal men at steady state, which was considered to be reached by the 3rd injection. Please refer to Clinical Pharmacology Review by Dr. Doanh Tran dated 05/05/2008 for detailed discussion regarding the steady state assessment.

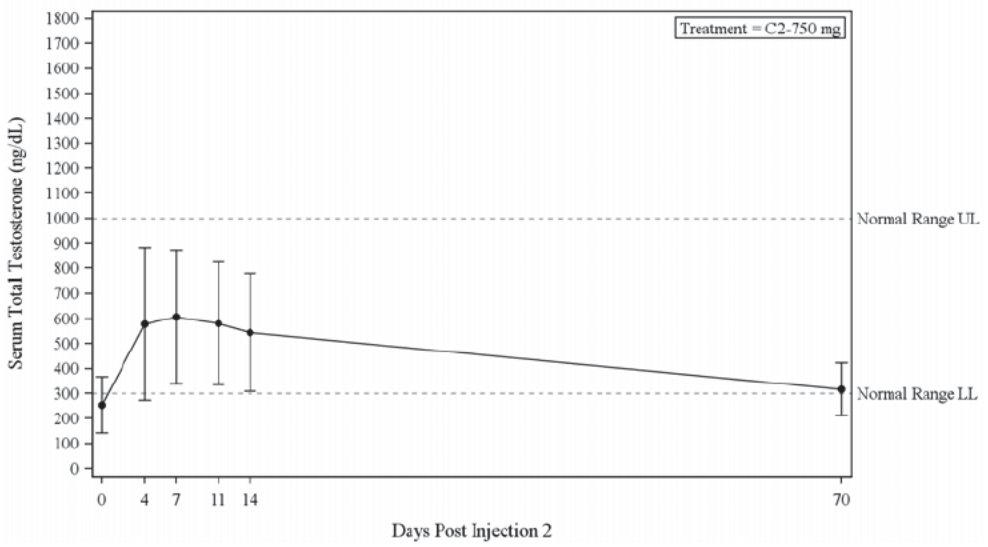
The full PK profiles of serum total testosterone were characterized following 2nd (in Part C2), 3rd and 4th (in Part C2) injections. The serum total testosterone had very similar PK profiles following the 3rd and 4th injections. Following the 3rd and 4th injections, the mean C_{avg} (calculated as $AUC_{0\text{-}tau}$/tau where tau is the dosing interval) was 494.9 ± 141.5 ng/dL and 514.3 ± 163.11 ng/dL, respectively, and the mean serum testosterone concentrations at each time point were within the normal range of 300 – 1000 ng/dL throughout both dosing intervals. Please refer to Clinical Pharmacology Review by Dr. Doanh Tran dated 05/05/2008 for detailed discussion.

Figure 1. Mean (SD) Serum Total Testosterone Concentrations (ng/dL) following the 3rd and 4th Injection Intervals (Part C)



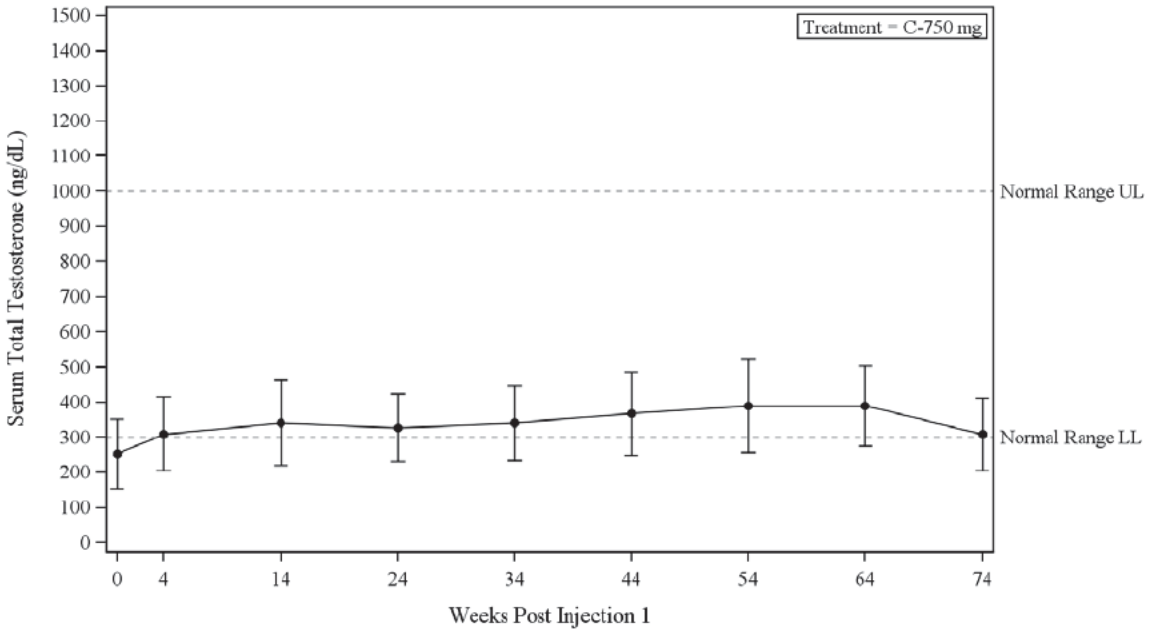
In this submission, the sponsor had also submitted new data that characterize the full PK profile of serum total testosterone level following the 2nd injection in Part C2 study as supportive data. Following the 2nd injections, the mean C_{avg} was 449.6 ± 157.01 ng/dL, and the mean serum testosterone concentrations remained within the normal range of 300 – 1000 ng/dL throughout the dosing intervals.

Figure 2. Mean (SD) Serum Total Testosterone Concentrations (ng/dL) following the 2nd Injection (Part C2)



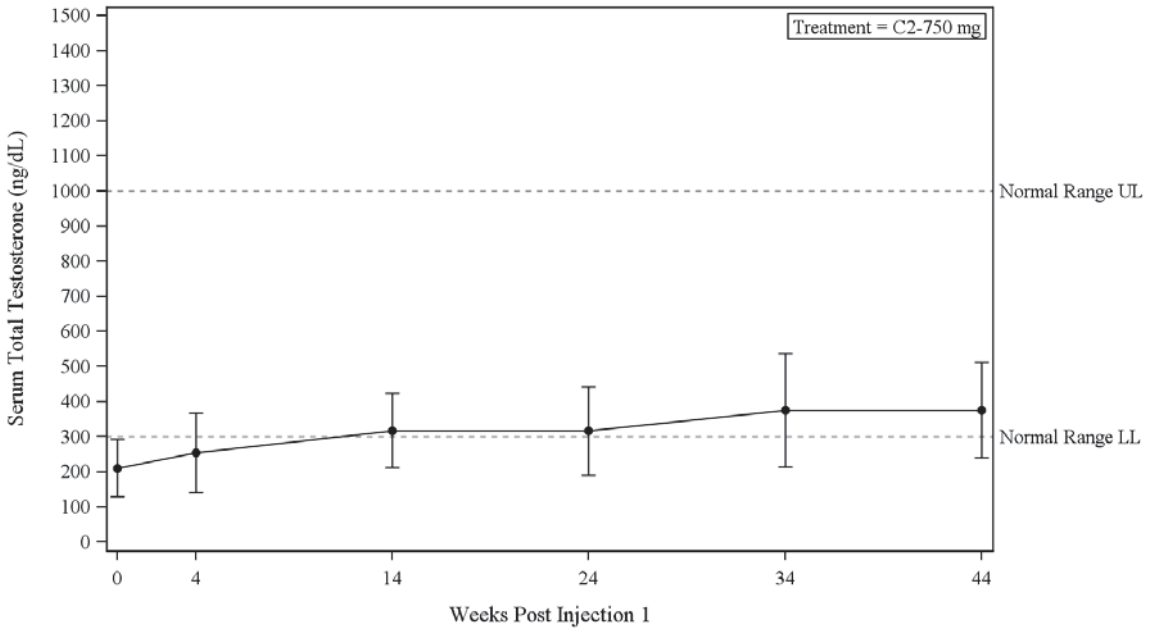
In Part C, the tough concentration (immediately prior to injection) of serum testosterone levels was measured up to 9 injections in (data up to 5 injections were submitted and reviewed during the 1st cycle of review) The mean trough concentrations of serum total testosterone after the first injection ranged from 307.8 to 389.8 ng/dL and were within the normal range (300 to 1000 ng/dL).

Figure 3. Mean (SD) Serum Total Testosterone Concentrations (ng/dL) at Trough Time Points Through the 9th Injection, Long-Term Pharmacokinetic Population (Part C)



Additionally, the sponsor had also measure trough concentration of serum total testosterone up to 6 injections in Study Part C2 (as supporting data). The mean trough concentrations of serum total testosterone after the 2nd injection ranged from 316.2 ng/dL to 375.8 ng/dL and were within the normal range (300 to1000 ng/dL).

Figure 4. Mean (SD) Serum Total Testosterone Concentrations (ng/dL) at Trough Time Points Through the 6th Injection (Part C2)



2.3.4 Does administered of TU 750 mg dose result in excessively high serum testosterone level in hypogonadal men?

Parameter C_{max}, based on the criteria in table 2, was used to decide whether the administered dose of TU resulted in excessively high serum testosterone level in hypogonadal men in this study.

Table 2. Decision Criteria for C_{max}

Serum Total Testosterone Maximum Concentration (C_{max}) Observed During the 3rd Injection Interval	**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.

The C_{max} was assessed following the 3rd (the steady state) and 4th injections in the study Part C and the following the 2nd injection in study Part C2. Following all injections, greater than 85% of patients had C_{max} value ≤1500 ng/dL. No patients following 2nd and 3rd injection and 4 (3.8%) patients following 4th injection had C_{max} value between 1800 and 2500 ng/dL; No patient had a C_{max} value >2500 ng/dL following any of the injections. Therefore, C_{max} criteria were met following all 2nd, 3rd, and 4th injections.

Table 3. Number (%) of Patients (and Two-sided 95% Confidence Interval) Meeting Serum Total Testosterone C_{max} Criteria for Success

Serum Total Testosterone C_{max}	**2nd Injection Interval Part C2 (N=23)**		**3rd Injection Interval Part C (N=117)**		**4th Injection Interval Part C (N=104)**	
	N (%)	95% (CI)	N (%)	95% (CI)	N (%)	95% (CI)

≤1500 ng/dL	22 (95.7%)		108 (92.3%)	(87.5%-97.1%)	96 (92.3%)	(87.2%, 97.4%)
>1500 to <1800 ng/dL	1 (4.3%)		9 (7.7%)	(2.9%- 12.3%)	4 (3.8%)	(0.2%, 7.5%)
1800-2500 ng/dL	0		0		4 (3.8%)	(0.2%, 7.5%)
>2500 ng/dL	0		0		0	
Meet C_{max} Criteria	**Yes**		**Yes**		**Yes**	

Therefore, TU 750 mg given intramuscularly at baseline, at 4 weeks, then at 10-week intervals thereafter does not result in excessively high serum total testosterone values in hypogonadal men.

2.4 Analytical Section

2.4.1 What bioanalytical methods were used to assess the concentration?

For both Part C and C2, the sponsor had used high performance liquid chromatography (HPLC) with tandem mass spectrometry (MS/MS) detection by [redacted] (b) (4) to measure the human serum concentration of T and DHT. Part C and C2 had same bioanalysis procedures and acceptance criteria (Please refer to the Clinical Pharmacology Review by Dr. Doanh Tran dated 05/05/2008 for further details) and both parts (C & C2) had acceptable reported precision and accuracy of assay runs.

2.4.2 Were the analytical assay methods adequately validated?

The bioanalytical method via HPLC with MS/MS detection to measure the concentration of T and DHT in human serum samples in study IP157-001 Part C and Part C2 was appropriately validated ([redacted] (b) (4) validation report 2100-801). Please see the Clinical Pharmacology Review by Dr. Doanh Tran dated 05/05/2008 for further details of the validation report.

In addition to the validation report that was submitted in the last cycle of review (validation report 2100-801 dated 08/16/2006), the sponsor had also submitted an addendum No. 1 to the validation report with the following updated validation information (report dated 06/06/2008) in this submission.

- Frozen matrix stability for testosterone and DHT in human serum was established for 463 day when stored in a freezer set to maintain -10 to -30°C.
- Frozen matrix stability for testosterone and DHT in PBS was established for 195 days when stored in a freezer set to maintain -10 to -30°C.
- Additional short-term matrix stability was confirmed for seven freeze/thaw cycles for testosterone and DHT in human serum.
- Intermediate (working) standard solution stability for solutions of testosterone and DHT, at each of the lowest and highest concentration levels, was confirmed for 105 days when stored in a refrigerator set to maintain 2 to 8°C.

3 Appendices

3.1 Individual Study Review

IP157-001 Parts C

TITLE: **A Two-Arm, Open-Label, Randomized, Multi-Center Pharmacokinetic and Long-Term Safety Study of Intramuscular Injections of 750 mg and 1000 mg Testosterone Undecanoate in Hypogonadal Men**

Study Site:

Sponsor:	Endo Pharmaceuticals Inc, Chadds Ford, PA
Clinical Site:	Multicenter study of 31 investigative centers in the U.S.A
Analytical Site:	(b) (4)

Phase of Study: Phase 3 study

Primary Objective:
The primary objective for Part C of the study was to evaluate the pharmacokinetics of testosterone (T) from Testosterone Undecanoate **(**TU) 750 mg given intramuscularly at baseline, at 4 weeks, and then every 10 weeks thereafter, over the 10-week interval following the 3rd injection, via multiple measurements of serum total testosterone, in up to approximately 130 hypogonadal men.

Secondary Objectives:
The secondary objectives for Part C of the study were:

- To evaluate the pharmacokinetics of testosterone from TU 750 mg given intramuscularly at baseline, at 4 weeks, and then every 10 weeks thereafter, over the 10-week interval following the 4th injection, via multiple measurements of serum total testosterone.
- To compare serum levels of DHT, estradiol, and SHBG to simultaneous levels of serum total testosterone over the 3rd injection interval.
- To evaluate safety in patients treated with TU 750 mg given intramuscularly at baseline, at 4 weeks, and then every 10 weeks thereafter, through up to 9 injections in hypogonadal men.

STUDY DESIGN:

Drug Products: Each (b) (4) TU contained 4 mL of Testosterone undecanoate drug product, in a concentration of 250 mg/mL in oily solution. In this study, the dose administered was 750 mg TU in 3 mL oily solution.

Part C was a multicenter, single-arm, open-label study with a planned enrollment of up to 130 patients. The treatment arm was TU 750 mg in 3 mL (250 mg/mL) oily solution, injected intramuscularly into the buttock (deep gluteal muscle) at baseline, at 4 weeks and then every 10 weeks thereafter. TU 750 mg was administered up to 9 intramuscular injections (approximately 20 months/84 weeks). Each dose comprised 3 mL of TU in oily solution (TU 750 mg) and was to be administered at 9 AM (±3 hours). The injection site was alternated for each consecutive injection (i.e., the left and right buttocks rotated from one injection to the next).

All patients underwent intensive pharmacokinetic (IPK) assessments during the 3rd and 4th injection intervals. In addition, patients also underwent a trough (immediately prior to injection) pharmacokinetic (PK) assessment at each 10-week dosing interval visit through Injection 9. Safety was assessed throughout the study (i.e., up to 9 injections [up to approximately 20 months/84 weeks]).

Part C had 4 defined periods: Screening, Baseline, Stage 1, and Stage 2:

- Screening: Approximately 1- to 5-week screening period (washout from select prior testosterone replacement therapies could extend this period for some patients).
- Baseline: Final pre-study measurements were captured and patients were enrolled.
- Stage 1 (the first 3 injections): This included the first injection at the baseline visit. The end of Stage 1 was the 4th injection visit. The Stage 1 analysis included only data through the 4th injection visit and this interim CSR have been previously submitted in 2007 and reviewed by Dr. Doanh Tran (clinical pharmacology review) dated 05/05/2008.
- Stage 2 (long-term safety extension): The study continued following the 4th injection visit, with up to 5 additional injections (at 10-week intervals) during an extended treatment phase. The Stage 2 analysis included all patients and all safety data.

Key inclusion criteria:

- Male with primary or secondary hypogonadism at least 18 years of age
- Morning screening serum testosterone concentration <300 ng/dL
- If receiving endocrine replacement hormones (eg, thyroid), antihypertensive, lipid lowering agents, antidepressants, or anxiolytic medications, the dose must be stable for at least 28 days prior to the first administration of the study drug or was not currently on such medications

Study Schedule:

	Injection Number and Week											
	Screening Phase		1	2	3	4	5	6	7	8	9	EOS
	Days -35 to -1	Post-Washout	Baseline Day 0	4	14	24	34	44	54	64	74	84[a]
Informed Consent	X											
Eligibility	X		X[b]									
Medical History (includes height)	X		X[b]									
Physical Examination	X											
Digital Rectal Examination, PSA	X		X	X	X	X	X	X	X	X		X
Vital Signs (includes pulse, blood pressure, weight, temperature)	X		X			X						
12-Lead Electrocardiogram (ECG)	X											
Hematology, Coagulation, Chemistry (includes lipids), Urinalysis, FSH, LH	X		X			X						X
Prostate Volume (via TRUS)[c]	X											
Pharmacokinetic Sampling (Total and Free Testosterone, DHT, SHBG, estradiol)	X only if Washout NOT Required	X if Washout Required	X	X	X	X	X	X	X	X		
Adverse Events			X	X	X	X	X	X	X	X	X	X
Prior/Concomitant Medications	X		X	X	X	X	X	X	X	X	X	X
750 mg injection (includes drug accountability)			X	X	X	X	X	X	X	X	X	
Local tolerability assessment[d]			X	X	X	X	X	X	X	X	X	X
Profile of Mood States			X									
AUA Symptom Score	X		X									
Male-Patient Global Assessment (M-PGA)				X	X	X						

Data Source: Protocol Amendment 10 (Appendix 16.1.1).

[a] Patients who discontinued prematurely from the study and who did not complete all of the treatment injections were to be assessed as listed under Week 84 or End of Study (EOS) Visit.

[b] Medical History and Eligibility pages were updated at baseline as appropriate

[c] TRUS could be repeated during the study at the Investigator's discretion.

[d] Injection site was assessed by the Investigator if, at any time, the patient indicated a tolerability issue with the injection site.

AUA=American Urological Association; DHT=Dihydrotestosterone; FSH=Follicle stimulating hormone; LH=Luteinizing hormone; PSA= Prostate specific antigen; SHBG=Sex hormone binding globulin; TRUS=Transrectal ultrasound

Note: Part D assessments were performed starting with Injection 8 visit as patients received their first subcutaneous injection at this visit (see Listing 16.2.5.2).

Study Population:
Of the 130 patients enrolled in Part C, 93 patients completed Part C and 37 patients discontinued early.

Table C-1. Summary of Demographic Characteristics, Total Patient Sample

Parameters	**Category/statistics**	**All subject (N= 130)**
Gender	Male	130
	Female	0
Age (years)	Mean ± SD	54.2 ± 10.25
	Range	24-75
Baseline Height (cm)	Mean ± SD	177.9 ±7.57
	Range	152-193
Baseline Weight (kg)	Mean ± SD	101.2 ±17.96
	Range	59-158
BMI (kg/m^2)	Mean ± SD	32.0 ± 5.40
	Range	17-51
Race	White	97 (74.6%)
	Asia	0
	Black	16 (12.3%)
	Hispanic	14 (10.8%)
	Other	3 (2.3%)
Inclusion Screening Total Testosterone (ng/dL)	Mean ± SD	214.7 ± 68.57
	Range	24 -299

PK Population:
Patients who had a minimum of 4 serum total testosterone concentration values within the 3rd injection dosing interval. The 4 values could include the Day 0 and/or Day 70 (4th injection visit) values from the interval. Additionally, patients had to have weighed ≥65 kg in order to be included in the PK Population.
The PK Population was used for the analysis of the primary and secondary efficacy outcomes during the 3rd injection interval.

Steady-State PK population:
All patients in the PK Population with non-missing 4^{th} and 5^{th} injection serum total testosterone concentrations.

Long term PK population**:**
All patients in the Steady-State PK Population with a non-missing 8^{th} injection serum total testosterone concentration.

Table C-2

	C-750 mg
Total Patient Enrolled	130
PK Population	117 (90%)
Steady-State PK Population	104 (80%)
Long–Term PK Population	98 (75.4%)
Patients Completed Treatment Phase	
Yes	93 (71.5%)
No	37 (28.5%)
Reason for Discontinuation	
Adverse Event	15 (11.5%)
Protocol Violation	0
Patient Withdrew Consent	10 (7.7%)
Patient Non-Compliance	5 (3.8%)
Lost to Follow-up	3 (2.3%)
Other	4 (3.1%)

The other reasons for early discontinuation for the 4 patients were withdrawn by Sponsor (2 patients; 031-7021 and 065-7121); a patient (032-7117) was moving to California and could not complete follow-up visits and a patient (044-7097) had an elevated PSA level (3.89 ng/mL) prior to Injection 1, which was confirmed with a repeat test (3.92 ng/mL)

Pharmacokinetic Measurements:

- In Part C, total testosterone (T), free testosterone [measured], DHT, SHBG, and estradiol were measured via PK blood sampling. However, TU and DHTU were not assessed in Part C.
- After the 3rd IM injection, PK blood samples were collected at Day 0 (pre-3rd injection), 4, 7, 11, 14, 21, 28, 42, 56, and 70 (pre-4th injection), where the 4th injection visit was defined as the end of the injection interval.
- After the 4th IM injection, PK blood samples were collected at Day 0 (pre-4th injection), 4, 7, 11, 42, and 70 (pre-5th injection), where the 5th injection visit was defined as the end of the injection interval.
- In addition, trough (immediately prior to injection) pharmacokinetic (PK) was assessed at each 10-week dosing interval visit through Injection 9.

Data Analysis:

PK:

PK parameters $AUC_{0\text{-}70days}$, C_{avg}, C_{max}, C_{trough}, T_{max}, Tl_{ast} were derived for each Intensive PK interval following the 3rd and 4th injection. PK parameters were estimated from the serum concentration data using non-compartmental analysis within each patient. Nominal (protocol-scheduled) time from dosing was used to estimate all individual (within-patient) PK parameters. All parameters, except C_{trough}, were derived for each IPK interval. C_{trough} was derived for both IPK and non-IPK injection intervals. WinNonLin® Professional version 5.3 was used to derive PK parameters, as appropriate.

Efficacy:

The primary efficacy endpoint analysis was based on PK assessments during the 3rd injection interval for PK population. Secondary efficacy endpoint analysis included PK and clinical symptomatology assessments during the same 3rd injection interval. Steady-state analysis was based on PK assessment during the 4th injection interval in Part C. Two-sided 95% CIs were constructed for the PK primary and secondary efficacy outcomes

Primary Hypothesis:

TU 750 mg given intramuscularly at baseline, at 4 weeks, and then every 10 weeks thereafter during the 3rd injection interval does provide adequate testosterone replacement in hypogonadal men.
A patient was considered a responder if his serum total testosterone C_{avg} was in the normal range (300 to 1000 ng/dL), where C_{avg} was derived as the AUC of the dose interval divided by the duration of the dosing interval, ie, $C_{avg} = AUC_{0\text{-}70\ days}/70$ days.

Secondary Hypothesis:
TU 750 mg given intramuscularly at baseline, at 4 weeks, and then every 10 weeks thereafter during the 3rd injection interval does not result in excessively high serum total testosterone values in hypogonadal men. The secondary hypothesis was tested as summarized below

Serum Total Testosterone Maximum Concentration (C_{max}) Observed During the 3rd Injection Interval	**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.

Additional Secondary Efficacy Outcomes
Based on Pharmacokinetic Data:
- The proportion of patients with serum total testosterone concentration values falling below 300 ng/dL at any time during the 3rd injection interval
- The time to first observation of serum total testosterone value below 300 ng/dL during the 3rd injection interval
- "Clinical Success": This was defined based on C_{avg} and the Day 70 concentration (C_{trough}) of serum total testosterone during the 3rd injection interval. Patients were classified as "Clinical Success" if both their C_{avg} and C_{trough} values fell within the normal range of 300 to 1000 ng/dL.
- Steady-state assessment of serum total testosterone concentrations during the 4th injection interval
- Serum total testosterone C_{max}

Based on Clinical Symptomatology:
- Male-Patient Global Assessment (M-PGA):
  - Proportion of patients for each M-PGA category
  - Correlation (Pearson coefficients) of each M-PGA category with serum total testosterone C_{max}, C_{avg}, and C_{trough} on Day 0 and Day 21 of the 3rd injection interval
- Body Weight and Body Mass Index (BMI)
  - Changes in body weight and BMI from pretreatment to 4th injection visit
  - Correlation (Pearson coefficients) of changes in body weight and BMI from pretreatment to 4th injection visit with serum total testosterone C_{max}, C_{avg}, and C_{trough}

Bioanalytical Analysis:
The concentration of T and DHT in human serum samples were determined by using high performance liquid chromatography (HPLC) with tandem mass spectrometry (MS/MS) detection by (b) (4) The bioanalysis procedures and acceptance criteria are discussed in the Clinical Pharmacology Review by Dr. Doanh Tran dated 05/05/2008

in detail. The part C (including stage 1 and 2) has acceptable reported precision and accuracy of assay runs.
The method used in this study was appropriately validated ([redacted](b) (4) validation report 2100-801). Please see the Clinical Pharmacology Review by Dr. Doanh Tran dated 05/05/2008 for details of the validation report.

RESULTS:

Efficacy:
The primary efficacy (C_{avg}) and safety (C_{max}) assessments were based on the PK sample collection during the 3rd injection interval, which is considered to be at the steady-state (please refer to the Clinical Pharmacology Review by Dr. Doanh Tran dated 05/05/2008 for details of steady state assessment).

C_{avg}
The mean $C_{avg\ for}$ serum total T concentrations was 494.9 ± 141.5 ng/dL and were within the normal range of 300 – 1000 ng/dL throughout the 3rd dosing interval. 94% of patients had serum total T C_{avg} within the 300 – 1000 ng/dL range and met the responder criteria, and 6% patients were non-responders.

Table C-3. Number (%) of Patients (and Two-Sided 95% Confidence Interval) Meeting Serum Total Testosterone C_{avg} Criteria for a Responder During the 3rd Injection Interval, PK Population

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

During the 3rd injection interval, the mean serum total testosterone concentrations remained within the normal range (300 to 1000 ng/dL), as demonstrated by the below FigureC-1.

Figure C-1. Mean (SD) Serum Total Testosterone Concentrations (ng/dL) following the 3rd Intramuscular Injection of Testosterone Undecanoate, PK Population

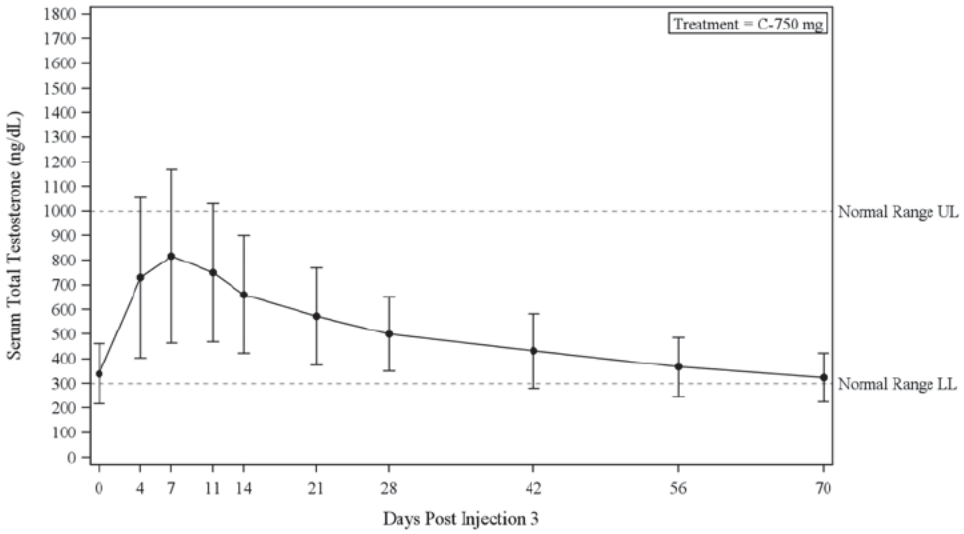
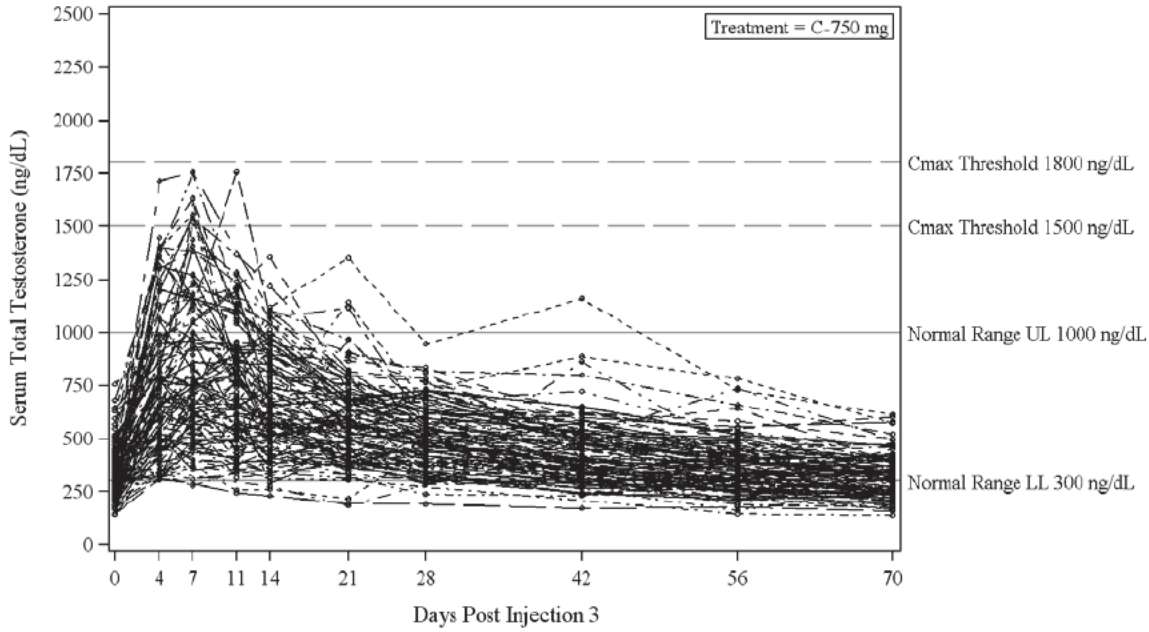


Figure C-2. By-Patient Serum Total Testosterone Concentrations (ng/dL) During the 3rd Injection Interval, Pharmacokinetic Population



No patient had a serum total testosterone concentration value that exceeded the 1800 ng/dL at any time during the 3rd injection interval.

Table C-4. Descriptive Statistics for Injection 3 Serum Total Testosterone (ng/dL) Pharmacokinetic Parameters, Pharmacokinetic Population

	C-750							
	N	**Mean**	**Std. Dev.**	**Min**	**Median**	**Max**	**%CV**	**Geometric Mean**

$AUC_{0\text{-}70days}$ (d·ng/dL)	117	34645.6	9902.45	13755.1	33342.2	70016.9	28.6	33263.6
C_{trough} (ng/dL)	117	323.5	99.11	138.2	316.9	611.1	30.6	309.0
C_{max} (ng/dL)	117	890.6	345.11	311.0	813.6	1758.5	38.8	826.8
T_{max} (days)	117	10.0	7.11	4.0	7.0	42.0	71.1	8.4
C_{avg} (ng/dL)	117	494.9	141.46	196.5	476.3	1000.2	28.6	475.2

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

C_{max}

108 patients (92.3%) had a serum total testosterone C_{max} value ≤1500 ng/dL; Nine patients (7.7%) had C_{max} > 1500 ng/dL. No patient had a C_{max} value between 1800 and 2500 ng/dL or C_{max} value >2500 ng/dL during the 3rd injection interval. Thus, the C_{max} criteria for success were met during the 3rd injection in this study. Therefore, TU 750 mg given intramuscularly at baseline, at 4 weeks, then at 10-week intervals thereafter does not result in excessively high serum total testosterone values in hypogonadal men.

Number (%) of Patients (and Two-sided 95% Confidence Interval) Meeting Serum Total Testosterone C_{max} Criteria for Success During the 3rd Injection Interval, Pharmacokinetic Population

Serum Total Testosterone C_{max} Observed During 3rd Injection Interval	**Criteria for Success[a]**	**C-750 mg (N=117)**	
		N (%)	**95% CI**
≤1500 ng/dL	≥85% of Patients	108 (92.3%)	(87.5%, 97.1%)
1800-2500 ng/dL	≤5% of patients	0	
>2500 ng/dL	No Patients	0	

Other Secondary analysis:

Table C-4. Other Secondary Efficacy Outcomes Based on Pharmacokinetic Assessments During the 3rd Injection Interval, Pharmacokinetic Population

Secondary Efficacy Outcome During the 3rd Injection Interval	**C-750 mg (N=117)**	
	N (%)	**95% CI**
Patients with Serum Total Testosterone Concentration <300 ng/dL at Any Time, n (%)		
At Least 1 Concentration <300 ng/dL	60 (51.3%)	(42.2%, 60.3%)
No Concentrations <300 ng/dL	57 (48.7%)	(39.7%, 57.8%)
N (%) of Patients with C_{avg} ≥300 ng/dL	111 (94.9%)	(90.9%, 98.9%)
Time (Days) to First Serum Total Testosterone below 300 ng/dL		
N	60	

Median	56.0	
Minimum, Maximum	5, 74	
N (%) of Patients with Clinical Success[b]		
Success	63 (53.8%)	(44.8%, 62.9%)
Not a Success	54 (46.2%)	(37.1%, 55.2%)
N (%) of Patients with C_{max} ≤1500, >1500 to <1800, 1800 to 2500, >2500 ng/dL		
≤1500 ng/dL	108 (92.3%)	(87.5%, 97.1%)
>1500 to <1800 ng/dL	9 (7.7%)	(2.9%, 12.5%)
1800 to 2500 ng/dL	0	
>2500 ng/dL	0	

Patients were classified as "clinical success" if both their C_{avg} and C_{trough} values fell within the normal range of 300 to 1000 ng/dL.

Table C-5. Number (%) of Patients with Serum Total Testosterone Concentrations Above or Below the Normal Range Post 3rd Injection Visit, Pharmacokinetic Population

Total Testosterone	C-750 n (%) Days Post 3rd Injection Visit									
	0 (N=117)	4 (N=111)	7 (N=111)	11 (N=107)	14 (N=114)	21 (N=115)	28 (N=111)	42 (N=109)	56 (N=115)	70 (N=116)
<300 ng/dL	53 (45.3%)	0	2 (1.8%)	2 (1.9%)	4 (3.5%)	3 (2.6%)	6 (5.4%)	20 (18.3%)	38 (33.0%)	52 (44.8%)
300 to 1000 ng/dL	64 (54.7%)	90 (81.1%)	80 (72.1%)	86 (80.4%)	99 (86.8%)	109 (94.8%)	105 (94.6%)	88 (80.7%)	77 (67.0%)	64 (55.2%)
>1000 ng/dL	0	21 (18.9%)	29 (26.1%)	19 (17.8%)	11 (9.6%)	3 (2.6%)	0	1 (0.9%)	0	0

Effect of body weight and BMI on serum total T concentration:
Please see the Clinical Pharmacology Review by Dr. Doanh Tran dated 05/05/2008.

Efficacy during the 4th injection interval:

C_{avg}:
During the 4th injection, the mean serum T concentrations were within the normal range of 300 – 1000 ng/dL with the mean (±SD) total serum T C_{avg} of 514.3 ± 163.11 ng/dL.
96.2% of patients were responders with C_{avg} within 300 - 1000 ng/dL range and 3.8% of the patients were non-responders with C_{avg} <300 ng/dL. No patient had a C_{avg} >1000 ng/dL.

Table C-6. Number (%) of Patients (and Two-Sided 95% Confidence Interval) Meeting Serum Total Testosterone C_{avg} Criteria for a Responder During the 4th Injection Interval, SS PK Population

Serum Total Testosterone C_{avg} Criteria	C-750 mg (N=104)	
	N (%)	2-sided 95%CI

Responder		
C_{avg} within 300-1000 ng/dL	100 (96.2%)	(92.5%-99.8%)
Not a Responder		
C_{avg} <300 ng/dL	4 (3.8%)	0.2%-7.5%
C_{avg} >1000 ng/dL	0	

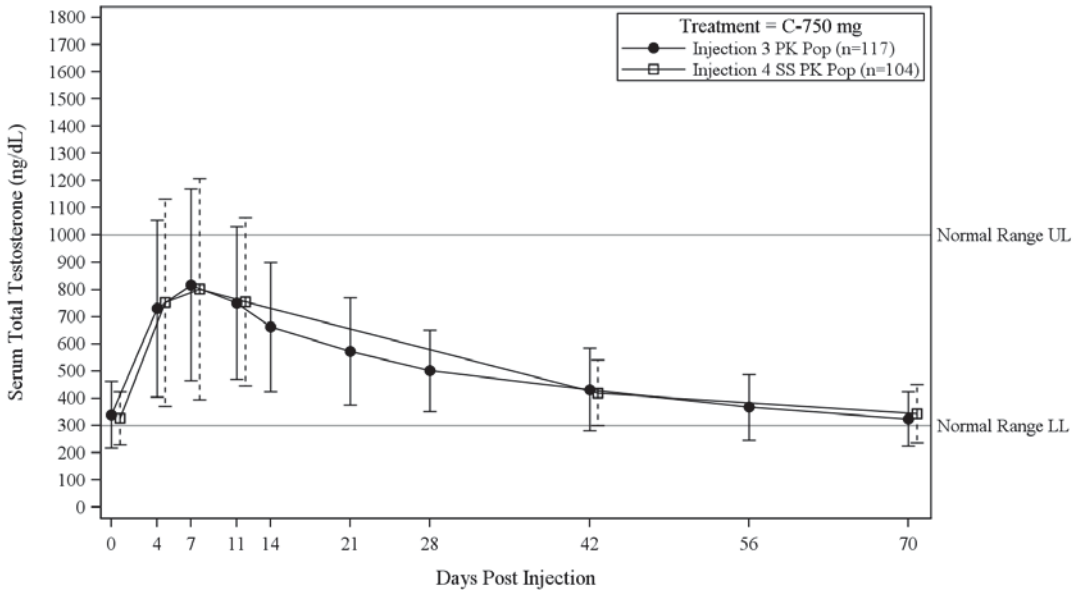
Table C-7. Descriptive Statistics for 4th Injection Serum Total Testosterone pharmacokinetic Parameters, Steady-State Pharmacokinetic Population (ng/dL)

	C-750 mg (N=104)							
	N	**Mean**	**Std. Dev.**	**Min**	**Median**	**Max**	**%CV**	**Geometric Mean**
$AUC_{0\text{-}70days}$ (d·ng/dL)	104	35999.5	11418.03	18970.2	33048.5	66485.4	31.7	34308.6
C_{trough} (ng/dL)	104	342.8	106.92	160.8	332.0	633.9	31.2	327.4
C_{max} (ng/dL)	104	837.6	412.07	327.1	748.1	2200.5	49.2	755.4
T_{max} (days)	104	10.1	12.65	0	7.0	70.0	125.4	7.6
C_{avg} (ng/dL)	104	514.3	163.11	271.0	472.1	949.8	31.7	490.1

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

The mean serum total testosterone concentrations during 3rd and 4th injection were very similar and all mean values were within the normal range during the both injection intervals.

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



C_{max}:
The C_{max} criteria for success were met during the 4th injection interval; 96 patients (92.3%) had a serum total testosterone C_{max} value ≤1500 ng/dL; 4 patients (3.8%) had a C_{max} value between 1800 and 2500 ng/dL; and no patient had a C_{max} value >2500 ng/dL during the 4th injection interval. This result, once again confirm that TU 750 mg given intramuscularly at baseline, at 4 weeks, then at 10-week intervals thereafter does not result in excessively high serum total testosterone values in hypogonadal men.

Table C-8. Number (%) of Patients (and Two-sided 95% Confidence Interval) Meeting Serum Total Testosterone C_{max} Criteria for Success During the 4th Injection Interval, SS PK Population

Serum Total Testosterone C_{max} Observed During 3rd Injection Interval	**C-750 mg (N=104)**	
	N (%)	**95% CI**
≤1500 ng/dL	96 (92.3%)	(87.2%, 97.4%)
>1500 to <1800 ng/dL	4 (3.8%)	(0.2%, 7.5%)
1800-2500 ng/dL	4(3.8%)	(0.2%, 7.5%)
>2500 ng/dL	0	

Long term
Trough (immediately prior to injection) concentration of serum total testosterone was assessed at each 10-week dosing interval visit through Injection 9. Trough concentrations level up to 5 injections were provided during the 1st submission. The sponsor had provided additional trough concentration data up to 9 injections in this submission. The mean trough concentrations of serum total testosterone after the first injection ranged from 307.8 to 389.8 ng/dL and were within the normal range (300 to 1000 ng/dL).

Figure C-4. Mean (SD) Serum Total Testosterone Concentrations (ng/dL) at Trough Time Points Through the 9th Injection Week (Week 74), Long-Term Pharmacokinetic Population

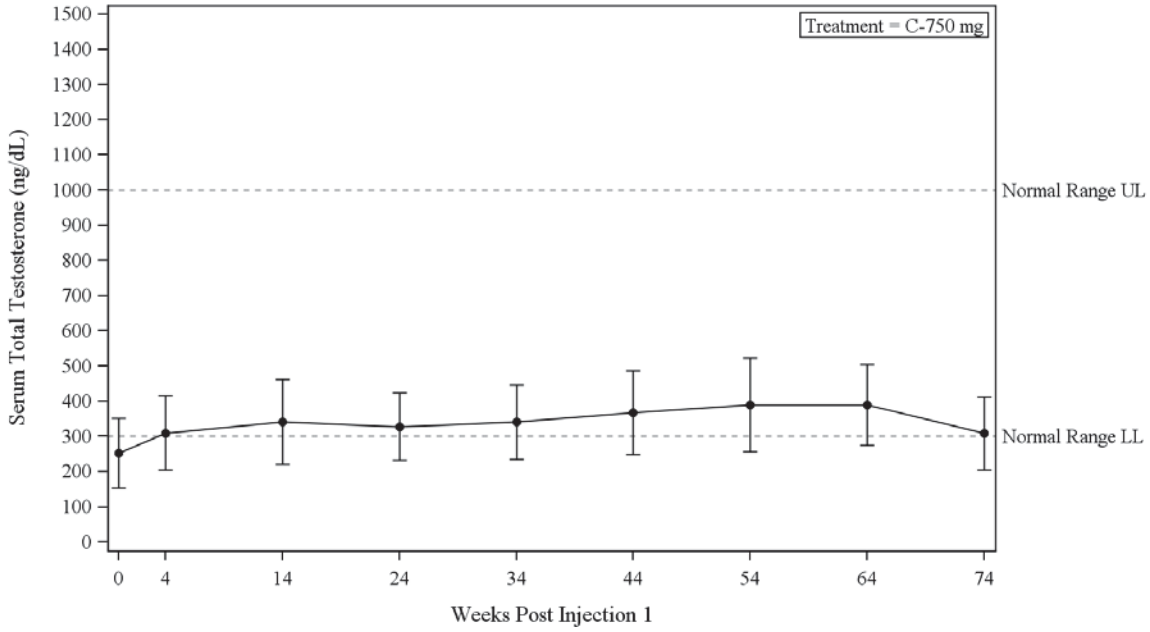


Table C-9. Descriptive Statistics for Serum Total Testosterone Concentration (ng/dL) by Trough Time Points Through All Injection Visits, Long-Term Pharmacokinetic Population

Visit	C-750 mg (N=98)							
	N	Mean	Std. Dev.	Min	Median	Max	%CV	Geometric Mean
Screening	98	219.3	71.05	24.3	239.0	343.0	32.4	200.8
Injection 1	98	251.6	98.86	0.0	254.4	538.4	39.3	230.7
Injection 2	97	309.6	104.91	133.4	304.3	705.5	33.9	293.5
Injection 3	98	340.5	120.69	141.4	310.6	754.1	35.4	321.5
Injection 4	98	327.6	96.11	165.4	319.2	611.1	29.3	314.2
Injection 5	98	339.9	105.87	160.8	330.1	633.9	31.1	324.8
Injection 6	97	367.1	119.12	185.1	354.3	795.7	32.4	349.7
Injection 7	98	389.4	133.13	178.3	362.9	781.5	34.2	369.0
Injection 8	98	389.8	114.45	172.8	380.2	706.8	29.4	373.3
Injection 9	6[a]	307.8	103.88	218.6	275.1	509.5	33.7	296.0

IP157-001 Parts C2

TITLE: **A Two-Arm, Open-Label, Randomized, Multi-Center Pharmacokinetic and Long-Term Safety Study of Intramuscular Injections of 750 mg and 1000 mg Testosterone Undecanoate in Hypogonadal Men**

Study Site:

Sponsor:	Endo Pharmaceuticals Inc, Chadds Ford, PA
Clinical Site:	Multicenter study of 8 investigative centers in the U.S.A
Analytical Site:	(b) (4)

Phase of Study: Phase 3 study

Primary Objective:
The primary objective for Part C2 of the study was to evaluate the maximum concentration (C_{max}) of testosterone from TU 750 mg, given intramuscularly at baseline, at 4 weeks, and then every 10 weeks thereafter, over the 10-week interval following the 2nd injection (through Day 14 post Injection 2), via multiple measurements of serum total testosterone, in up to approximately 20 hypogonadal men. In order to provide a complete pharmacokinetic (PK) profile of TU 750 mg during the 2nd injection interval, Day 70 of the 2nd injection interval was included in the evaluations.

Secondary Objectives:
- To compare serum levels of dihydrotestosterone (DHT), estradiol, and sex hormone binding globulin (SHBG) to simultaneous levels of serum total testosterone
- To evaluate safety in patients treated with TU 750 mg at baseline, at 4 weeks, and then every 10 weeks thereafter, through up to 6 injections in hypogonadal men

STUDY DESIGN:

Drug Products: Each (b) (4) TU contained 4 mL of Testosterone undecanoate drug product, in a concentration of 250 mg/mL in oily solution. In this study, the dose administered was 750 mg TU in 3 mL oily solution.

Part C2 was a multicenter, single-arm, open-label study with a planned enrollment of up to 20 patients. Part C2 functioned as a second cohort to Part C. The treatment arm was TU 750 mg in 3 mL (250 mg/mL) oily solution, injected intramuscularly into the buttock (deep gluteal muscle) at baseline, at 4 weeks and then every 10 weeks thereafter. TU 750 mg was administered up to 6 intramuscular injections (approximately 12 months/54 weeks). Each dose comprised 3 mL of TU in oily solution (TU 750 mg) and was to be administered at 9 AM (±3 hours). The injection site was alternated for each consecutive injection (i.e., the left and right buttocks rotated from one injection to the next).

All patients underwent intensive pharmacokinetic (IPK) assessments during the 2nd injection intervals. In addition, patients also underwent a trough (immediately prior to injection) pharmacokinetic (PK) assessment at each 10-week dosing interval visit through Injection 6. Safety was assessed throughout 6 injections (up to approximately 12 months/54 weeks).

Part C had 4 defined periods: Screening, Baseline, Stage 1, and Stage 2:

- Screening: Approximately 1- to 5-week screening period (washout from select prior testosterone replacement therapies could extend this period for some patients).
- Baseline: Final pre-study measurements were captured and patients were enrolled.
- Stage 1 (The first 2 injections, plus 4 post Injection 2 PK sample collection visits): This included the first injection at the baseline visit. The end of Stage 1 was to be the Day 14 post Injection 2 visit. The Stage 1 analysis was to include only data through the Day 14 post Injection 2 visit, which was to be the primary analysis for this part of the study. However, in order to provide a complete PK profile of TU 750 mg during the 2nd injection interval, Day 70 of the interval was included in the primary analysis
- Stage 2 (long-term safety extension): Followed Stage 1 and included 4 additional injections (at 10-week intervals) during an extended treatment phase.

Key inclusion criteria:

- Male with primary or secondary hypogonadism at least 18 years of age, weighing ≥143.3 lb (≥65 kg)
- Morning screening serum testosterone concentration <300 ng/dL
- If receiving endocrine replacement hormones (e.g., thyroid), antihypertensive, lipid lowering agents, antidepressants, or anxiolytic medications, the dose must be stable for at least 28 days prior to the first administration of the study drug or was not currently on such medications

Study Schedule:

	Injection Number and Week								
	Screening Phase		1	2	3	4	5	6	EOS
	Days -35 to -1	Post-Washout	Baseline Day 0	4	14	24	34	44	54[a]
Informed Consent	X								
Eligibility	X		X[b]						
Medical History (includes height)	X		X[b]						
Physical Examination	X								
Digital Rectal Examination, PSA	X		X	X	X	X	X	X	X
Vital Signs (includes pulse, blood pressure, weight, temperature)	X		X			X			
12-Lead Electrocardiogram	X								
Hematology, Coagulation, Chemistry (includes lipids), Urinalysis, FSH, LH	X		X						X
Prostate Volume (via TRUS)[c]	X								
Pharmacokinetic Sampling (Total and Free Testosterone, DHT, SHBG, estradiol)	X only if Washout NOT Required	X if Washout Required	X	X	X	X	X	X	
Adverse Events			X	X	X	X	X	X	X
Prior/Concomitant Medications	X		X	X	X	X	X	X	X
750 mg injection (includes drug accountability)			X	X	X	X	X	X	
Local tolerability assessment[d]			X	X	X	X	X	X	X
AUA Symptom Score	X								

Data Source: Protocol Amendment 10 (Appendix 16.1.1).

[a] Patients who discontinued prematurely from the study and who did not complete all of the treatment injections were to be assessed as listed under Week 54 or End of Study (EOS) visit. (Patients who discontinued prematurely from the study prior to Protocol Amendment 10 [see section 9.8.1] were to complete physical examination, vital signs, PK labs, and AUA Symptom Score.)

[b] Medical History and Eligibility pages were updated at baseline as appropriate.

[c] TRUS could be repeated during the study at the Investigator's discretion

[d] Injection site was assessed by Investigator if, at any time, the patient indicated a tolerability issue with the injection site.

AUA=American Urological Association; DHT=Dihydrotestosterone; FSH=Follicle stimulating hormone; LH=Luteinizing hormone; PK=Pharmacokinetic; PSA=Prostate specific antigen; SHBG=Sex hormone binding globulin; TRUS=Transrectal ultrasound

Study Population:

Of the 23 patients enrolled in Part C2, 21 of them completed Part C2, and 2 patients discontinued early. Reasons for early discontinuation were AE (1 patient [4.3%]) and patient withdrew consent (1 patient [4.3%])

Table C2-1. Summary of Demographic Characteristics, Total Patient Sample

Parameters	Category/statistics	All subject (N= 130)
Gender	Male	23
	Female	0
Age (years)	Mean ± SD	53.3 ± 10.35
	Range	30-71
Baseline Height (cm)	Mean ± SD	178.7 ±8.85
	Range	160-196
Baseline Weight (kg)	Mean ± SD	107.3 ±21.24
	Range	72-152
BMI (kg/m^2)	Mean ± SD	33.6 ± 6.31
	Range	23-48
Race	White	18 (78.3%)
	Asia	0
	Black	4 (17.4%)
	Hispanic	1 (4.3%)
	Other	0
Inclusion Screening Total Testosterone (ng/dL)	Mean ± SD	197.6 ± 75.81
	Range	29 -279

Pharmacokinetic Measurements:

- Intensive PK samples were collected after the 2nd injection on Days 0 (pre-injection), 4, 7, 11, 14, and 70. Theses intensive PK samples were used for the determination of serum total testosterone and DHT concentrations.
- Trough concentrations (immediately prior to each injection) were measured at every injection visit until the end of the study (up to 6 injections) or at early discontinuation from the study.

Data Analysis:

PK:

PK parameters $AUC_{0\text{-}70days}$, Dose-normalized AUC, C_{avg}, C_{max}, Dose-normalized C_{max}, C_{trough}, T_{max}, Tl_{ast} were derived for each Intensive PK interval following the 2nd injection. PK parameters were estimated using non-compartmental analysis within each patient using nominal (protocol-scheduled) time. Except C_{trough}, all parameters were derived for each IPK interval where C_{trough} was derived for both IPK and non-IPK injection intervals. WinNonLin® Professional version 5.3 was used to derive PK parameters.

Efficacy:

The primary study endpoint was to be based on the total testosterone C_{max} observed during the 2nd injection interval through Day 14 post Injection 2.

Primary Hypothesis:

TU 750 mg given intramuscularly at baseline, at 4 weeks, and then every 10 weeks thereafter during the 2nd injection interval does not result in excessively high serum total testosterone values in hypogonadal men. The primary hypothesis was tested as summarized below

Serum Total Testosterone Maximum Concentration (C_{max}) Observed During the 3rd Injection Interval	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.

Although the time period for assessment of this primary PK outcome, C_{max}, was to be based on the post 2nd injection period through Day 14, Day 70 of the interval was included in the evaluation in order to provide a complete PK profile of TU 750 mg during the 2nd injection interval.

Bioanalytical Analysis:
The concentration of serum Testosterone (T) and DHT in human serum samples were determined by using high performance liquid chromatography (HPLC) with tandem mass spectrometry (MS/MS) detection by (b) (4) The bioanalysis procedures and acceptance criteria are the same in Part C and Part C2 and are discussed in detail in the Clinical Pharmacology Review by Dr. Doanh Tran dated 05/05/2008 for Part C. The part C2 (including stage 1 and 2) has acceptable reported precision and accuracy of assay runs.
The method was appropriately validated ((b) (4) validation report 2100-801). Please see the Clinical Pharmacology Review by Dr. Doanh Tran dated 05/05/2008 for details of the validation report.

RESULTS:

Efficacy:

The primary study endpoint was to be based on the total testosterone C_{max} observed during the 2nd injection interval through Day 14 post Injection 2.

C_{max}:
22 patients (95.7%) had a serum total testosterone C_{max} value ≤1500 ng/dL; One patient (4.3%) had serum total testosterone C_{max} of >1500 ng/dL, but less than 1800 ng/dL. no patient had a C_{max} value between 1800 and 2500 ng/dL or Cmax value >2500 ng/dL during the 2nd injection interval. The mean C_{max} was 689.0 ng/dL. Thus, the C_{max} criteria for success were met during the 2nd injection. Therefore, TU 750 mg given intramuscularly at baseline, at 4 weeks, then at 10-week intervals thereafter does not result in excessively high serum total testosterone values in hypogonadal men.

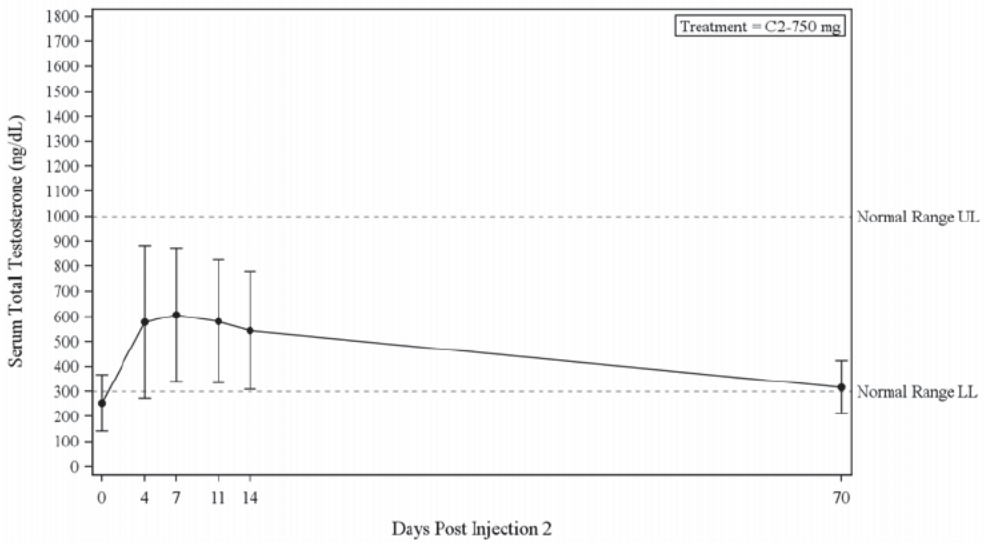
Table C2-2. Number (%) of Patients Meeting Serum Total Testosterone C_{max} Criteria for Success During the 2nd Injection Interval, Total Patient Sample / Pharmacokinetic Sample

	Criteria for Success	C2-750 mg (N=23)
Serum Total Testosterone C_{max} Observed During 2nd Injection		
≤1500 ng/dL	≥85% of Patients	22 (95.7%)

1800-2500 ng/dL	≤5% of patients	0
>2500 ng/dL	No Patients	0
Other Serum Total Testosterone C_{max} Observed During 2nd		
>1500 to <1800 ng/dL		1 (4.3%)

The mean serum total testosterone concentrations were within the normal range (300 to 1000 ng/dL) post Injection 2 and remained within the normal range through Day 70 of the interval.

Figure C2-1. Mean (SD) Serum Total Testosterone Concentrations (ng/dL) following the 2nd Injection



The majority of patients' serum total testosterone concentrations maintained within the normal range post 2nd injection.

Figure C2-2. By-Patient Serum Total Testosterone Concentrations (ng/dL) During the 2nd Injection

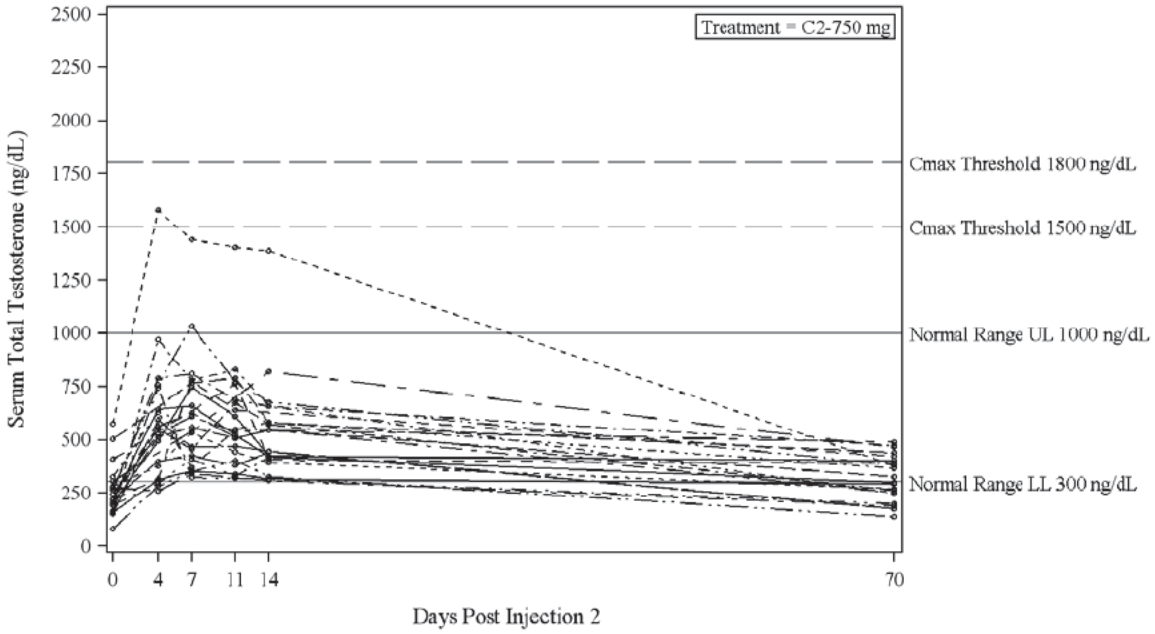


Table C2-3. Descriptive Statistics for Injection 2 Serum Total Testosterone (ng/dL) Pharmacokinetic Parameters, Pharmacokinetic Population

	C2-750 mg							
	n	**Mean**	**Std. Dev.**	**Min**	**Median**	**Max**	**%CV**	**Geometric Mean**
$AUC_{0\text{-}70days}$ (d·ng/dL)	23	31475.2	10990.41	17114.4	30436.2	68092.8	34.9	29910.2
C_{trough} (ng/dL)	23	317.4	105.31	135.8	298.9	487.5	33.2	299.1
C_{max} (ng/dL)	23	689.0	266.94	338.6	657.2	1576.3	38.7	646.6
T_{max} (days)	23	8.0	3.27	4.0	7.0	14.0	41.1	7.3
C_{avg} (ng/dL)	23	449.6	157.01	244.5	434.8	972.8	34.9	427.3

$AUC_{0\text{-}70days}$=Area under curve from Day 0 through Day 70; C_{avg}=Average concentration; C_{max}=Maximum concentration; C_{trough}=Day 70 concentration; CV=Coefficient of variation; T_{max}=Time of maximum concentration.

Secondary PK outcomes:

Table C2-4. Secondary Pharmacokinetic Outcomes During the 2nd Injection Interval

Pharmacokinetic Outcome	C2-750 mg (N=23) n (%)
Number (%) of Patients with At Least 1 Total Testosterone >1000 ng/dL	
At least 1 concentration >1000 ng/dL	2 (8.7%)
No concentration >1000 ng/dL	21 (91.3%)
Number (%) of Patients with At Least 1 Total Testosterone >1100 ng/dL	
At least 1 concentration >1100 ng/dL	1 (4.3%)

No concentration >1100 ng/dL	22 (95.7%)
Number (%) of Patients with At Least 1 Total Testosterone >1250 ng/dL	
At least 1 concentration >1250 ng/dL	1 (4.3%)
No concentration >1250 ng/dL	22 (95.7%)
Number (%) of Patients with At Least 1 Total Testosterone <300 or >1000 ng/dL	
At least 1 concentration <300 or >1000 ng/dL	14 (60.9%)
No concentration <300 or >1000 ng/dL	9 (39.1%)

Serum Dihydrotestosterone Concentrations

The serum DHT concentration-time-curve was similar to that of total testosterone. The mean ratio of DHT to total testosterone concentration dropped at Day 4 and then began to slowly rise following the 2nd injection of TU 750 mg.

Figure C2-3. Mean (SD) Dihydrotestosterone (pg/mL) for the 2nd Injection Interval

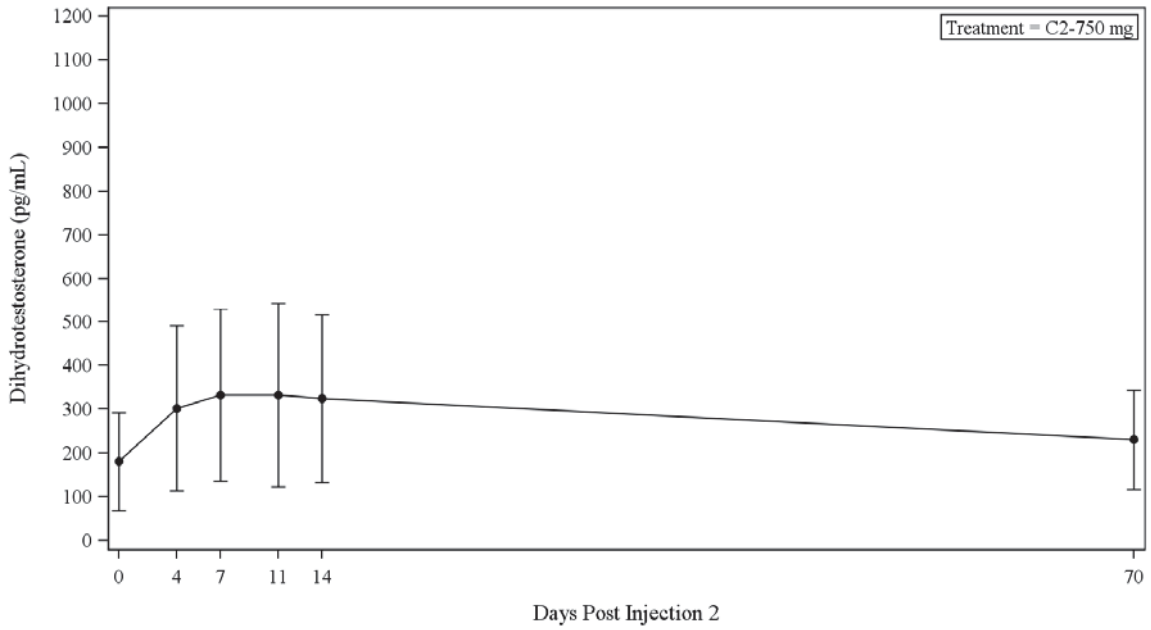
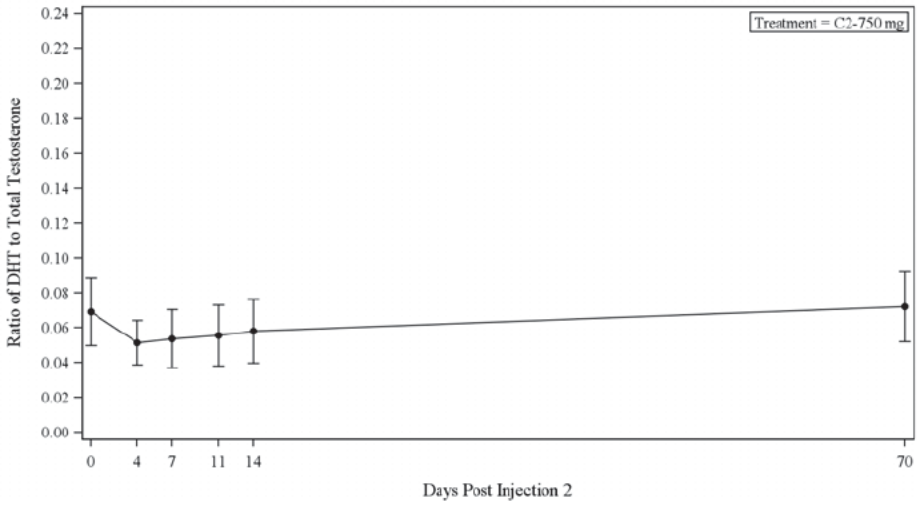


Figure C2-4. Mean (SD) Ratio of Dihydrotestosterone (ng/dL) to Total Testosterone (ng/dL) for the 2nd Injection Interval



Long Term:

Trough concentration of serum total testosterone was assessed up to Injection 6. The mean trough concentrations of serum total testosterone after the 2nd injection ranged from 316.2 ng/dL to 375.8 ng/dL and were within the normal range (300 to1000 ng/dL).

Figure C2-5. Mean (SD) Serum Total Testosterone Concentrations (ng/dL) at Trough Time Points Through the 6th Injection (Week 44)

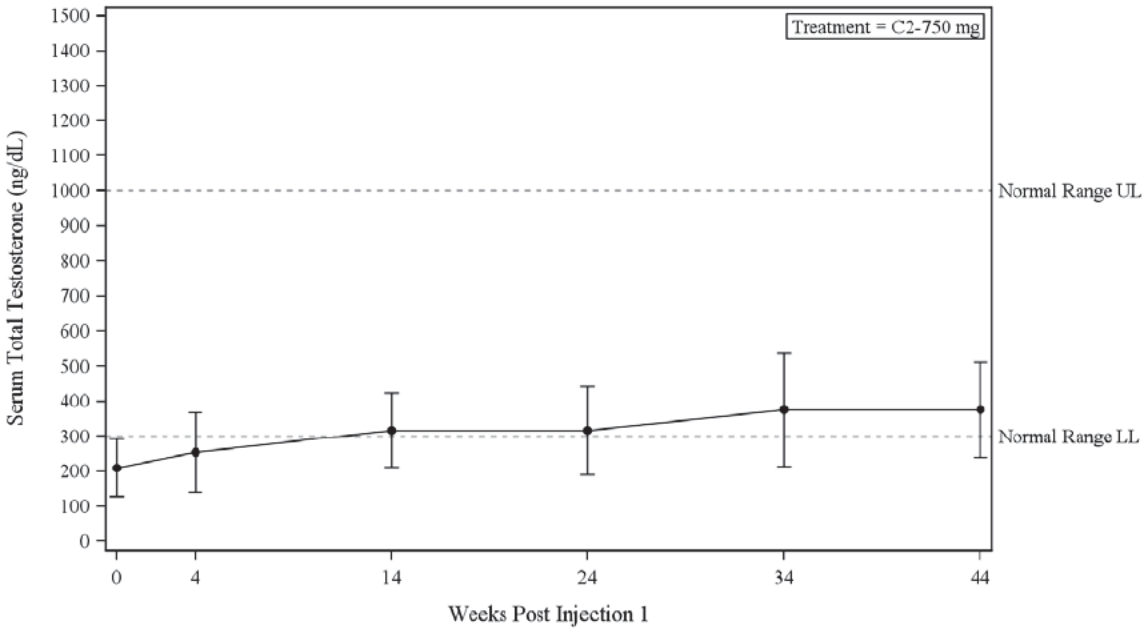


Table C2-5. Descriptive Statistics for Serum Total Testosterone Concentrations (ng/dL) by Trough Time Points Through All Injection Visits, Total Patient Sample / Pharmacokinetic Sample

Visit	C2-750 mg (N=23)

	n	Mean	Std. Dev.	Min	Median	Max	%CV	Geometric Mean
Screening	22	197.6	75.81	29.4	220.6	279.1	38.4	177.1
Injection 1	23	210.4	81.68	27.3	226.1	419.7	38.8	189.6
Injection 2	23	254.7	112.73	80.7	220.9	576.6	44.3	234.2
Injection 3	23	317.4	105.31	135.8	298.9	487.5	33.2	299.1
Injection 4	23	316.2	126.14	147.5	319.1	662.4	39.9	294.8
Injection 5	22	374.7	161.76	163.9	346.7	865.6	43.2	345.0
Injection 6	20	375.8	136.53	188.9	353.9	757.9	36.3	354.3

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/s/

DILARA JAPPAR
05/24/2013

EDWARD D BASHAW
05/24/2013

OFFICE OF CLINICAL PHARMACOLOGY REVIEW AMENDMENT

NDA: 22-219	Submission Dates: 3/2/2009, 6/8/2009, 6/15/2009, 6/22/2009, 8/14/2009
Brand Name	Aveed
Generic Name	Testosterone undecanoate
Reviewer	Doanh Tran, Ph.D.
Team Leader	Myong-Jin Kim, Pharm.D.
OCP Division	Division of Clinical Pharmacology 3
OND Division	Division of Reproductive and Urologic Products
Sponsor	Endo Pharmaceuticals, Inc.
Relevant IND	72,297
Submission Type	Resubmission
Formulation; Strength(s)	Intramuscular injection solution, 250 mg/mL
Indication	Testosterone replacement therapy in males

The Clinical Pharmacology review of NDA 22-219 resubmission (DFS, date 7/10/2009) recommended that NDA 22-219 was acceptable, provided that labeling recommendations are adequately addressed. This review amendment is to document that the sponsor has adequately addressed our labeling recommendations. The agreed labeling was submitted on 8/14/2009; it is attached in section 1.3 of this review amendment.

1.1 Recommendation

The Division of Clinical Pharmacology 3/Office of Clinical Pharmacology finds NDA 22-219 for testosterone undecanoate acceptable.

1.2 Phase IV Commitments

None

1.3 Labeling

The following is the agreed labeling.

10 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/ TS) immediately following this page.

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
NDA 22219	GI 1		NEBIDO
NDA 22219	ORIG 1		NEBIDO
NDA 22219	ORIG 1		NEBIDO
NDA 22219	ORIG 1		NEBIDO
NDA 22219	ORIG 1		NEBIDO
NDA 22219	ORIG 1		NEBIDO

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/s/

DOANH C TRAN
08/17/2009

MYONG JIN KIM
08/17/2009

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA: 22-219	Submission Dates: 3/2/2009, 6/8/2009, 6/15/2009, 6/22/2009
Brand Name	Aveed
Generic Name	Testosterone undecanoate
Reviewer	Doanh Tran, Ph.D.
Team Leader	Myong-Jin Kim, Pharm.D.
OCP Division	Division of Clinical Pharmacology 3
OND Division	Division of Reproductive and Urologic Products
Sponsor	Endo Pharmaceuticals, Inc.
Relevant IND	72,297
Submission Type	Resubmission
Formulation; Strength(s)	Intramuscular injection solution, 250 mg/mL
Indication	Testosterone replacement therapy in males

Table of Contents

1 Executive Summary

Testosterone undecanoate (TU) is an ester prodrug of testosterone (T). It is being proposed for the indication of T replacement therapy in males for conditions associated with a deficiency or absence of endogenous T. TU is proposed to be administered intramuscularly (IM) in the buttock. The dose being sought is 750 mg TU at start of therapy, 4 weeks later, and then every 10 weeks.

Original NDA 22-219 was submitted on 8/27/2007. It was considered acceptable from a clinical pharmacology perspective pending labeling negotiation (Clinical Pharmacology review, DFS date, 5/5/2008). There were safety and chemistry, manufacturing, and controls (CMC) issues that prevented the approval of NDA 22-219 during the original review cycle. An Approvable Letter was issued on 6/27/2008 listing Clinical and CMC deficiencies. There was no Clinical Pharmacology deficiency listed in the Approvable letter.

In this resubmission, the sponsor provided responses to the Clinical and CMC deficiencies. No new pharmacokinetic (PK) information was provided. This review primarily involved labeling recommendations.

A Clinical Pharmacology memorandum was entered into DFS on 5/13/2009 to document a labeling comment to Sponsor regarding the safety of administering the current TU product in patients with body weight < 65 kg. This comment was sent to Sponsor in an Information Request letter on 5/19/2009. The current labeling recommendations are included in section 2 of this review.

The Sponsor requested a full waiver from the requirement to submit assessments of TU in pediatric patients (boys) <18 years old. The Division of Reproductive and Urologic Products (DRUP) recommended granting a full waiver because there are too few children with the condition to study. The full waiver was reviewed by the Pediatric Review Committee (PeRC) Pediatric Research Equity Act of 2007 (PREA) Subcommittee on 4/29/2009. The PeRC agreed with the DRUP to grant a full waiver for this product.

1.1 Recommendation

The Division of Clinical Pharmacology 3/Office of Clinical Pharmacology finds NDA 22-219 for testosterone undecanoate acceptable, provided the labeling recommendations are adequately addressed.

1.2 Phase IV Commitments

None

2 Labeling Recommendations

Recommended revisions to the Sponsor's proposed label are presented below. The additions are shown as double underlined and deletions are shown as ~~strikethrough~~.

9 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page.

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/s/

Doanh Tran
7/10/2009 09:34:36 AM
PHARMACOLOGIST

Myong-Jin Kim
7/10/2009 11:03:28 AM
BIOPHARMACEUTICS

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA: 22-219	Submission Dates: August 24, 2007, December 20, 2007, February 8, 2008, and April 2, 2008
Brand Name	Nebido
Generic Name	Testosterone undecanoate
Reviewer	Doanh Tran, R.Ph., Ph.D.
Team Leader	Myong-Jin Kim, PharmD
OCP Division	Division of Clinical Pharmacology 3
OND division	Division of Reproductive and Urologic Products
Sponsor	Indevus
Relevant IND(s)	72,297
Submission Type	Original
Formulation; Strength(s)	Intramuscular injection solution, 250 mg/mL
Indication	Testosterone replacement therapy

Table of Contents

1 Executive Summary

1.1 Recommendation

The Office of Clinical Pharmacology/ Division of Clinical Pharmacology 3 has reviewed NDA 22-219. We find this NDA acceptable from a Clinical Pharmacology perspective, pending labeling discussion.

1.2 Phase IV Commitments

None

1.3 Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

Testosterone undecanoate (TU) is an ester prodrug of testosterone (T). It is being proposed for the indication of T replacement therapy in males for conditions associated with a deficiency or absence of endogenous T. TU is administered intramuscularly (IM) in the buttock. The dose being sought is 750 mg TU at start of therapy, 4 weeks later, and then every 10 weeks (± 3 days) (hereafter referred to as TU 750 mg LOADING regimen).

The NDA is supported by 2 phase 3 safety and efficacy studies (Study IP157-001 Part C and Study IP157-001 Part A). Study IP157-001 Part C evaluated the TU 750 mg LOADING (n=117) regimen and study IP157-001 Part A evaluated doses of 750 mg (n=102) or 1000 mg (n=97) given every 12 weeks to hypogonadal men. Because the primary endpoints in the phase 3 studies are pharmacokinetic (PK) endpoints, they are also the primary sources of PK data. Eleven other phase 1, phase 2, and phase 3 studies (JPH01495, JPH04995, JPH04995 Follow-up, ME98096, ME98096 Follow-up, ME98096 Final Follow-up, ME97029, ME97029 Follow-up, ME97029 Final Follow-up, 306605, and 306605 Follow-up) were provided in the NDA. However, these studies were not reviewed in depth because they used regimens that are not being sought in this NDA and used older assay methods (radioimmunoassay or electrochemoluminescence immunoassay) that are not as accurate as the current HPLC/MS/MS method used in the primary PK studies IP157-001 Part A and Part C.

(b) (4)

The sponsor requested the DRUP in a teleconference on 1/15/2008 to consider the TU 750 mg LOADING regimen studied in study IP157-001 Part C (study report submitted to the Division on 12/20/2007) for approval. Due to this change, data from study IP157-001 Part C were used as the source of steady state PK for the TU 750 mg LOADING regimen. Data from study IP157-001 Part A were used to assess the PK of TU 750 mg following a single IM injection because Part C did not evaluate first dose PK. Part A also served as the primary source of data on serum TU and dihydrotestosterone undecanoate (DHTU) because they were not measured in study IP157-001 Part C.

Steady state PK of the TU 750 mg LOADING regimen:
Following IM administration to the buttock, TU is slowly released from the injection site. TU is metabolized to T via ester cleavage of the undecanoic acid group. For the TU 750 mg LOADING regimen, the 3rd injection interval was determined to be the first injection interval that would represent steady state conditions for serum total T concentration. Steady state was assessed based on trough serum total T concentration following the 2nd, 3rd, and 4th injections. The 3rd injection interval was used as the primary PK and efficacy assessment. The following are the total T PK parameters from the 3rd injection interval:

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

Ninety four percent of patients (110 of 117) (95% confidence interval, CI, 89.6 - 98.5) had serum total T C_{ave} within the 300 – 1000 ng/dL range. Nine of 117 patients (7.7%) had C_{max} > 1500 ng/dL and no patient had C_{max} ≥ 1800 ng/dL during the 3rd injection interval. However, analysis of the data from the 4th injection interval indicated that 4 of 100 patients (4%) had C_{max} > 1800 ng/dL with values of 1994, 2000, 2178, and 2201 ng/dL, respectively.

Single dose PK of 750 mg TU:
The serum total T PK profile following a first injection of 750 mg TU (n=19) was similar to that at steady state but the C_{max} and C_{ave} values were lower. The mean (±SD) C_{max} and C_{ave} (over 84 days dosing interval) were 611 (224) ng/dL and 328 (96) ng/dL, respectively. The median T_{max} was 7 days.

Effect of body mass index (BMI) on exposure to T following a 3rd injection of 750 mg:
Post hoc exploratory analyses of data from study IP157-001 Part C indicate that baseline body weight and BMI were correlated with serum total T exposure. The mean total T C_{ave} were 578, 567, and 445 ng/dL for patients with baseline BMI of <26, 26-30, and >30 kg/m^2, respectively. The respective mean C_{max} were 1234, 1062, and 751 ng/dL for these 3 BMI groups. There was a trend that as body weight and BMI decreased, the exposure to total T increased. A similar trend was observed for both 750 mg and 1000 mg TU arms in study IP157-001 Part A following the 4th injection of the once every 12 weeks regimen.

The sponsor excluded 2 patients from PK analysis of study IP157-001 Part C due to their pre-treatment body weights being less than 65 kg. Only one patient (patient 031-7021) had serum T concentration available from the primary PK 3rd injection interval. He had a body weight of 59 kg and a BMI of 17.2. He exhibited high C_{max} and C_{ave} serum total T concentrations of 2888 ng/dL and 1164 ng/dL, respectively.

Effects on other hormones:
In addition to the increase in serum total T concentration following administration of IM TU, serum Free T, dihydrotestosterone (DHT) and estradiol (E2) were increased. TU administration did not affect concentration of sex hormone binding globulin (SHBG). The increases in serum DHT and E2 were expected since they are downstream metabolites of T. Because T binds mainly to SHBG and albumin, the increase in Free T concentration was consistent with the increase in total T and lack of SHBG effect. The concentration versus time profiles for Free T, DHT and E2 generally paralleled total T profile. The group mean concentrations at measured timepoints during the 3rd injection interval ranged from 203 – 544 pg/mL for Free T, 244 – 451 pg/mL for DHT, 14.4 – 35.6 pg/mL for E2, and 18.9 – 20.1 nmol/L for SHBG. TU was also observed in serum, generally only at the earliest sampling times of 4 and 7 days post injection. Concentration values of DHTU were below the limit of quantification (LLOQ = 100 ng/dL) for all but a few samples. None of the samples in the 1000 mg dose group had measurable DHTU concentration.

Method validation:
The primary PK studies IP157-001 Part C and IP157-001 Part A used an HPLC/MS/MS assay for T and DHT and a separate HPLC/MS/MS assay for TU and DHTU. Both assays were validated and acceptable.

Briefing: An optional inter-division Clinical Pharmacology briefing occurred on 4/15/2008 with the following in attendance: Edward D Bashaw, Myong-Jin Kim, Suresh Kaul, Harry Handelsman, Sandhya Apparaju, Chongwoo Yu, LaiMing Lee, Hyunjin Kim, and Lydia Velazquez.

2 Question Based Review

2.1 General Attributes

2.1.1 What is the proposed indication for testosterone undecanoate (TU)?

TU is indicated for testosterone (T) replacement therapy in males for conditions associated with a deficiency or absence of endogenous T:

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

2.1.2 What is male hypogonadism?

Male hypogonadism is characterized by a deficiency of endogenous T production resulting in abnormally low concentrations of circulating T, i.e., serum T concentration of <300 ng/dL. Male hypogonadism is classified in primary and secondary causes. Primary or hypogonadotropic hypogonadism, congenital or acquired, may be derived from numerous causes, including testicular failure due to cryptorchidism, bilateral testicular torsion, orchitis, orchidectomy, Klinefelter's syndrome, chemotherapy or toxic damage from alcohol or heavy metals. Secondary hypogonadism, congenital or acquired, is caused by idiopathic gonadotropin releasing hormone (GnRH) deficiency or pituitary-hypothalamic injury from tumors, trauma, or radiation. In the vast majority of cases, hypogonadism is related to a primary defect of the testes. Hypogonadism in adult men may vary with respect to the clinical presentation. T deficiency is accompanied by symptoms of different severity which include sexual dysfunction, reduced muscle mass and muscle strength, depressed mood and osteoporosis.

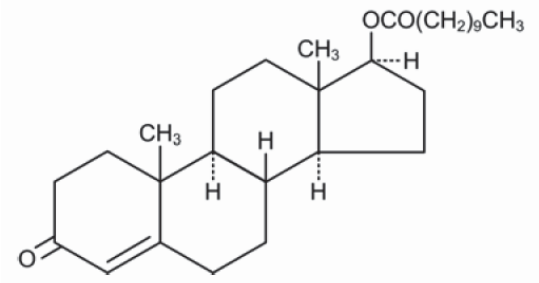
2.1.3 What is the main goal of T replacement therapy (TRT)? What are the current pharmacologic treatments?

T replacement has been used clinically to treat primary and secondary male hypogonadism. The goal of TRT is to achieve normal physiologic concentrations of T. This may help manage the symptoms associated with androgen deficiency. The available T replacement products include orally administered formulations, transdermal patches and gels, buccal formulations, as well as subcutaneous and intramuscular injections.

2.1.4 What is Nebido?

Nebido is a long-acting depot formulation of TU in castor oil and benzyl benzoate solution intended as T replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous T. TU is an ester of T that is metabolized to the active T by cleavage of the undecanoic acid side chain, presumably via serum esterases. The dosage form is an oily solution of 250 mg/mL TU (equivalent to 157.9 mg/mL T) intended for intramuscular (IM) injection. An injection of 3 mL yields 750 mg TU (b) (4)

Figure 1: Testosterone undecanoate



$C_{30}H_{48}O_3$

MW: 456.7

Endogenous T is synthesized mainly in the testes and in small amounts in the adrenal cortex. In men, T is responsible for the development of the male sex characteristics during fetal and neonatal development and pubertal maturation. T is required for maintenance of the male phenotype and other androgen-dependent functions, such as spermatogenesis and sexual behavior. Depending on the target organ, T's spectrum of action is primarily androgenic (e.g., prostate, seminal vesicles, epididymides) or protein-anabolic (musculature, bone, haematopoiesis, kidney, liver). The generally accepted "Normal" T value range in healthy (eugonadal) males is from 300 to 1000 ng/dL.

The half-life of T in the plasma is short, ranging from 10 to 100 minutes. Therefore, chemically modified T is used as one method of overcoming this limitation. Chemical modifications of T resulting in increased half-life, as compared to T, include T 1-alkylated derivatives and 17P-hydroxylated esters of T, such as TU and T enanthate (e.g., Delatestryl).

2.1.5 What are the sponsor's proposed dosage and route of administration?

TU is administered intramuscularly. The dose is 750 mg TU at start of treatment, at 4 weeks, and every 10 weeks thereafter (hereafter referred to as TU 750 mg LOADING regimen). TU is administered with slow deep IM injection into the buttock (deep gluteal muscle). For each consecutive injection, the injection site is alternated between buttocks.

2.1.6 What studies were conducted in support of this NDA?

The sponsor initially submitted the final study report for study IP157-001, Part A, Stage 1 to provide the primary evidence of efficacy and safety for TU (b) (4) the sponsor submitted the final study report for study IP157-001, Part C, Stage 1 which evaluated the TU 750 mg LOADING regimen (i.e., 750 mg TU at start of treatment, at 4 weeks, and every 10 weeks thereafter). During a teleconference with the Division of Reproductive and Urologic Products on January 15, 2008, the sponsor decided to only seek approval for the TU 750 mg LOADING regimen.

Since the primary efficacy endpoints in the phase 3 trials are PK endpoints, these studies (Part A and Part C) also provided PK characterization of TU following both single and multiple dosing.

In addition to the primary PK data obtained from studies IP157-001 Part A and IP157-001 Part C, the results from 11 other clinical studies (single dose study: JPH01495, multiple dose studies: JPH04995, JPH04995 Follow-up, ME98096, ME98096 Follow-up, ME98096 Final Follow-up, ME97029, ME97029 Follow-up, ME97029 Final Follow-up, 306605, and 306605 Follow-up) conducted in Europe were provided as supporting data. These supporting studies did not use the same TU 750 mg LOADING regimen that is being sought in this NDA and they were not used to directly support the TU 750 mg LOADING regimen. The results of these studies helped in the design of the phase 3 studies during drug development. However, the results are no longer applicable to the efficacy assessment (i.e., T PK) of the final regimen being sought in this NDA. In addition, these studies used older assay methodologies, namely radioimmunoassay (RIA) or electrochemoluminescence immunoassay, that are not as accurate as the HPLC/MS/MS method used in the primary PK study IP157-001 (see section 2.6.2 for additional details on these older assays). Therefore, these supporting studies were not reviewed in depth and the results are not reported in this review except for the single dose PK study JPH01495.

2.1.7 What are the preset primary and secondary endpoints for the phase 3 study?

The primary efficacy endpoint is C_{ave} (calculated as $AUC_{0\text{-}tau}$/tau where tau is the dosing interval) within the range of 300 – 1000 ng/dL. To meet the efficacy criteria, the point estimate for the primary endpoint must be at least 75% and the lower bound of the two-sided 95% confidence interval about the defined primary efficacy variable must be not lower than 65%.

Additionally, a secondary endpoint on C_{max} is based on the criteria in table 1. The primary and secondary endpoints were assessed based on data from the 3rd injection interval of the TU 750 mg LOADING regimen.

Table 1: 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).		

2.2 General Clinical Pharmacology

2.2.1 What is the pharmacokinetics of TU?

Based on observed serum concentration of TU, T, dihydrotestosterone (DHT) and estradiol (E2) and known properties of T we can deduce that TU is metabolized to T and subsequently to DHT and E2. TU may also be metabolized, to a lesser extent, to dihydrotestosterone undecanoate (DHTU). No new data were provided on the metabolism of T. Sponsor relied exclusively on known properties of T based on class labeling of T replacement products to address distribution, metabolism, and excretion of T. Based on the most recent labeling approval for a T replacement product, the following is known:

Distribution
Circulating T is primarily bound in the serum to sex hormone-binding globulin (SHBG) and albumin. Approximately 40% of T in plasma is bound to SHBG, 2% remains unbound (free) and the rest is bound to albumin and other proteins.
Metabolism
There is considerable variation in the half-life of T as reported in the literature, ranging from 10 to 100 minutes. T is metabolized to various 17-keto steroids through two different pathways. The major active metabolites of T are E2 and DHT.
Excretion
About 90% of a dose of T given intramuscularly is excreted in the urine as glucuronic and sulfuric acid conjugates of T and its metabolites; about 6% of a dose is excreted in the feces, mostly in the unconjugated form. Inactivation of T occurs primarily in the liver.

The remainder of this section will be divided into 3 main subsections to address the following: 1) PK of the TU-Loading regimen that is being sought in this NDA, 2) 1st injection PK up to 12 weeks post injection, and 3) PK of the standard 12-week regimen.

2.2.1.1 What is the pharmacokinetics of TU following IM injections to the buttock using the TU 750 mg LOADING regimen?

The PK of the TU 750 mg LOADING regimen was examined in a Phase 3 study IP157-001 Part C entitled, 'A Two-Arm, Open-Label, Randomized, Multi-Center Pharmacokinetic and Long-term Safety Study of Intramuscular Injections of 750 mg and 1000 mg TU In Hypogonadal Men.' The study enrolled 130 male patients with primary or secondary hypogonadism at least 18 years of age with morning screening serum T concentration < 300 ng/dL. Each patient received 750 mg TU (250 mg/mL) in 3 mL oily solution, injected at baseline, 4 weeks later and then every 10

weeks thereafter. Study IP157-001 was divided into 2 stages. Stage 1 was from start of treatment through the end of the 3rd injection interval. Stage 2 was from the 4th injection through the 9th injection. Data for Stage 1 and the 4th injection interval part of Stage 2 were reported in this NDA.

PK results:

Steady state assessment:
Assurance of the presence of steady state conditions during the 3rd injection interval is important because the PK parameters calculated from data obtained during the 3rd injection interval are used to help assess the safety and efficacy of chronic TU administration.

Trough serum total T concentrations following the 2nd, 3rd, and 4th injection of the TU 750 mg LOADING regimen were used to assess whether steady state conditions were reached during the 3rd injection interval. The mean data indicated that the serum T C_{trough} values were similar at end of 2nd, 3rd, and 4th injection intervals (figure 2 and table 2). An analysis of individual data did not reveal any particular trend of shift in C_{trough} with each subsequent injection (data not shown). A comparison of serum total T concentration at several time points post injection during the 3rd and 4th injection intervals indicates similar PK profiles (figure 3). Together, these data indicated that steady state conditions were achieved during the 3rd injection interval.

Figure 2: Mean (±SD) serum total T concentrations at each injection visit (trough) from pre-treatment through 5th injection – Steady state PK population, study IP157-001 Part C

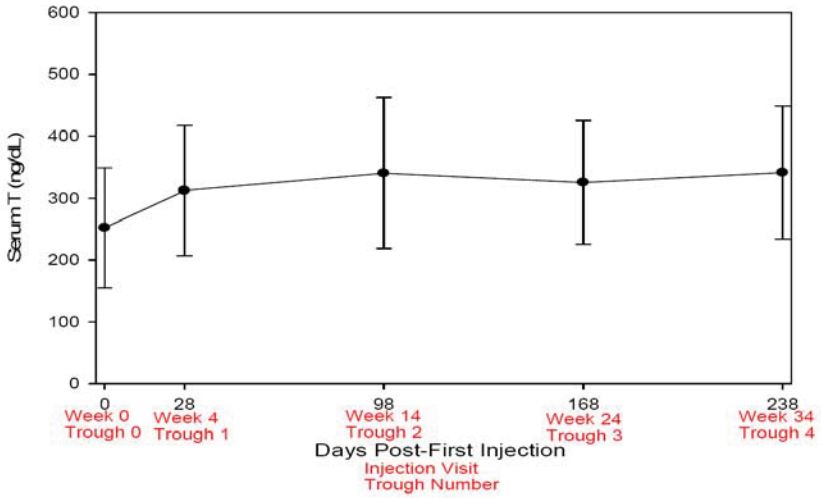
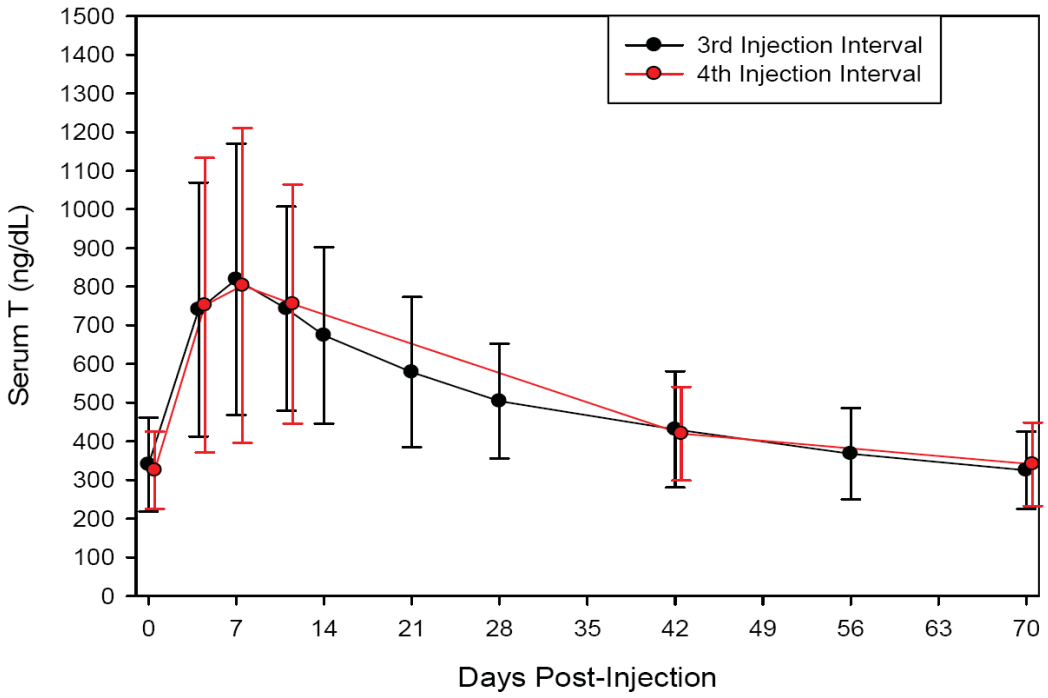


Table 2: Descriptive statistics for Serum total T concentration at each injection visit (trough) from pre-treatment through 5th injection – weeks post-first injection – Steady State Population, study IP157-001 Part C Stage 1 and Stage 2

	Serum Total Testosterone (ng/dL) (N=105)		
Time	**Mean**	**Standard Deviation**	**Range**
Week 0/Injection 1	251.3	96.79	0 to 538
Week 4/Injection 2	312.2	104.85	133 to 706
Week 14/Injection 3	340.1	122.17	141 to 754
Week 24/Injection 4	325.0	99.64	107 to 611
Week 34/Injection 5	340.9	108.09	148 to 634
Source: Table 9.2.1.2.1.1			

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



It was noted that the mean steady state T average concentration (C_{ave}) of the TU 750 mg LOADING regimen of 494.9 ng/dL (see C_{ave} assessment below) is similar to the estimated steady state T C_{ave} of 489 ng/dL following TU administration using the standard 750 mg regimen that uses a longer dosing interval of every 12 weeks (Study IP157-001 Part A and Section 2.2.1.5). Theoretically, the same dose given at shorter dosing interval of 10 weeks should yield a steady state C_{ave} that is about 20% higher than one given every 12 weeks, assuming linear PK. This brings into questions whether the C_{ave} following the 3rd dose of the TU 750 mg LOADING regimen truly represents steady state. A possible reason for the apparent lower than expected C_{ave} of the TU 750 mg LOADING regimen relative to the every 12 weeks regimen may be differences in study cohorts. Another reason could be any potential differences in injection site properties due to the different washout times between injections (10 vs. 12 weeks). Mean pre-treatment body weight and baseline serum total T concentration were similar between the 2 cohorts.

However, as noted previously the T C_{trough} concentrations following the 2nd, 3rd, and 4th injections were similar, indicating that the 3rd dose interval would represent steady state conditions. Additionally, examination of individual C_{trough} T concentrations following the 2nd, 3rd, and 4th injections did not reveal a specific increasing or decreasing trend with each subsequent injection. In the absence of convincing evidence to indicate that the 3 trough concentrations are erroneous, this reviewer concurs that steady state conditions have been achieved during the 3rd injection interval.

Average serum concentration (C_{ave} or C_{avg}, used interchangeably in this review) assessment:

C_{ave} was calculated by dividing the area under the concentration vs. time curve (AUC) from 0 to 70 days by the dosing interval of 70 days. The primary analysis was based on the 3rd injection interval which represents steady state conditions.

Following TU injection at steady state, serum total T concentration rose to a mean C_{max} of 891 ng/dL at a median T_{max} of 7 days. The T concentration declines gradually over the remainder of the 7-day dosing interval due to slow release of the drug from the injection site. The mean serum T concentrations was within the normal range of 300 – 1000 ng/dL throughout the dosing interval (figure 4). The mean (±SD) total T C_{ave} was 494.9 (141.5) ng/dL. 5% of patients (6 of 117) had serum C_{ave} < 300 ng/dL and did not get sufficient T replacement. 1 patient out of 117 had C_{ave} > 1000 ng/dL. 94% (95% CI 89.6 – 98.45) of patients (110 of 117) had serum total T C_{ave} within the 300 – 1000 ng/dL range. These data indicate that the TU 750 mg LOADING regimen met the primary C_{ave} PK efficacy criteria. The validity of the statistical calculation is reviewed by the Statistics reviewer.

Figure 4: Mean (±SD) serum total T concentrations following the 3rd injection interval of TU 750 mg LOADING regimen (Study IP157-001 Part C)

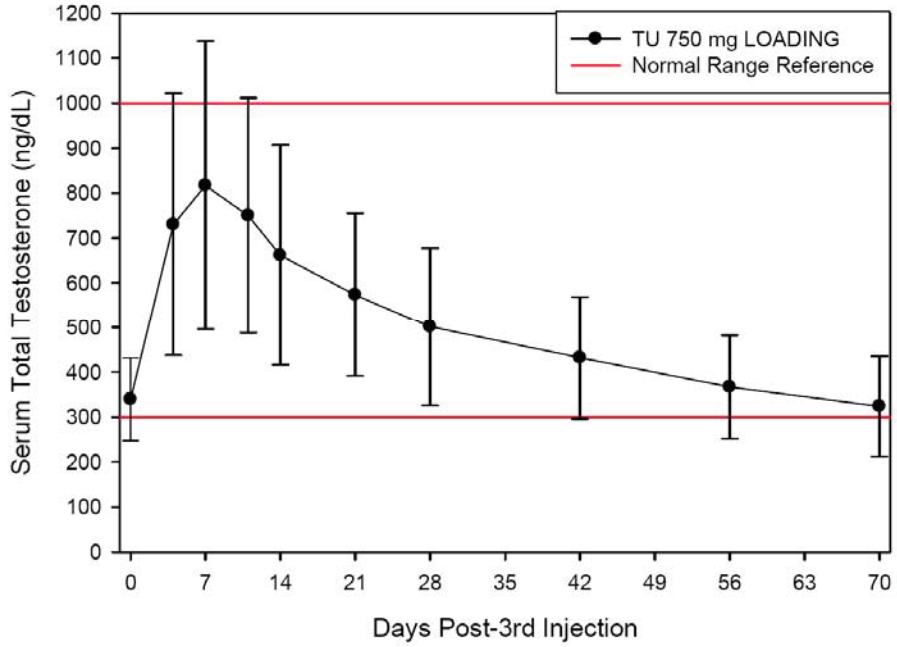


Figure 5: Composite of individual serum total T concentration following the 3rd injection of the TU 750 mg LOADING regimen – PK population, study IP157-001 Part C

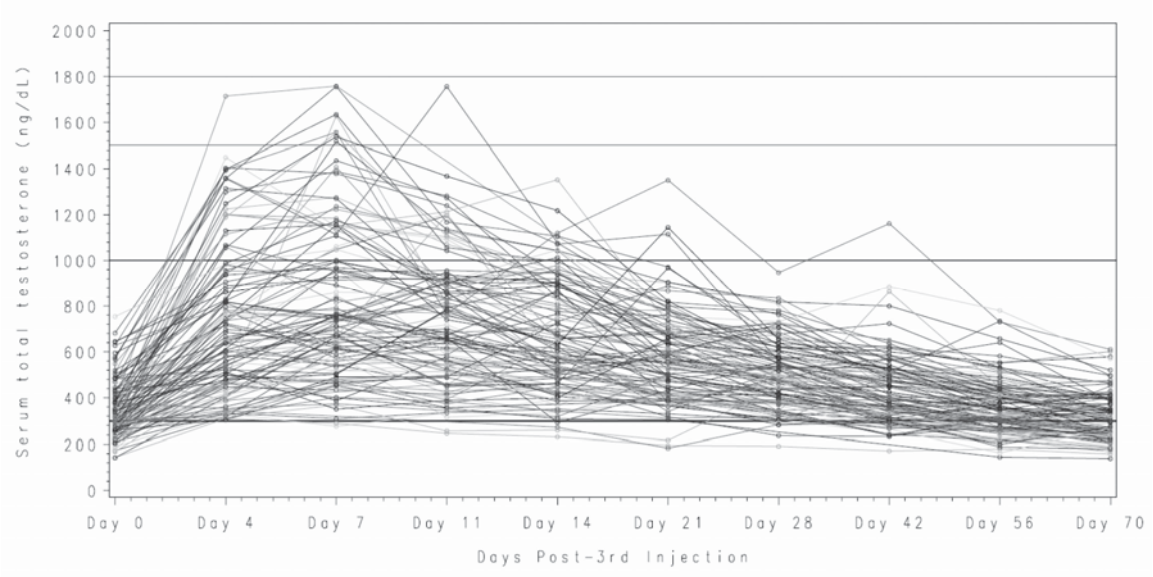


Table 3: PK parameters of serum total T (ng/dL) following the 3rd injection interval of TU 750 mg LOADING regimen (PK population, study IP157-001 Part C)

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

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

C_{max} assessment:

The assessment of C_{max} was based on the observed maximum serum T concentration in each individual during his 3rd injection interval using the PK population. Additional analyses of 1 patient excluded from the 3rd injection PK population and total T concentration from the sparse samplings during the 4th injection interval were also conducted.

Based on the PK population (n=117), no patient experienced $C_{max} \geq 1800$ ng/dL during the 3rd injection interval (figure 5). Nine patients (7.7%) had $C_{max} > 1500$ ng/dL (Table 4). The C_{max} criteria were met based on the PK population.

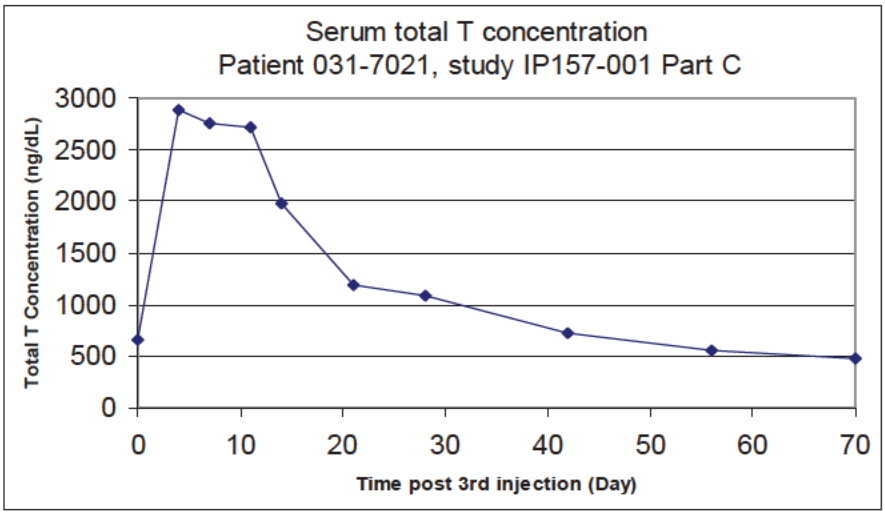
However, there was one patient in Part C (Patient 031-7021) who was excluded from the PK population due to a body weight below 65 kg. The sponsor indicated that this additional PK population exclusion criterion was added after the statistical analysis plan was finalized. It is not clear if the assay results were known to the sponsor before this exclusion criterion was added. This patient experienced serum T concentrations above 2500 ng/dL at 3 consecutive sampling days (days 4, 7, and 11) during the 3rd injection interval (figure 6). His serum total T C_{max} and C_{ave} were 2888 ng/dL and 1164 ng/dL, respectively. The sponsor indicated that the intended population for treatment with TU is hypogonadal men with a body weight of at least 65 kg. However, the protocol did not exclude patients based on body weight or BMI. This information should be considered for risk vs. benefit assessment and appropriate labeling should be done. This issue has been brought to the attention of the NDA review team for consideration.

Table 4: Summary of C_{max} assessment of serum total T concentrations during the 3rd injection interval compared to C_{max} thresholds approvability criteria – PK population, study IP157-001 Part C

	Number of Patients Exceeding/Number of Patients Assessed (Percent of Patients Exceeding)
C_{max} Outcome	**TU 750 mg LOADING (N=117)**
> 1500 ng/dL[1]	9 of 117 (7.7%)
≥ 1800 ng/dL and < 2500 ng/dL	0 of 117 (0%)
≥ 2500 ng/dL	0 of 117 (0%)
Did Dose Meet Threshold Limits?	**Yes**

Reference: Section 14.2 Table 9.2.1.3
[1] The > 1500 ng/dL classification includes all patients with at least one T concentration > 1500 ng/dL (and thus also includes any patients with a T ≥ 1800 ng/dL).
Note: The PK Population excluded patients who weighed less than 65 kg.

Figure 6: Serum total T concentration in patient 031-7021 who was excluded (post hoc) from the PK population due to his body weight <65 kg. He had a body weight of 59 kg and a BMI of 17.2.



An analysis of the 4th injection interval total T data (sparse PK sampling on days 4, 7, 11, 42, and 70 post injection) revealed that 4 patients (of 100 with PK data) had C_{max} between 1800 ng/dL and 2500 ng/dL (Table 4A). Within-subject comparisons of the 4th injection C_{max} to the 3rd injection C_{max} indicated increases of 24 – 62% in these 4 patients. Correlation analysis of 3rd injection C_{trough} and 4th injection C_{max} of data from these 4 patients indicated an inverse relationship. This suggests that the high C_{max} observed during the 4th injection interval may be due to variability in the PK instead of a trend of increasing concentration with subsequent dose. It should be noted that while the sparse sampling times likely captured the C_{max} in most patients, some patients might have had C_{max} at other times.

Table 4A: Maximum observed total T concentrations for 4 patients with high C_{max} during the 4th injection interval (Study IP157-001 Part C)

Patient ID	4th injection C_{max} (ng/dL)	3rd injection C_{max} (ng/dL)	3rd injection C_{trough} (ng/dL)
063-7123	1994	1236	465
078-7135	2000	1554	463
054-7109	2178	1756	338
031-7030	2201	1404	293

2.2.1.2 What is the single-dose pharmacokinetics of TU following IM injection to the buttock?

The sponsor did not capture the first dose PK in study IP157-001 using the TU 750 mg LOADING regimen. However, single dose PK of TU was characterized in 2 subgroups of patients enrolled in study IP157-001, Part A. Study IP157-001 Part A enrolled hypogonadal men of at least 18 years of age. First dose PK measurements were obtained from small subpopulations for both the 750 mg dose (n=19) and 1000 mg dose (n=19). The sampling times are Day 0 (pre-dosing), Day 4, 7, 11, 14, 21, 28, 42, 56, 70, and at the end of the injection interval Day 84 (pre-second injection).

Serum T concentration was elevated following the first injection of 750 mg or 1000 mg TU with a median T_{max} of 7 days. The IM depot formulation allowed for a prolonged profile of elevated serum T concentration. Most patients had C_{trough} <300 ng/dL at the end of the 84-day dosing interval in this first dose PK assessment.

Figure 7: By-treatment mean (+SD) serum total T concentrations over 84 days resulting from a single injection of TU - 1st IPK population (Study IP157-001 Part A)

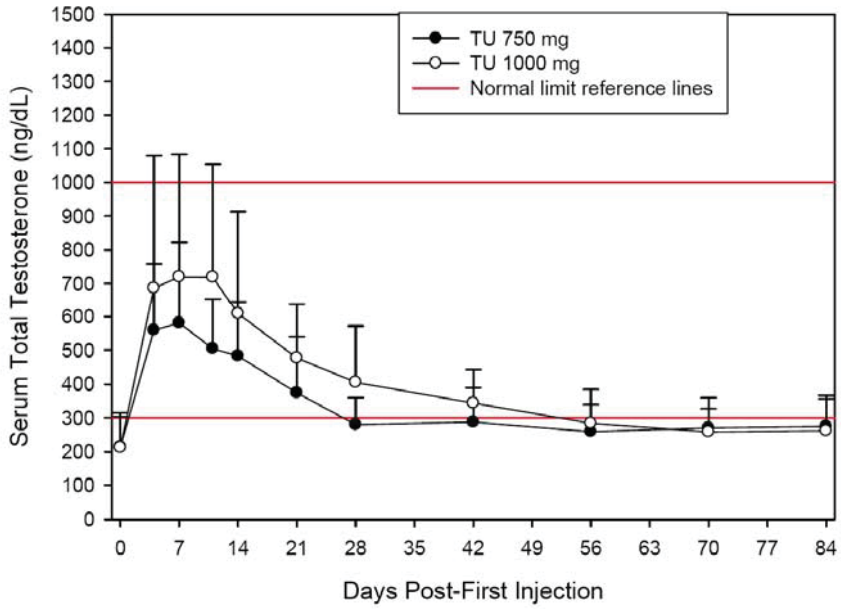


Figure 8: Individual (n=19) serum total T concentrations during first injection interval of 750 mg TU (Study IP157-001 Part A).

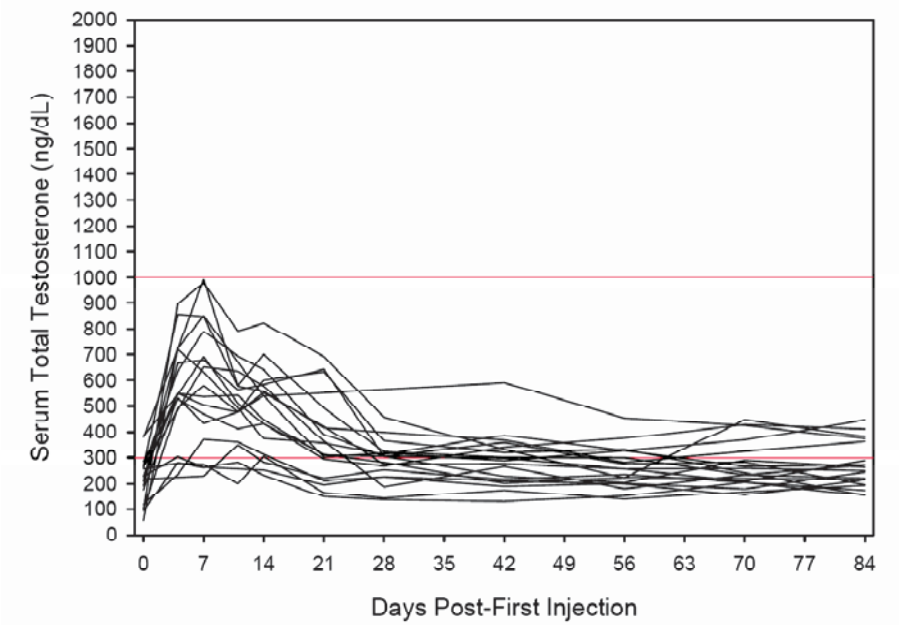


Figure 9: Individual (n=19) serum total T concentrations during first injection interval of 1000 mg TU (Study IP157-001 Part A).

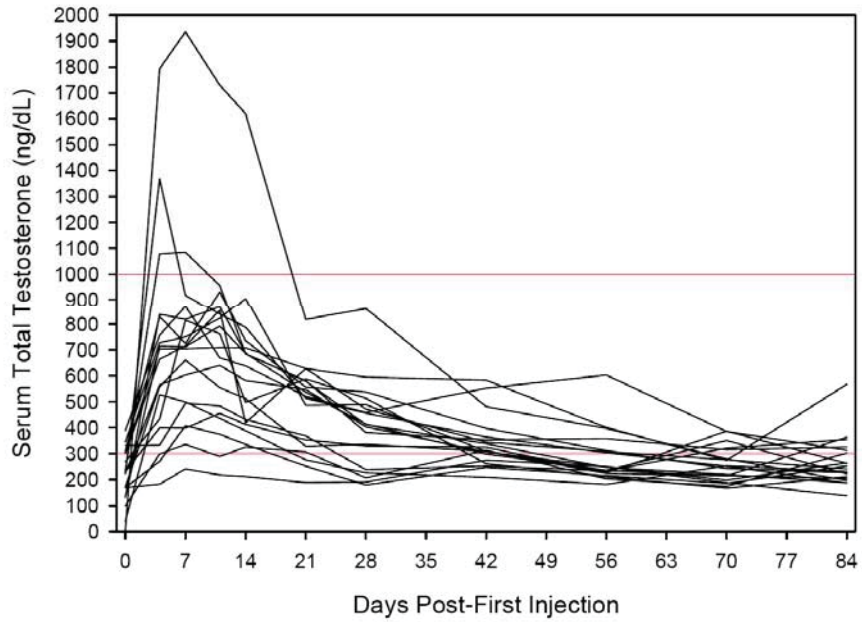


Table 5: PK parameters of serum total T resulting from a single injection of TU – 1st IPK population in study IP157-001 Part A.

TU Dose	Pharmacokinetic Parameter	Number Patients	Mean	Standard Deviation	Minimum	Median	Maximum	CV (%)	Geometric Mean
750 mg	$AUC_{(0-84)}$ (days*ng/dl)	19	27513.0	8045.18	14515.5	27723.6	43609.6	29.2	26329.4
	C_{Trough} (Day 84)	19	267.3	88.36	152.8	248.6	446.8	33.1	254.3
	C_{max} (ng/dL)	19	611.1	223.69	281.0	633.5	991.9	36.6	568.9
	Dose-normalized C_{max}(ng/dL)[1]	19	0.8	0.30	0.4	0.8	1.3	36.6	0.8
	T_{Last} (days)	19	84.0	0.00	84.0	84.0	84.0	0.0	84.0
	T_{max}	19	8.5	4.59	4.0	7.0	21.0	54.1	7.5
	Dose-normalized $AUC_{(0-84)}$ (days*ng/dl)[1]	19	36.7	10.73	19.4	37.0	58.1	29.2	35.1
	$C_{avg, 0-84}$ (ng/dL)[2]	19	327.5	95.78	172.8	330.0	519.2	29.2	313.4
1000 mg	$AUC_{(0-84)}$ (days*ng/dl)	19	32713.7	9894.60	18944.0	32419.8	59561.7	30.2	31384.7
	C_{Trough} (Day 84)	19	265.9	94.65	137.3	240.8	567.5	35.6	252.9
	C_{max} (ng/dL)	19	785.5	388.07	275.2	792.2	1935.1	49.4	706.1
	Dose-normalized C_{max}(ng/dL)[1]	19	0.8	0.39	0.3	0.8	1.9	49.4	0.7
	T_{Last} (days)	19	84.0	0.00	84.0	84.0	84.0	0.0	84.0
	T_{max}	19	10.4	8.13	4.0	7.0	42.0	78.4	8.9
	Dose-normalized $AUC_{(0-84)}$ (days*ng/dl)[1]	19	32.7	9.89	18.9	32.4	59.6	30.2	31.4
	$C_{avg, 0-84}$ (ng/dL)[2]	19	389.4	117.79	225.5	386.0	709.1	30.2	373.6

Reference: Section 14.2 Table 9.2.1.1.2
CV = Coefficient of Variation
[1] Statistics for the dose normalized AUC were derived by dividing the mean of the original parameter ($AUC_{(0-84)}$) by the dose amount (750 mg or 1000 mg).
[2] C_{avg} derived as $AUC_{(0-84)}$/84 days

Review note on the next 3 sections:

Sections 2.2.1.3, 2.2.1.4, and 2.2.1.5 discuss the PK following the once every 12 weeks regimen. They are presented to provide 1) additional support for the TU formulation, 2) link to measured TU and DHTU concentrations that were not measured in the TU 750 mg LOADING regimen, and 3) documentation that the 4th injection interval of the TU 1000 mg every 12 weeks regimen did not represent steady state and that it likely would not meet the C_{max} criteria at steady state.

(b) (4)

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(b) (4)

2.2.2 What is the relative dose-exposure relationship?

Based on data obtained during the 4th injection interval of study IP157-001 Part A where hypogonadal men were administered 750 mg or 1000 mg TU IM Q12WK, relative to the 1000 mg dose, the 750 mg dose yield about (b) (4) C_{max} and AUC of total T (Table 12). (b) (4)

(b) (4)

Table 12: Ratios of dose-normalized C_{ma} and AUC (TU 750 mg versus TU 1000 mg) of serum total T following the 4th injection (b) (4) – PK population (study IP157-001 Part A)

(b) (4)

Table 13: Ratios of dose-normalized C_{max} and AUC (TU 750 mg versus TU 1000 mg) of serum total T following the 1st injection – 1st IPK population (study IP157-001 Part A)

Parameter[1]	Ratio of Means	Ratio of Geometric Means
Dose-normalized C_{max}	1.00	1.14
Dose-normalized $AUC_{(0-84)}$	1.12	1.12

Reference: Section 14.2 Table 9.2.1.1.1

[1] Ratio of dose-normalized C_{max} and $AUC_{(0-84)}$ derived by dividing the dose-normalized mean (or geometric mean) for the 750 mg arm by the corresponding mean (or geometric mean) for the 1000 mg arm. A ratio of '1' indicates the dose-normalized means were equal. A ratio above '1' indicates the 750 mg arm dose-normalized mean (or geometric mean) was higher than the dose-normalized mean (or geometric mean) in the1000 mg arm.

2.2.3 What is the relative concentration of Free T (unbound T), DHT, E2, SHBG and total T following IM administration of TU?

Relative concentration of Free T, DHT, E2 and total T were evaluated in both Part A and Part C of study IP157-001. The results were similar between the 2 parts. Since the sponsor is only seeking approval of the regimen used in Part C and for simplicity of discussion, only data from Part C will be discussed here. The results of both parts may be viewed in their respective individual study reports attached at the end of this review.

Following administration of IM TU, elevation of serum Free T, DHT and E2 were observed. TU administration did not affect concentration of SHBG. The increases in serum DHT, and E2 were expected since they are downstream metabolites of T. Since T binds mainly to SHBG and albumin, with SHBG concentration unchanged (assuming no change in albumin concentration), the increase in Free T concentration was also expected. The concentration versus time profiles for Free T, DHT and E2 generally paralleled the T profile. The mean concentrations during the 3rd injection interval ranged from 203 – 544 pg/mL for Free T, 244 – 451 pg/mL for DHT, 14.4 – 35.6 pg/mL for E2, and 18.9 – 20.1 nmol/L for SHBG.

The following section describes the data obtained during the 3rd injection interval of the TU 750 mg LOADING regimen (i.e., weeks 14 – 24 after start of TU treatment).

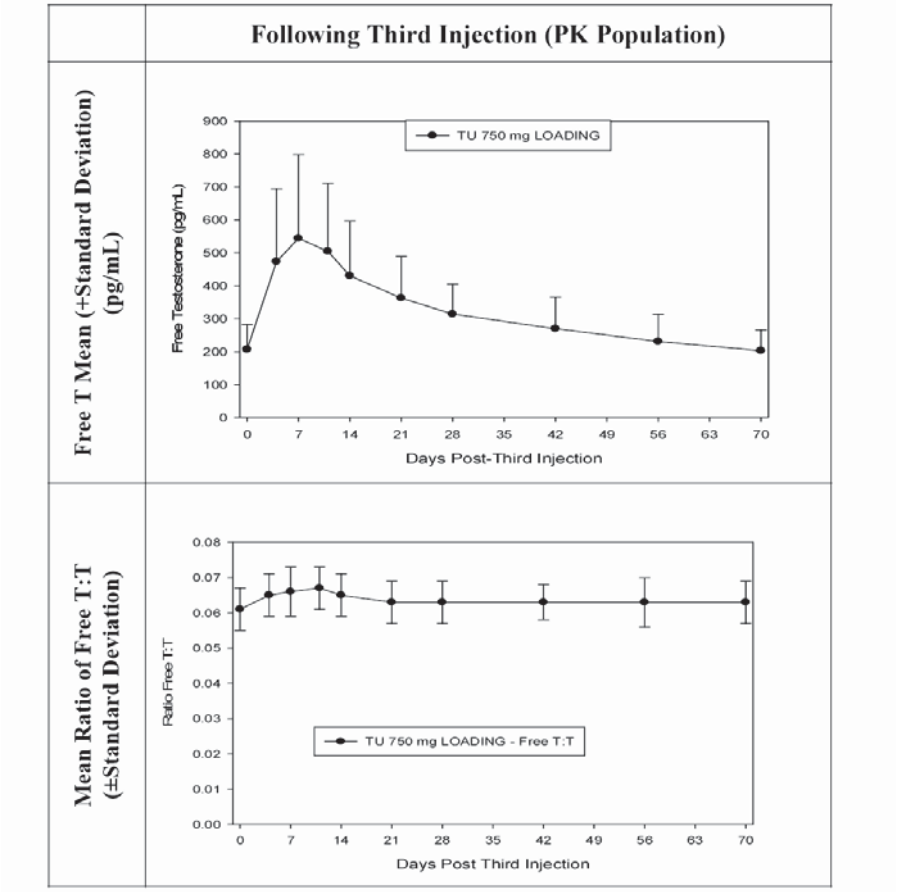
Serum Free T concentration:

Average Free T concentrations generally paralleled T concentrations (figure 14). Average Free T concentrations were generally above the normal range of 50 – 210 pg/mL (as provided by the central laboratory). Variability was moderate at most time points (coefficients of variation (CV%)

appoximately 45%), with slightly higher standard deviations at the T_{max} time points (Day 4 to Day 7).

Reflecting the parallel tracking of Free T to T, the mean ratios of Free T:T remained relatively constant. The average ratios remained essentially unchanged from pre-treatment, ranging on average from 0.060 to 0.065.

Figure 14: Free T and ratio of Free T to total T following the 3rd injection of TU 750 mg LOADING – PK population, study IP157-001 Part C

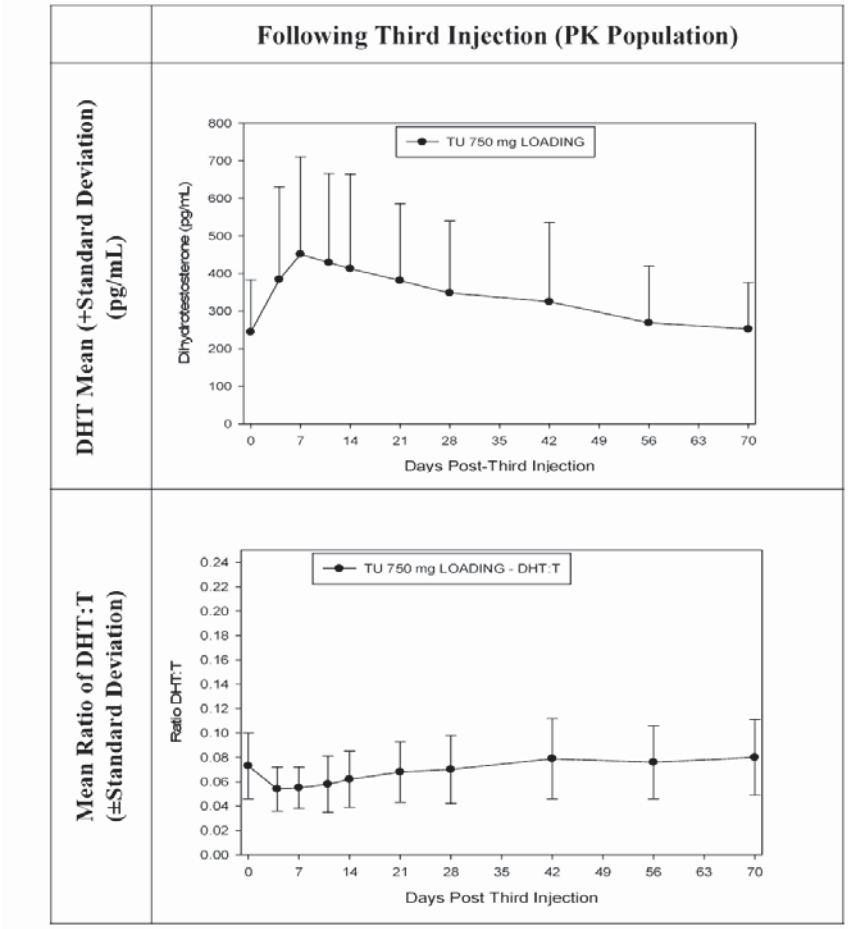


DHT concentration:

Average DHT concentrations closely paralleled total T concentrations but had smaller magnitude of increase at T_{max} (figure 15). Average DHT concentrations were in the range of approximately 250 – 450 ng/dL. Variability was moderate at most time points (CV%, 50% to 70%), with slightly higher standard deviations at the T_{max} time points (Day 4 to Day 7).

Reflecting the parallel tracking of DHT to T, the mean ratios of DHT:T remained relatively constant. The DHT:T ratios ranged from, on average, 0.05 to 0.07, with relatively low variability observed across the time points.

Figure 15: DHT and ratio of DHT to total T following the 3rd injection of TU 750 mg LOADING – PK population, study IP157-001 Part C

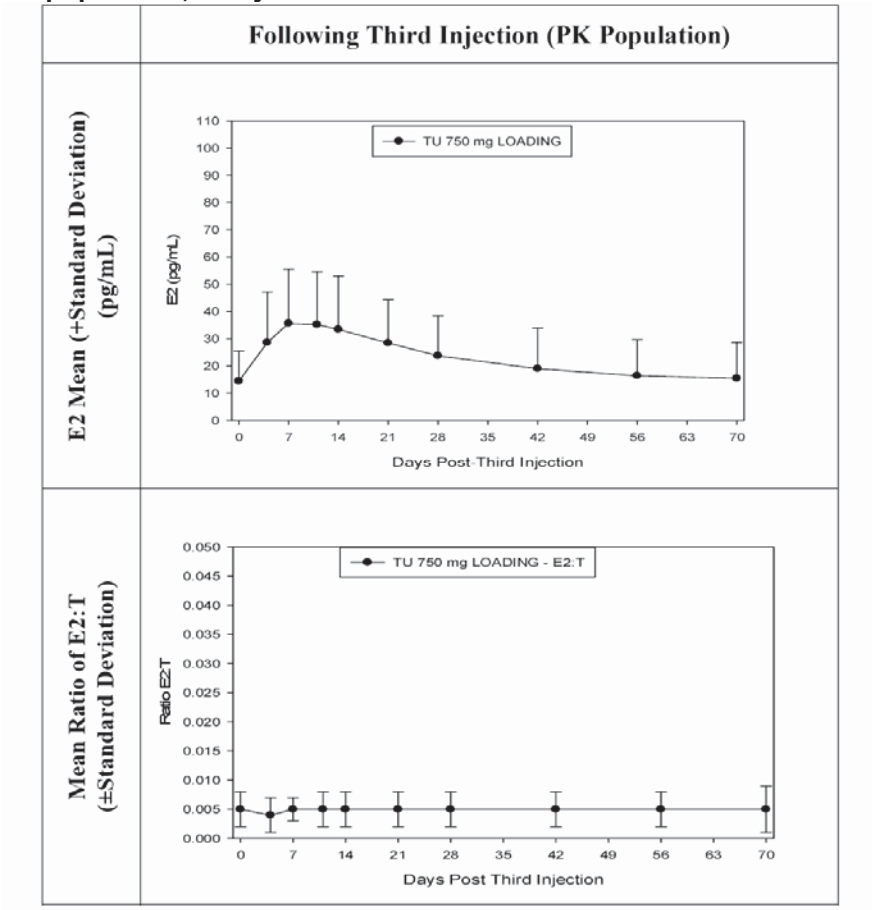


E2 concentration:

Average E2 concentrations generally paralleled total T concentrations (figure 16). Average E2 concentrations tended to remain within the normal range of 0 – 35 pg/mL (as provided by the central laboratory). E2 tended to demonstrate higher relative variability than the other hormones (CV%,,55% -80%).

Reflecting the parallel tracking of E2 to T, the mean ratios of E2:T remained relatively constant. The average on-treatment ratios remained similar to the average pre-treatment ratios. The E2:T ratios ranged from, on average, 0.004 to 0.005, with relatively low variability observed across the time points.

Figure 16: E2 and ratio of E2 to total T following the 3rd injection of TU 750 mg LOADING – PK population, study IP157-001 Part C

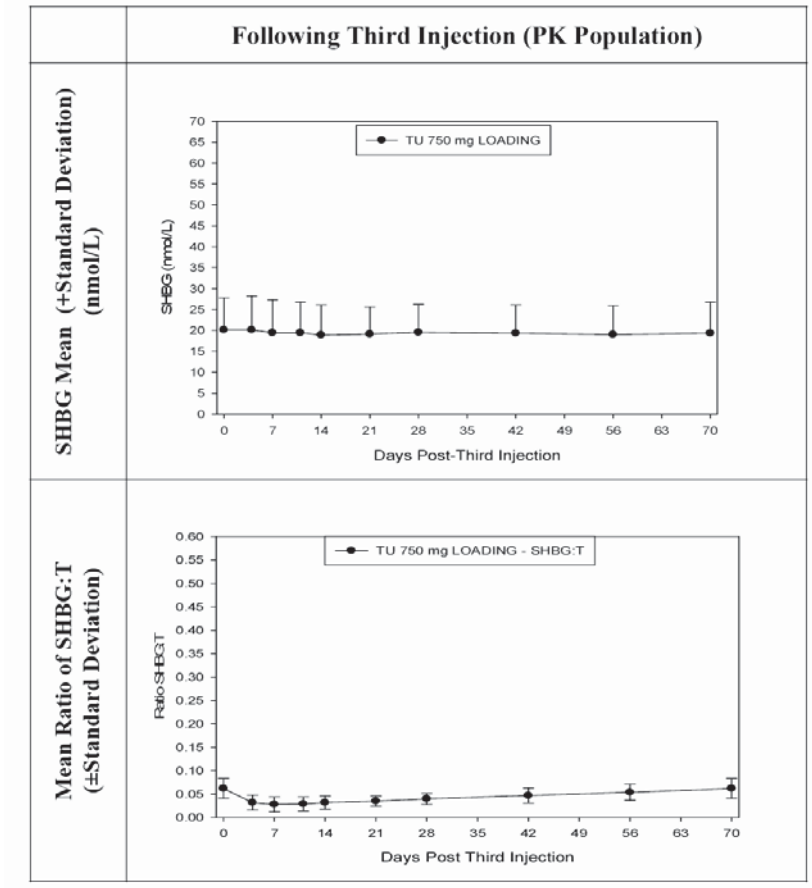


SHBG concentration:

Average SHBG concentrations remained constant (figure 17) and similar to the baseline values obtained prior to injection 1 (mean ± SD of 20.3 ± 8.6 nmol/L). Average SHBG concentrations tended to remain within the lower end of the normal range of 13 – 71 nmol/L (as provided by the central laboratory). Variability was moderate at all time points (CV%, 40% - 50%). Data from study IP157-001 Part A showed that the average SHBG concentrations were similar between the 1st and 4th injection, indicating that TU administration did not affect SHBG concentration.

The mean ratios of SHBG:T tended to drop immediately following the injection (at the Day 4 time point). Based on the stable mean SHBG concentrations during the interval, the changes in the ratio were due to the changes in T concentrations (and not changes in SHBG concentrations). The SHBG:T ratios ranged from, on average, 0.02 to 0.06, with relatively low variability observed across the time points.

Figure 17: SHBG and ratio of SHBG to total T following the 3rd injection of TU 750 mg LOADING – PK population, study IP157-001 Part C

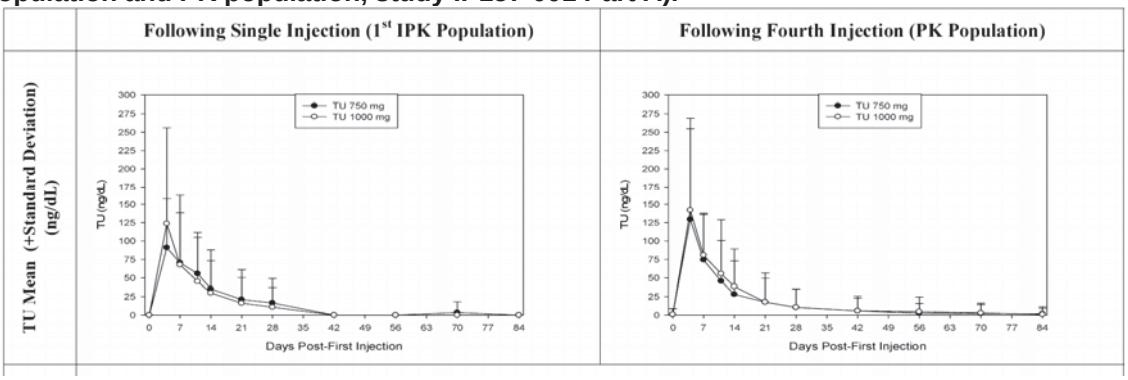


2.2.4 What is the serum concentration of TU and DHTU following IM administration of TU?

Serum TU and DHTU were assessed following the first injection (1st IPK subgroup) and the 4th injection (PK population) in study IP157-001 Part A for both 750 mg and 1000 mg once every 12 weeks regimens. They were not assessed in Part C of same study. Since the dose and formulation being sought in the NDA, namely 750 mg in oil, are the same as the 750 mg dose used in Part A, the relative concentration of TU and DHTU obtained in part A should provide reasonable estimates of the relative concentration to be expected in Part C even thought he dosing schedules are different between Part A and Part C.

TU: TU concentration was measurable in human serum following IM administration of TU 750 mg and 1000 mg. The observed individual concentration vs. time profiles were generally discontinuous with many samples being below the limit of quantitation (BLQ, LLOQ = 50 ng/dL). Most patients had one or two measurable samples to give a peak of TU concentration (usually on Day 4, the first measured time point post injection, and declined on Day 7) with other sampling times listed as BLQ. The data suggest that the true peak of TU might have occurred before Day 4 post injection. The highest observed serum TU concentrations were 1220 and 735 ng/dL following administration of 750 and 1000 mg TU doses, respectively. They were both observed during the 4th injection interval, Day 4. Figure 18 shows the mean (+SD) of serum TU concentrations following IM administration of TU (Note that BLQ samples were set to be zero and there were large numbers of BLQ samples.

Figure 18: TU concentration following the 1st and 4th injections of TU (1st dose IPK population and PK population, study IP157-001 Part A).

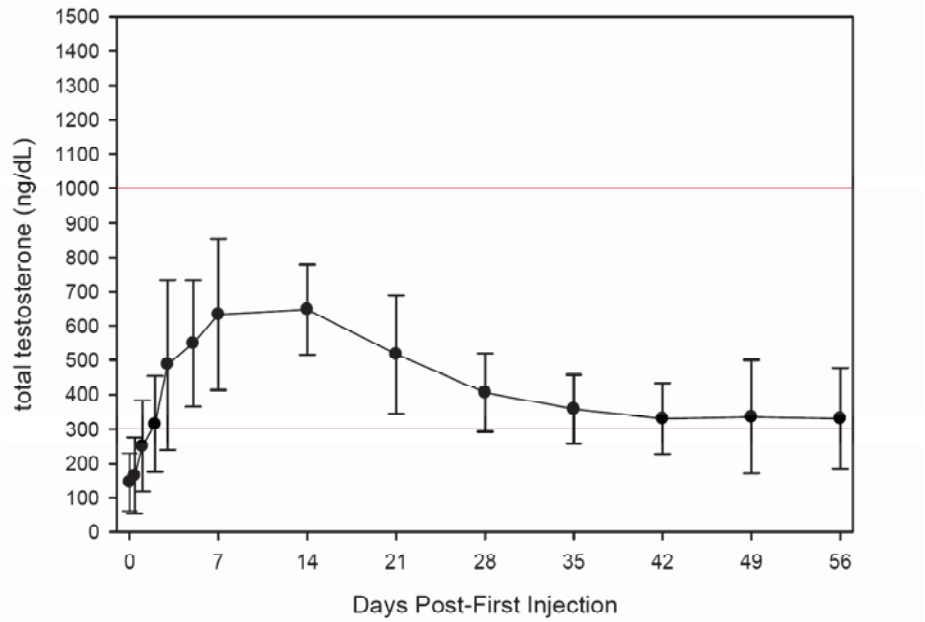


DHTU: As measured in Study IP157-001, Part A, (1st and 4th injection intervals), concentration values of DHTU were below the limit of quantification (LLOQ = 100 ng/dL) for all but a few samples. There were 3 measurable samples with concentrations of 101, 170, and 238 ng/dL. They came from 3 separate patients. None of the samples in the 1000 mg dose group had measurable DHTU concentration.

2.2.5 How were the doses chosen for Phase 3 study?

Prior to conduct of study IP157-001, a single dose PK study of 1000 mg TU was evaluated in phase 1 study JPH01495 (n=14 hypogonadal men) in Europe. This study evaluated serum total T up to 8 weeks post dose. The results showed a mean C_{max} of approximately 700 ng/dL. The median (range) T_{max} was 14 (3 – 21) days. Mean $T_{1/2}$ was 53.46 days. One subject had serum total T concentration exceeding the upper limit of 1000 ng/dL on measurement days 3, 5, and 7. This subject had a C_{max} of 1177 ng/dL three days after TU injection. Figure 19 shows the mean total T PK profile for study JPH01495.

Figure 19: Mean ± SD serum total T from a single injection of TU from an early phase 1 study JPH01495 (n=14).



Pharmacokinetic modeling was used to estimate the dose and dosing intervals that would produce a steady state C_{ave} within the range of 300 – 1000 ng/mL and C_{max} values that would meet the FDA safety criteria.

2.3 Intrinsic Factors

2.3.1 What are the effects of intrinsic factors (e.g., age, weigh, race, renal and hepatic insufficiency, etc.) on the PK of TU?

The sponsor did not conduct separate studies to examine the effect of intrinsic factors on the PK of TU. However, correlation analyses of body weight and BMI to serum total T exposure were explored by the sponsor using the phase 3 data. Both body weight and BMI were correlated with T exposure. Effects of BMI on T exposure were consistent between the 2 dosing regimens studied in Part A and Part C of study IP157-001.

Higher serum T concentration can be expected from patients with lower BMI or lower body weight. The data are not sufficient to predict serum T exposure following TU injections on an individual patient basis. Figures 19A and 19B show scatter plots of serum total T C_{ave} and baseline body weight or BMI. The line represents a linear regression of the scatter plot.

Figure 19A: Scatter plot of individual serum total T C_{ave} versus baseline body weight

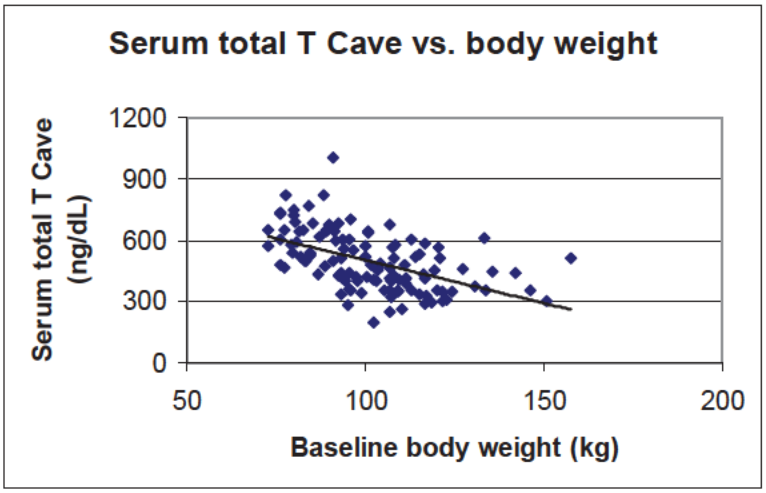
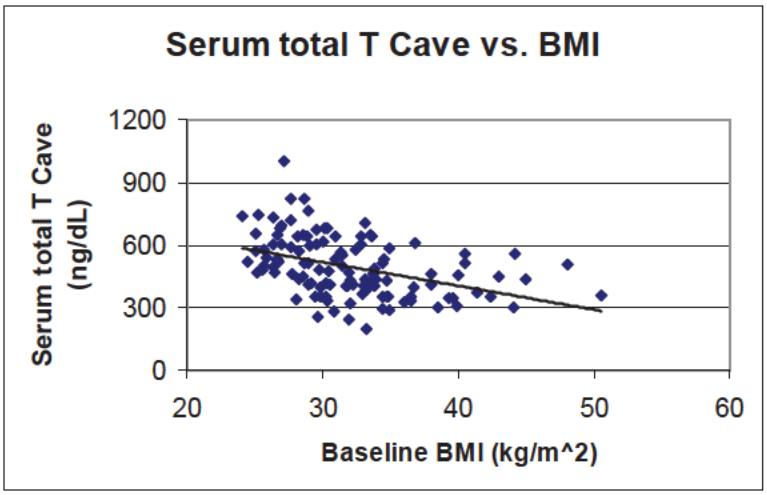


Figure 19B: Scatter plot of individual serum total T C_{ave} versus baseline BMI



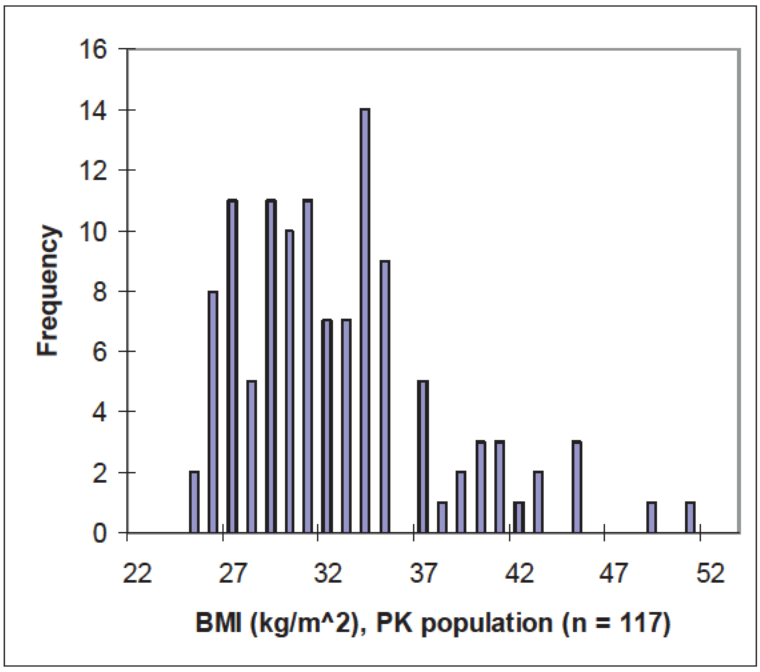
Patients with pretreatment body weight of <100 kg (n=57) had mean (SD) serum total T C_{max} and C_{ave} of 1088 (345) ng/dL and 568 (139) ng/dL, respectively, during the 3rd injection interval of the TU 750 mg LOADING regimen. Patients with higher body weight of ≥100 kg (n=60) had lower serum total T C_{max} and C_{ave} (mean ± SD) of 703 ± 218 ng/dL and 426 ± 104 ng/dL, respectively.

A similar trend was observed with BMI. Table 14 shows the mean (SD) for serum total T C_{max} and C_{ave} stratified by BMI of <26, 26-30, and >30 kg/m^2. The group with the lowest BMIs had the highest mean T exposure and the group with the highest BMIs had the lowest mean T exposure. The patients in the BMI <26 group had BMI in the range of 22.9 – 25.9 (note that patient 031-7021 with a BMI of 17.2 was excluded from PK analyses due to his low body weight). Figure 20 shows the distribution of BMI values for the PK population (n=117).

Table 14: Mean (SD) serum total T C_{ave} and C_{max} during the 3rd injection interval by BMI subgroups – PK population, study IP157-001 Part C

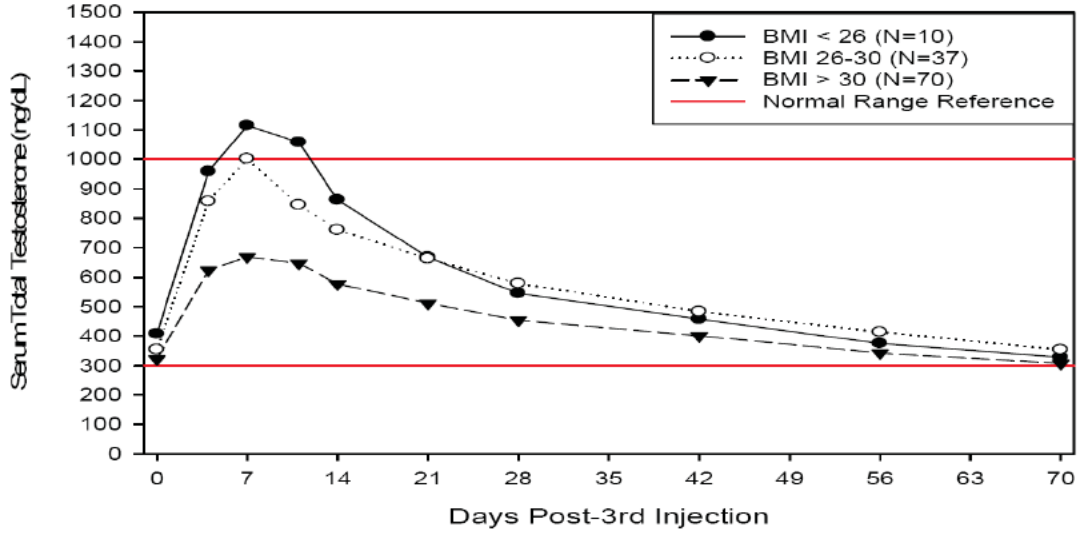
	TU 750 mg LOADING (N=117)		
	<26 kg/m² (N=10)	26-30 kg/m² (N=37)	>30 kg/m² (N=70)
	Mean (SD)	Mean (SD)	Mean (SD)
C_{max} (ng/dL)	1233.8 (339.57)	1061.5 (394.43)	751.2 (277.14)
C_{avg} (ng/dL)	578.8 (100.86)	566.7 (154.60)	445.0 (116.33)
Reference: Section 14.2 Table 9.2.1.8.3			

Figure 20: Distribution of BMI values – PK population, study IP157-001 Part C



The apparent effect of BMI was not due to differences in pre-dose serum T concentration. Even though the pre-dose and trough T concentrations were similar across the BMI subgroups, patients in the highest BMI category tended to have the lowest average T concentration through the majority of the steady state dosing interval. Figure 21 provides the average concentration-time profiles for T by BMI subgroup.

Figure 21: Mean serum total T concentration by time point during 3rd injection interval by BMI subgroups – PK population, study IP157-001 Part C



2.4 Extrinsic Factors

2.4.1 What are the effects of extrinsic factors (e.g., drugs, herbal products, diet, smoking, alcohol use, etc.) on the PK of TU?

The sponsor did not conduct any studies to examine effects of extrinsic factors on the PK of TU. TU metabolizes into T by cleavage of the ester bond. T is an endogenous hormone that is present in normal men at concentration similar to that being targeted by treatment with TU in hypogonadal men. Few drug interactions with T are known from the literature (see approved labeling for other T replacement therapy, e.g., Androgel).

2.5 General Biopharmaceutics

2.5.1 Is the to-be-marketed formulation the same as the clinical trial formulation?

Yes. The formulation of TU was not changed during drug development. Bridging studies for changes in manufacturing sites are not needed since TU is formulated as a solution.

2.5.2 What is the formulation of TU?

TU is formulated as a solution for IM injection. Table 15 lists the ingredients in TU formulation. (b) (4)

Table 15: TU formulation

Names of ingredients	Dosage unit (b) (4)		Function
		750 mg strength	
Testosterone undecanoate		750 mg	Active substance
Benzyl benzoate		1500.0 mg	(b) (4)
Castor oil		885.0 mg	
(b) (4		-	
Total mass		3135.0 mg	
Total volume		3 mL	

2.6 Analytical Section

Analysis of the Phase 3 study IP157-001 was conducted using different bioanalytical methods than other studies. This section will first discuss the assays for study IP157-001,followed by discussions of methods utilized in other supporting studies.

2.6.1 What are the bioanalytical methods used for the Phase 3 study IP157-001 Part A and Part C? Were the assay validated?

Samples from study IP157-001, Part A, and Part C were analyzed using a validated assay for T and DHT (Part A and Part C) and a separate validated assay for TU and DHTU (Part A only).

T and DHT validation:
Validation for a method to determine T and DHT in human serum by HPLC with MS/MS detection was conducted by (b) (4) in study number 2100-801. The method utilized a sample size of 0.5 mL and liquid-liquid extraction. The method was validated over the concentration ranges of 20.0 to 5000 ng/dL for T and 5.00 to 1250 ng/dL for DHT. Initially, validation for DHT failed and the method was only used for measurement of T. Following additional method development, validation vas repeated and both T and DHT passed validation. Sensitivity, linearity, and recovery were acceptable. Precision and accuracy results were within the normal range recommended by FDA (i.e., within ±20% at LLOQ and ±15% at other concentrations). The validation results were acceptable and the data for T and DHT may be used.

Stability for T and DHT was evaluated and summarized below.

Table 16: Minimum stability of T and DHT under a variety of conditions (validation report 2100-801). *Note: stability of T and DHT in frozen matrix was confirmed up to 74 days at time of bioanalysis of study IP157-001 Part A, Stage 1 data.*

Test	Conditions	Minimum Stability
Standard stock solution of testosterone	(b) (4)	(b) (4) hours
Standard stock solution of DHT		hours
Internal standard stock solution of testosterone-d_3		hours
Internal standard stock solution of dihydrotestosterone-d_4		hours
Short-term in matrix (human serum)		(b) (4) cycles for testosterone; (b) (4) cycles for DHT
Short-term in matrix (PBS)		(b) (4) cycles for testosterone (b) (4) cycles for DHT
Short-term in matrix (human serum)		(b) (4) hours
Short-term in matrix (PBS)		hours
Frozen in matrix		days for testosterone
Processed-sample viability		(b) (4) hours

TU and DHTU validation:
Validation for a method for the determination of TU and DHTU in human serum by HPLC with MS/MS detection was conducted by (b) (4) in study number 6530-109. The method utilized a sample size of 0.2 mL and solid phase extraction. The method was validated over the concentration ranges of 50.0 to 10,000 ng/dL for TU and 100 to 20,000 ng/dL for DHTU. Sensitivity and linearity were acceptable. Recovery was low for both TU (48.2%) and DHTU (52.0%). Recovery was lower for both TU and DHTU at the low QC concentrations (42.9% for TU and 41.6% for DHTU) compared to the high QC concentration (55.2% for TU and 69.4% for DHTU). The recovery of the internal standards also followed a similar pattern. Precision and accuracy results were within the normal range recommended by FDA. The overall validation results were acceptable and the data for TU and DHTU may be used.

Table 17: Minimum stability of TU and DHTU under a variety of conditions (validation report 6530-109).

Test	Conditions	Minimum Stability
Standard stock solution of TU and DHTU	(b) (4)	(b) (4) hours
Standard stock solution of TU and DHTU		(b) (4) days
Internal standard stock solution of TU-d_{21} and DHTU-d_{21}		(b) (4) hours
Short-term in matrix for TU and DHTU		(b) (4) cycles and (b) (4) cycles
Short-term in matrix for TU and DHTU		At least (b) (4) hours
Frozen in matrix for TU and DHTU		(b) (4) days
Processed-sample viability for TU and DHTU		(b) (4) hours

Bioanalytical report for Part A:

Samples were originally analyzed singly. At a minimum, each batch included a calibration curve, a matrix blank, a control zero (matrix blank containing internal standard), and duplicate quality control (QC) samples at three concentrations within the calibration range. The samples were interspersed with calibration standards and QC samples within the batch. Dilution QC samples were also included in batches where samples were diluted prior to analysis.

Acceptance Criteria:

Sample results were accepted if calibration curve and QC data from the reported batches indicated that the method met the acceptance criteria for those batches. Reported data met the following criteria:

- Batches were considered acceptable if no more than one-fourth of the calibration standards were excluded, and a minimum of six non-zero back-calculated concentrations for calibration standards were within the range of 85.0% to 115.0% of theoretical [80.0% to 120.0% at the lower limit of quantitation (LLOQ)].
- Batches were considered acceptable if at least one-half of the undiluted QC samples at each concentration and two-thirds of all undiluted QC samples in the curve range were within the range of 85.0% to 115.0% of theoretical.
- Dilution QC samples were included, at least in duplicate, for each analytical batch containing samples requiring dilution. These QC samples were diluted with blank matrix to the same extent as the most highly diluted sample, and were included at least at every order of magnitude utilized for dilutions. At least one-half of the dilution QC samples were within the range of 85.0% to 115.0% of theoretical for the results of diluted samples to be accepted.

The reported precision and accuracy of assay runs during analysis of Part A were acceptable.

Select assay deviation note for Part A:

TU concentration for subject 002-4151, week 48 (just prior to 5th injection) was not reported due to apparent large discrepancy between the original and backup tubes. The original analysis reported a concentration of 5718.73 ng/dL. Re-analysis in duplicates for the original tube and the backup tube was performed. However, the analysis run failed to meet acceptance criteria at a single QC level. Further analysis was not possible since all samples had been consumed. Data

from the failed analysis runs showed that the original tube results were still high while the backup tube results were near or below the limit of quantitation. Examination of the TU PK profile in this subject shows the typical expected profile with TU's T_{max} at day 4. Samples at day 21 post dose and beyond were all below LOQ of 50 ng/dL. It is likely that the sample at week 48 (84 days post dose) would be very low as suggested by the backup tube results. It is acceptable that this sample is listed as not reportable.

Bioanalytical report for Part C:

The bioanalysis procedures and acceptance criteria for Part C are the same as that described above for Part A. The reported precision and accuracy of assay runs during analysis of Part C were acceptable.

2.6.2 What are the bioanalytical methods used in supporting study JPH01495?

The 11 supporting studies (listed in section 2.1.6) used commercially available RIA or electrochemoluminesence immunoassay to assay T and its metabolites. Full method validation reports for the various assays were not available. Studies ME98096 and ME97029 used a commercially available RIA kit "Coat-A-Count total testosterone solid-phase RIA" by Diagnostic Corporation DPC, Biermann GmbH, Grmany. Study 306605 used a commercially available electrochemoluminescence immunoassay (Roche Elecsys). Studies JPH01495 and JPH04995 used the RIA described below.

Bioanalytical report with assessment of quality control samples was provided for study JPH01495. A commercially available RIA kit was used (Double antibody radioimmunoassay for testosterone, Kit DSL-4100, Diagnostic System laboratories, Sinsheim, Germany) was used for the determination of T in human serum. This kit was also used in study JPH04995 and its extensions.

The DSL-4100 T assay has a calibration range of up to 86.7 nmol/L or 2500 ng/dL. The calibrator concentrations are 0.0, 0.4, 1.7, 8.7, 34.7, 86.7 nmol/L. The manufacturer stated the assay has a lower limit of detection of 0.17 nmol/L and an intra-assay precision of <10% for quality control (QC) concentrations of 1.8, 17.5, and 3.19 nmol/L. In the sponsor's laboratory, the intra-assay and inter-assay precision did not meet current standards for bioanalytical assays (i.e., within ±20% at LLOQ and ±15% at other concentrations). The inter-assay precision CV% for 3 QC concentrations of 3.1, 18, and 41 nmol/L were 16.9, 7.9, and 7.4% at start of assay, respectively. Similar variability was observed when the quality control samples were assessed at the end of the assay. Accuracy were acceptable for the 2 higher QC concentration (i.e., within the range of 85 – 115% nominal value). However, the intra-assay accuracy of the 3.1 nmol/L QC were usually off by 40 – 50% with overall inter-assay accuracy of 66.8% at start of assay and 57.1% at end of assay. This assay was not accurate at the lower end of the calibration curve.

3 Detailed Labeling Recommendations

Labeling was not reviewed at the time of this review.

4 Appendices

4.1 Proposed labeling (Original and Annotated)

Labeling was not reviewed at the time of this review.

4.2 Individual Study Reviews

Individual study review for the 2 phase 3 studies, namely Study IP157-001 Part A and Study IP157-001 Part C, are included at the end of this review.

4.3 Consult Review

There is no consult review for this NDA.

4.4 Cover sheet and OCPB Filing/Review Form

They are attached at the end of the document.

Individual study review of study IP157-001, Part C, Stage 1 and part of Stage 2

Title:
A Two-Arm, Open-Label, Randomized, Multi-Center Pharmacokinetic and Long-term Safety Study of Intramuscular Injections of 750 mg and 1000 mg Testosterone Undecanoate (TU) In Hypogonadal Men. (*Note: Part C evaluated only one specific regimen using the 750 mg dose*)

Primary objectives:
- To evaluate the pharmacokinetics of TU 750 mg, given at baseline, at 4 weeks, and then every 10 weeks thereafter, over the 10-week interval following the 3rd injection, via multiple measurements of serum total T, in up to approximately 130 hypogonadal men. This dosing regimen (with a 4-week loading injection and injections every 10 weeks thereafter) is referred to as TU 750 mg LOADING.

Secondary objectives:
- To evaluate the pharmacokinetics of TU 750 mg LOADING over the 10-week interval following the 4th injection, via multiple measurements of serum total T
- To compare serum levels of DHT, E2, and SHBG to simultaneous levels of serum total T over the 3rd injection interval.
- To evaluate safety in patients treated with TU 750 mg LOADING, through up to 9 injections in hypogonadal men.

Study design:
Part C is a multicenter, 1-arm, open-label part of the study. The treatment arm was:

- TU 750 mg LOADING: Each patient received 750 mg TU (250 mg/mL) in 3 mL oily solution, injected at baseline, 4 weeks later and then every 10 weeks thereafter.

Select inclusion criteria:
- Male with primary or secondary hypogonadism at least 18 years of age
- Morning screening serum T concentration < 300 ng/dL
- If receiving endocrine replacement hormones (e.g., thyroid), antihypertensives, lipid lowering agents, antidepressants or anxiolytic medications, the dose must be stable for at least 28 days prior to the first administration of the study drug OR is not currently on such medications.

Reviewer's note: 2 enrolled patients (Patient 065-7121 and Patient 031-7021) had body weight <65kg and they were discontinued. PK data obtained from patient 031-7021 were excluded from PK assessment for the 3rd injection interval. This patient had serum total T concentration above 2500 ng/dL on days 4, 7, and 11 post 3rd injection.

The study enrolled 130 patients. All patients were to undergo intensive pharmacokinetic (IPK) assessments during the 3rd injection interval. The study has 4 defined periods: Screening, Baseline, Stage 1, and Stage 2.

- Screening: Approximately 1-5 week screening period (washout from select prior T replacement therapies may have extended this period for some patients)
- Baseline: Final pre-study measurements were captured and patients were enrolled.
- Stage 1: The first 3 injection intervals (through the 4th injection visit). This included the first injection at the Baseline visit. The end of Stage 1 was the 4th injection visit. This Stage 1 analysis and report includes only data through the 4th injection visit, and is the primary analysis for this Part of the study submitted in support of the NDA.
- Stage 2: (Long-term safety extension): The study will continue following the 4th injection visit, with 5 additional injections (at 10-week intervals) during an extended treatment phase. The

Stage 2 analysis will include all patients and all data. At FDA's request, the sponsor provided serum T concentration obtained during the 4th injection interval in this NDA.

PK samples collection:

- Intensive PK (IPK) collection: After the 3rd injection was given, PK draws were collected at Day 0 (pre-3rd injection), 4, 7, 11, 14, 21, 28, 42, 56, and 70 (pre-4th injection), where the 4th injection visit was defined as the end of the injection interval. The following were measured: Serum total T, free T, DHT, E2, and SHBG. TU and DHTU were not assessed in Part C.
- Additional PK collection: After the 4th injection was given, PK draws were collected at Day 0 (pre-4th injection), 4, 7, 11, 42, and 70 (pre-5th injection), where the 5th injection visit was defined as the end of the injection interval.
- Trough T concentrations will be collected at each injection visit up to the 9th injection in stage 2.

The primary analysis for Part C was based on the post-3rd injection IPK collections. Patients continued to have sampling for PK assessment during the 4th injection interval and trough samples (prior to each injection) captured at each 10-week dosing interval visit through the remainder of the study.

Drug product:
Each (b) (4) TU contained 4 mL of drug product, in a concentration of 250 mg/mL. In this study, the dose administered was 750 mg TU in 3 mL oily solution. Injections were made into the deep gluteal muscle.

Study schedule:
Table 18: Schedule of events for TU 750 mg LOADING (study IP157-001 Part C)

	Injection Number and Week											
	Screening Phase		1	2	3	4	5	6	7	8	9	EOS
	Days -35 to -1	Post-Washout	Baseline Day 0	4	14	24	34	44	54	64	74	84[4]
Informed Consent	X											
Eligibility	X		X[1]									
Medical History (includes height)	X		X[1]									
Physical Exam	X											X
Digital Rectal Examination, PSA	X		X	X	X	X	X	X	X	X	X	X
Vital Signs (includes pulse, blood pressure, weight, temperature)	X		X			X						X
12 Lead ECG	X											X
Hematology, Coagulation, Chemistry (includes lipids), Urinalysis, FSH, LH	X		X			X						X
Prostate Volume (via TRUS)[2]	X											
Pharmacokinetic Sampling (T, DHT, FREE T, SHBG, E2)	X only if Washout NOT Required	X if Washout Required	X	X	X	X	X	X	X	X	X	X
Adverse Events			X	X	X	X	X	X	X	X	X	X
Prior/Concomitant Medications	X		X	X	X	X	X	X	X	X	X	X
Injection (includes drug accountability)			X (750 mg)	X (750 mg)	X (750 mg)	X (750 mg)	X (750 mg)	X (750 mg)	X (750 mg)	X (750 mg)	X (750 mg)	X (750 mg)	
Local tolerability assessment[3]			X	X	X	X	X	X	X	X	X	X
Profile of Mood States			X									X
AUA Symptom Score	X		X									X
Male Patient Global Assessment				X	X	X						X

1 Medical History and Eligibility pages were updated at Baseline visit as appropriate.
2 TRUS may be repeated during the study at the investigator's discretion.
3 Injection site was assessed by investigator if, at any time, the patient indicates a tolerability issue with the injection site.
4 Patients who discontinued prematurely from the study and who did not complete all of the treatment injections were to be administered assessments as listed under Week 84 or End of Study (EOS) Visit

Table 19: Schedule of PK intensice sampling for TU 750 mg LOADING (study IP157-001 Part C)

Intensive PK Collection Time Points (All time points collected Post-Injection 3 and GRAY shaded region time points collected Post-Injection 4)										
	Day									
Assessments	**0[a]**	**4**	**7**	**11**	**14**	**21**	**28**	**42**	**56**	**70[b]**
Serum Total Testosterone	X	X	X	X	X	X	X	X	X	X
DHT	X	X	X	X	X	X	X	X	X	X
Estradiol	X	X	X	X	X	X	X	X	X	X
Free T (measured)	X	X	X	X	X	X	X	X	X	X
SHBG	X	X	X	X	X	X	X	X	X	X
Male Patient Global Assessment						X				

a Day 0 and Day 70 assessments are also described in Table 9. The assessments are not different nor intended to be duplicative.
b Day 70 of Injection Period 3 is the same as Day 0 of Injection Period 4

Data analysis:
The concentration of T and DHT in human serum samples was assessed by HPLC with MS/MS detection by (b) (4) located at (b) (4)

The method was validated ((b) (4) validation report 2100-801). The study specific bioanalytical report was provided in (b) (4) report 6657-213 (Draft report, issued Dec 6, 2007 and Final report, issued March 26, 2008). Both reports are acceptable.

Special note: The sponsor indicated because T concentrations above 2500 ng/dL were identified in the C_{max} approvability criteria as important values of interest, whenever a T concentration was originally found to be above the FDA threshold of 2500 ng/dL, the sample was to be re-assayed in duplicate by the bioanalytical laboratory to confirm the finding. For purposes of PK analysis the mean of the repeats was to be derived and used in the PK assessments for these values.

This reanalysis of only samples above the safety threshold and method of computation (mean of the repeats) may introduce bias in the statistical analysis of the C_{max} end point. However, since reanalysis was not needed for any sample from Part C, no further discussion is needed.

PK Population:
Pharmacokinetic assessments were to be performed on those patients who receive the 3rd injection and complete the 3rd injection interval pharmacokinetic assessments. Patients in the PK Population were to be used for all PK summaries and for all summaries of the metabolites and other hormone assessments. Patients were to be included in the PK Population if they satisfied the following:

- Patients must have had a minimum of 4 T concentration values within the 3rd injection dosing interval. The 4 values could include the Day 0 and/or Day 70 (4th injection visit) values.
- If any patients were found to be noncompliant with respect to dosing or have incomplete data, a decision was to be made on a case-by-case basis as to their inclusion in the PK Population.
- Finally, patients had to have weighed at least 65 kg in order to be included in the PK Population. [*Note that this criterion was added after the Statistical Analysis Plan was finalized.]*

A total of 117 qualified to be included in the PK population. One patient (Patient 031-7058) did not have a Day 168 T (prior to 4th injection) concentration. Curve stripping was used to estimate the Day 168 T concentration for purpose of AUC calculation. This patient did not contribute to the 3rd injection C_{trough} descriptive analysis. In addition, since he did not have a Day 168 concentration, he was not counted in Table 20 as having completed the 4th injection visit.

Table 20: Patient Accounting (Study IP157-001 Part C)

	Number of patients
	TU 750 mg LOADING
Screened	354
Enrolled[1]	130
Completing 4th Injection Visit N (% Based on Enrolled Patients)	116 (89.2)
Premature Discontinuation N (% Based on Enrolled Patients)	14 (10.8)
Reference: Section 14.1 Tables 9.1.2 and 9.1.3 [1] Enrolled was defined as randomized and treated with at least one injection of study medication.	

One patient was excluded from PK analysis dues protocol violation. Patient 002-7022 was confirmed as taking concomitant DHEA, a known androgenic steroid hormone that was prohibited in this study (based on Exclusion Criteria 16). The T concentration values from this patient were excluded from the pharmacokinetic analyses.

Efficacy results:

Steady state conditions were determined to have been achieved following the third injection interval (Please see discussion at the end of this section and within the QBR for details). The primary efficacy (C_{ave}) and safety (C_{max}) assessments were based one the intensive PK collection during the 3rd injection interval of the TU 750 mg LOADING regimen.

The mean serum T concentrations were within the normal range of 300 – 1000 ng/dL throughout the dosing interval (figure 22 and table 21). The mean (±SD) total T C_{ave} was 494.9 ± 141.5 ng/dL. 94% (95% CI 89.6 – 98.45) of patients had serum total T C_{ave} within the 300 – 1000 ng/dL range.

Figure 22: Mean (±SD) serum total T concentrations following the 3rd injection interval of TU 750 mg LOADING regimen (Study IP157-001 Part C)

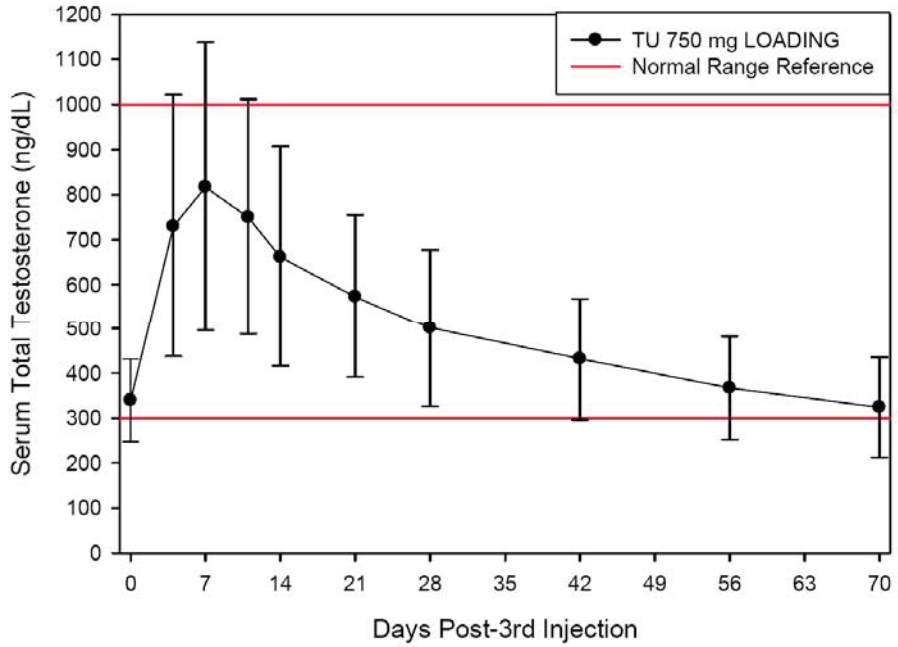


Figure 23: Composite of individual serum total T concentration following the 3rd injection of the TU 750 mg LOADING regimen – PK population, study IP157-001 Part C

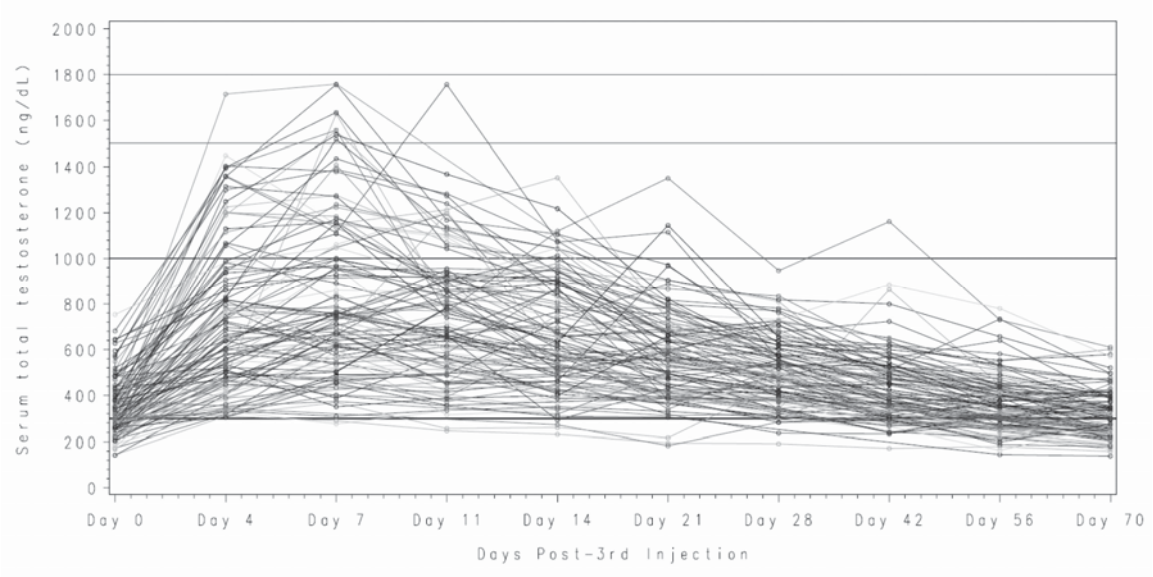


Table 21: Serum total T concentrations (ng/dL) over 70 day following the 3rd injection interval of TU 750 mg LOADING regimen (PK population, Study IP157-001 Part C)

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

Reference: Section 14.2 Table 9.2.1.2.1

Table 22: 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 23: Number (%) of patients (and 95% CI) meeting C_{ave} criteria – PK population, studu IP157-001 Part C

	Number (%) of Patients and 95% CI	
	TU 750 mg LOADING (N=117)	
Outcome	**N (%)**	**95% CI**
C_{avg} within [300,1000] ng/dL	110 (94.0)	(89.6, 98.4)
C_{avg} NOT within [300,1000] ng/dL	7 (6.0)	

Reference: Section 14.2 Table 9.2.1.3
95% CI based on normal approximation to the binomial, using a critical value Z=1.96.

Steady state assessment:

Trough serum total T concentrations following the 2nd, 3rd, and 4th injection of the TU 750 mg LOADING regimen was used to assess whether steady state conditions were reached during the 3rd injection interval. The mean data indicates that the serum T C_{trough} values were similar at end of 2nd, 3rd, and 4th injection interval. An analysis of individual data did not reveal any particular trend of shift in C_{trough} with each subsequent injection (data not shown). This is consistent with the mean data. A comparison of serum total T concentration at several time point post injection during the 3rd and 4th injection intervals indicates similar PK profiles. Together, these data indicate that steady state conditions were achieved during the 3rd injection interval.

Figure 24: Mean (±SD) serum total T concentrations at each injection visit (trough) from pre-treatment through 5th injection – Steady state PK population, study IP157-001 Part C

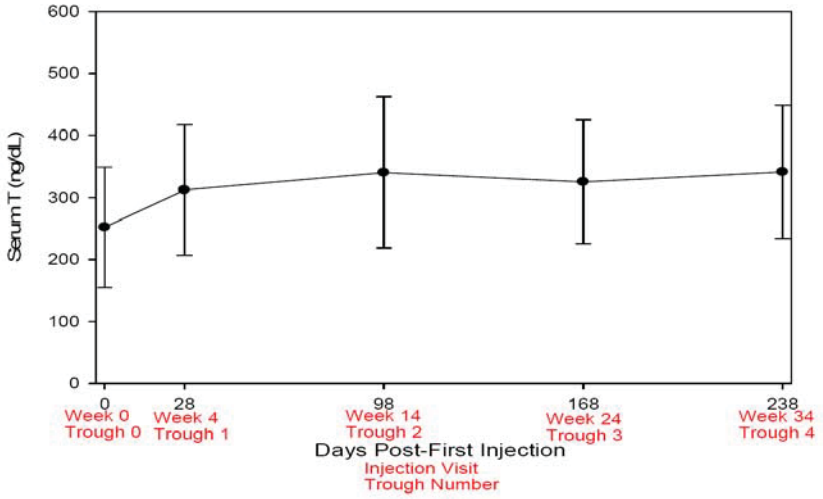
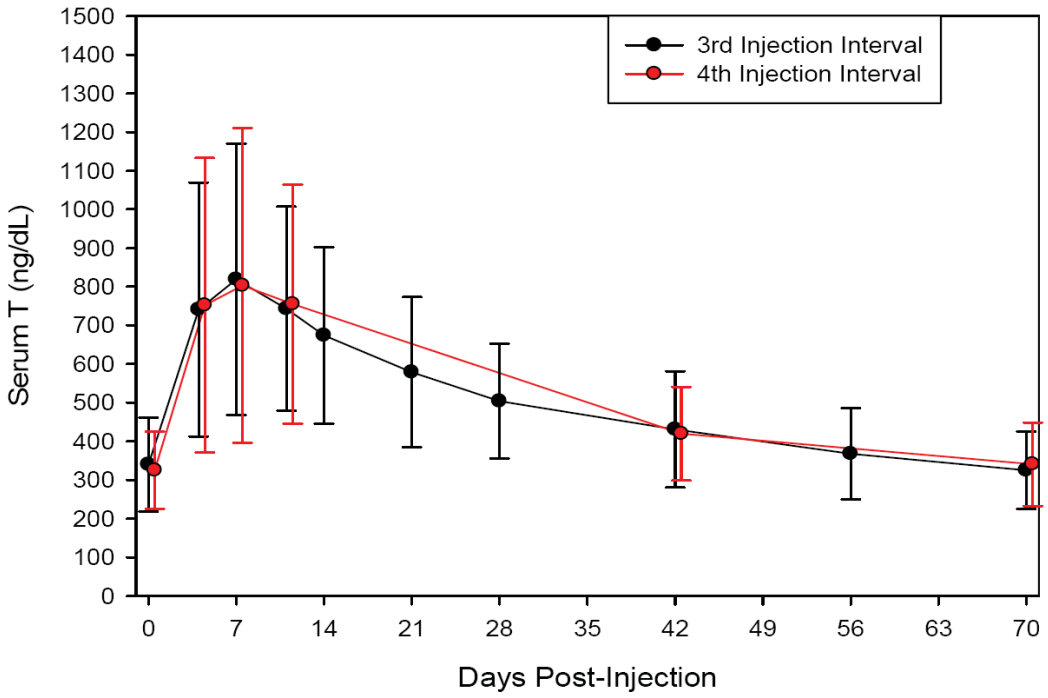


Table 24: Descriptive statistics for Serum total T concentration at each injection visit (trough) from pre-treatment through 5th injection – weeks post-first injection – Steady State Population, study IP157-001 Part C Stage 1 and Stage 2

	Serum Total Testosterone (ng/dL) (N=105)		
Time	**Mean**	**Standard Deviation**	**Range**
Week 0/Injection 1	251.3	96.79	0 to 538
Week 4/Injection 2	312.2	104.85	133 to 706
Week 14/Injection 3	340.1	122.17	141 to 754
Week 24/Injection 4	325.0	99.64	107 to 611
Week 34/Injection 5	340.9	108.09	148 to 634
Source: Table 9.2.1.2.1.1			

Figure 25: comparison of serum total T concentrations between the 3rd and 4th injection intervals – Steady State PK population, study IP157-001 Part C



C_{max} assessment:

Based on the PK population, no patient experienced C_{max} ≥ 1800 ng/dL during the 3rd injection interval. Nine patients (7.7%) had C_{max} > 1500 ng/dL (Table 25). The C_{max} criteria were met based on the PK population. However, there was one patient in Part C (Patient 031-7021) who was excluded from the PK population due to a body weight below 65 kg. This patient did experience a T concentration above 2500 ng/dL during the 3rd injection interval (figure 26). The sponsor indicated that the intended population for treatment with TU is hypogonadal men with a body weight of at least 65 kg. This information should be considered for risk vs. benefit assessment and appropriate labeling should be done.

Table 25: Summary of C_{max} assessment of serum total T concentrations during the 3rd injection interval compared to C_{max} thresholds approvability criteria – PK population, study IP157-001 Part C

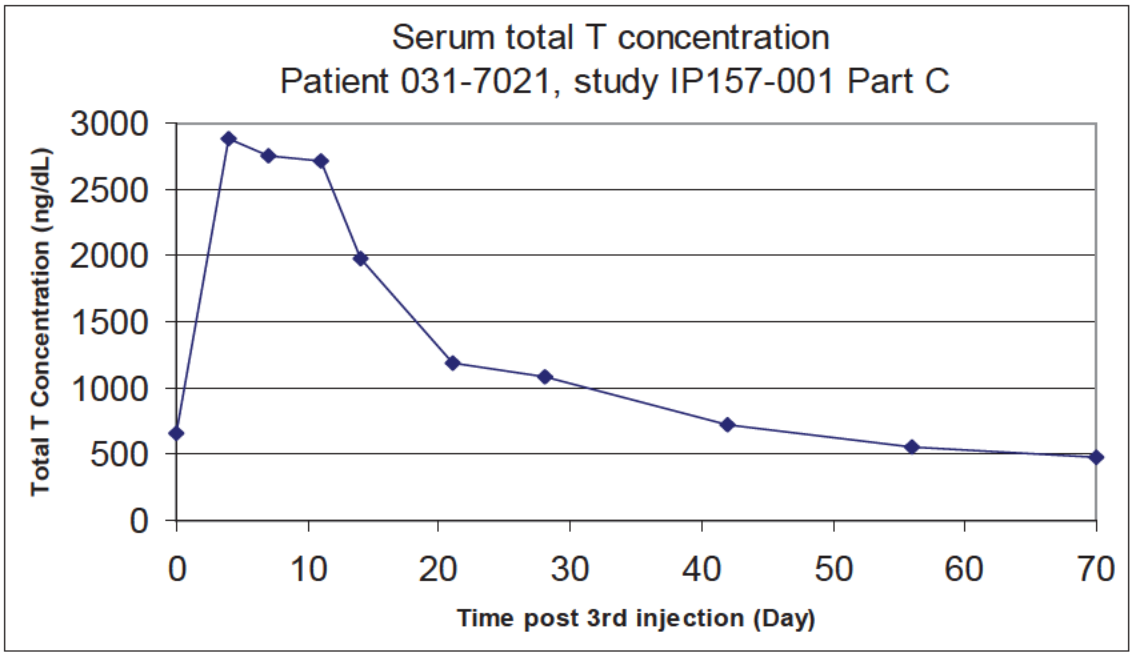
	Number of Patients Exceeding/Number of Patients Assessed (Percent of Patients Exceeding)
C_{max} Outcome	**TU 750 mg LOADING (N=117)**
> 1500 ng/dL[1]	9 of 117 (7.7%)
≥ 1800 ng/dL and < 2500 ng/dL	0 of 117 (0%)
≥ 2500 ng/dL	0 of 117 (0%)
Did Dose Meet Threshold Limits?	**Yes**

Reference: Section 14.2 Table 9.2.1.3

[1] The > 1500 ng/dL classification includes all patients with at least one T concentration > 1500 ng/dL (and thus also includes any patients with a T ≥ 1800 ng/dL).

Note: The PK Population excluded patients who weighed less than 65 kg.

Figure 26: Serum total T concentration in patient 013-7021 who was excluded from the PK population due to his body weight <65 kg. He had a body weight of 59 kg and a BMI of 17.2.



Other results:

Summary of secondary endpoints:

Table 26: Secondary efficacy outcomes during the 3rd injection interval of TU 750 mg LOADING regimen – PK population, study IP157-001 Part C

Secondary Outcome Parameter	TU 750 mg LOADING (N=117)
Number Patients with C_{avg} < 300, 300 - 1000, > 1000 ng/dL	
<300 ng/dL	6 (5.1)
300 to 1000 ng/dL	110 (94.0)
>1000 ng/dL	1 (0.9)
Number Patients with C_{avg} ≥ 300 ng/dL	
<300 ng/dL	6 (5.1)
≥300 ng/dL	111 (94.9)
Number Patients with at least one serum total testosterone below 300 ng/dL	
At least one concentration < 300 ng/dL	61 (52.1)
No concentration < 300 ng/dL	56 (47.9)
Number Patients with C_{max} ≤1500, > 1500 - < 1800, 1800 - <2500, ≥ 2500 ng/dL	
≤ 1500 ng/dL	108 (92.3)
> 1500 - < 1800 ng/dL	9 (7.7)
1800 - <2500 ng/dL	0 (0.0)
≥ 2500 ng/dL	0 (0.0)
Number Patients with at least one serum total testosterone > 1000 ng/dL	
At least one T concentration > 1000 ng/dL	35 (29.9)
No T concentration > 1000 ng/dL	82 (70.1)
Reference: Section 14.2, Table 9.2.1.3	

Effect of body weight and BMI on serum total T concentration:

Sponsor conducted exploratory correlation analysis and revealed that, consistent with finding in Part A of Study IP157-001, the pre-injection T concentration, the pre-treatment body mass index (BMI) of the patient, and the pre-treatment body weight of the patient were each predictive of T exposure. Higher serum T concentration can be expected from patients with higher pre-injection T concentration, lower BMI, or lower body weight. The data are not sufficient to predict serum T exposure following TU injections on an individual patient basis.

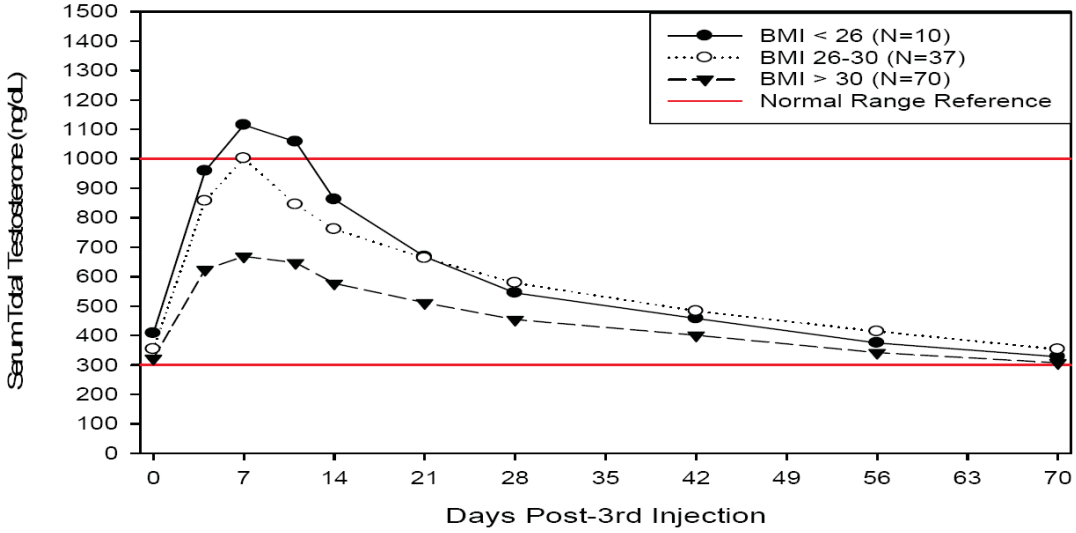
Table 27 shows the mean (SD) for serum total T C_{max} and C_{ave} stratified by BMI of <26, 26-30, and >30 kg/m^2. The group with the lowest BMIs had the highest mean T exposure and the group with the highest BMIs had the lowest mean T exposure. The patients in the BMI <26 group had BMI in the range of 22.9 – 25.9 kg/m^2.

Table 27: Mean (SD) serum total T C_{ave} and C_{max} during the 3rd injection interval by BMI subgroups – PK population, study IP157-001 Part C

	TU 750 mg LOADING (N=117)		
	<26 kg/m^2 (N=10)	26-30 kg/m^2 (N=37)	>30 kg/m^2 (N=70)
	Mean (SD)	Mean (SD)	Mean (SD)
C_{max} (ng/dL)	1233.8 (339.57)	1061.5 (394.43)	751.2 (277.14)
C_{avg} (ng/dL)	578.8 (100.86)	566.7 (154.60)	445.0 (116.33)
Reference: Section 14.2 Table 9.2.1.8.3			

While the pre-dose and trough T concentrations were similar across the BMI subgroups, patients in the highest BMI category tended to have the lowest average T concentration through the majority of the steady state dosing interval. Figure 27 provides the average concentration-time profiles for T by BMI subgroup.

Figure 27: Mean serum total T concentration by time point during 3rd injection interval by BMI subgroups – PK population, study IP157-001 Part C

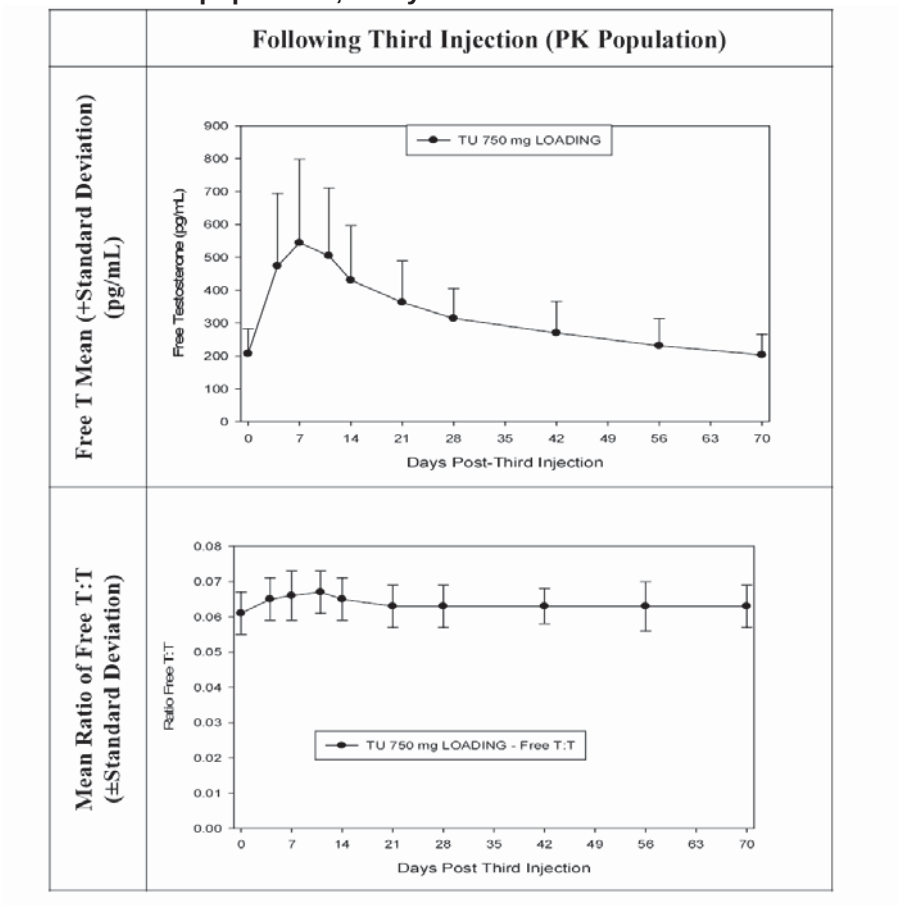


Serum Free T concentration:

Average Free T concentrations generally paralleled total T concentrations (figure 28). Average Free T concentrations were generally above the normal range of 50 – 210 pg/mL (as provided by the central laboratory). Variability was moderate at most time points (coefficients of variation averaged around 45%), with slightly higher standard deviations at the Tmax time points (Day 4 to Day 7).

Reflecting the parallel tracking of Free T to T, the mean ratios of Free T:T remained relatively constant. The average ratios remained essentially unchanged from pre-treatment, ranging on average from 0.060 to 0.065.

Figure 28: Free T and ratio of Free T to total T following the 3rd injection of TU 750 mg LOADING – PK population, study IP157-001 Part C

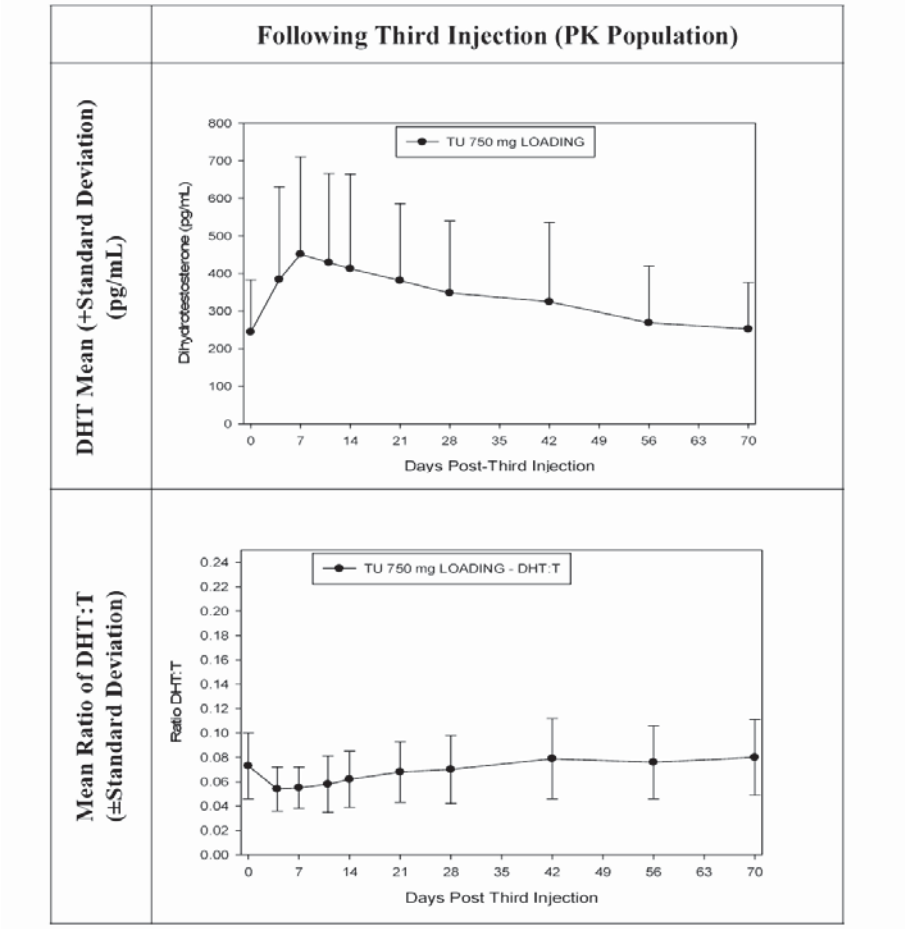


DHT concentration:

Average DHT concentrations generally paralleled total T concentrations but had smaller magnitude of increase at T_{max} (figure 29). Average DHT concentrations were in the range of approximately 250 – 450 ng/dL. Variability was moderate at most time points (coefficients of variation averaged around 50% to 70%), with slightly higher standard deviations at the Tmax time points (Day 4 to Day 7).

Reflecting the parallel tracking of DHT to T, the mean ratios of DHT:T remained relatively constant. The DHT:T ratios ranged from, on average, 0.05 to 0.07, with relatively low variability observed across the time points.

Figure 29: DHT and ratio of DHT to total T following the 3rd injection of TU 750 mg LOADING – PK population, study IP157-001 Part C

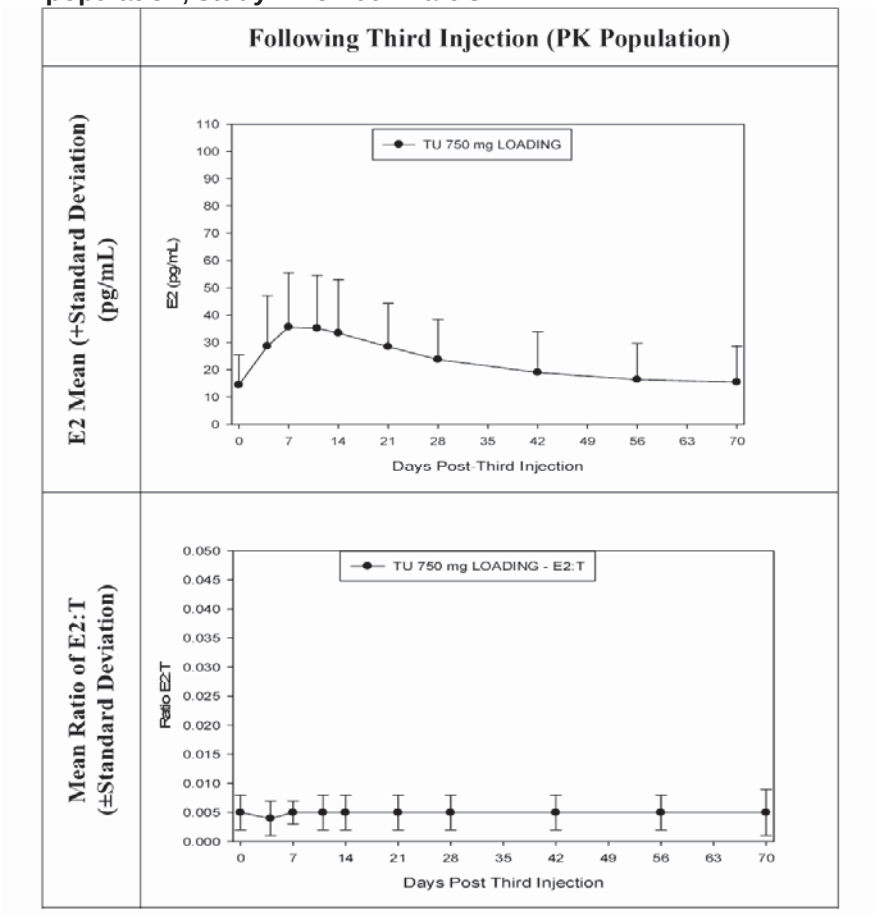


Estradiol concentration:

Average E2 concentrations generally paralleled total T concentrations (figure 30). Average E2 concentrations tended to remain within the normal range of 0 – 35 pg/mL (as provided by the central laboratory). E2 tended to demonstrate higher relative variability than the other hormones (as measured by the coefficients of variation for E2 concentrations, which ranged from 55% to upwards of 80%).

Reflecting the parallel tracking of E2 to T, the mean ratios of E2:T remained relatively constant. The average on-treatment ratios remained similar to the average pre-treatment ratios. The E2:T ratios ranged from, on average, 0.004 to 0.005, with relatively low variability observed across the time points.

Figure 30: E2 and ratio of E2 to total T following the 3rd injection of TU 750 mg LOADING – PK population, study IP157-001 Part C

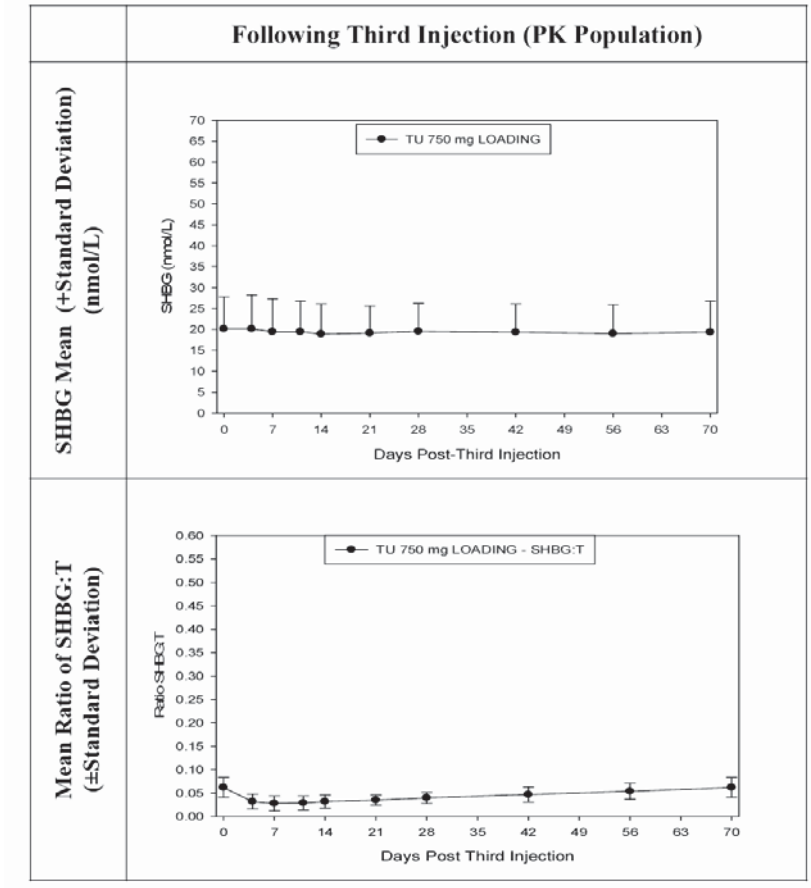


SHBG concentration:

Average SHBG concentrations remained constant (figure 31) and similar to baseline values. Average SHBG concentrations tended to remain within the lower end of the normal range of 13 – 71 nmol/L (as provided by the central laboratory). Variability was moderate at all time points (coefficients of variation averaged around 40 to 50%).

The mean ratios of SHBG:T tended to drop immediately following the injection (at the Day 4 time point). Based on the stable mean SHBG concentrations during the interval, the changes in the ratio were due to the changes in T concentrations (and not changes in SHBG concentrations). The SHBG:T ratios ranged from, on average, 0.02 to 0.06, with relatively low variability observed across the time points.

Figure 31: SHBG and ratio of SHBG to total T following the 3rd injection of TU 750 mg LOADING – PK population, study IP157-001 Part C



Individual study review of study IP157-001, Part A, Stage 1 and part of Stage 2

(b) (4)

Title:
A Two-Arm, Open-Label, Randomized, Multi-Center Pharmacokinetic and Long-term Safety Study of Intramuscular Injections of 750 mg and 1000 mg Testosterone Undecanoate (TU) In Hypogonadal Men

Primary objective:
- To evaluate the pharmacokinetics of TU 750 mg and TU 1000 mg, given every 12 weeks, over the 12-week interval following the 4th injection, via multiple measurements of serum total T, in approximately 110 hypogonadal men per treatment arm.

Secondary objectives:
- To evaluate the pharmacokinetics of TU 750 mg and TU 1000 mg over the 12-week intervals following the 1st, 2nd and 3rd injections, via multiple measurements of serum total T, in 20 hypogonadal men per treatment arm.
- To compare serum levels of DHT, E2, SHBG, TU, and DHTU to simultaneous levels of serum total T.
- To evaluate long-term safety in all patients via treatment with TU 750 mg and TU 1000 mg, given every 12 weeks in hypogonadal men, for up to 48 weeks.

Study design:
This is a multicenter, 2-arm, randomized, open-label part of the study. Treatment arms are:

- 750 mg TU (250 mg/mL) in 3 mL oily solution (TU 750 mg), injected every 12 weeks
- 1000 mg TU (250 mg/mL) in 4 mL oily solution (TU 1000 mg), injected every 12 weeks

Select inclusion criteria:
- Male with primary or secondary hypogonadism at least 18 years of age
- Morning screening serum T concentration < 300 ng/dL
- If receiving endocrine replacement hormones (e.g., thyroid), antihypertensives, lipid lowering agents, antidepressants or anxiolytic medications, the dose must be stable for at least 28 days prior to entry OR is not currently on such medications.

Approximately 110 patients were to be randomized into each treatment dose arm for a total of up to approximately 220 patients. The randomization schedule for patients was to be stratified by the screening T concentration level as follows:

- T < 150 ng/dL, and;
- T = 150 to < 250, and;
- T = 250 < 300 ng/dL.

The last screening T measurement prior to randomization was used to determine the patient stratification level.

The first 40 patients (20 per treatment group) were to be included as the sub-group of patients who would undergo intensive pharmacokinetic (IPK) assessments during both the 1st (1st dose IPK subgroup) and 4th injection intervals with sparse additional T/DHT PK assessments post 2nd and 3rd injection, while the remaining 180 patients were to have IPK captured after only the 4th injection.

The study has 4 defined periods: Screening, Baseline, Stage 1, and Stage 2.

- Screening: Approximately 1-5 week screening period (washout from select prior T replacement therapies may have extended this period for some patients)
- Baseline: Final pre-study measurements were to be captured, and patients were to be randomized to one or the other treatment group.
- Stage 1: From the day of the 1st injection to the day of the 5th injection, hence, the first 5 injections at 12-week intervals. This included the first injection at the Baseline visit. The end of Stage 1 was the 5th injection visit at approximately 48 weeks post-first injection. The Stage 1 analysis includes only data through the 5th injection visit in each treatment group. In addition, the 1st injection (single-dose) IPK data as well as the post 2nd and 3rd injection sparse T/DHT data of approximately the initial 20 patients from each treatment dose arm are included in Stage 1 report.
- Stage 2 (Long-term safety extension): The study is continuing following the 5th injection visit, with 8 additional injections (at 12-week intervals) planned during an extended treatment phase. The Stage 2 analysis will include all patients and all data.

The primary analysis was performed following the completion of the post-4th injection IPK collections.

Patients were to have a trough PK at the 2nd and 3rd injection and were to continue to have trough PK captured thereafter (following the 5th injection, i.e., during the extension portion of the study) at each 12-week dosing interval visit through the remainder of the study. Additionally, the first 40 patients were to have T and DHT levels assessed at three timepoints each post 2nd and 3rd injection (on Days 42, 56, and 70).

Stage 2 is ongoing and will include an additional 9 injections; thus, the total exposure for individual patients will be up to 13 injections (approximately 3 years). Long-term safety will be assessed through 13 injections up to approximately 3 years (the "Stage 2" analysis). Data from Stage 2 is not included in this NDA with the exception of mean trough concentrations at the end of the 5^{th} and 6^{th} injection intervals as provided in a response to FDA's 74-Day letter and again discussed in the study report for Study IP157-001 Part C. Those data are not discussed in this individual study review. [redacted] (b) (4)

PK samples collection:

- In the first 20 patients in each treatment arm after the 1st injection, at Day 0 (measured pre-injection), and at Day 4, 7, 11, 14, 21, 28, 42, 56, 70, and the end of the 1st injection interval at Day 84, i.e., at 2nd injection visit (measured pre-injection), and;

- In up to 110 patients in each treatment arm after the 4th injection (at 36 weeks post-first injection), at Day 0 (measured pre-injection), 4, 7, 11, 14, 21, 28, 42, 56, 70, and Day 84 of the 4th injection interval, where the 5th injection visit is defined as the end of the injection interval.

The 1st injection IPK data was to be used to characterize the single-injection concentration-time profile for each treatment group. Additionally, the first 40 patients were to have sparse PK assessment of T and DHT levels assessed at three timepoints each post 2nd and 3rd injection.

The 4th injection IPK data will be used to determine the primary pharmacokinetic outcomes (based on the FDA criteria for C_{ave} and C_{max}).

Drug product:
Each [redacted] (b) (4) TU contained 4 mL of drug product, in a concentration of 250 mg/mL. In this study, doses contained either 750 mg TU in 3 mL oily solution or 1000 mg TU in 4 mL oily

solution. Injections were made into the deep gluteal muscle. Dosing was to have been provided at 9 a.m. ± 3 hours. Trough PK was to be collected prior to dosing. All PK (hormone testing) samples were to be collected in the morning.

Study schedule:

Table 28: Schedule of events (study IP157-001 Part A)

	Injection Number and Week														
	Screening Phase		1	2	3	4	5	6	7	8	9	10	11	12	13	EOS
	Days -35 to -7	Post-Washout	Day 0	12	24	36	48	60	72	84	96	108	120	132	144	156[5]
Informed Consent	X															
Eligibility	X		X[1]													
Medical History	X		X[1]													
Physical Exam	X					X		X				X				X
Digital Rectal Examination	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital Signs (includes pulse, blood pressure, temperature)	X		X			X		X				X				X
12 Lead ECG	X					X		X				X				X
Hematology, Coagulation, Chemistry, Urinalysis, FSH, LH	X		X	X		X		X				X				X
Lipid Profile - Preferred Fasting (Total, LDL, HDL cholesterol & triglycerides) and PSA	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Prostate Volume (via TRUS)[2]	X															
Pharmacokinetic Sampling (T, DHT, FREE T,TU, DHTU, E2, SHBG) TU/DHTU are not collected at screening	X only if Washout NOT Required	X if Washout Required	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events			X	X	X	X	X	X	X	X	X	X	X	X	X	X
Prior/Concomitant Medications	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Injection (includes drug accountability)			X	X	X	X	X	X	X	X	X	X	X	X	X	
Local tolerability assessment[3]			X	X	X	X	X	X	X	X	X	X	X	X	X	X
Body Measurements (hip-and-waist circumference, hand grip strength and weight; height is captured at Baseline only; DEXA[4])			X			X		X				X				X
Profile of Mood States			X	X	X	X	X	X	X	X	X	X	X	X	X	X
Psychosexual Daily Questionnaire (7-day diary to begin 7 days prior to Baseline)	X only if Washout NOT Required	X if Washout Required	Patient Returns Diary													
International Index of Erectile Function			X	X		X		X				X				X
AUA Symptom Score	X		X	X		X		X				X				X
Male Patient Global Assessment				X		X		X				X				X

[1]Medical History and Eligibility pages will be updated at Baseline visit as appropriate.
[2]TRUS may be repeated during the study at the investigator's discretion.
[3]Injection site will be assessed by investigator if, at any time, the patient indicates a tolerability issue with the injection site.
[4]Optional DEXA will be performed at baseline and annually (ie, week 60, week 108 and week 156) thereafter at specified investigator sites, and is not a requirement for study entry.
[5]Patients who discontinue prematurely from the study and who will not complete all of the treatment injections are to be administered assessments as listed under Week 156 or End of Study (EOS) Visit.

Table 29: Schedule of IPK samplings (study IP157-001 Part A)

Intensive PK Collection Time Points (Post-Injection 1[a] ,2[a] ,3[a] ,and 4[b] Only)											
	Day										
Assessments	0[c]	4	7	11	14	21	28	42	56	70	84[c,d]
Serum Total Testosterone[e]	X	X	X	X	X	X	X	X	X	X	X
DHT[e]	X	X	X	X	X	X	X	X	X	X	X
TU	X	X	X	X	X	X	X	X	X	X	X
DHTU	X	X	X	X	X	X	X	X	X	X	X
Estradiol	X	X	X	X	X	X	X	X	X	X	X
SHBG	X	X	X	X	X	X	X	X	X	X	X
Free T (measured)	X	X	X	X	X	X	X	X	X	X	X
Psychosexual Daily Questionnaire (7-day diary)						X (start on Day 21)	X (return on Day 28)				
International Index of Erectile Function & AUA Symptom Score						X					
Profile of Mood States						X					
Male Patient Global Assessment						X					
Local tolerability assessment			X Post injection 4 only								

[a] First 20 patients of each treatment dose arm
[b] All patients of each treatment dose arm
[c] Day 0 and Day 84 assessments are described in the protocol Table 9
[d] Day 84 of Injection Periods 1 and 4 is the same as Day 0 of Injection Periods 2 and 5, respectively
[e] Day 42, 56, 70: Sparse PK assessment of T & DHT performed during Injection Periods 2 and 3 on first 20 patients of each treatment dose arm – see GRAY shaded region above

Data analysis:
The concentration of T, DHT, TU and DHTU in human serum samples was assessed by HPLC with MS/MS detection by (b) (4) located at (b) (4)

The methods were validated ((b) (4) validation reports 2100-801 (T and DHT) and 6530-109 (TU and DHTU)). The study specific bioanalytical report was provided in Covance report 6657-213 (final Part A, Stage 1 report, issued July 20, 2007). The reports were acceptable.

Special note:

The sponsor indicated because T concentrations above 1800 ng/dL were identified in the FDA C_{max} threshold criteria as important values of interest, whenever a T concentration was originally found to be above the FDA threshold of 1800 ng/dL, the sample was re-assayed in duplicate by the bioanalytical laboratory to confirm the finding. The mean of the repeats was derived and used in the PK assessments for these values. There were 6 samples that were reassayed for this reason. All 3 raw T concentrations (the original and the 2 repeat values) as well as the reported value (median) and the mean of the repeats for these 6 samples are listed in Table 30.

Table 30: List of all serum total T concentration values exceeding 1800 ng/dL during 4th injection interval – PK population, study IP157-001 Part A

Patient Number and Days Post-Fourth Injection	Treatment Group	Reported Value (ng/dL)[1]	Original Result (ng/dL)	Repeat 1 (ng/dL)	Repeat 2 (ng/dL)	Mean of Repeat 1 and 2 (ng/dL)[2]
041-4057 Day 7	1000 mg	1909.49	1999.18	1909.49	1862.91	**1886.20**
035-4035 Day 7	1000 mg	1961.64	2067.93	1922.50	1961.64	**1942.07**
002-4050 Day 7	1000 mg	1929.92	2054.07	1925.04	1929.92	**1927.48**
021-4017 Day 7	1000 mg	1901.21	2015.38	1892.03	1901.21	**1896.62**
002-4074 Day 4	1000 mg	1826.59	1946.97	1826.59	1737.37	**1781.98**
057-4104 Day 7	1000 mg	1632.52	1848.36	1602.40	1632.52	**1617.46**

Reference: Appendix 16.4 Data Listing 12.2.17.1
[1] Reported value was the median of the 3 T concentrations (the original and the 2 repeat values), as reported by the bioanalytical laboratory in the study database. See the bioanalytical report for more details.
[2] Repeat values 1 and 2 were processed (within patient) in the same bioanalytical run. The mean of the repeated values was used in the pharmacokinetic analysis.

Reviewer's notes: This method of select reanalysis on samples with concentration >1800 ng/dL introduces bias to the results. As observed in this report, all reanalysis samples reported lower concentrations than the original results. Additionally, the sponsor chose to use the mean of repeats rather than the usually applied method of using the median of original and the duplicate repeats. Depending on whether the original, median of original and repeats, or mean of the repeats was used, the number of patients with C_{max} >1800 ng/dL were 6, 5, or 4, respectively.

The small decreases in total T concentration due to these reassays should not significantly affect the calculation of C_{ave}.

PK Population:
Pharmacokinetic assessments were to be performed on those patients who receive the 4th injection and complete the 4th injection interval pharmacokinetic assessments. Patients in the PK Population were to be used for all PK summaries and for all summaries of the metabolites and other hormone assessments. Patients were to be included in the PK Population if they satisfied the following:

- Patients must have had a minimum of 4 T concentration values within the 4th injection dosing interval. The 4 values could include the Day 0 and/or Day 84 values.
- If any patients were found to be noncompliant with respect to dosing or have incomplete data, a decision was to be made on a case-by-case basis as to their inclusion in the PK Population.

1st IPK subgroup:
A separate population was to be identified as the patients who had intensive PK collected during the 1st injection interval. This population was to have no more than 20 patients per treatment group.

- Patients must have had a minimum of 4 T concentration values within the 1st injection dosing interval. The 4 values could include the Day 0 and/or Day 84 values.

1st and 4th IPK population:
A separate population was to be identified as the patients who had intensive PK collected during both the 1st and 4th injection intervals. The intent of this population was to allow for comparison of the PK from the 1st interval to the 4th interval, for derivation of accumulation ratios for AUC and Cmax.

Table 31 list the number of patients in each population.

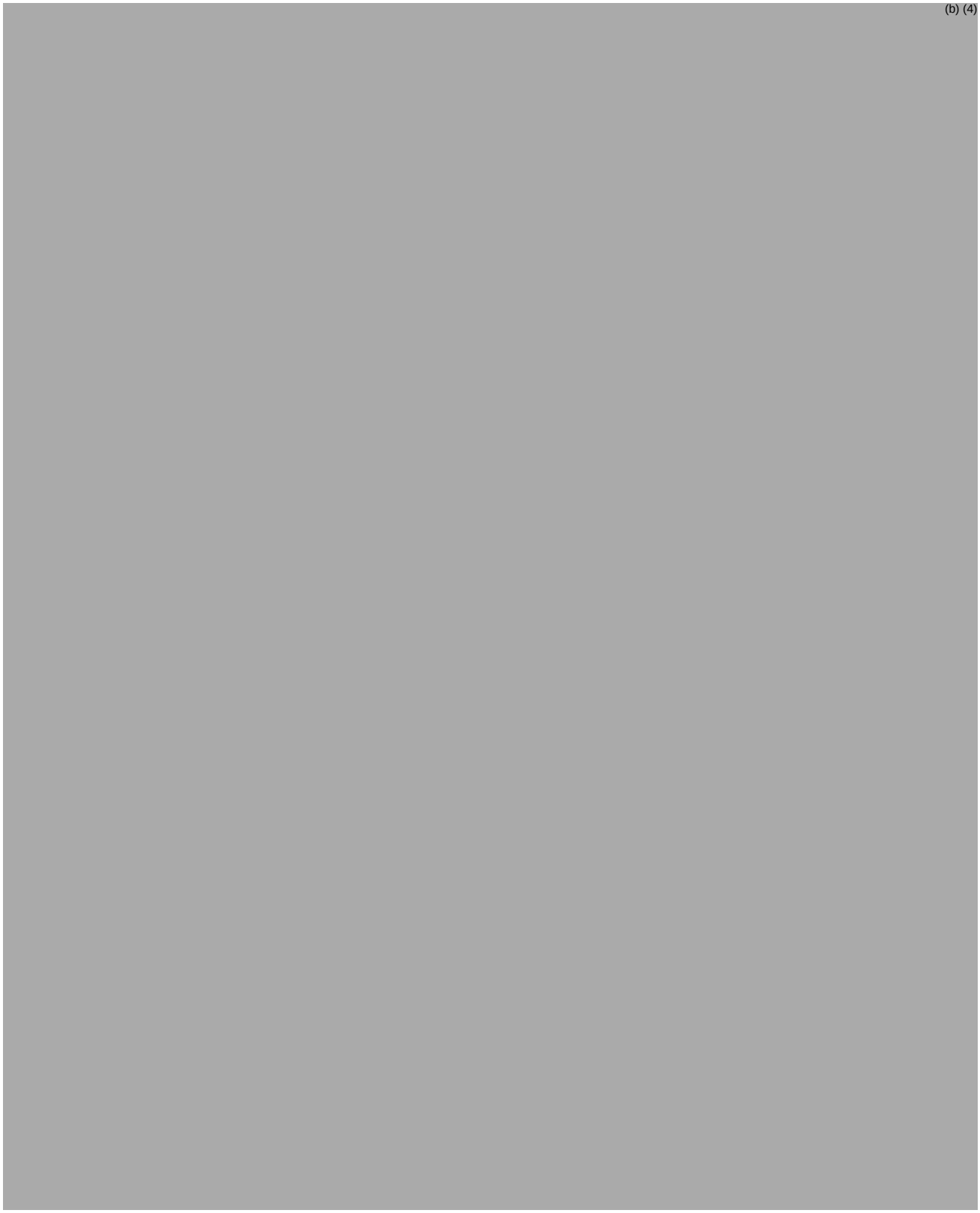
Table 31: Patient samples for analysis (Study Ip157-001 Part A)

Population (Patient Sample)	TU 750 (N=120)	TU 1000 (N=117)
Total Patient Sample	120 (100.0)	117 (100.0)
PK Population	102 (85.0)	97 (82.9)
Patients Eligible for 1st Injection Interval PK Assessment[1]	20	20
1st IPK Population	19 (95.0)	19 (95.0)
1st and 4th IPK Population	16 (80.0)	16 (80.0)

Reference: Section 14.1 Table 9.1.3
[1] As per the study design, only 40 patients (20 per treatment group) were eligible for intensive PK sampling during the 1st injection interval. Percentages are based only on those 20 patients per treatment group.

(b) (4)

(b) (4)



1st IPK population:
This study included an intensive PK sampling (in a subgroup of 20 patients per treatment group) for T concentrations during the 1st injection interval. The intent of this sampling was to allow for a

characterization of the T PK profile over the 12 weeks following the 1st injection of either the TU 750 mg or TU 1000 mg dose. PK sampling was performed in this subgroup of patients pre- 1st injection and then following the 1st injection at Days 4, 7, 11, 14, 21, 28, 42, 56, 70, and the end of the injection interval at Day 84, ie, at the 2nd injection visit. Further sampling was performed in this IPK subgroup at Days 42, 56 and 70 post 2nd injection and post 3rd injection.

Figure 36 shows the mean PK profile for a single dose of either 750 or 1000 mg TU given IM to the buttock to hypogonadal men. Figures 37 and 38 show composites of the individual PK profiles. Table 40 shows the PK parameters for single dose TU. Please note that baseline correction was not used because the goal of TRT is to return the serum T concentration (regardless of endogenous or exogenous contribution) in hypogonadal men to its normal physiologic concentration.

Serum T concentration is elevated following the first injection of 750 mg or 1000 mg TU with a median T_{max} of 7 days. The IM depot formulation allowed for a prolonged profile of elevated serum T concentration. Most patients had C_{trough} <300 ng/dL by the end of the 84-day dosing interval in this first dose PK assessment.

Figure 36: By-treatment mean (+SD) serum total T concentrations over 84 days resulting from a single injection of TU - 1st IPK population (Study IP157-001 Part A)

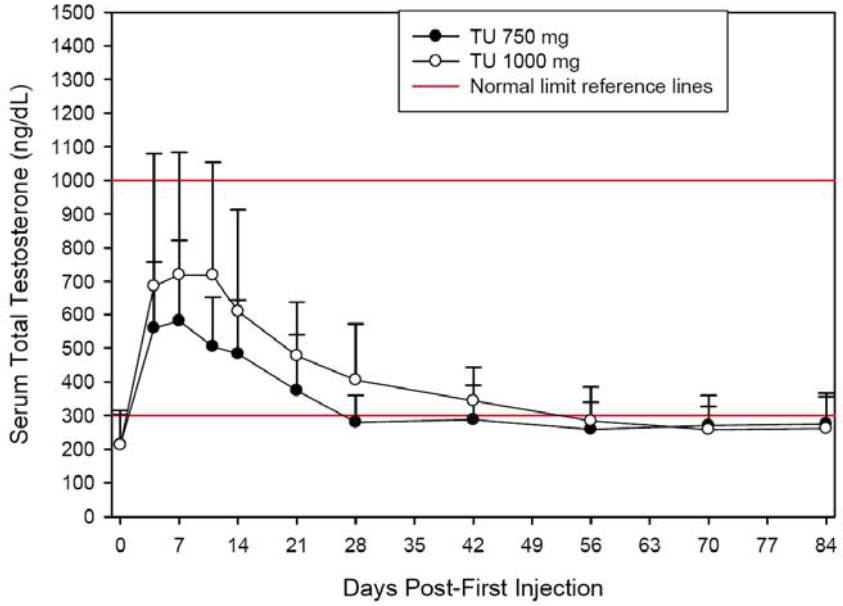


Figure 37: Individual (n=19) serum total T concentrations during first injection interval of 750 mg TU (Study IP157-001 Part A).

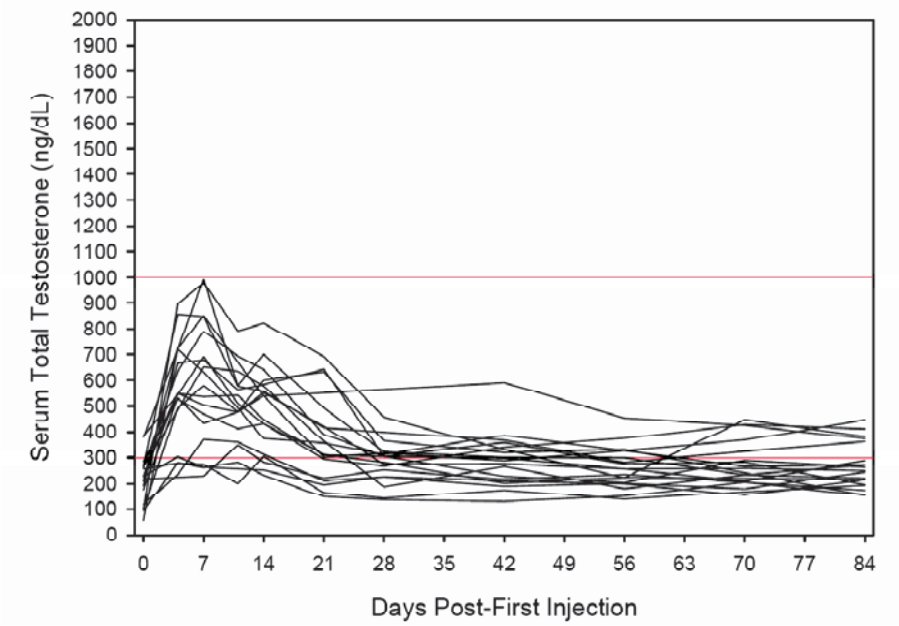


Figure 38: Individual (n=19) serum total T concentrations during first injection interval of 1000 mg TU (Study IP157-001 Part A).

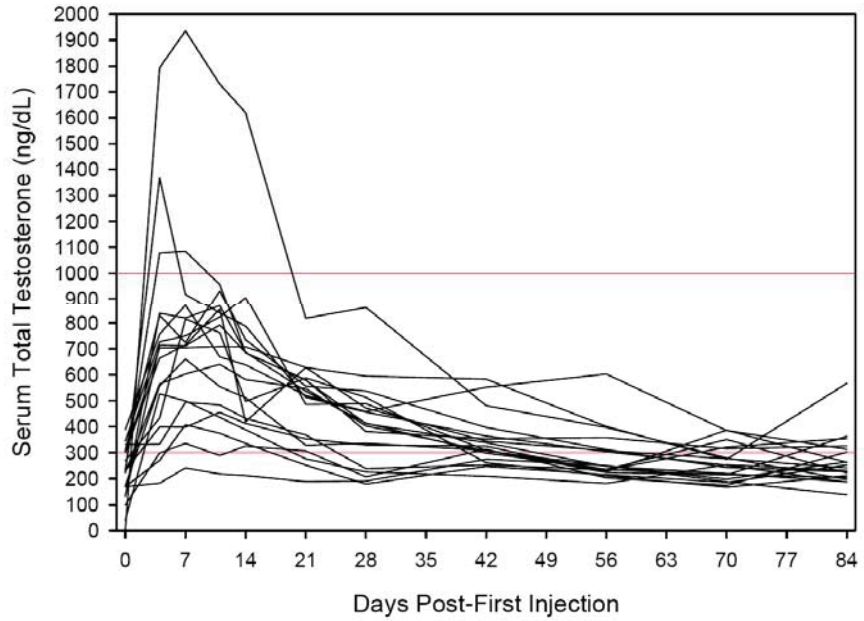


Table 39: Serum total T concentrations (ng/dL) following the 1st injection of TU – 1st IPK population, study IP157-001 Part A

Treatment Group (Number of Patients in 1st IPK Population)	Time (Days Post-Injection)	Number Patients	Mean	Standard Deviation	Minimum	Median	Maximum	CV%
TU 750 mg (N=19)	0 (Baseline)	19	214.8	91.38	57.0	227.3	385.1	42.5
	4	17	559.0	199.17	234.5	548.2	896.4	35.6
	7	19	580.4	241.99	228.6	579.1	991.9	41.7
	11	18	504.7	149.18	199.7	501.2	792.1	29.6
	14	19	482.7	162.16	231.9	537.8	821.8	33.6
	21	19	374.1	164.78	147.5	355.5	691.9	44.0
	28	17	274.7	78.71	135.3	280.8	456.8	28.7
	42	19	287.4	102.40	128.9	287.5	590.1	35.6
	56	19	259.3	79.39	137.8	255.7	453.5	30.6
	70	19	270.1	89.56	154.2	240.7	447.3	33.2
	84	19	267.3	88.36	152.8	248.6	446.8	33.1
TU 1000 mg (N=19)	0 (Baseline)	19	214.3	104.78	0.0	224.2	388.5	48.9
	4	19	686.2	394.19	182.8	664.9	1792.7	57.4
	7	19	720.4	363.92	241.4	711.6	1935.1	50.5
	11	18	719.4	335.14	218.0	735.9	1729.6	46.6
	14	19	608.9	305.05	212.2	582.1	1619.9	50.1
	21	19	476.8	160.81	188.2	520.8	817.7	33.7
	28	19	405.3	166.22	178.9	411.7	860.5	41.0
	42	19	343.5	99.23	209.5	314.2	583.1	28.9
	56	19	284.1	100.17	181.5	246.9	603.2	35.3
	70	19	258.0	68.41	166.5	252.0	386.4	26.5
	84	19	265.9	94.65	137.3	240.8	567.5	35.6
Reference: Section 14.2 Table 9.2.1.2.2								

Table 40: PK parameters of serum total T resulting from a single injection of TU – 1st IPK population in study IP157-001 Part A.

TU Dose	Pharmacokinetic Parameter	Number Patients	Mean	Standard Deviation	Minimum	Median	Maximum	CV (%)	Geometric Mean
750 mg	$AUC_{(0-84)}$ (days*ng/dl)	19	27513.0	8045.18	14515.5	27723.6	43609.6	29.2	26329.4
	C_{Trough} (Day 84)	19	267.3	88.36	152.8	248.6	446.8	33.1	254.3
	C_{max} (ng/dL)	19	611.1	223.69	281.0	633.5	991.9	36.6	568.9
	Dose-normalized C_{max}(ng/dL)[1]	19	0.8	0.30	0.4	0.8	1.3	36.6	0.8
	T_{Last} (days)	19	84.0	0.00	84.0	84.0	84.0	0.0	84.0
	T_{max}	19	8.5	4.59	4.0	7.0	21.0	54.1	7.5
	Dose-normalized $AUC_{(0-84)}$ (days*ng/dl)[1]	19	36.7	10.73	19.4	37.0	58.1	29.2	35.1
	$C_{avg\ 0-84}$ (ng/dL)[2]	19	327.5	95.78	172.8	330.0	519.2	29.2	313.4
1000 mg	$AUC_{(0-84)}$ (days*ng/dl)	19	32713.7	9894.60	18944.0	32419.8	59561.7	30.2	31384.7
	C_{Trough} (Day 84)	19	265.9	94.65	137.3	240.8	567.5	35.6	252.9
	C_{max} (ng/dL)	19	785.5	388.07	275.2	792.2	1935.1	49.4	706.1
	Dose-normalized C_{max}(ng/dL)[1]	19	0.8	0.39	0.3	0.8	1.9	49.4	0.7
	T_{Last} (days)	19	84.0	0.00	84.0	84.0	84.0	0.0	84.0
	T_{max}	19	10.4	8.13	4.0	7.0	42.0	78.4	8.9
	Dose-normalized $AUC_{(0-84)}$ (days*ng/dl)[1]	19	32.7	9.89	18.9	32.4	59.6	30.2	31.4
	$C_{avg\ 0-84}$ (ng/dL)[2]	19	389.4	117.79	225.5	386.0	709.1	30.2	373.6

Reference: Section 14.2 Table 9.2.1.1.2
CV = Coefficient of Variation
[1] Statistics for the dose normalized AUC were derived by dividing the mean of the original parameter ($AUC_{(0-84)}$) by the dose amount (750 mg or 1000 mg).
[2] C_{avg} derived as $AUC_{(0-84)}$/84 days

Second and third injection T concentrations:

The analysis in this section includes data from the 1st and 4th IPK Population, which included 16 patients in each group. Patients must have completed IPK in both the 1st and the 4th injection intervals in order to be included in this population.

Figures 39 and 40 show the serum T concentrations vs. time post-injection for the 750 mg and 1000 mg doses, respectively. Based on the sparse samplings on days 0, 42, 56, 70, and 84 post-injection, the serum T concentrations increases with each subsequent injection but there appears to be a similar profile across the injection intervals.

Figure 39: TU 750 mg mean total T concentrations during first, second, third, and 4th injection intervals (Days 0, 42, 56, 70, and 84 within each interval) – 1st and 4th IPK population, study IP157-001 Part A

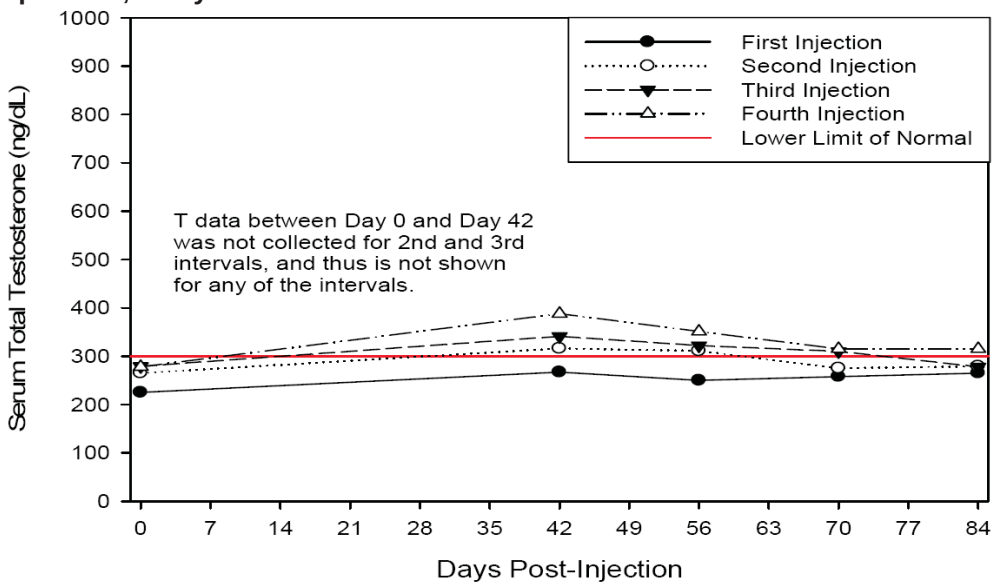
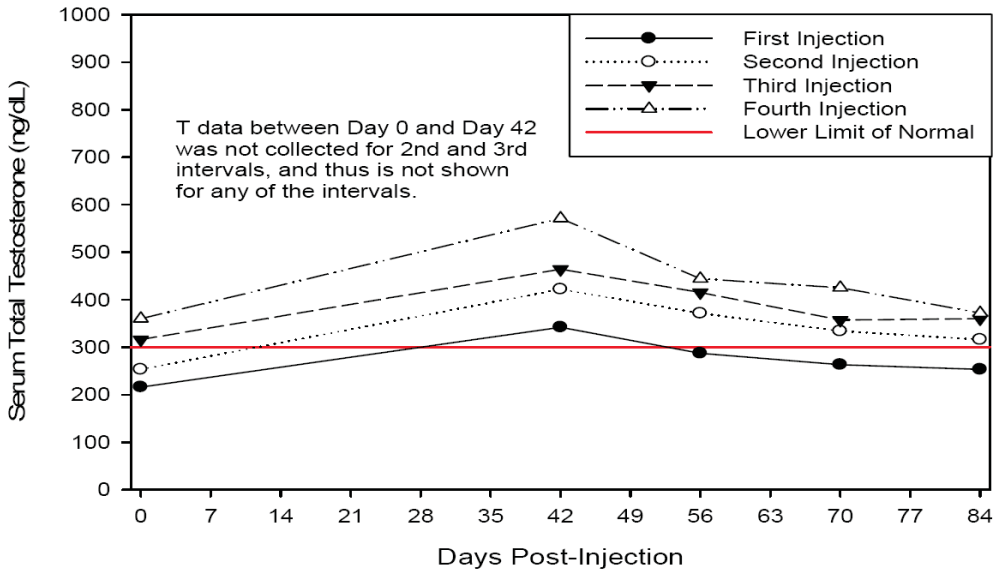


Figure 40: TU 1000 mg mean total T concentrations during first, second, third, and 4th injection intervals (Days 0, 42, 56, 70, and 84 within each interval) – 1st and 4th IPK population, study IP157-001 Part A



Factors associated with T Exposure

Sponsor investigated several factors that may have been predictive of T exposure, as measured by PK parameters C_{max} and C_{ave} during the 4th Injection interval. Included in this assessment were variables for age, pre-treatment or pre-dose T concentration, baseline BMI (or baseline weight), prior TRT use, and race.

This exploratory analysis revealed that most of these variables were not predictive of C_{max} or C_{ave}. Three variables were predictive of exposure for both treatment groups: the pre-injection T concentration, the pre-treatment body mass index (BMI) of the patient, and the pre-treatment body weight of the patient.

As expected, patients with a higher pre-dose T (i.e., their Day 0 T concentration collected on the day of the 4th injection) tended to have a higher C_{max} and C_{ave} during the 4th injection interval compared to patients with a lower pre-dose T. The strength of this association was not sufficient to allow for prediction of individual patient values for C_{max} or C_{ave}, but was sufficient to allow for an overall population-based conclusion that patients with higher pre-injection T tended to have slightly higher PK exposure when at steady state. [Note that the association between pre-dose T and post-dose T concentrations was not detected for the 1st injection; patients in the study were required to have a pre-treatment T below 300 ng/dL (thus, all patients had T below the lower limit of normal to start with), and only 19 patients in each arm had the intensive serum sampling during the 1st injection interval (the small sample size limiting the sensitivity of any subgroup assessments).]

To demonstrate the association between pre-injection T and post-injection T, subgroups were defined (in a post-hoc manner) by their pre-4th injection T concentrations using the following classifications;

- T < 300 ng/dL
- T between 300 and 450 ng/dL
- T > 450 ng/dL.

For both treatment arms, patients in the lowest T subgroup (those patients with a pre-fourth injection T < 300 ng/dL) had approximately 25% less exposure to T than patients in the highest T subgroup (i.e., those patient with a pre-4th injection T > 450 ng/dL).

Pre-treatment (study baseline) BMI and weight were both univariately (and similarly) predictive of these PK parameters. The univariate association between BMI (and weight) and exposure was characterized by lower average C_{max} and C_{ave} values as average BMI (and weight) increased. For both treatment arms, patients in the highest BMI subgroup had approximately 25% less exposure to T than patients in the lowest BMI subgroup (table 41). These differences were observed despite of similar pre-injection T concentrations among the BMI subgroups.

Table 41: Summary of mean (SD) serum total T C_{ave} and C_{max} during 4th injection intervals by BMI subgroups – PK population, study IP157-001 Part A

	TU 750 (N=102)			TU 1000 (N=97)		
	<26 kg/m² (N=11)	26-30 kg/m² (N=32)	>30 kg/m² (N=58)	<26 kg/m² (N=12)	26-30 kg/m² (N=32)	>30 kg/m² (N=52)
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
C_{max} (ng/dL)	1084.8 (344.96)	837.2 (333.17)	713.1 (260.57)	1271.5 (383.67)	1108.4 (396.81)	858.0 (344.27)
C_{avg} (ng/dL)	535.0 (99.49)	457.2 (150.42)	409.6 (110.78)	623.0 (131.88)	603.6 (167.86)	498.5 (164.22)

Reference: Section 14.2 Table 9.2.1.8.3
Note: One patient in each treatment group was missing a pre-treatment weight, did not have a pre-treatment BMI derived, and thus is not included in this table.

Figure 41: TU 750 mg mean serum total T concentration during 4th injection interval by BMI subgroups – PK population, study IP157-001 Part A

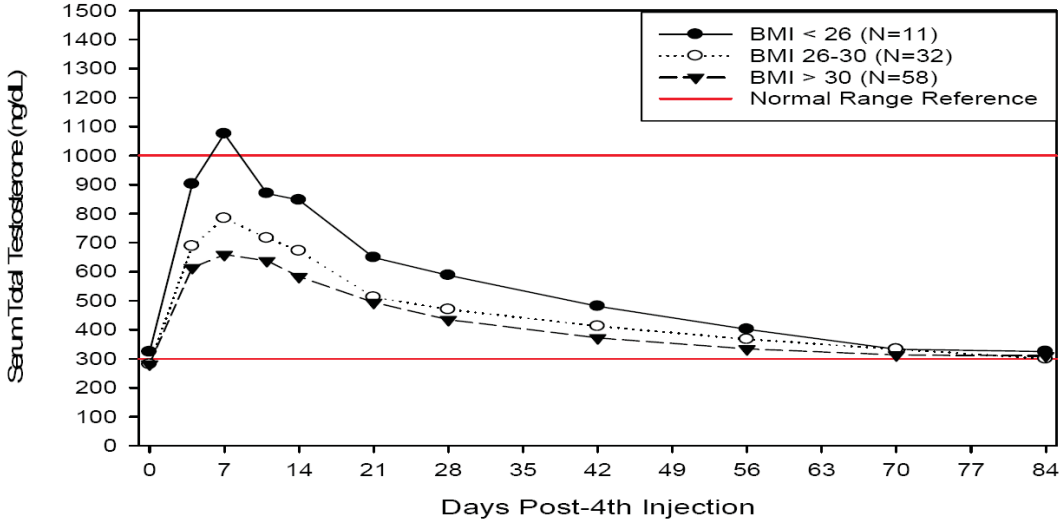
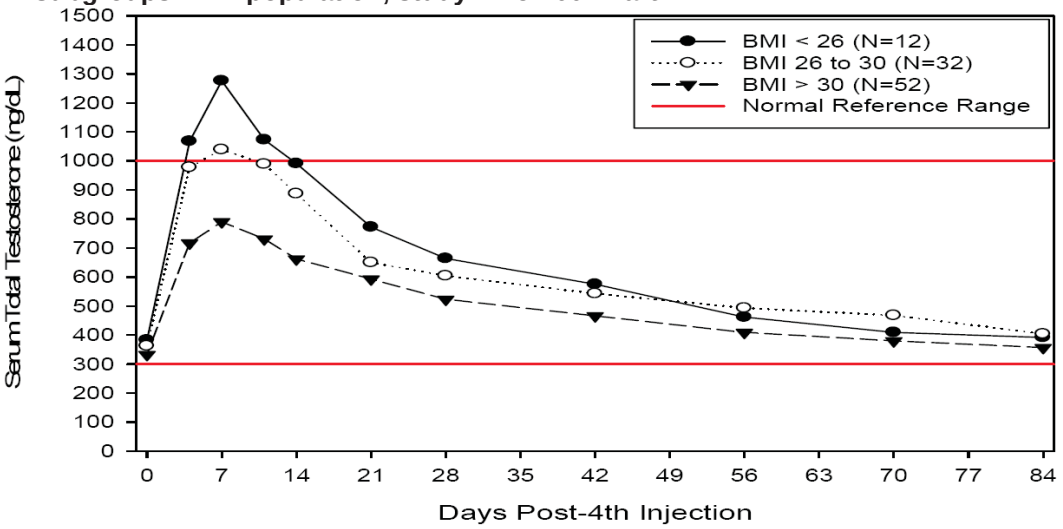


Figure 42: TU 1000 mg mean serum total T concentration during 4th injection interval by BMI subgroups – PK population, study IP157-001 Part A



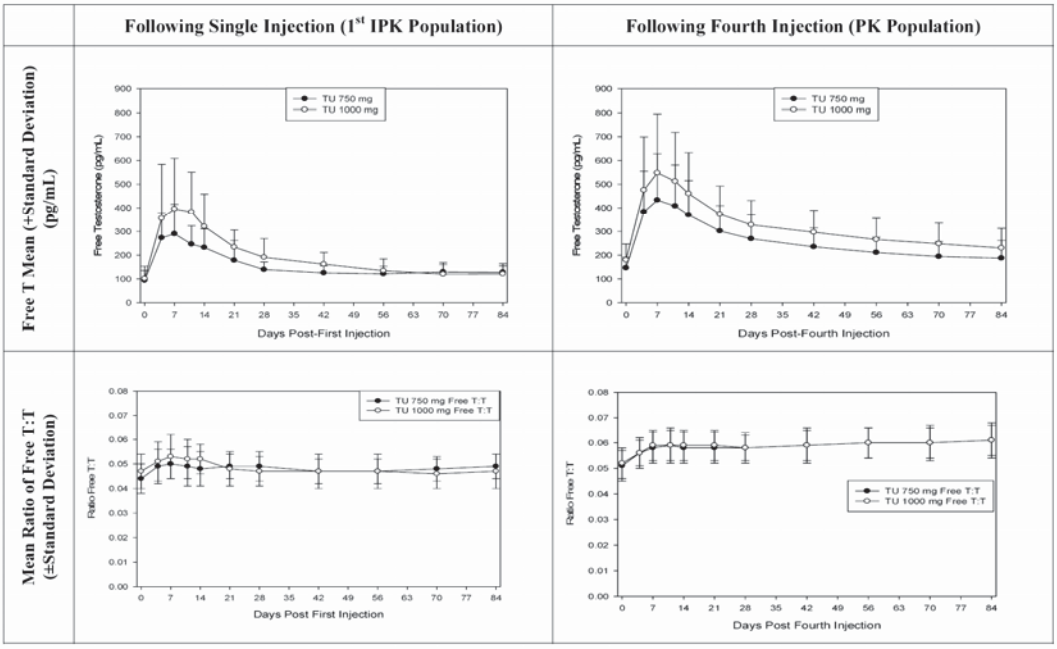
Hormones and T

Administration of exogenous T may lead to changes of other hormones and factors such as free T concentration (from unbound T), E2 (from metabolism of T), DHT (from metabolism of T), and SHBG. Serum free T, E2, DHT, and SHBG concentration were measured and compared to normal ranges. Their ratios to total T were also evaluated.

Serum Free T concentration:
For both treatment groups, average Free T concentrations generally paralleled T concentrations following both the 1st injection and the 4th injection. Average Free T concentrations tended to remain within or above the normal range of 50 – 210 pg/mL (as provided by the central laboratory), with concentrations of Free T in the TU 1000 mg arm higher than those in the TU 750 mg arm at most time points post-1st and 4th injection. Variability was moderate at most time points (coefficients of variation averaged around 40%), with slightly higher standard deviations at the T_{max} time points (Day 7 to Day 14).

Reflecting the parallel tracking of Free T to T, the mean ratios of Free T:T remained relatively constant throughout the 1st and 4th injection intervals. The average ratios remained essentially unchanged from pre-treatment through the 4th injection time points, ranging on average from 0.045 to 0.060.

Figure 43: Free T concentration and ratio of free T to total T following the 1st and 4th injection of TU – 1st IPK population and PK population, study IP157-001 Part A

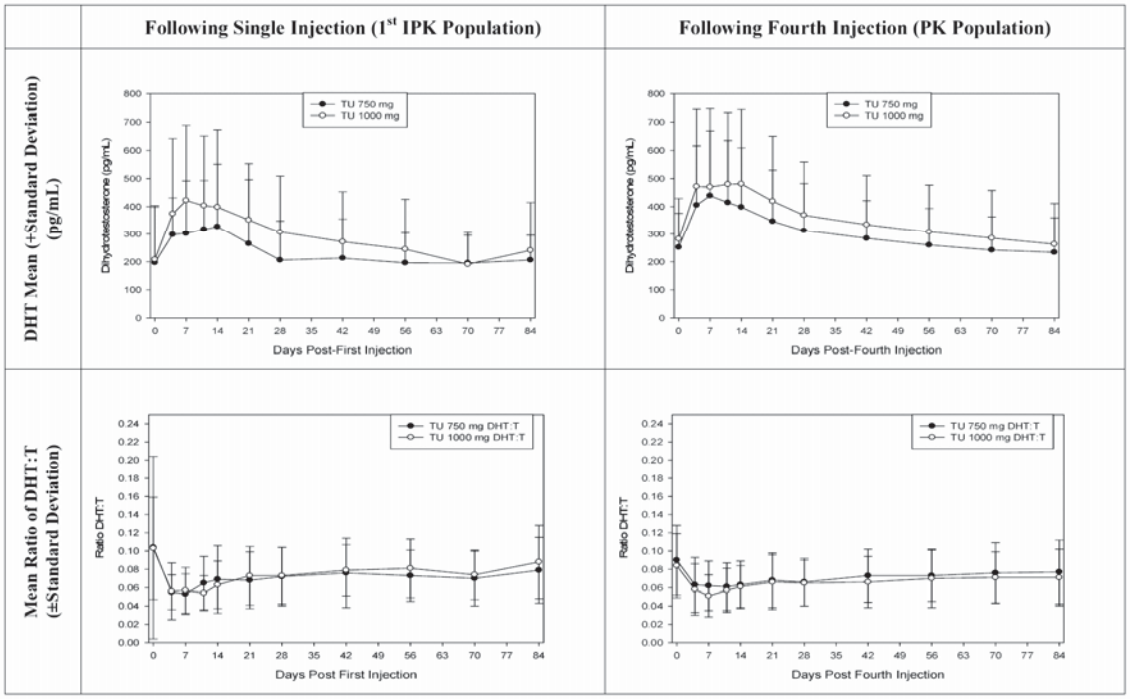


DHT:
For both treatment groups, average DHT concentrations generally paralleled T concentrations following both the 1st injection and the 4th injection. Average DHT concentrations were in the range of approximately 200 – 500 ng/dL, with concentrations of DHT in the TU 1000 mg arm higher than those in the TU 750 mg arm at most time points post-1st and 4th injection. Variability was moderate at most time points (coefficients of variation averaged around 55%), with slightly higher standard deviations at the Tmax time points (Day 7 to Day 14).

Reflecting the parallel tracking of DHT to T, the mean ratios of DHT:T remained relatively constant throughout the 1st and 4th injection intervals. The average ratios did drop slightly from the average pre-treatment values, and tended to remain on average below the pre-treatment ratios. The sponsor noted that the pre-treatment ratios were marked by a small number of

exceptionally high DHT:T ratios; these high pre-treatment values contributed to the higher variability observed at the pre-treatment time point. This may explain for part of the drop in ratio following the 1st injection. The drop in DHT:T ratio between Day 0 and Day 4 post dose was less prominent during the 4th injection but was still significant. The DHT:T ratios ranged from, on average, 0.05 to 0.07 during the 4th injection interval, with relatively low variability observed across the time points.

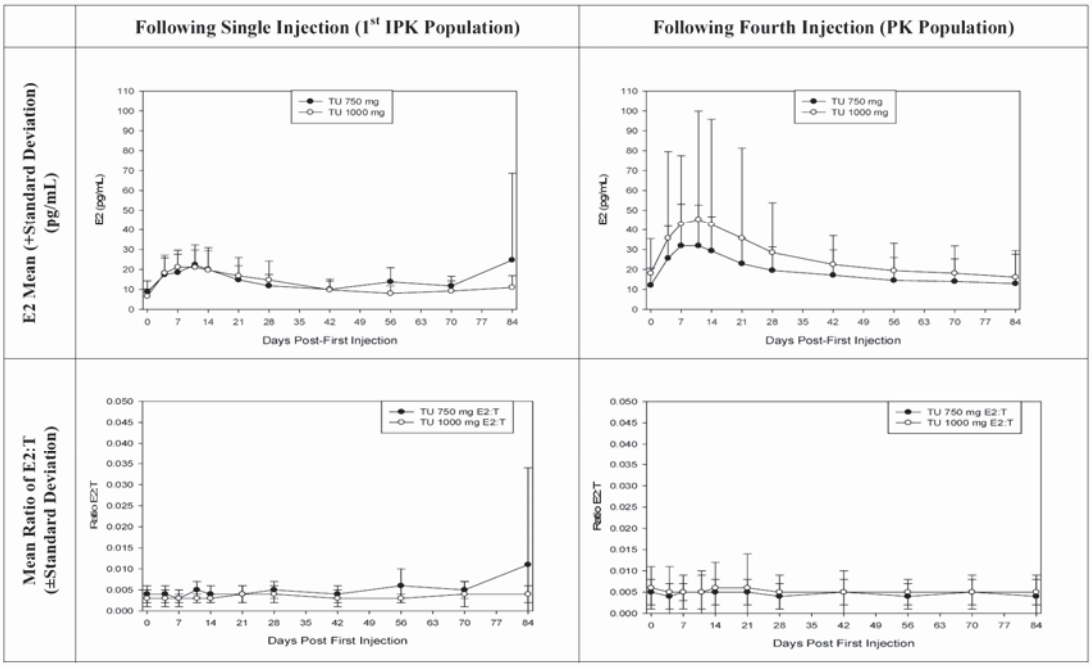
Figure 44: DHT and ratio of DHT to total T following the 1st and 4th injections of TU - 1st IPK population and PK population, study IP157-001 Part A



Estradiol:
For both treatment groups, average E2 concentrations generally paralleled T concentrations following both the 1st injection and the 4th injection. Average E2 concentrations tended to remain within or slightly higher than the normal range of 0 – 35 pg/mL (as provided by the central laboratory), with concentrations of E2 in the TU 1000 mg arm higher than those in the TU 750 mg arm at most time points post-4th injection. The 1st-injection Day 84 average for the TU 750 mg arm was marked by a single high E2 concentration; this value contributed to the higher variability observed at that time point for both the E2 concentration and the ratio of E2:T. E2 tended to demonstrate higher relative variability than the other hormones (as measured by the coefficients of variation for E2 concentrations, which ranged from 56% to upwards of 125%). There were also higher standard deviations observed for the TU 1000 mg arm as compared to the TU 750 mg arm.

Reflecting the parallel tracking of E2 to T, the mean ratios of E2:T remained relatively constant throughout the 1st and 4th injection intervals. The average on-treatment ratios remained similar to the average pre-treatment ratios. The E2:T ratios ranged from, on average, 0.045 to 0.055 during the 4th injection interval, with relatively low variability observed across the time points.

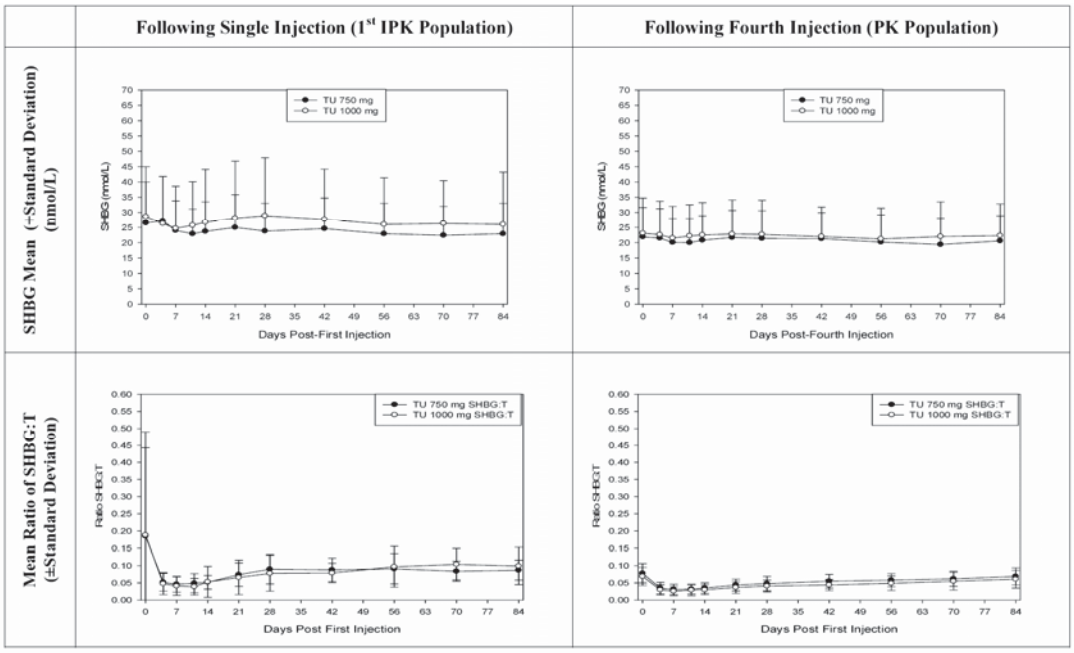
Figure 45: E2 and ratio of E2 to total T following the 1st and 4th injections of TU - 1st IPK population and PK population, study IP157-001 Part A



SHBG:
For both treatment groups, average SHBG concentrations remained constant following both the 1st injection and the 4th injection. The average SHBG concentrations were similar between the 1st and 4th injection, indicating that TU administration did not affect SHBG concentration. Average SHBG concentrations tended to remain within the middle of the normal range of 13 – 71 nmol/L (as provided by the central laboratory), with concentrations of SHBG in the TU 1000 mg arm slightly higher than those in the TU 750 mg arm at most time points post-1st and 4th injection. The sponsor noted that the TU 1000 mg arm also demonstrated slightly higher average concentrations pre-treatment and the differences between the groups during the on-treatment time points were similar in magnitude to those observed at the pre-treatment time point. Coefficients of variation averaged around 40 to 50% during the 4th interval and were consistent throughout each injection interval. Higher variability was observed with the 1st IPK population, likely due to the smaller sample size.

The mean ratios of SHBG:T tended to drop immediately following the injection (at the Day 4 time point). Based on the stable mean SHBG concentrations during the interval, the changes in the ratio were due to the changes in T concentrations (and not changes in SHBG concentrations). The pre-treatment average ratios for both groups were marked by at least one high SHBG:T ratio; these values contributed to the higher variability observed at pre-treatment for the ratios observed in the plots of the 1st IPK population. The SHBG:T ratios ranged from, on average, 0.02 to 0.08 during the 4th injection interval, with relatively low variability observed across the time points.

Figure 46: SHBG and ratio of SHBG to total T following the 1st and 4th injections of TU - 1st IPK population and PK population, study IP157-001 Part A



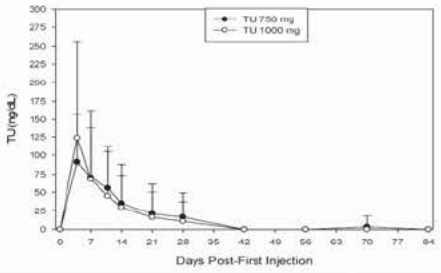
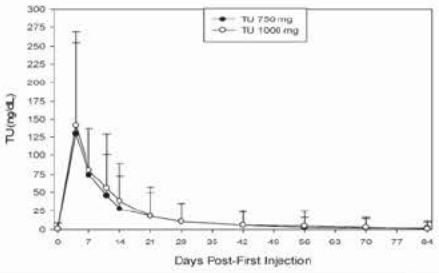
TU and DHTU:

Serum TU and DHTU were assessed following the first injection (1st IPK subgroup) and the 4th injection (total PK population).

TU: TU concentration was measurable in human serum following IM administration of TU 750 mg and 1000 mg. The observed individual concentration vs. time profiles were generally discontinuous with many samples being below the limit of quantitation (BLQ, LLOQ = 50 ng/dL). Most patients had one or two measurable samples to give a peak of TU concentration (usually on Day 4, the first measured time point post injection, and declined on Day 7) with other sampling times listed as BLQ. The data suggest that the true peak of TU might have occurred before Day 4 post injection. The highest observed serum TU concentrations were 1220 and 735 ng/dL following administration of 750 and 1000 mg TU doses, respectively. They were both observed during the 4th injection interval, Day 4. Figure 47 shows the mean (+SD) of serum TU concentrations following IM administration of TU (Note that BLQ samples were set to be zero and there were large numbers of BLQ samples.

DHTU: As measured in Study IP157-001, Part A, (1st and 4th injection intervals), concentration values of DHTU were below the limit of quantification (LLOQ = 100 ng/dL) for all but a few samples. There were 3 measurable samples with concentrations of 101, 170, and 238 ng/dL. They came from 3 separate patients. None of the samples in the 1000 mg dose group had measurable DHTU concentration.

Figure 47: TU concentration following the 1st and 4th injections of TU (1st dose IPK population and PK population, study IP157-001 Part A).

	Following Single Injection (1st IPK Population)	Following Fourth Injection (PK Population)
TU Mean (+Standard Deviation) (ng/dL)		
	Note: the assay for TU had a lower limit of 50 ng/dL. For generation of these plots, concentration values below the limit of quantification (BLQ) were set to 0 (zero). Generally, half or more of the values at each time point were BLQ; thus, these data are characterized by primarily unquantifiable concentrations of TU. Geometric means are presented in Section 14.2 Tables 9.2.3.1, and provide a measure of central tendency that excludes values BLQ.	

Office of Clinical Pharmacology
New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	**22-219**	**Brand Name**	**Nebido**
OCP Division	**DCP3**	**Generic Name**	**Testosterone undecanoate**
Medical Division	**DRUP**	**Drug Class**	**Androgen**
OCP Reviewer	**Doanh Tran, R.Ph., Ph.D**	**Indication(s)**	**Replacement therapy in males for conditions associated with a deficiency or absence of endogenous testosterone**
OCP Team Leader	**Myong Jin Kim, Pharm. D.**	**Dosage Form**	**Injectable solution**
		Dosing Regimen	(b) (4)
Date of Submission	**August 24, 2007**	**Route of Administration**	**Intramuscular injection**
Estimated Due Date of OCP Review	**April 26, 2008**	**Sponsor**	**Indevus**
PDUFA Due Date	**June 27, 2008**	**Priority Classification**	**Standard**
Division Due Date	**May 9, 2008**		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	**Number of studies submitted**	**Number of studies reviewed**	**Critical Comments If any**
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	x			
Tabular Listing of All Human Studies	x			
HPK Summary	x			
Labeling	x			
Reference Bioanalytical and Analytical Methods	x			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:	x	1		JPH01495
multiple dose:	x	5		JPH04995, JPH04995 Follow-up, ME98096, ME98096 Follow-up, ME98096 Final Follow-up
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:	x			Part of IP157-001
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				

pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:	x	6		ME97029, ME97029 Follow-up, ME97029 Final Follow-up, 306605, 306605 Follow-up, IP157-001 part A
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References	x	23		
Total Number of Studies		35		

Filability and QBR comments

	"X" if yes	Comments
Application filable?	x	Reasons if the application is not filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?
Comments sent to firm?	x	Comments have been sent to firm (or attachment included). FDA letter date if applicable.
QBR questions (key issues to be considered)	(b) (4) [redacted]	
Other comments or information not included above		
Primary reviewer Signature and Date		
Secondary reviewer Signature and Date		

Filing Memo

Clinical Pharmacology Review

NDA: 22-219
Compound: Testosterone undecanoate 250 mg/mL in castor oil intramuscular injection solution
Sponsor: Indevus

Date: 09/20/2007
Reviewer: Doanh Tran, R.Ph., Ph.D.

Introduction:

Nebido is a solution of testosterone undecanoate (TU) 250 mg/mL in castor oil and benzyl benzoate. It is intended to be given as an intramuscular injection (b) (4) for replacement therapy in males for conditions associated with a deficiency or absence of endogenous testosterone. TU is an ester pro-drug that is hydrolysed in the body to form testosterone (T), which serves the purpose of T replacement in hypogonadal men. The NDA contains a primary phase 3 study of efficacy (base on a primary end point of serum T concentration) and safety (study IP157-001) that was conducted in the US. Additionally, the results from 11 clinical studies (phase 1, phase 2, and phase 3, including the 6 follow-up studies) conducted in Europe were provided as supporting data. There appears to be sufficient data to evaluate the pharmacokinetics of Nebido in the target men population. However, no studies were conducted to evaluate the effect of intrinsic and extrinsic factors on the PK of Nebido.

Bioavailability:

Increase in serum T concentration was observed following injection of Nebido 1000 mg. Following 4 injections of 1000 mg Nebido at 12-week intervals, the mean ± SD C_{ave} and C_{max} were 551 ± 169 and 997 ± 395 ng/dL, respectively. In a subgroup of patients with available PK data for both the first and fourth dose, the fourth dose/first dose ratios for C_{max}, C_{trough}, and $AUC_{0\text{-}84\ days}$ were 1.4, 1.5, and 1.5 respectively. Serum concentration of dihydrotestosterone (DHT) and estradiol (E2) were also elevated following administration of Nebido and paralleled the profile of serum T. Serum concentrations of dihydrotestosterone undecanoate (DHTU) were mostly (99%) below the limit of quantification (100 ng/dL). However, serum concentrations of TU were measurable with observable concentrations as high as 735 ng/dL.

Absorption:

Intramuscularly injected Nebido forms a depot that releases the drug slowly (b) (4)

(b) (4)

Distribution:

No new data is provided. The sponsor relies exclusively on known properties of testosterone.

Metabolism:

Based on serum measurements, TU is metabolized to T and subsequently to DHT and E2. TU may also be metabolized to DHTU to a lesser extent. No new data is provided on the metabolism of testosterone. Sponsor relies exclusively on known properties of testosterone.

Excretion:

No new data is provided. Sponsor relies exclusively on known properties of testosterone.

Drug-drug interactions:

The sponsor did not conduct any drug interaction studies.

Special population:

The sponsor did not conduct studies in any special population.

Clinical vs. to-be-marketed formulation:

The drug formulation and manufacturing process were not changed during development and are the same as the to-be-marketed product. The clinical supplies were (b) (4) manufactured by (b) (4) The to-be-marketed product (in vials) will be manufactured in (b) (4) site. This drug product is a solution and a manufacturing site change would not require bridging studies.

Method validation:

The primary study IP157-001 used a HPLC-MS/MS assay to measure T, TU, DHT, and DHTU. The bioanalytical analysis was conducted by (b) (4) This assay was validated and data are available for review. Other supporting studies used commercially available radioimmunoassay or electrochemiluminescence immunoassay.

Recommendation:

The Office of Clinical Pharmacology/Division of Clinical Pharmacology 3 finds that the Human Pharmacokinetics and Bioavailability section for NDA 22-219 is fileable. The following review comment should be conveyed to the Sponsor in a 74-day letter.

Comments for sponsor:

(b) (4)

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

/s/

Doanh Tran
5/1/2008 05:23:49 PM
BIOPHARMACEUTICS

Myong-Jin Kim
5/5/2008 08:34:09 AM
BIOPHARMACEUTICS

Office of Clinical Pharmacology
New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	22-219	Brand Name	Nebido
OCP Division	DCP3	Generic Name	Testosterone undecanoate
Medical Division	DRUP	Drug Class	Androgen
OCP Reviewer	Doanh Tran, R.Ph., Ph.D	Indication(s)	Replacement therapy in males for conditions associated with a deficiency or absence of endogenous testosterone
OCP Team Leader	Myong Jin Kim, Pharm. D.	Dosage Form	Injectable solution
		Dosing Regimen	(b) (4)
Date of Submission	August 24, 2007	Route of Administration	Intramuscular injection
Estimated Due Date of OCP Review	April 26, 2008	Sponsor	Indevus
PDUFA Due Date	June 27, 2008	Priority Classification	Standard
Division Due Date	May 9, 2008		

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Patients-				
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multiple dose:	x	5		JPH04995, JPH04995 Follow-up, ME98096, ME98096 Follow-up, ME98096 Final Follow-up
Dose proportionality -				
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In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
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gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:	x	6		ME97029, ME97029 Follow-up, ME97029 Final Follow-up, 306605, 306605 Follow-up, IP157-001 part A
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Phase 1 and/or 2, proof of concept:				
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replicate design; single / multi dose:				
Food-drug interaction studies:				
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(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References	x	23		
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	"X" if yes	Comments
Application filable?	x	Reasons if the application is not filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?
Comments sent to firm?		Comments have been sent to firm (or attachment included) FDA letter date if applicable
QBR questions (key issues to be considered)		(b) (4)
Other comments or information not included above		
Primary reviewer Signature and Date		
Secondary reviewer Signature and Date		

Filing Memo

Clinical Pharmacology Review

NDA: 22-219
Compound: Testosterone undecanoate 250 mg/mL in castor oil intramuscular injection solution
Sponsor: Indevus

Date: 09/20/2007
Reviewer: Doanh Tran, R.Ph., Ph.D.

Introduction:

Nebido is a solution of testosterone undecanoate (TU) 250 mg/mL in castor oil and benzyl benzoate. It is intended to be given as an intramuscular injection [redacted] (b) (4) for replacement therapy in males for conditions associated with a deficiency or absence of endogenous testosterone. TU is an ester pro-drug that is hydrolysed in the body to form testosterone (T), which serves the purpose of T replacement in hypogonadal men. The NDA contains a primary phase 3 study of efficacy (base on a primary end point of serum T concentration) and safety (study IP157-001) that was conducted in the US. Additionally, the results from 11 clinical studies (phase 1, phase 2, and phase 3, including the 6 follow-up studies) conducted in Europe were provided as supporting data. There appears to be sufficient data to evaluate the pharmacokinetics of Nebido in the target men population. However, no studies were conducted to evaluate the effect of intrinsic and extrinsic factors on the PK of Nebido.

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Increase in serum T concentration was observed following injection of Nebido 1000 mg. Following 4 injections of 1000 mg Nebido at 12-week intervals, the mean ± SD C_{ave} and C_{max} were 551 ± 169 and 997 ± 395 ng/dL, respectively. In a subgroup of patients with available PK data for both the first and fourth dose, the fourth dose/first dose ratios for C_{max}, C_{trough}, and $AUC_{0\text{-}84\ days}$ were 1.4, 1.5, and 1.5 respectively. Serum concentration of dihydrotestosterone (DHT) and estradiol (E2) were also elevated following administration of Nebido and paralleled the profile of serum T. Serum concentrations of dihydrotestosterone undecanoate (DHTU) were mostly (99%) below the limit of quantification (100 ng/dL). However, serum concentrations of TU were measurable with observable concentrations as high as 735 ng/dL.

Absorption:

Intramuscularly injected Nebido forms a depot that releases the drug slowly. [redacted] (b) (4)

(b) (4)

Distribution:

No new data is provided. The sponsor relies exclusively on known properties of testosterone.

Metabolism:

Based on serum measurements, TU is metabolized to T and subsequently to DHT and E2. TU may also be metabolized to DHTU to a lesser extent. No new data is provided on the metabolism of testosterone. Sponsor relies exclusively on known properties of testosterone.

Excretion:

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Drug-drug interactions:

The sponsor did not conduct any drug interaction studies.

Special population:

The sponsor did not conduct studies in any special population.

Clinical vs. to-be-marketed formulation:

The drug formulation and manufacturing process were not changed during development and are the same as the to-be-marketed product. The clinical supplies were [redacted] (b) (4) manufactured by [redacted] (b) (4) The to-be-marketed product (in vials) will be manufactured in Bayer Schering AG at Berlin, Germany site. This drug product is a solution and a manufacturing site change would not require bridging studies.

Method validation:

The primary study IP157-001 used a HPLC-MS/MS assay to measure T, TU, DHT, and DHTU. The bioanalytical analysis was conducted by [redacted] (b) (4) This assay was validated and data are available for review. Other supporting studies used commercially available radioimmunoassay or electrochemiluminescence immunoassay.

Recommendation:

The Office of Clinical Pharmacology/Division of Clinical Pharmacology 3 finds that the Human Pharmacokinetics and Bioavailability section for NDA 22-219 is fileable. The following review comment should be conveyed to the Sponsor in a 74-day letter.

Comments for sponsor:

[redacted] (b) (4)

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

/s/

Doanh Tran
10/17/2007 01:35:07 PM
BIOPHARMACEUTICS

Myong-Jin Kim
10/22/2007 09:09:10 AM
BIOPHARMACEUTICS