CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206089Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY REVIEW ADDENDUM

NDA: 206089	Submission Dates: 9/27/2018, 1/7/2019, 3/19/2019, 3/22/2019, and 3/25/2019
Proposed Brand Name	JATENZO
Generic Name	Testosterone undecanoate (TU)
Clinical Pharmacology Primary Reviewer	Chongwoo Yu, PhD
Clinical Pharmacology Secondary Reviewer	Doanh Tran, PhD
OCP Signatory	Shirley Seo, PhD
OCP Divisions	Division of Clinical Pharmacology III (DCP III)
OND Division	Division of Bone, Reproductive, and Urologic Products (DBRUP)
Sponsor	Clarus Therapeutics
Submission Type	Resubmission / 505(b)(2)
Relevant IND	IND 78104
Formulation, Strength, and Dosing Regimen	Oral soft-gel capsules; 158 mg, 198 mg, 237 mg; twice daily (BID) in the morning and in the evening with food (starting dose is 237 mg TU BID and can be titrated up to 396 mg or down to 158 mg TU BID)
Indication	Testosterone replacement therapy in adult males with primary or hypogonadotropic hypogonadism

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1 INTRODUCTION & BACKGROUND

This addendum documents the final labeling language that the Division and the Sponsor has reached agreement on. Reference is made to Dr. Chongwoo Yu's Clinical Pharmacology review dated February 27, 2019 in DARRTS for the Clinical Pharmacology review team's original labeling recommendations.

1.1 Recommendation

The Office of Clinical Pharmacology (OCP)/Division of Clinical Pharmacology III has reviewed NDA 206089 submitted on September 27, 2018, January 7, 2019, March 19, 2019, March 22, 2019, and March 25, 2019. The overall Clinical Pharmacology information submitted to support this NDA is **acceptable** and JATENZO is **recommended for approval** from a Clinical Pharmacology standpoint.

1.2 Final Labeling Language

An agreement on the final labeling language for the following Clinical Pharmacology related sections were reached between the Division and Sponsor.

HIGHLIGHTS

----------DOSAGE AND ADMINISTRATION----------

- Prior to initiating JATENZO, confirm the diagnosis of hypogonadism by ensuring that serum testosterone concentrations have been measured in the morning on at least two separate days and that these concentrations are below the normal range (2.1).
- Take JATENZO with food (2.2).
- Starting dose: 237 mg orally once in the morning and once in the evening.
- Adjust the dose to a minimum of 158 mg twice daily and a maximum of 396 mg twice daily based on serum testosterone drawn 6 hours after the morning dose at least 7 days after starting treatment or following dose adjustment and periodically thereafter (2.2).

----------DRUG INTERACTIONS----------

- Androgens may decrease blood glucose and therefore may decrease insulin requirements in diabetic patients (7.1).
- Changes in anticoagulant activity may be seen with androgens. More frequent monitoring of International Normalized Ratio (INR) and prothrombin time is recommended in patients taking warfarin (7.2).
- Use of testosterone with corticosteroids may result in increased fluid retention. Use with caution, particularly in patients with cardiac, renal, or hepatic disease (7.3).
- Concomitant administration of medications that are known to increase blood pressure may lead to additional increases in blood pressure when used with JATENZO (7.4).

FULL PRESCRIBING INFORMATION

2 DOSAGE AND ADMINISTRATION

2.1 Confirmation of Hypogonadism Before Initiation of JATENZO

Prior to initiating JATENZO, confirm the diagnosis of hypogonadism by ensuring that serum testosterone concentrations have been measured in the morning on at least two separate days and that these testosterone concentrations are below the normal range.

2.2 Dosing and Dose Adjustment Information

Individualize the dosage of JATENZO based on the patient's serum testosterone concentration response to the drug. The recommended starting dose is 237 mg taken orally twice daily, once in the morning and once in the evening. Take JATENZO with food.

Dose Adjustment

To ensure proper dose adjustment, measure serum testosterone concentrations 6 hours after the morning dose in plain tubes, clotted at room temperature for 30 minutes prior to centrifugation. Adjust the JATENZO dose based on this serum testosterone measurement as shown in Table 1. Wait seven days after starting treatment or adjusting the dose before checking the serum testosterone concentration. Thereafter, periodically monitor serum testosterone concentrations 6 hours after the morning dose.

Administer the same dose in the morning and evening. The minimum recommended dose is 158 mg twice daily. The maximum recommended dose is 396 mg (two 198 mg capsules) twice daily.

Table 1: JATENZO Dose Adjustment Scheme

Testosterone Concentration in Serum From Plain Tube Drawn 6 hours After Morning Dose	Current JATENZO Dose (mg, twice daily)	New JATENZO Dose (mg, twice daily)
Less than 425 ng/dL	158	198
	198	237
	237	316 (two 158 mg capsules)
	316 (two 158 mg capsules)	396 (two 198 mg capsules)
425 ng/dL – 970 ng/dL	No Dose Change	
More than 970 ng/dL	396 (two 198 mg capsules)	316 (two 158 mg capsules)
	316 (two 158 mg capsules)	237
	237	198
	198	158
	158	Discontinue Treatment

7 DRUG INTERACTIONS

7.1 Insulin

Changes in insulin sensitivity or glycemic control may occur in patients treated with androgens. In diabetic patients, the metabolic effects of androgens may decrease blood glucose and, therefore, may necessitate a decrease in the dose of anti-diabetic medication.

7.2 Oral Vitamin K Antagonist Anticoagulants

Changes in anticoagulant activity may be seen with androgens; therefore, more frequent monitoring of international normalized ratio (INR) and prothrombin time are recommended in patients taking warfarin, especially at the initiation and termination of androgen therapy.

7.3 Corticosteroids

The concurrent use of testosterone with corticosteroids may result in increased fluid retention and requires careful monitoring particularly in patients with cardiac, renal or hepatic disease.

7.4 Medications that May Also Increase Blood Pressure

Some prescription medications and nonprescription analgesic and cold medications contain drugs known to increase blood pressure. Concomitant administration of these medications with JATENZO may lead to additional increases in blood pressure *[See Boxed Warning and Warnings and Precautions (5.1)]*.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Endogenous androgens, including testosterone and dihydrotestosterone (DHT), are responsible for the normal growth and development of the male sex organs and for maintenance of secondary sex characteristics. These effects include the growth and maturation of prostate, seminal vesicles, penis and scrotum; the development of male hair distribution, such as facial, pubic, chest and axillary hair; laryngeal enlargement, vocal cord thickening, alterations in body musculature and fat distribution.

Male hypogonadism, a clinical syndrome resulting from insufficient secretion of testosterone, has two main etiologies. Primary hypogonadism is caused by defects of the gonads, such as Klinefelter syndrome or Leydig cell aplasia, whereas secondary hypogonadism (also known as hypogonadotropic hypogonadism) is the failure of the hypothalamus (or pituitary) to produce sufficient gonadotropins (FSH, LH).

12.2 Pharmacodynamics

No specific pharmacodynamic studies were conducted using JATENZO.

12.3 Pharmacokinetics

Absorption

JATENZO delivers physiologic amounts of testosterone, producing testosterone concentrations that approximate normal concentrations seen in healthy men.

JATENZO was taken orally at a starting dose of 237 mg twice per day with meals in a multicenter, open-label, randomized, 2-arm, active-controlled trial in hypogonadal males. The dose was adjusted, as needed, on Days 14 and 56 between a minimum of 158 mg twice per day and a maximum of 396 mg twice per day based on the average plasma testosterone concentration obtained over 24 hours after the morning dose. The average daily NaF-EDTA plasma testosterone concentration was 403 (± 128) ng/dL at the end of treatment, where the normal eugonadal range in NaF-EDTA plasma was 252-907 ng/dL in this study. Note that the titration scheme for use in clinical practice is based on serum total testosterone [*see Dosage and Administration (2.2)*].

Table 3 summarizes the pharmacokinetic (PK) parameters for plasma total testosterone in patients completing at least 105 days of JATENZO treatment administered twice daily.

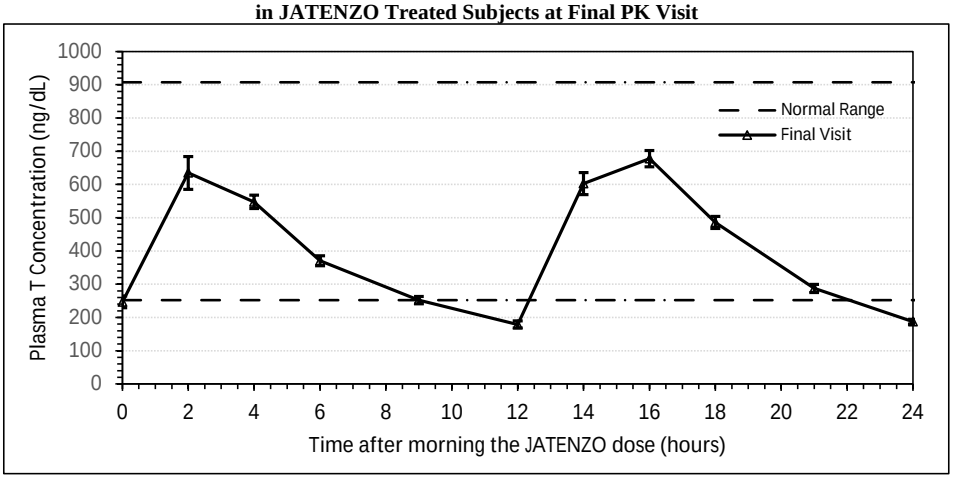
Table 3: NaF-EDTA Plasma Testosterone C_{avg} and C_{max} at Final PK Visit

PK Parameter		All Doses (N=151)
C_{avg} (ng/dL)	Mean	403
	SD	128
C_{max} (ng/dL)	Mean	1008
	SD	581

PK = pharmacokinetic; C_{avg} = 24-hour average concentration; C_{max} = maximum concentration

Figure 2 summarizes the mean plasma total testosterone profile for the patients at the final PK visit.

Figure 2: Mean (±SEM) Concentration-Time Profile for NaF-EDTA Plasma Total Testosterone in JATENZO Treated Subjects at Final PK Visit



SEM = standard error of the mean; T = testosterone

When JATENZO was dosed with different breakfasts containing various amounts of fat, the bioavailability with the 30 g fat, 45 g fat, and high-calorie high-fat breakfasts was comparable, but there was a food effect with the 15 g fat breakfast compared to the 30 g fat breakfast. The 15 g fat breakfast had a 25% decrease in testosterone exposure compared to the 30 g fat breakfast.

Distribution

Circulating testosterone is primarily bound in serum to sex hormone-binding globulin (SHBG) and albumin. Approximately 40% of testosterone in plasma is bound to SHBG, 2% remains unbound (free) and the rest is loosely bound to albumin and other proteins.

Metabolism

The androgenic activity of testosterone undecanoate occurs after the ester bond linking the testosterone to the undecanoic acid is cleaved by endogenous non-specific esterases. Undecanoic acid is metabolized like all fatty acids via the beta-oxidation pathway.
Testosterone is metabolized to various 17-keto steroids through two different pathways. The major active metabolites of testosterone are dihydrotestosterone (DHT) and estradiol.

Excretion

About 90% of a dose of testosterone given intramuscularly is excreted in the urine as glucuronic and sulfuric acid conjugates of testosterone and its metabolites. About 6% of a dose is excreted in the feces, mostly in the unconjugated form. Inactivation of testosterone occurs primarily in the liver.

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/s/

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OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA: 206089	Submission Dates: 9/27/2018 and 1/7/2019
Proposed Brand Name	JATENZO
Generic Name	Testosterone undecanoate (TU)
Clinical Pharmacology Primary Reviewer	Chongwoo Yu, PhD
Clinical Pharmacology Secondary Reviewer	Doanh Tran, PhD
OCP Signatory	Shirley Seo, PhD
OCP Divisions	Division of Clinical Pharmacology III (DCP III)
OND Division	Division of Bone, Reproductive, and Urologic Products (DBRUP)
Sponsor	Clarus Therapeutics
Submission Type	Resubmission / 505(b)(2)
Relevant IND	IND 78104
Formulation, Strength, and Dosing Regimen	Oral soft-gel capsules; 158 mg, 198 mg, 237 mg; twice daily (BID) in the morning and in the evening with food (starting dose is 237 mg TU BID and can be titrated up to 396 mg or down to 158 mg TU BID)
Indication	Testosterone replacement therapy in adult males with primary or hypogonadotropic hypogonadism

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1 EXECUTIVE SUMMARY

Clarus Therapeutics submitted the original NDA 206089 for JATENZO on January 3, 2014 and upon completion of review, the DBRUP took a Complete Response (CR) action on November 3 2014. Subsequently, the Sponsor submitted a resubmission to NDA 206089 for JATENZO on June 22, 2017 and the DBRUP took a CR action on March 22, 2018. On September 27, 2018, the Sponsor submitted the current 505(b)(2) resubmission to NDA 206089 for JATENZO. This NDA resubmission is relying on prior findings of nonclinical safety from literature.

JATENZO is a soft gelatin capsule containing testosterone undecanoate (TU), developed as an oral testosterone replacement therapy (TRT) in adult males for conditions associated with a deficiency or absence of endogenous testosterone (T). JATENZO is for oral use only and is available in three strengths: 158 mg, 198 mg, and 237 mg. **A new dose titration scheme based on serum T is being proposed for JATENZO in this resubmission**. The recommended starting dose of JATENZO is 237 mg of TU, taken orally twice daily (BID), once in the morning with food and once in the evening with food (i.e., not on an empty stomach). To ensure proper dosing, the Sponsor is proposing that T concentrations should be measured in serum from blood drawn into plain tubes (red-top tubes) 6 hours after the morning dose and at least 7 days after starting treatment or following dose adjustment.

To support the approval of JATENZO, the Sponsor submitted 5 new Clinical Pharmacology/ Biopharmaceutics studies in this resubmission, which includes three TU to T *ex vivo* conversion studies – following JATENZO administration (CLAR-18019), Andriol® administration (CLAR-18016), and *in vitro* TU spiking (CLAR-18021), bioanalytical method correlation study (CLAR-18020), and a TU cross-reactivity study with commercially available T immunoassays (CLAR-18018). Only Study CLAR-18019 had JATENZO orally administered to study participants. This review will focus on the 5 studies newly submitted in this resubmission.

1.1 Recommendation

The Office of Clinical Pharmacology (OCP)/Division of Clinical Pharmacology III has reviewed NDA 206089 submitted on September 27, 2018, and January 7, 2019. The overall Clinical Pharmacology information submitted to support this NDA is **acceptable** and JATENZO is **recommended for approval** from a Clinical Pharmacology standpoint.

1.2 Post-marketing Requirements or Commitments

In the CR letter issued on March 22, 2018, the Division stated that the Sponsor need to address the drug-drug interaction (DDI) potential of TU as the perpetrator. The Sponsor is proposing to conduct the TU DDI study as a post-marketing study. The Sponsor's proposal is acceptable from the Clinical Pharmacology standpoint. The following post-marketing requirement should be included in the approval letter.

> Conduct *in vitro* studies to assess the potential of testosterone undecanoate to inhibit or induce drug metabolizing enzymes and transporters. If *in vitro* studies suggest a potential for interaction, additional *in vivo* studies may be required.

1.3 Summary of Important Clinical Pharmacology Findings

Proposed Dose Titration Scheme

In the pivotal Phase 3 study, CLAR-15012, dose-titration was based on T concentrations measured in plasma from NaF/EDTA tubes kept on ice for 30 minutes prior to centrifugation. A T dose-titration boundary range of 350 to 800 ng/dL was used to guide dose adjustment. The Sponsor is proposing to base the dose-titration decision on the 6 hour post-dose sample (in Study CLAR-15012, the T concentration at 6 hours post-dose had the highest concordance with C_{avg}). After applying the correction factor, 1.214 (1/0.824), the lower boundary value of 350 ng/dL was changed to **425 ng/dL** (350 × 1.214) and the upper boundary value of 800 ng/dL was changed to **970 ng/dL** (800 × 1.214). The Sponsor is proposing the new titration threshold of 425 to 970 ng/dL based on T concentrations measured from serum in plain tubes. Table 1 shows the dose adjustment scheme that is based on serum testosterone concentration from a sample drawn 6 hours after the morning dose.

Table 1: JATENZO Dose Adjustment Scheme

Testosterone Concentration in Serum From Plain (Red-Top) Tube Drawn 6 hours After Dose	Current JATENZO Dose (mg, BID)	New JATENZO Dose (mg, BID)
< 425 ng/dL	158	198
	198	237
	237	316
	316	398
425 – 970 ng/dL	No Dose Change	
> 970 ng/dL	396	316
	316	237
	237	198
	198	158
	158	Discontinue Treatment

BID = twice daily

Based on the following, the Clinical Pharmacology review team believes that the Sponsor's proposed dose titration scheme based on 6 hr post-dose using serum T concentration is reasonable because:

- T concentration at 6 hr post-dose (C_6) has the highest concordance with T C_{avg} → Clinically relevant
- Lower TU concentration at 6 hr post-dose compared to 4 hr post-dose → Lower variability due to TU to T ex vivo conversion.
- Successful establishment of conversion factor that enables the correlation between measured T serum concentrations at 6 hours post-dose (in future clinical settings, using plain tubes) to T plasma concentrations from blood collected in NaF/EDTA tubes at 6 hours post-dose that was used in the pivotal Phase 3 study, CLAR-15012.

The following subsections will briefly outline the analyses and considerations were undertaken to reach the conclusion above.

TU to T *ex vivo* Conversion

The Sponsor conducted a new study (CLAR-18019) to assess the TU to T ex *vivo* conversion following oral administration of JATENZO. Blood was collected into 3 different types of tubes

(i.e., plain, EDTA, and NaF/EDTA) approximately 5 hours post-morning dose on Day 8 to assess the 5-hour T concentration (C_5).

Matrix Effect

Prior to starting the TU dosing, blood samples were collected in each of the tube types and incubation temperature combinations so that the effects could be quantified for each combination. A previous study (CLAR-16014) showed the ratio of matrix effect to be 0.858 while the current study showed a ratio of 0.869. The geometric mean ratio of 0.858 is used in subsequent calculations since Study CLAR-16014 had a more robust dataset (i.e., 97 subjects vs. 13 subjects).

Rate of TU to T *ex vivo* Conversion

T concentrations in all tubes showed increases as incubation time at room temperature increased. No increase in T concentrations was observed in plasma (NaF/EDTA tubes) when placed on ice. This indicates that temperature plays a significant role in the TU to T *ex vivo* conversion.

In an *in vitro* TU spiking study (CLAR-18021), it was found that the extent of conversion during the second 30-minute incubation interval (30 minutes to 60 minutes) ranged between 40% and 85% of the extent of conversion during the first 30 minutes of incubation in the different tubes and incubation conditions.

TU to T *ex vivo* conversion rate and TU concentrations

The rate of TU to T *ex vivo* conversion depends on the substrate (i.e., TU) concentration present in the tube.

Conversion Factor

The 3 factors that translate a T concentration measured under one set of tube type/incubation temperature/time condition (i.e., serum from blood collected in a plain tube and held at room temperature for 30 minutes) to an alternative set of tube type/incubation temperature/time condition (i.e., plasma collected in a NaF/EDTA tube and kept for 30 minutes on ice) were determined. These 3 factors are:

- Extent of TU to T *ex vivo* conversion occurring in serum plain tube at the incubation temperature over the processing time between sample collection and centrifuging
- Extent of TU to T *ex vivo* conversion occurring in NaF/EDTA plasma tube at the incubation temperature over the processing time between sample collection and centrifuging
- Matrix effect associated with the pair of tube type/incubation temperature combinations

Overall Conversion Factor

An overall conversion factor was derived to be 0.824 (0.959 × 0.858 × 1.001) for a sample collected 6 hours post-dose as shown in Figure 1 (Section 2.2.5). This allows the conversion of a serum T concentration to a NaF/EDTA plasma T concentration. When converting T concentrations from plasma in NaF/EDTA tube to T concentrations for serum in plain tube, the conversion factor is (1/0.959) x (1/0.858) x (1/1.001) = 1.214. It should be noted that this conversion factor is only applicable for samples taken at about 6 hours post-dosing of JATENZO.

Applying Conversion Factor to Clinical Data

At Visit 7 in the pivotal Phase 3 study, CLAR-15012, matched pairs (contemporaneously collected) of samples were collected into plain and NaF/EDTA tubes, which were incubated for 30 minutes at room temperature or on ice, respectively, before centrifugation. The differences between the measured serum T concentration and the derived serum T concentration (derived from measured NaF/EDTA plasma T concentration and relevant conversion factor) are 1.3% to 3.1% with 95% CIs range of less than ±6%. This provided support that the chosen conversion factor is appropriate.

Prolongation of Incubation Time

A sensitivity analysis to see how different serum processing times (e.g., 60, 90, and 120 minutes post-collection) would affect the T concentration ratios when compared to the 30 minute post-collection samples was conducted. It was reported that for the 60, 90, and 120 minute clotting times, the arithmetic mean values were 0.24%, 2.28%, and 3.55% greater than the value at 30 minutes incubation. A clinically meaningful difference is not expected due to the prolongation of the clotting time up to 120 minutes.

TU Concentration and Sensitivity Analysis

A sensitivity analysis was performed to assess how the potential variability of TU concentrations would affect the correction factors and how that would affect the overall conversion factors for T concentrations in NaF/EDTA plasma to those in serum (e.g., 1.263 at 4 hours post-dose and 1.214 at 6 hours post-dose).

The mean deviations in predicted T values at 4- and 6-hours post-dose at both the upper and lower bounds of the 95% CI for TU (67.3 and 169.3 ng/mL for 4 hours; 28.1 and 75.2 ng/mL for 6 hours) range from -3.06% to 5.78%.

2 QUESTION BASED REVIEW

2.1 General Attributes

2.1.1 What is the regulatory history of JATENZO since the last review cycle?

The Sponsor submitted a resubmission to NDA 206089 for JATENZO on June 22, 2017 and the Division took a CR action on March 22, 2018.

A Type A, post-action meeting was held on June 12, 2018. At the meeting, the Division recommended that further investigation of the rate and extent of TU to T *ex vivo* conversion during the time course of plasma sample preparation is warranted to determine whether T concentration measurements from plasma in NaF/EDTA tubes in their Phase 3 trial are accurate, reliable, and reproducible.

On September 27, 2018, the Sponsor submitted the current resubmission to NDA 206089 for JATENZO.

2.1.2 What are the relevant data submitted to support the approval of JATENZO?

To support the approval of JATENZO, the Sponsor submitted 5 Clinical Pharmacology studies in this resubmission, which included the following:

- CLAR-18019: TU to T *ex vivo* conversion study following administration of JATENZO
- CLAR-18021: TU to T *ex vivo* conversion study following *in vitro* TU spiking
- CLAR-18016: TU to T *ex vivo* conversion study following administration of Andriol®
- CLAR-18020: Bioanalytical method correlation study
- CLAR-18018: TU cross-reactivity study with commercially available T immunoassays

Study participants were administered with JATENZO only in Study CLAR-18019.

In addition, the Sponsor submitted the following information:

- Draft labeling in physician labeling rule (PLR) format
- Bioanalytical study reports and method validation reports

2.2 General Clinical Pharmacology

2.2.1 What are the factors that affect the different outcome of T concentration measurements from serum in plain tubes and plasma in NaF/EDTA tubes?

There is a matrix effect that makes a difference in the T concentration measured even without TU administration or spiking. The other factor is the TU to T *ex vivo* conversion. The following are known to contribute to the TU to T ex vivo conversion:

- Post-collection incubation temperature: Lowering the temperature reduces conversion.
- Post-collection incubation time: TU to T ex vivo conversion occurs most rapidly during the first 30 minutes post-collection. Reducing the incubation time will help reducing the TU to T *ex vivo* conversion.
- TU concentration: The TU to T ex vivo conversion is TU concentration-dependent.
- Presence of esterase inhibitor (e.g., NaF) and test tube: The presence of esterase inhibitor (e.g., NaF in NaF/EDTA tube) further reduces the TU to T *ex vivo* conversion.

2.2.2 How was the matrix effect evaluated?

In an open-label, non-randomized, single-sequence study (CLAR-18019) conducted in 13 healthy males (18-45 years of age) to evaluate the TU to T *ex vivo* conversion, study participants were dosed with JATENZO and had blood drawn into 3 different types of blood-collection tubes (i.e., Plain, EDTA, and NaF/EDTA). Prior to starting the TU dosing, blood samples were collected in each of the tube type / incubation temperature combinations so that the matrix effect could be compared between each combination. Study CLAR-16014 identified the matrix effect as 0.858 (multiply by factor to convert a T concentration in serum to a corresponding value in NaF/EDTA plasma), or its reciprocal 1.166 (to convert a T concentration value in NaF/EDTA plasma to a corresponding value in serum). The new study, CLAR-18019 showed a ratio of 0.869 (or its reciprocal 1.151). The geometric mean ratio of 0.858 was used in subsequent matrix effect or conversion factor calculations since Study CLAR-16014 had a more robust dataset (i.e., 97 subjects vs. 13 subjects).

2.2.3 How was the effect of post-collection incubation time and temperature on TU to T *ex vivo* conversion concentrations evaluated?

In Study CLAR-18019 mentioned above, study participants took 396 mg of JATENZO (i.e., 198 mg x 2 capsules) by mouth immediately prior to their meals (containing 30 g fat) for 7 days (Days 1-7). Blood samples were collected at approximately 5 hours post-morning dose on Day 8 to assess the 5-hour T concentration (C_5). Blood was collected into 3 different types of tubes (i.e., Plain, EDTA, and NaF/EDTA). T concentrations in all tubes showed increases as incubation time at room temperature increased. No increase in T concentrations was observed in plasma (NaF/EDTA tubes) when placed on ice. This indicates that temperature plays a significant role in the TU to T *ex vivo* conversion.

There was a large difference between Time 0 and the 30 minute post-collection mean T concentration ratios for serum in plain tube processed at room temperature. The Time 0 time point does not fit well with the regression line for time points of 30-120 minutes post-collection. This is likely because blood is at body temperature (37°C) when initially drawn but then cools to room temperature (approximately, 21°C) over the subsequent 30 minutes. As a result, the TU to T *ex vivo* conversion proceeds more rapidly during the first 30 minutes than in subsequent time periods. This observation was also made in an *in vitro* TU spiking study (CLAR-18021).

The extent of conversion at 60 minutes was somewhat less than double that during the first 30 minutes for both types of tubes incubated at room temperature. The extent of conversion during the second 30-minute incubation interval (30 minutes to 60 minutes) ranged between 40% and 85% of the extent of conversion during the first 30 minutes of incubation in the different tubes and incubation conditions. This reduced rate of TU to T conversion might be due to the change (reduction) in esterase activity as the blood-sample cools from body temperature (37°C) to the incubation temperature, decreasing catalytic activity with time, or due to reductions in TU concentrations with elapsed incubation time.

2.2.4 How was the effect of TU concentration on TU to T *ex vivo* conversion evaluated?

In Study CLAR-18019, the magnitude of the TU concentration dependence was assessed by plotting the rate of conversion of TU to T versus the initial (time = 0 or baseline) TU concentration and determining the slope and intercept of the relationship. The slopes for tubes containing NaF and/or EDTA kept on ice are relatively flat comparted to those held at room temperature. It should be noted that TU to T *ex vivo* conversion still existed in plasma in NaF/EDTA tubes at room

temperature. In summary, the rate of TU to T *ex vivo* conversion depends on the substrate (i.e., TU) concentration present in the tube.

2.2.5 How was the conversion factor between T concentrations in serum collected in plain tubes and plasma collected in NaF/EDTA tubes derived? Was the derived conversion factor tested with clinical data?

The 3 factors that translate a T concentration measured under one set of tube type / incubation temperature and time conditions (i.e., serum from blood collected in a plain tube and held at room temperature for 30 minutes) to an alternative set of tube type / incubation temperature and time conditions (i.e., plasma collected in a NaF/EDTA tube and kept for 30 minutes on ice) were determined. These 3 factors are:

- Extent of TU to T *ex vivo* conversion occurring in serum plain tube at the incubation temperature over the processing time between sample collection and centrifuging
- Extent of TU to T *ex vivo* conversion occurring in NaF/EDTA plasma tube at the incubation temperature over the processing time between sample collection and centrifuging
- Matrix effect associated with the pair of tube type / incubation temperature combinations

TU to T *ex vivo* conversion factor

It should be noted that TU concentrations were not measured in the pivotal Phase 3 study, CLAR-15012. The estimated TU concentrations for Study CLAR-15012 was derived by performing linear interpolation to derive 4- and 6-hour post-dose TU in Study CLAR-09007 and applying a scaling factor for TU concentration to account for the inter-study difference between Studies CLAR-09007 and CLAR-15012 due to slightly different observed T concentrations. The TU concentration was estimated to be approximately 118 ng/mL at 4 hours post-dose and 52 ng/mL at 6 hours post dose.

The conversion factor for overestimation of T concentration due to present of TU was calculated based on results of regression analysis. In the case for serum in plain tubes kept at room temperature for 30 minutes, for 4 hour post-dose (TU concentration = 118 ng/mL), the conversion factor for the overestimation in plain tube will be 1((1+overestimation) = 1/(1+0.0856) = 0.921. For 6 hour post-dose (TU concentration = 52 ng/mL), the conversion factor for the overestimation in plain tube will be 1/(1+overestimation) = 1/(1+0.0429) = 0.959.

In the case for plasma in NaF/EDTA tubes kept on ice for 30 minutes, for 4 hour post-dose (TU concentration = 118 ng/mL), the conversion factor for the overestimation in NaF/EDTA tube is 1((1+overestimation) = 1/(1+0.0022) = 0.998 For 6 hour post-dose (TU concentration = 52 ng/mL), the conversion factor for the overestimation in NaF/EDTA tube is 1((1+overestimation) = 1/(1+0.0013) = 0.999

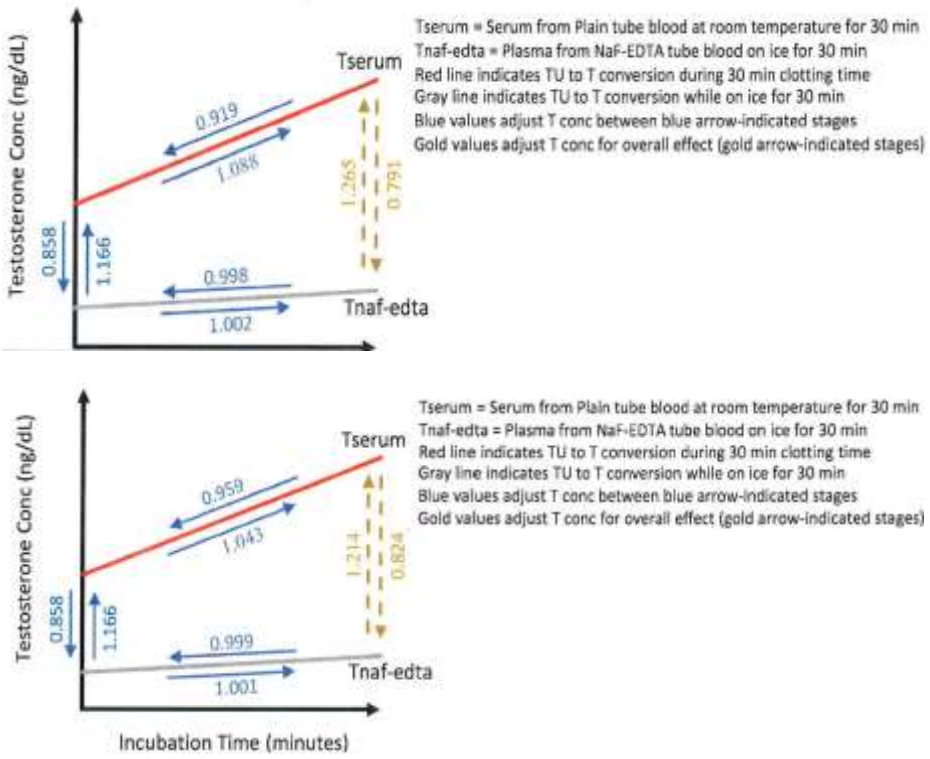
Matrix effect conversion factor

As shown in Table 2, the T concentration ratio of NaF/EDTA tube/plain tube obtained in Study CLAR-16014 is 0.858.

Overall Conversion Factor

Using the 3 factors mentioned above, an overall conversion factor was derived which allows the conversion of a serum T concentration to a NaF/EDTA plasma T concentration (or vice versa).

Figure 1: Conversion Diagram for T Concentration Measured from Serum in Plain Tube (Incubated at Room Temperature for 30 Minutes) to an Equivalent Value for Plasma in NaF/EDTA Tube (Incubated on Ice for 30 Minutes) for a Sample Collected 4 hours post-dose (Top) and 6 hours post-dose (Bottom) (Study CLAR-18019)



The diagram shown in Figure 1 helps visualize the relationship between the multiple effects on the T concentration assessment described above and an overall conversion factor that can be used to translate the T concentration in one setting to an equivalent actionable T concentration in a second setting. As shown in Figure 6, conversion for a sample collected 6 hours post-dose (bottom) (i.e., at estimated TU concentration of 52 ng/mL) in a plain tube (and allowed to clot at room temperature for 30 minutes) into the expected T concentration if the sample had been collected in a NaF/EDTA tube (and kept on ice for 30 minutes):

- First (top arrow), reducing the T concentration in the serum (from the plain tube) by the factor compensating for TU to T *ex vivo* conversion at room temperature for 30 minutes (0.959)
- Second, by further reducing the measured T concentration by the matrix effect associated with NaF/EDTA plasma compared to serum (0.858)
- Third, by increasing the resulting T concentration by the TU to T *ex vivo* conversion that occurs when a sample in a NaF/EDTA tube is held on ice for 30 minutes (1.001)

The combined effect, 0.959 × 0.858 × 1.001, is equal to 0.824 (i.e., the product of the 3 effects known to affect the serum concentration). The expected value of the equivalent T concentration in plasma from a NaF/EDTA tube is 82.4% of the serum value when the incubation temperature, incubation time, and the underlying TU concentration are as stated. When deriving the T concentration from plasma in NaF/EDTA tube to concentration in serum, the combined effect is (1/0.959) x (1/0.858) x (1/1.001) = 1.214.

It should be noted that because TU concentration in a sample affects the amount of T formed, the overall conversion factor of 1.214 is only applicable to samples collected at 6 hours post dosing of JATENZO where the estimated concentration of TU is about 52 ng/mL. Significant deviation in TU concentrations would introduce error to the applied conversion factor.

Applying Conversion Factor to Clinical Data

At Visit 7 in the pivotal Phase 3 study, CLAR-15012, matched pairs (contemporaneously collected) of samples were collected into plain and NaF/EDTA tubes, which were incubated for 30 minutes at room temperature or on ice, respectively, before centrifugation. T concentrations were measured in the serum/plasma from these tubes. Table 2 presents an analysis of the Study CLAR-15012, Visit 7, 4- and 6-hour post-dose serum T concentrations. The differences between the measured serum T concentration and the derived serum T concentration (derived from measured NaF/EDTA plasma T concentration and relevant conversion factor) are 1.3% to 3.1% with 95% CIs of were less than ±6%.

Reviewer's Comment: *It should be noted that the Sponsor inadvertently used the conversion factor of 1.263 instead of 1.265 in the calculation below for samples collected 4 hours post-dose. However, a meaningful difference due to this error is not expected.*

Table 2: Comparison between Serum T Concentrations Measured at 4- and 6-hours post-dose Samples and Serum T Concentrations Calculated from Measured NaF/EDTA Plasma T Concentrations using Conversion Factor for 4- and 6-hour post-dose Samples (Study CLAR-15012, Visit 7)

Parameter	N	Mean (SD)	Median	95% CI
4-Hour Postdose Sample				
Measured serum testosterone (ng/dL)	154	696.0 (327.95)	648.0	643.78, 748.20
Calculated testosterone[a] (ng/dL)	154	688.2 (312.12)	654.8	638.46, 737.84
% difference (actual – derived)		-1.3% (24.09)	1.9	-5.12%, 2.55%
6-Hour Postdose Sample				
Measured serum testosterone (ng/dL)	155	477.1 (267.40)	430.5	434.71, 519.57
Calculated testosterone[b] (ng/dL)	155	449.6 (223.94)	408.4	414.05, 485.11
% difference (actual – derived)		3.1% (16.78)	3.42	0.43%, 5.76%

CI = confidence interval; EDTA = ethylenediaminetetraacetic acid; NaF = sodium fluoride; SD = standard deviation
a Calculated serum testosterone = conversion factor (1.263) × measured NaF-EDTA plasma testosterone.
b Calculated serum testosterone = conversion factor (1.214) × measured NaF-EDTA plasma testosterone.

2.2.6 How does prolongation of post-collection incubation time and variability of TU concentrations affect the overall conversion factor?

Effect of Prolongation of Post-collection Incubation Time

A sensitivity analysis to see how different serum processing time (e.g., 60, 90, and 120 minute post-collection) would affect the T concentration ratios when compared to the 30 minute post-collection samples was conducted. It was reported that for the 60, 90, and 120 minute clotting times, the arithmetic mean values were 0.24%, 2.28%, and 3.55% greater than the value at 30 minutes incubation. This translates into an increase of 0.045 and 0.043 of the overall conversion factors at 4 hours post-dose and 6 hours post-dose, respectively. A meaningful clinical difference is not expected due to the prolongation of the clotting time up to 120 minutes.

Effect of TU Concentration Variability

A sensitivity analysis was performed to assess how the potential variability of TU concentrations (e.g., variability of the estimated mean TU of 118 ng/mL and 52 ng/mL) would affect the correction

factors (e.g. , 0.959 and 0.919) and how that would affect the overall conversion factors for T concentrations in NaF/EDTA plasma to those in serum (e.g., 1.265 at 4 hours post-dose and 1.214 at 6 hours post-dose).

As a sensitivity analysis, the mean deviations in T (and 95% CI) were calculated at the mean TU concentrations estimated for 4- and 6-hours post-dose and at the lower and upper bounds of the 95% CI for the mean 4- and 6-hour post-dose TU values.

Table 3: Summary of Conversion Factors for Incubation Time, Temperature, and Matrix Effects in Serum and NaF/EDTA Plasma for Conversion of Serum T Concentrations to Plasma T Concentrations (Study CLAR-18019; N=13)

Serum RT => NaF-EDTA on ice	TU	Time & Temp in Serum Effect	Matrix Effect	Time & Temp in Plasma Effect	Com-bined Effects	Error in Predicting Observed Plasma T Conc		
Rationale for Selected TU	ng/mL	Step 1	Step 2	Step 3	Overall	Mean	LB 95% CI	UB 95% CI
1 Original report TU at 4 h	115	0.921	0.858	1.0022	0.792	0.15%	-9.62%	9.92%
2 Original report TU at 6 h	52	0.959	0.858	1.0013	0.824	4.17%	-5.99%	14.32%
3 Revised mean TU at 4 h	118	0.919	0.858	1.0022	0.791	-0.03%	-9.78%	9.72%
4 Revised mean TU at 6 h	52	0.959	0.858	1.0013	0.824	4.17%	-5.99%	14.32%
5 LB of revised mean TU at 4 h	67.3	0.949	0.858	1.0015	0.816	3.16%	-6.90%	13.22%
6 UB of revised mean TU at 4 h	169.3	0.891	0.858	1.0029	0.767	-3.06%	-12.52%	6.39%
7 LB of revised mean TU at 6 h	28.1	0.974	0.858	1.0010	0.837	5.78%	-4.54%	16.09%
8 UB of revised mean TU at 6 h	75.2	0.945	0.858	1.0016	0.812	2.65%	-7.36%	12.66%

Table 3 summarizes the sensitivity analysis results in Rows 5-8. The mean deviations in predicted T values at 4- and 6-hours post-dose at both the upper and lower bounds of the 95% CI for TU (67.3 and 169.3 ng/mL for 4 hours; 28.1 and 75.2 ng/mL for 6 hours) range from -3.06% to 5.78%.

2.2.7 What dose titration scheme is the Sponsor proposing for labeling and is it acceptable?

In the pivotal Phase 3 study, CLAR-15012, dose-titration was based on T concentrations measured in plasma from NaF/EDTA tubes kept on ice for 30 minutes prior to centrifugation. A T dose-titration boundary range of 350 to 800 ng/dL was used to guide dose adjustment. In 'real world' clinical practice, T concentrations are typically measured in serum from plain tubes that are allowed to clot for 30 minutes at room temperature. Serum T concentration value could be directly compared to an equivalent titration boundary range derived from Study CLAR-15012 using the correction factor 1.214 (i.e., 1 / 0.824). This factor, 1.214, converts the lower boundary value of 350 ng/dL to 425 ng/dL (350 × 1.214) and the upper boundary value of 800 ng/dL to 970 ng/dL (800 × 1.214). The Sponsor is proposing a new titration threshold of 425 to 970 ng/dL based on T concentrations measured from serum in plain tubes.

Tables 4 and 5 show the dose titration thresholds at 6 hour post-dose and 4 hour post-dose, respectively, calculated using the T concentration dose titration thresholds from plasma in NaF/EDTA tubes that were used in Study CLAR-15012 and the mean, lower bound (LB), and upper bound (UB) conversion factors. Table 6 summarizes the mean and worst-case scenario dose titration thresholds based on the serum T concentrations at 4- and 6-hour post-dose samples.

Table 4: Dose Titration Thresholds Calculated Using T Concentrations from Plasma in NaF/EDTA Tubes and Corresponding Conversion Factors at 6 hour post-dose

Time (hr post-dose)	T NaF/EDTA Plasma (ng/dL)	Conversion Factor	T serum (ng/dL)
6 hr, Mean, Low	350	1.214	425
6 hr, Mean, High	800	1.214	971
6 hr, LB, Low	350	1.195	418
6 hr, LB, High	800	1.195	956
6 hr, UB, Low	350	1.232	431
6 hr, UB, High	800	1.232	986

Table 5: Dose Titration Thresholds Calculated Using T Concentrations from Plasma in NaF/EDTA Tubes and Corresponding Conversion Factors at 4 hour post-dose

Time (hr post-dose)	T NaF/EDTA Plasma (ng/dL)	Conversion Factor	T serum (ng/dL)
4 hr, Mean, Low	350	1.265	443
4 hr, Mean, High	800	1.265	1012
4 hr, LB, Low	350	1.226	429
4 hr, LB, High	800	1.226	981
4 hr, UB, Low	350	1.304	456
4 hr, UB, High	800	1.304	1043

Table 6: Comparison of Mean and Worst-case Scenario Dose Titration Thresholds Based on Serum T Concentrations at 4- and 6-hour post-dose Samples

Titration Sampling Time Point	Titration Threshold based on T Serum (ng/dL)
6 hr Post-dose Mean	425-971
6 hr Post-dose Worst Case Scenario	418-986
4 hr Post-dose Mean	443-1012
4 hr Post-dose Worst Case Scenario	429-1043

Worst-case scenario used the low threshold of the lower bound and the high threshold of the upper bound

Based on the following the Clinical Pharmacology review team believes that the Sponsor's proposed dose titration scheme based on 6 hr post-dose using serum T concentration is reasonable:

- T concentration at 6 hr post-dose (C_6) has the highest concordance with T C_{avg} → Clinically relevant
- Lower TU concentration at 6 hr post-dose compared to 4 hr post-dose → Lower variability due to TU to T ex vivo conversion.
- Successful establishment of conversion factor that enables to correlate measured T serum concentrations at 6 hour post-dose to T NaF/EDTA plasma concentrations at 6 hour post-dose that was used in pivotal Phase 3 study, CLAR-15012.

2.3 Extrinsic Factors

2.3.1 Did the Sponsor conduct any DDI studies?

No DDI studies were conducted with JATENZO. In the CR letter issued on March 22, 2018, the Division told the Sponsor to address the drug-drug interaction potential of TU as the perpetrator. The Sponsor is proposing to conduct the TU DDI study as a post-marketing study. The Sponsor's proposal is acceptable from the Clinical Pharmacology standpoint.

2.4 Bioanalytical Methods

2.4.1 Did the Sponsor use validated bioanalytical methods to generate the study data?

Yes. The acceptance criteria and performance of the total T bioanalytical methods were in compliance with the Agency's Bioanalytical Method Validation Guidance. The method validation and performance of the bioanalytical methods used in the submitted studies are acceptable and there are no unresolved bioanalytical issues related to the approvability of JATENZO.

The correlation data (Section 4.1.3) collected from the two different laboratories used were evaluated and found to be acceptable.

2.4.2 Was the cross-reactivity of TU with T when using immunoassays evaluated?

Yes. A study conducted to determine whether TU cross-reacts with T in four different FDA-approved commercially available immunoassays, following *in vitro* spiking of serum samples with predetermined amounts of TU.

Serum T concentrations were not affected by the spiking of charcoal stripped or male serum samples with 0 to 320 ng/mL of TU in any of the immunoassay methods tested. QC samples showed good reproducibility across immunoassays.

3 PROPOSED PRODUCT LABEL

The Clinical Pharmacology review team has the following labeling recommendations in response to the Sponsor's proposed product label:

Highlights

- Information conveying that concomitant administration of medication that are known to increase blood pressure (BP) with JATENZO may lead to additional increases in BP should be added to Section 7 to be consistent with the class labeling language of the most recently approved TRT product, XYOSTED.

Full Prescribing Information

- Information conveying that concomitant administration of medication that are known to increase blood pressure (BP) with JATENZO may lead to additional increases in BP should be added to Section 7 to be consistent with the class labeling language of the most recently approved TRT product, XYOSTED.
- (b) (4)
- The PK profile and parameters should be moved from Section (b) (4) to Section 12.3 *Pharmacokinetics* to be consistent with other TRT product labels.
- The PK parameters should be presented in a combined manner instead of being presented by (b) (4)
- Information on metabolism of TU should be added to Section 12.3 *Pharmacokinetics*.
- Minor edits need to be made to keep the labeling language consistent with the class labeling language of the most recently approved TRT product, XYOSTED.

4 APPENDICES

4.1 Individual Study Reviews

4.1.1 TU to T ex vivo Conversion Evaluation (following TU administration) Study (CLAR-18019)

Title: A Study to Assess Post-Collection Conversion of TU to T in Blood from Men Receiving Oral TU Collected into Different Types of Sample Tubes

Primary Objective: To determine the rate of post-collection TU to T conversion, as manifested by increases in T concentration, in plain tubes held at room temperature and NaF/EDTA tubes held at room temperature or on ice prior to centrifugation.

Study Design, Treatments, and Drug Administration:
This was an open-label, non-randomized, single-sequence study conducted in 13 healthy males (18-45 years of age). Study participants were dosed with 396 mg of JATENZO (i.e., 198 mg x 2 capsules) immediately prior to meals for 7 days and once in the morning of day 8 and had blood drawn into 3 different types of blood-collection tubes (i.e., Plain, EDTA, and NaF/EDTA). Blood samples were collected at approximately 5 hours post-dose to assess the 5-hour T concentration (C_5). These tubes were then processed in different ways (i.e., different durations between phlebotomy and centrifugation, different holding temperatures [room temperature or on ice] between phlebotomy and centrifugation. After defined periods of incubation, the tubes were centrifuged and the serum or plasma transferred into vials and frozen. The T and TU concentrations in the serum or plasma were then measured using validated LC-MS/MS methods.

Reviewer's Comment: *For this study, JATENZO (TU) capsules were supplied at a strength of 198 mg TU. The drug lot number for JATENZO dispensed in this study was 3166139.*

The Sponsor followed the Division's recommendation conveyed at the Type A meeting on June 12, 2018 regarding the study design in conducting this study.

Meals:
Subjects were provided meals on Day 1 and during the confinement period on Days 7 and 8. The breakfasts provided on Days 1 and 8 and dinner provided on Day 7 contained about 30 g of fat (approximately 30% of calories in the meal). Meals were consumed immediately after dosing. The entire meal was consumed within 20 minutes. When the subjects were not in the clinic, they were told to take the capsules with their morning and evening meal. The content of the meal was not specified.

PK Sampling and Characterization:
The effects of tube additives and incubation temperature on the rate of *ex vivo* conversion of TU to T were evaluated. As summarized in Table A-1-1, the blood samples were collected into 3 tube types: (a) Plain (red-top) tubes, (b) EDTA (lavender-top) tubes, and (c) NaF/EDTA (gray-top) tubes. The tube additives EDTA and NaF acted as an anticoagulant and an esterase inhibitor, respectively. Blood from the Plain tubes was processed to serum; blood from the other 2 tube types was processed to plasma. The blood collected in various plain tubes was allowed to sit for 30, 60, 90, or 120 minutes at room temperature to allow clotting prior to processing. The blood collected in EDTA tubes was divided into 2 sets based on their designated incubation temperature (at room temperature or on ice) with various of the tubes sitting for 0, 15, 30, 60, 90, or 120 minutes prior to centrifugation. The blood collected into NaF/EDTA tubes was processed in the same manner as

the EDTA tubes. This approach resulted in each subject providing 28 samples divided among the 5 tube type / incubation temperature combinations on Day 8 of treatment, as summarized in Table A-1-1. Both T and TU concentrations were measured in each sample.

Table A-1-1: Collection Tubes and Sample Handling for Blood Collected on Day 8 at 5 hours Post-dose

Tube Type	Plain	EDTA		NaF-EDTA	
Incubation Condition	RT	RT	Ice	RT	Ice
Incubation Period					
0 – centrifuge immediately	NA[a]	X	X	X	X
15 minutes	NA[a]	X	X	X	X
30 minutes	X	X	X	X	X
60 minutes	X	X	X	X	X
90 minutes	X	X	X	X	X
120 minutes	X	X	X	X	X

EDTA = ethylenediaminetetraacetic acid; NA = not appropriate; NaF = sodium fluoride; RT = room temperature

[a]It is recommended that blood be allowed to clot for 30 minutes at RT prior to centrifugation; therefore, these samples are not available since the blood was not fully clotted.

PK Assessments

This study explored the impact of the variables, namely the hold period between phlebotomy and centrifugation, TU concentration, temperature that the tube was held at (e.g., room temperature or on ice), and whether or not the tube type contained esterase inhibitors (e.g., NaF) that determine the rate of TU to T *ex vivo* conversion. TU concentrations were not controlled, but the blood samples were drawn at the mid-point of the sample window that is being considered for collection of the status-sample (i.e., dose titration sample), and thus approximates the clinical setting for titration of JATENZO.

Reviewer's Comment: *Based on the analysis, the difference in the T concentration between serum and EDTA plasma was estimated for particular sample handling conditions. The Sponsor used the outcome of this assessment to derive a conversion factor that can be used to relate T concentrations in NaF/EDTA plasma (whole blood drawn into NaF/EDTA tubes then held on ice for 30 minutes prior to centrifugation), the matrix used in the pivotal Phase 3 study, CLAR-15012, to equivalent serum T concentration values as they are now proposing to use serum T concentrations for dose titration.*

Bioanalytical Methods:

Sample Preparation

Plain Collection Tubes, Incubated at Room Temperature (Serum):

Collected blood tubes were incubated at room temperature for a minimum of 30 minutes. Centrifugation earlier than 30 minutes was not appropriate since the blood would not have been fully clotted. Each sample was centrifuged at the specified time point for 20 minutes at > 1000 g. For each blood collection tube, serum was separated promptly after centrifugation and transferred into appropriately labelled polypropylene tubes.

EDTA Collection Tubes, Incubated at Room Temperature (Plasma):

Collected blood tubes were incubated at room temperature for the specified incubation time points, and then centrifuged for 20 minutes at > 1000 g. For each blood collection tube, plasma was separated promptly after centrifugation and transferred into appropriately labelled polypropylene tubes.

EDTA Collection Tubes, Incubated in Ice Bath (Plasma):
Collected blood tubes incubated in an ice bath for the specified incubation time points, and then centrifuged at the specified time point for 20 minutes at > 1000 g. For each blood collection tube, plasma was separated promptly after centrifugation and transferred into appropriately labelled polypropylene tubes.

NaF/EDTA Tubes, Incubated at Room Temperature (Plasma):
Collected blood tubes incubated at room temperature for the specified incubation time points, and then centrifuged for 20 minutes at > 1000 g. For each blood collection tube, plasma was separated promptly after centrifugation and transferred into appropriately labelled polypropylene tubes.

NaF/EDTA Tubes, Incubated in Ice Bath (Plasma):
Collected blood tubes incubated in an ice bath for the specified incubation time points, and then centrifuged for 20 minutes at > 1000 g. For each blood collection tube, plasma was separated promptly after centrifugation and transferred into appropriately labelled polypropylene tubes.

All samples were then stored at -20°C (± 5°C) prior to analysis.

T Bioanalysis
The concentrations of T and TU were determined in serum and plasma samples of all subjects using validated LC-MS/MS methods at (b) (4) (formerly called (b) (4)) located in (b) (4). The analytical procedures were conducted in compliance with the laboratory's Standard Operating Procedures.

For T concentrations, blood samples were collected from plain, EDTA, and NaF/EDTA blood collection tubes and analyzed using a validated UPLC-MS/MS method. The dynamic range was 10 ng/dL to 3,000 ng/dL.

T were extracted from serum or plasma by liquid-liquid extraction (LLE). The extracted samples were dried under a stream of nitrogen, the residue was reconstituted. Reconstituted sample extracts were analyzed using a Waters UPLC System (injection volume: 20 mcL) equipped with an Applied Biosystems Sciex API 5000 triple quadrupole mass spectrometer. Chromatographic separation was performed on an ACE Excel 2 C18-PFP, 100 x 3.0 mm, 2 µm-reversed phase column (column temperature: 25°C) for T using gradient elution. Positive ions generated from the electrospray ion source were detected using the multiple reaction monitoring (MRM) mode. Quantitation was performed using a weighted linear regression ($1/concentration^2$) of the determined peak area ratios for T and T-d_3 (internal standard [IS]).

A total of 455 study samples (195 samples in human NaF/Na_2EDTA plasma, 65 samples in human serum and 195 samples in human EDTA K_2 plasma) were analyzed. Inter-run assay accuracy (% RE) demonstrated biases of -4.25% to -1.16% and precision (% CV) ranged from 4.70% to 8.52%, while intra-run assay accuracy demonstrated biases of -7.18% to -0.56% and precision ranged from 0.76% to 1.21%. Incurred sample reanalysis (ISR) was conducted for a total of 20 samples in human NaF/Na_2EDTA plasma and 20 samples in human EDTA K_2 plasma and 12 samples in human serum from this study all (100%) of the ISR results met the acceptability criteria.

Reviewer's Comment: *For this study, T validated method in human NaF/Na_2EDTA plasma was used to measure the T concentrations in NaF/Na_2EDTA plasma, EDTA K_2 plasma and serum investigational samples. The main reason for analyzing all sample types within one analytical run from one validated matrix method is to minimize as much as possible variability that could arise from using three different methods (for the same analyte quantitation) and processed in different analytical runs. Therefore,*

serum and EDTA K_2 plasma T concentrations measured using the NaF/Na_2EDTA method for investigational purpose are considered reliable although it cannot be considered being covered by the validated method. Calibration standards and QC samples were prepared in different matrices as follows for this study:

- *Calibration Standards: in stripped human NaF/Na_2EDTA plasma*
- *QCs at low, intermediate and high levels: in unstripped human NaF/Na_2EDTA plasma*
- *QCs at low and high levels: in unstripped human serum and in unstripped human EDTA K_2 plasma*

Table A-1-2: Summary of Accuracy and Precision Assessments for T and TU Assays by Matrix

Analyte	Testosterone			Testosterone Undecanoate		
Calibration Standards	10 to 3000 ng/dL			1.0 to 1000 ng/mL		
LLOQ	10 ng/dL			1.0 ng/mL		
Sample Matrix	Serum	NaF-EDTA Plasma	EDTA Plasma	Serum	NaF-EDTA Plasma	EDTA Plasma
Accuracy	96.67% to 102.63%	95.23% to 103.08%	97.45% to 100.12%	100.33% to 102.33%	98.94% to 100.73%	102.22% to 102.33%
Between Run Precision (CV)	1.83% to 4.95%	1.23% to 3.85%	1.79% to 3.55%	2.34% to 5.21%	1.99% to 3.32%	2.09% to 3.91%

CV = coefficient of variation; EDTA = ethylenediaminetetraacetic acid; LLOQ = lower limit of quantitation; NaF = sodium fluoride

During this ex vivo conversion study, a set of serum and EDTA K_2 QC samples were prepared as mentioned above and were analyzed along with investigational samples in order to confirm that NaF/Na_2EDTA calibration standards did quantify properly serum and EDTA K_2 plasma samples. As shown in Table A-1-2, the accuracy and precision for T concentrations were comparable among different matrices (i.e., serum, NaF/EDTA plasma, and EDTA plasma).

In order to calculate the increase in T concentrations due to TU to T ex vivo conversion, it is necessary to know the initial T concentration (e.g., T concentration in circulation). When TU to T ex vivo conversion is calculated in experiments where oral TU is administered, the closest approximation to the "true" baseline value is the T concentration in a blood sample which is processed immediately after phlebotomy (e.g., centrifuged at time = 0). Since samples in Plain tubes need 30 minutes to clot, it is not possible to get a "true" baseline value for serum. Therefore, as a surrogate for a serum "true" baseline, the Day 8, EDTA "true" baseline (time = 0) was used.

<u>TU Bioanalysis</u>

TU concentrations were measured in serum or plasma samples isolated from whole blood drawn into NaF/EDTA containing blood collection tubes collected on each of the 5 PK days. The TU was analyzed using a sensitive and specific validated LC-MS/MS method. The dynamic range was 1 ng/mL to 1,000 ng/mL.

TU were extracted from serum or plasma by LLE with methyl tert-butyl ether. The extracted samples were dried under a stream of nitrogen, the residue was reconstituted. Reconstituted sample extracts were analyzed using an Agilent HP 1100 HPLC System (injection volume: 10 mcL) equipped with an Applied Biosystems Sciex API 5000 triple quadrupole mass spectrometer. Chromatographic separation was performed on an BEH phenyl, 50 x 3.0 mm, 1.7 µm-reversed phase column (column temperature: 35°C) for TU using isocratic elution. Positive ions generated from the electrospray ion source were detected using the MRM mode. Quantitation was performed using a weighted linear regression (1/concentration^2) of the determined peak area ratios for TU and TU-d_5 (IS).

A total of 364 study samples (156 samples in human NaF/Na_2EDTA plasma, 52 samples in human serum and 156 samples in human EDTA K_2 plasma) were analyzed. Inter-run assay accuracy demonstrated biases of -1.02% to 0.49% and precision ranged from 3.70% to 5.90%, while intra-run assay accuracy demonstrated biases of -2.50% to 1.66% and precision ranged from 1.62% to 5.83%. ISR was conducted for a total of 21 samples in human NaF/Na_2EDTA plasma, 12 samples in human EDTA K_2 plasma, and 20 samples in human serum from this study all (100%) of the ISR results met the acceptability criteria.

Reviewer's Comment: *For this study, TU validated method in human NaF/Na_2EDTA plasma was used to measure the TU concentrations in NaF/Na_2EDTA plasma, EDTA K_2 plasma and serum investigational samples. The main reason for analyzing all sample types within one analytical run from one validated matrix method is to minimize as much as possible variability that could arise from using three different methods (for the same analyte quantitation) and processed in different analytical runs. Therefore, serum and EDTA K_2 plasma TU concentrations measured using the NaF/Na_2EDTA method for investigational purpose are considered reliable although it cannot be considered being covered by the validated method. Calibration standards and QC samples were prepared in different matrices as follows for this study:*

- *Calibration Standards: in stripped human NaF/Na_2EDTA plasma*
- *QCs at low, intermediate, and high levels: in unstripped human NaF/Na_2EDTA plasma*
- *QCs at low and high levels: in unstripped human serum and in unstripped human EDTA K_2 plasma*

During this ex vivo conversion study, a set of serum and EDTA K_2 QC samples were prepared as mentioned above and were analyzed along with investigational samples in order to confirm that NaF/Na_2EDTA calibration standards did quantify properly serum and EDTA K_2 plasma samples. As shown in Table A-1-2, the accuracy and precision for TU were comparable among different matrices (i.e., serum, NaF/EDTA plasma, and EDTA plasma).

The acceptance criteria and performance of the total T and TU bioanalytical methods are in compliance with the Agency's Bioanalytical Method Validation Guidance. In summary, the method validation and performance of the bioanalytical methods in clinical studies are acceptable and there are no unresolved bioanalytical issues related to the approvability of JATENZO.

Dose Rationale

In order to accurately estimate the magnitude of overestimation likely to be seen in clinical practice, it was necessary for the circulating TU concentration to reflect the expected circulating TU concentration in clinical practice. Practically, this meant dosing with the highest JATENZO dose proposed in clinical trials and dosing such that the TU concentration reached steady state. In clinical practice, a patient's ultimate dose will be based on dose titration using a dose-titration regimen tested in Study CLAR-15012. In that study, the highest dose was 396 mg TU twice daily (two 198 mg TU capsules twice daily). Therefore, this was the dose studied in this study.

PK Results

Matrix Effect

Matrix effects were assessed in this study because they are anticipated to affect the comparison of T concentrations in one matrix to that in another, as well as because it was proposed that T concentrations measured in EDTA plasma (Day 8 immediate spin) would be used as a Day 8 baseline (time = 0) value for serum from plain tubes (plain tubes require 30 minutes to clot so it is not feasible to collect a time = 0 sample). Prior to starting the TU dosing, blood samples were collected in each of the tube type / incubation temperature combinations so that the effects could be quantified for each combination. Table A-1-3 presents the matrix effects (e.g., ratios of T

concentrations measured in matrix from selected pairs of tube types) calculated from this study, as well as the matrix effect determined in Study CLAR-16014.

Table A-1-3: Ratio of T Concentrations Measured in Two Matrices (Serum or Plasma) from Blood Drawn into Plain, EDTA, or NaF/EDTA Tubes Without TU Administration

Analyte	Testosterone Ratios		Testosterone Ratio
Study	Current Study		CLAR-16014
	EDTA / Plain	NaF-EDTA / Plain	NaF-EDTA / Plain
Tube Type / Tube Type	Ratio	Ratio	Ratio
Ratio	0.973	0.869[a]	0.858
Reciprocal ratio (1/ratio)	1.028	1.151[a]	1.166

CSR = clinical study report; EDTA = ethylenediaminetetraacetic acid; NaF = sodium fluoride; TU = testosterone undecanoate

[a] These values were not used in subsequent matrix effect calculations since matrix effect calculated in Study CLAR-16014 has a more robust dataset (97 subjects versus 13 subjects).

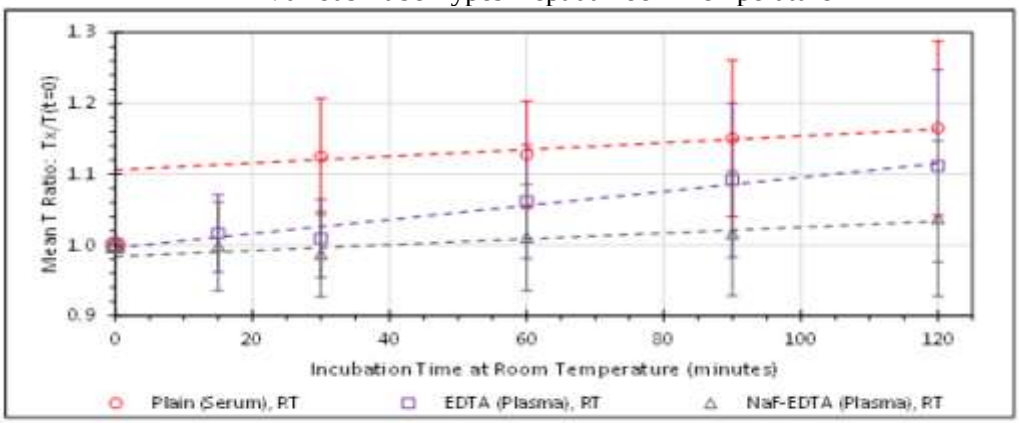
Reviewer's Comment: *It should be noted that Study CLAR-16014 (submitted in the last review cycle) demonstrated that in 97 healthy young men, T concentrations measured in plasma from NaF/EDTA tubes (held for 30 minutes on ice prior to centrifugation) and serum from plain tubes (held for 30 minutes at room temperature prior to centrifugation) showed a consistent and systematic difference in their results. This blood was collected from men who did not have TU in their circulation, so the matrix effect was solely due to the additives in the sample collection tubes. Study CLAR-16014 identified the matrix effect as 0.858 (multiply by factor to convert a T value in serum to a corresponding value in NaF/EDTA plasma), or its reciprocal 1.166 (to convert a T concentration value in NaF/EDTA plasma to a corresponding value in serum).*

For historical comparison purposes of the NaF/EDTA vs. plain tube matrix effect, the NaF/EDTA plasma/serum geometric ratio value from the current study at 0.869 differed by just 1.3% from the previously reported geometric mean value of 0.858 (Study CLAR-16014). The ratio identified in the current study is well within the 95% confidence interval (CI) (0.844, 0.873) for the previously reported result, which utilized 97 subjects. The Sponsor used geometric mean ratio of 0.858 in subsequent conversion factor calculations since Study CLAR-16014 had a more robust dataset (i.e., 97 subjects vs. 13 subjects). The Sponsor's approach is reasonable.

Rate of TU to T *ex vivo* Conversion

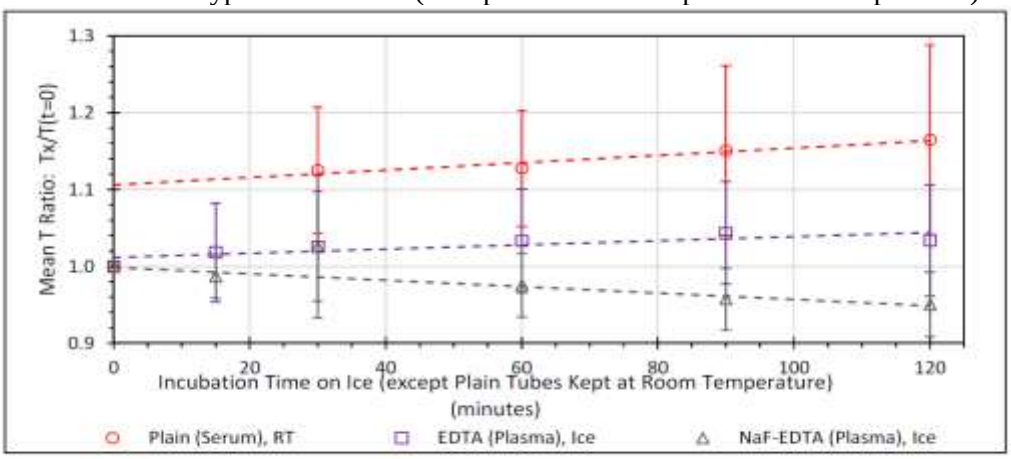
Figure A-1-1 and Figure A-1-2 present the mean baseline-normalized (ratio-transformed) T concentration patterns of *ex vivo* T formation over the first 120 minutes post-collection for each of the 5 tube type / incubation temperature combinations. T concentrations in all tubes showed increases as incubation time at room temperature increased. No increase in T concentrations was observed in plasma (NaF/EDTA tubes) when placed on ice. It appears that temperature plays a significant role in the TU to T *ex vivo* conversion.

Figure A-1-1: Mean T Ratios (with 95% CIs) Versus Incubation Time (and Their Regressions) in Various Tube Types Kept at Room Temperature



EDTA = ethylenediaminetetraacetic acid; NaF = sodium fluoride; RT = room temperature; T = testosterone
Regression lines from mean intercept and slope of 13 individual regression relationships (Table 14, Table 18, and Table 26)

Figure A-1-2: Mean T Ratios (with 95% CIs) Versus Incubation Time (and Their Regressions) in Various Tube Types Held on Ice (Except Plain Tube Kept at Room Temperature)



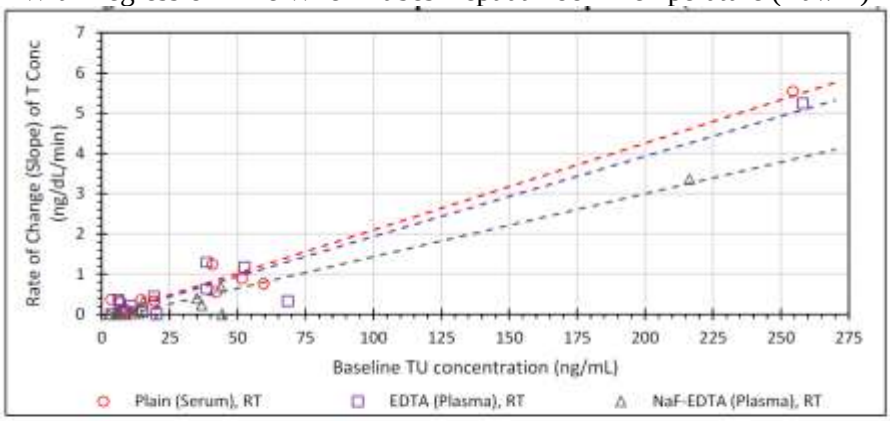
EDTA = ethylenediaminetetraacetic acid; NaF = sodium fluoride; RT = room temperature; T = testosterone
Regression lines from mean intercept and slope of 13 individual regression relationships (Table 14, Table 22, and Table 30)

TU to T *ex vivo* conversion rate and TU concentrations

The rate of TU to T *ex vivo* conversion depends on the substrate (i.e., TU) concentration present in the tube. The magnitude of the dependence was assessed by plotting the rate of conversion of TU to T versus the initial (time = 0 or baseline) TU concentration and determining the slope and intercept of the relationship. The plots of the 13 adjusted slope values for each of the 5 tube type / incubation temperature combinations are shown in Figure A-1-3 and Figure A-1-4 for the raw concentration data. Figure A-1-3 shows the results when the tube types were incubated at room temperature, Figure A-1-4 shows the results when the tube types were incubated on ice. The serum tube incubated at room temperature is shown in both graphs of each set to aid in comparing results between room temperature and ice incubations.

The slopes for tubes containing NaF and/or EDTA kept on ice are relatively flat comparted to those held at room temperature. It should be noted that TU to T *ex vivo* conversion still existed in plasma in NaF/EDTA tubes at room temperature.

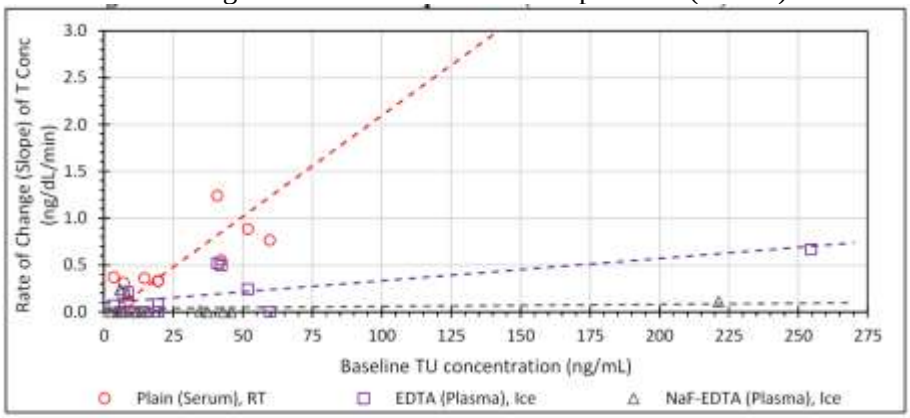
Figure A-1-3: Rate of TU to T Conversion as a Function of TU Concentration (Adjusted Slopes) With Regression Line When Tubes Kept at Room Temperature (Raw T)



Conc = concentration; EDTA = ethylenediaminetetraacetic acid; NaF = sodium fluoride; RT = room temperature; T = testosterone; TU = testosterone undecanoate

Note: Rate of change of T conc = slope of T(time) versus time plot (Table 51, Table 52, and Table 53). Uses adjusted slopes; ie, if regression slope for an individual's testosterone versus time plot calculated to < 0.0, then slope was set equal to zero.

Figure A-1-4: Rate of TU to T Conversion as a Function of TU Concentration (Adjusted Slopes) With Regression Line When Tubes Kept on Ice (Raw T)



Conc = concentration; EDTA = ethylenediaminetetraacetic acid; NaF = sodium fluoride; RT = room temperature; T = testosterone; TU = testosterone undecanoate

Note: Rate of change of T conc = slope of T(time) vs. time plot (Table 51, Table 52, and Table 53). Uses adjusted slopes; ie, if regression slope for an individual's testosterone versus time plot calculated to < 0.0, then slope was set equal to zero. Serum tube versus TU shown to facilitate comparison between tubes with fast and slow TU-to-testosterone conversion.

Reviewer's Comment: *It appears that both matrix effect (i.e., serum vs. NaF/EDTA plasma without TU dosing) and TU to T ex vivo conversion following TU dosing affect T concentrations. When TU was not administered, T concentrations from serum in plain tubes were higher compared to plasma in NaF/EDTA tubes (See Table A-1-3). Sponsor believes that NaF causes change in T partitioning and lowers the observed T concentration. Regarding the TU to T ex vivo conversion, it appears that post-collection (incubation) temperature plays a significant role. Overall, TU concentration, post-collection (incubation) time, and the presence of esterase inhibitor (e.g., NaF) contributes to the difference in measured T concentrations.*

Conversion Factor

The 3 factors that translate a T concentration measured under one set of tube type / incubation temperature and time conditions (i.e., serum from blood collected in a plain tube and held at room temperature for 30 minutes) to an alternative set of tube type / incubation temperature and time

conditions (i.e., plasma collected in a NaF/EDTA tube and kept for 30 minutes on ice) were determined. These 3 factors are:

- Extent of TU to T *ex vivo* conversion occurring in serum plain tube at the incubation temperature over the processing time between sample collection and centrifuging
- Extent of TU to T *ex vivo* conversion occurring in NaF/EDTA plasma tube at the incubation temperature over the processing time between sample collection and centrifuging
- Matrix effect associated with the pair of tube type / incubation temperature combinations

TU to T *ex vivo* conversion factor

It should be noted that TU concentrations were not measured in the pivotal Phase 3 study, CLAR-15012. The estimated TU concentrations for Study CLAR-15012 was derived by performing linear interpolation to derive 4- and 6-hour post-dose TU in Study CLAR-09007 and applying a scaling factor for TU concentration to account for the inter-study difference between Studies CLAR-09007 and CLAR-15012 due to slightly different observed T concentrations. The TU concentration was estimated to be approximately 118 ng/mL at 4 hours post-dose and 52 ng/mL at 6 hours post dose.

The conversion factor for overestimation of T concentration due to present of TU was calculated based on results of regression analysis (Tables A-1-4 and A-1-5). In the case for serum in plain tubes kept at room temperature for 30 minutes, for 4 hour post-dose (TU concentration = 118 ng/mL), the conversion factor for the overestimation in plain tube will be 1((1+overestimation) = 1/(1+0.0856) = 0.921. For 6 hour post-dose (TU concentration = 52 ng/mL), the conversion factor for the overestimation in plain tube will be 1/(1+overestimation) = 1/(1+0.0429) = 0.959.

Table A-1-4: Overestimation of T Concentrations (%) Due to TU to T *ex vivo* Conversion at Various TU Concentrations Based on Regression Analysis (plain tube at room temperature for 30 min)

Using Adjusted[a] Conversion Slopes	Plain at RT	EDTA on Ice	NaF-EDTA on Ice	EDTA at RT	NaF-EDTA at RT
Intercept (1/minute)	0.0002556	0.0002707	0.0000214	0.0002355	-0.0000684
Slope [(1/minute)/ng/mL TU]	0.0000226	0.0000024	0.000000441	0.0000213	0.0000194
R^2	0.8686	0.0861	0.0859	0.6964	0.9415
TU (ng/mL)	% increase	% increase	% increase	% increase	% increase
0	0.77%	0.81%	0.06%	0.71%	-0.21%
5	1.11%	0.85%	0.07%	1.03%	0.09%
25	2.46%	0.99%	0.10%	2.30%	1.25%
50	4.16%	1.17%	0.13%	3.90%	2.71%
52[b]	4.29%[b]	1.19%[b]	0.13%[b]	4.03%[b]	2.82%[b]
63	5.04%	1.26%	0.15%	4.73%	3.46%
75	5.85%	1.35%	0.16%	5.50%	4.16%
94	7.14%	1.49%	0.19%	6.72%	5.27%
100	7.55%	1.53%	0.20%	7.10%	5.62%
115[c]	8.56%[c]	1.64%[c]	0.22%[c]	8.06%[c]	6.49%[c]

In the case for plasma in NaF/EDTA tubes kept on ice for 30 minutes, for 4 hour post-dose (TU concentration = 118 ng/mL), the conversion factor for the overestimation in NaF/EDTA tube is 1((1+overestimation) = 1/(1+0.0022) = 0.998 For 6 hour post-dose (TU concentration = 52 ng/mL), the conversion factor for the overestimation in NaF/EDTA tube is 1((1+overestimation) = 1/(1+0.0013) = 0.999

Table A-1-5: Overestimation of T Concentrations (%) Due to TU to T *ex vivo* Conversion at Various TU Concentrations Based on Regression Analysis (NaF/EDTA tube on ice for 30 min)

Using Adjusted[a] Conversion Slopes	Plain at RT	EDTA on Ice	NaF-EDTA on Ice	EDTA at RT	NaF-EDTA at RT
Intercept (1/minute)	0.0002556	0.0002707	0.0000214	0.0002355	-0.0000684
Slope [(1/minute)/ng/mL TU]	0.0000226	0.0000024	0.000000441	0.0000213	0.0000194
R^2	0.8686	0.0861	0.0859	0.6964	0.9415
TU (ng/mL)	% increase	% increase	% increase	% increase	% increase
0	0.77%	0.81%	0.06%	0.71%	-0.21%
5	1.11%	0.85%	0.07%	1.03%	0.09%
25	2.46%	0.99%	0.10%	2.30%	1.25%
50	4.16%	1.17%	0.13%	3.90%	2.71%
52[b]	4.29%[b]	1.19%[b]	0.13%[b]	4.03%[b]	2.82%[b]
63	5.04%	1.26%	0.15%	4.73%	3.46%
75	5.85%	1.35%	0.16%	5.50%	4.16%
94	7.14%	1.49%	0.19%	6.72%	5.27%
100	7.55%	1.53%	0.20%	7.10%	5.62%
115[c]	8.56%[c]	1.64%[c]	0.22%[c]	8.06%[c]	6.49%[c]

Reviewer's Comment: *It should be noted that the Sponsor inadvertently used the TU concentration of 115 ng/mL instead of 118 ng/mL and its corresponding overestimation (%) when calculating the conversion factor. However, a meaningful difference due this error is not expected.*

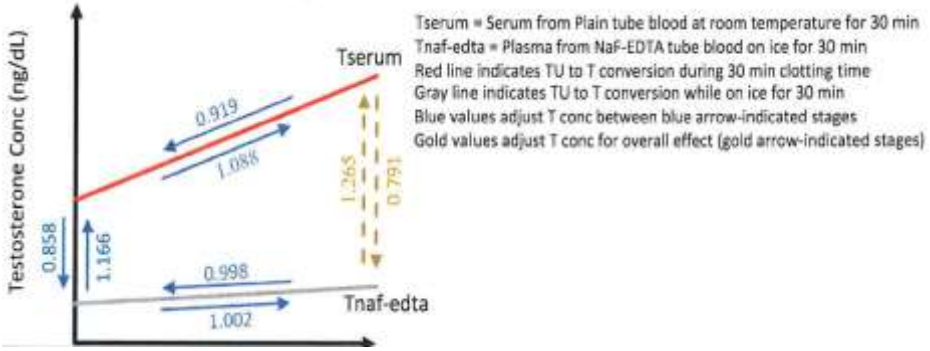
Matrix effect conversion factor

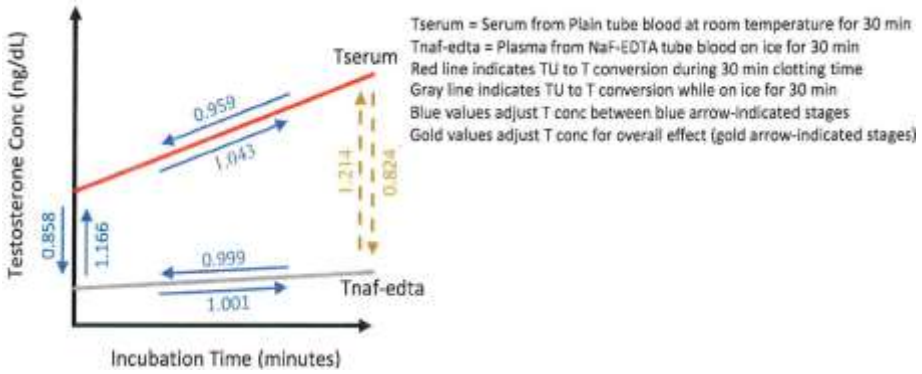
As shown in Table A-1-3, the T concentration ratio of NaF/EDTA tube/plain tube obtained in Study CLAR-16014 is 0.858.

Overall Conversion Factor

Using the 3 factors mentioned above, an overall conversion factor was derived which allows the conversion of a serum T concentration to a NaF/EDTA plasma T concentration (or vice versa).

Figure A-1-5: Conversion Diagram for T Concentration Measured from Serum in Plain Tube (Incubated at Room Temperature for 30 Minutes) to an Equivalent Value for Plasma in NaF/EDTA Tube (Incubated on Ice for 30 Minutes) for a Sample Collected 4 hours post-dose (Top) and 6 hours post-dose (Bottom)





The diagram shown in Figure A-1-5 helps visualize the relationship between the multiple effects on the T concentration assessment described above and an overall conversion factor that can be used to translate the T concentration in one setting to an equivalent actionable T concentration in a second setting. In the example in Figure A-1-5, conversion for a sample collected 6 hours post-dose (bottom) (e.g., TU concentration of 52 ng/mL) in a plain tube (and allowed to clot at room temperature for 30 minutes) into the expected T concentration if the sample had been collected in a NaF/EDTA tube (and kept on ice for 30 minutes):

- First (top arrow), reducing the T concentration in the serum (from the plain tube) by the factor compensating for TU to T *ex vivo* conversion at room temperature for 30 minutes (0.959)
- Second, by further reducing the measured T concentration by the matrix effect associated with NaF/EDTA plasma compared to serum (0.858)
- Third, by increasing the resulting T concentration by the TU to T *ex vivo* conversion that occurs when a sample in a NaF/EDTA tube is held on ice for 30 minutes (1.001)

The combined effect, 0.959 × 0.858 × 1.001, is equal to 0.824 (i.e., the product of the 3 effects known to affect the serum concentration). The expected value of the equivalent T concentration in plasma from a NaF/EDTA tube is 82.4% of the serum value when the incubation temperature, incubation time, and the underlying TU concentration are as stated. When deriving the T concentration for plasma in NaF/EDTA tube, the combined effect is (1/0.959) x (1/0.858) x (1/1.001) = 1.214.

As a sensitivity analysis, the mean deviations in T (and 95% CI) were calculated at the mean TU concentrations estimated for 4- and 6-hours post-dose and at the lower and upper bounds of the 95% CI for the mean 4- and 6-hour post-dose TU values.

Table A-1-6: Summary of Conversion Factors for Incubation Time, Temperature, and Matrix Effects in Serum and NaF/EDTA Plasma for Conversion of Serum T Concentrations to Plasma T Concentrations (Study CLAR-18019; N=13)

Serum RT => NaF-EDTA on ice	TU	Time & Temp in Serum Effect	Matrix Effect	Time & Temp in Plasma Effect	Com-bined Effects	Error in Predicting Observed Plasma T Conc		
Rationale for Selected TU	ng/mL	Step 1	Step 2	Step 3	Overall	Mean	LB 95% CI	UB 95% CI
1 Original report TU at 4 h	115	0.921	0.858	1.0022	0.792	0.15%	-9.62%	9.92%
2 Original report TU at 6 h	52	0.959	0.858	1.0013	0.824	4.17%	-5.99%	14.32%
3 Revised mean TU at 4 h	118	0.919	0.858	1.0022	0.791	-0.03%	-9.78%	9.72%
4 Revised mean TU at 6 h	52	0.959	0.858	1.0013	0.824	4.17%	-5.99%	14.32%
5 LB of revised mean TU at 4 h	67.3	0.949	0.858	1.0015	0.816	3.16%	-6.90%	13.22%
6 UB of revised mean TU at 4 h	169.3	0.891	0.858	1.0029	0.767	-3.06%	-12.52%	6.39%
7 LB of revised mean TU at 6 h	28.1	0.974	0.858	1.0010	0.837	5.78%	-4.54%	16.09%
8 UB of revised mean TU at 6 h	75.2	0.945	0.858	1.0016	0.812	2.65%	-7.36%	12.66%

Table A-1-6 summarizes the sensitivity analysis results in Rows 5-8. The mean deviations in predicted T values at 4- and 6-hours post-dose at both the upper and lower bounds of the 95% CI for TU (67.3 and 169.3 ng/mL for 4 hours; 28.1 and 75.2 ng/mL for 6 hours) range from -3.06% to 5.78%.

Applying Conversion Factor to Clinical Data

At Visit 7 in the pivotal Phase 3 study, CLAR-15012, matched pairs (contemporaneously collected) of samples were collected into plain and NaF/EDTA tubes, which were incubated for 30 minutes at room temperature or on ice, respectively, before centrifugation. T concentrations were measured in the serum/plasma from these tubes. These data were used to assess how well the conversion factor works with actual clinical trial data. As graphically depicted in Figure A-1-5 (bottom), to convert the T concentration from NaF/EDTA plasma (kept on ice for 30 minutes) drawn 6 hours post-dose to an analogous value from serum from a plain tube (kept at room temperature for 30 minutes), multiply by 1.214 (for samples collected 6 hours post-dose) or 1.263 (for samples collected 4 hours post-dose). Table A-1-7 presents an analysis of the Study CLAR-15012 Visit 7 4- and 6-hour post-dose serum T concentrations. The differences between the measured serum T concentration and the derived serum T concentration (derived from measured NaF/EDTA plasma T concentration and relevant conversion factor) are 1.3% to 3.1% with 95% CIs of less than ±6%.

Table A-1-7: Comparison between Serum T Concentrations Measured at 4- and 6-hours post-dose Samples and Serum T Concentrations Calculated from Measured NaF/EDTA Plasma T Concentrations using Conversion Factor for 4- and 6-hour post-dose Samples (Study CLAR-15012, Visit 7)

Parameter	N	Mean (SD)	Median	95% CI
4-Hour Postdose Sample				
Measured serum testosterone (ng/dL)	154	696.0 (327.95)	648.0	643.78, 748.20
Calculated testosterone[a] (ng/dL)	154	688.2 (312.12)	654.8	638.46, 737.84
% difference (actual – derived)		-1.3% (24.09)	1.9	-5.12%, 2.55%
6-Hour Postdose Sample				
Measured serum testosterone (ng/dL)	155	477.1 (267.40)	430.5	434.71, 519.57
Calculated testosterone[b] (ng/dL)	155	449.6 (223.94)	408.4	414.05, 485.11
% difference (actual – derived)		3.1% (16.78)	3.42	0.43%, 5.76%

CI = confidence interval; EDTA = ethylenediaminetetraacetic acid; NaF = sodium fluoride; SD = standard deviation
a Calculated serum testosterone = conversion factor (1.263) × measured NaF-EDTA plasma testosterone.
b Calculated serum testosterone = conversion factor (1.214) × measured NaF-EDTA plasma testosterone.

Prolongation of Incubation Time

For the 60, 90, and 120 minute clotting times, the arithmetic mean values were 0.24%, 2.28%, and 3.55% greater than the value at 30 minutes incubation.

Table A-1-8: Effect of Prolonging Incubation – Ratio of T Concentrations to Baseline T Concentration(Plasma in EDTA Tubes at t=0)

Matrix	Plasma	Serum	Serum	Serum	Serum	Serum	Serum	Serum	Serum
Tube	EDTA	Plain	Plain	Plain	Plain	Plain	Plain	Plain	Plain
Day	Day 8	Day 8	Day 8	Day 8	Day 8	Day 8	Day 8	Day 8	Day 8
Hold Temperature	Ice	RT	RT	RT	RT	RT	RT	RT	RT
Hold Time	0 Minutes[a]	30 Minutes	60 Minutes	90 Minutes	120 Minutes	Intercept	Slope	Adjusted Slope	R^2
N	13	13	13	13	13	13	13	13	13
Mean	1.0000	1.1249	1.1275	1.1505	1.1648	1.0425	0.001185	0.001190	0.44333
SD	0.00000	0.13590	0.12553	0.18317	0.20358	0.04921	0.0016226	0.0016185	0.329390
SEM	0.00000	0.03769	0.03482	0.05080	0.05646	0.01365	0.0004500	0.0004489	0.091356
CV%	0.0%	12.1%	11.1%	15.9%	17.5%	4.7%	137.0%	136.1%	74.3%
Gmean	1.0000	1.1178	1.1214	1.1382	1.1510	1.0414	NE	0.001188	0.15983
Median	1.000	1.089	1.086	1.114	1.105	1.038	0.00063	0.00063	0.4270
Minimum	1.000	0.976	0.938	0.886	0.987	0.971	-0.00006	0.00000	0.0002
Maximum	1.000	1.453	1.406	1.604	1.741	1.173	0.00601	0.00601	0.9809
Amean 95% LCB	NE	1.0427	1.0517	1.0399	1.0418	1.0127	0.000204	0.000211	0.24428
Amean 95% UCB	NE	1.2070	1.2034	1.2612	1.2879	1.0722	0.002165	0.002168	0.64238

Amean = arithmetic mean; CV = coefficient of variation; EDTA = ethylenediaminetetraacetic acid; Gmean = geometric mean; LCB = lower confidence bound; NE = not evaluated; RT = room temperature; SD = standard deviation; SEM = standard error of the mean

[a] EDTA plasma immediate spin sample (time = 0) serves as baseline for serum, since Plain tube needs 30 minutes to clot. (see Section 7.7.1)

Table A-1-9: Effect of Prolonging Incubation on Conversion Factors for Samples collected at 4 hours post-dose (Left) and 6 hours post-dose (Right)

	Serum CF	Matrix CF	Plasma CF	Overall CF
Inner Numbers [Outer Numbers*]				
30 min** (Reference)	1.086 [0.921]	1.166 [0.858]	0.998 [1.002]	1.263 [0.792]
60 min	1.089 [0.918]	NC	NC	1.266 [0.790]
90 min	1.111 [0.900]	NC	NC	1.292 [0.774]
120 min	1.125 [0.889]	NC	NC	1.308 [0.765]

NC- no change.

*Outer numbers are mathematical reciprocals of inner numbers

**values shown in CLAR-18019 PK Report Figure 23

Outer numbers: NaF/EDTA plasma → Serum

Inner numbers: Serum → NaF/EDTA plasma

	Serum CF	Matrix CF	Plasma CF	Overall CF
Inner Numbers [Outer Numbers*]				
30 min** (Reference)	1.043 [0.959]	1.166 [0.858]	0.999 [1.001]	1.214 [0.824]
60 min	1.046 [0.956]	NC	NC	1.217 [0.822]
90 min	1.067 [0.937]	NC	NC	1.242 [0.805]
120 min	1.080 [0.926]	NC	NC	1.257 [0.795]

NC- no change.

*Outer numbers are mathematical reciprocals of inner numbers

**values shown in CLAR-18019 PK Report Figure 24

Reviewer Comment: *As shown in Table A-1-8, the mean T concentrations were 3.55% higher at 120 minutes when compared to the 30 min clotting time. This translates into an increase of 0.045 and 0.043 of the overall conversion factors at 4 hours post-dose and 6 hours post-dose, respectively (Table A-1-9). A meaningful clinical difference is not expected due to the prolongation of the clotting time up to 120 minutes.*

Proposed Dose Titration Scheme

In the pivotal Phase 3 study, CLAR-15012, dose-titration was based on T concentrations measured in plasma from NaF/EDTA tubes kept on ice for 30 minutes prior to centrifugation. A T dose-titration boundary range of 350 to 800 ng/dL was used to guide dose adjustment. If a status-sample,

upon which the dose-titration decision will be based, is drawn 6 hours post-dose (in Study CLAR-15012, the T concentration at 6 hours post-dose had the highest concordance with C_{avg}), then that T value could be converted to an equivalent expected NaF/EDTA plasma value by multiplying by 0.824. Alternately, that same serum T value could be directly compared to an equivalent titration boundary range derived from Study CLAR-15012 using the correction factor 1.214 (1 / 0.824). This factor, 1.214, converts the lower boundary value of 350 ng/dL to 425 ng/dL (350 × 1.214) and the upper boundary value of 800 ng/dL to 970 ng/dL (800 × 1.214).

Table A-1-10 and Table A-1-11 show the dose titration thresholds at 6 hour post-dose and 4 hour post-dose calculated using the T concentration dose titration thresholds from plasma in NaF/EDTA tubes that were used in Study CLAR-15012 and the mean, lower bound (LB), and upper bound (UB) conversion factors.

Table A-1-10: Dose Titration Thresholds Calculated Using T Concentrations from Plasma in NaF/EDTA Tubes and Corresponding Conversion Factors at 6 hour post-dose

Time (hr post-dose)	T NaF/EDTA Plasma (ng/dL)	Conversion Factor	T serum (ng/dL)
6 hr, Mean, Low	350	1.214	425
6 hr, Mean, High	800	1.214	971
6 hr, LB, Low	350	1.195	418
6 hr, LB, High	800	1.195	956
6 hr, UB, Low	350	1.232	431
6 hr, UB, High	800	1.232	986

Table A-1-11: Dose Titration Thresholds Calculated Using T Concentrations from Plasma in NaF/EDTA Tubes and Corresponding Conversion Factors at 4 hour post-dose

Time (hr post-dose)	T NaF/EDTA Plasma (ng/dL)	Conversion Factor	T serum (ng/dL)
4 hr, Mean, Low	350	1.265	443
4 hr, Mean, High	800	1.265	1012
4 hr, LB, Low	350	1.226	429
4 hr, LB, High	800	1.226	981
4 hr, UB, Low	350	1.304	456
4 hr, UB, High	800	1.304	1043

Table A-1-12: Comparison of Mean and Worst-case Scenario Dose Titration Thresholds Based on Serum T Concentrations at 4- and 6-hour post-dose Samples

Titration Sampling Time Point	Titration Threshold based on T Serum (ng/dL)
6 hr Post-dose Mean	425-971
6 hr Post-dose Worst Case Scenario	418-986
4 hr Post-dose Mean	443-1012
4 hr Post-dose Worst Case Scenario	429-1043

Worst-case scenario used the low threshold of the lower bound and the high threshold of the upper bound

Table A-1-12 summarizes the mean and worst-case scenario dose titration thresholds based on the serum T concentrations at 4- and 6-hour post-dose samples

Based on the following this reviewer believes that the Sponsor's proposed dose titration scheme based on 6 hr post-dose using serum T concentration appears to be reasonable:

- T concentration at 6 hr post-dose (C_6) has the highest concordance with T C_{avg} → Clinically relevant
- Lower TU concentration at 6 hr post-dose compared to 4 hr post-dose → Lower variability due to TU to T ex vivo conversion.
- Successful establishment of conversion factor that enables to correlate measured T serum concentrations at 6 hour post-dose to T NaF/EDTA plasma concentrations at 6 hour post-dose that was used in pivotal Phase 3 study, CLAR-15012.

Conclusion:

- The TU to T *ex vivo* conversion, as manifested by increases in T concentration after sample collection, depends on temperature, type of collection tube, and TU concentration.
- In addition to TU to T ex vivo conversion, matrix effect also contributes to the difference of T concentrations obtained from different matrix.
- Conversion factors were successfully derived and were tested using clinical data.
- The factor of 0.824 can be used to convert the measured T concentration in serum (from Plain tube and allowed to clot for 30 minutes) at 6 hours post-dose (proposed time of status-sample, upon which the dose titration decision will be based) to an equivalent T concentration in plasma (from NaF/EDTA tube incubated on ice for 30 minutes). This equivalent plasma value could then be used for dose-titration decisions using the titration boundaries tested in Study CLAR-15012, namely 350 to 800 ng/dL.
- Alternatively, the serum T value could be directly compared to an equivalent titration boundary range using the conversion factor 1.214 (1 / 0.824). This factor, 1.214, converts the lower boundary value of 350 ng/dL to 425 ng/dL (350 × 1.214) and the upper boundary value of 800 ng/dL to 970 ng/dL (800 × 1.214).

4.1.2 TU to T ex vivo Conversion Evaluation (following TU spiking) Study (CLAR-18021)

Title: Bioanalytical Study to Evaluate the Impact of the Table Type, Incubation Temperature, and Duration on T Concentration After Spiking Blood with TU

Primary Objectives:
To compare the TU to T *ex vivo* conversion in plain and NaF/EDTA tubes after spiking blood samples with TU.

Study Design:
Eighteen (18) healthy men aged 18 to 65 years, inclusive, were enrolled based on selection criteria designed to identify healthy men. No study drug was administered. Blood samples were drawn into plain (red-top) tubes for serum collection and NaF/EDTA tubes for plasma collection. The blood was promptly aliquoted, spiked with TU (or vehicle), and then allowed to incubate for 30 or 60 minutes at room temperature or on ice. Blood sample TU spiking, incubation temperature, and incubation duration parameters utilized in the study are summarized in Table A-2-1.

Table A-2-1: Blood Sample TU Spiking, Incubation, and Incubation Duration Parameters

Parameter	Plain Tube (Serum)		NaF-EDTA Tube (Plasma)			
Temperature	Room Temperature		Room Temperature		On Ice	
Incubation duration	30 min	60 min	30 min	60 min	30 min	60 min
TU (ng added per mL blood[a])	0, 60, 300	0, 60, 300	0, 60, 300	0, 60, 300	0, 60, 300	0, 60, 300

EDTA = ethylenediaminetetraacetic acid; min = minutes; NaF = sodium fluoride; TU = testosterone undecanoate
[a] TU was dissolved in methanol such that the final methanol concentration in the blood was 1% v/v. For the TU 0 ng/mL samples, methanol was added to a final concentration of 1% v/v.

Primary Endpoint:
The primary endpoint was the measured concentration of T in the 2 types of sample collection tubes used for each subject.

Bioanalytical Methods:
Freshly collected blood samples were spiked with TU dissolved in methanol for a final concentration of 60 or 300 ng TU per mL of blood. The amount of methanol in all the spiked samples (0, 60, and 300 ng/mL TU) was equal and was 1% v/v. The T concentration in unspiked samples (i.e., spiked with 0 ng/mL TU; methanol only) served as the true baseline for each subject.

The spiked blood samples were incubated for 30 or 60 minutes. Plain tubes were incubated at room temperature. NaF/EDTA tubes were incubated at room temperature or on ice. At the end of the incubation, the tubes were centrifuged and the matrix (serum or plasma) was removed and frozen.

The concentrations of T and TU were determined in the serum or plasma samples using the same validated LC-MS/MS methods used in Study CLAR-18019. See Section 4.1.1 of this review for details. Table A-2-2 summarizes the run time assay characteristics based on the QC samples.

Table A-2-2: Summary of Accuracy and Precision Assessments for T and TU Measurements

Parameter	Testosterone	Testosterone	Testosterone Undecanoate	Testosterone Undecanoate
Sample Matrix	Plasma (NaF-EDTA)	Serum (Plain Tube)	Plasma (NaF-EDTA)	Serum (Plain Tube)
Calibration Standards	10 to 3000 ng/dL	10 to 3000 ng/dL	1 to 1000 ng/mL	1 to 1000 ng/mL
LLOQ	10 ng/dL	10 ng/dL	1 ng/mL	1 ng/mL
Accuracy[a]	97.68% to 100.51%	99.37% to 100.86%	100.56% to 106.67%	95.47% to 100%
Between Run Precision (CV)	2.34% to 3.67%	1.50% to 3.15%	2.75% to 3.44%	2.82% to 4.33%

CV = coefficient of variation; EDTA = ethylenediaminetetraacetic acid; LLOQ = lower limit of quantitation; NaF = sodium fluoride, TU= testosterone undecanoate

[a] Accuracy presented as 100 + % bias in Syneos CLAR-18021 Bioanalytic Report Methods Validation Summary

Reviewer's Comment: *The acceptance criteria and performance of the total T and TU bioanalytical methods were in compliance with the Agency's Bioanalytical Method Validation Guidance and are found to be acceptable.*

Results:

Targeted and Measured TU Concentrations

TU (in methanol) was added to whole blood such that the amount of TU added was 0, 60, or 300 ng/mL of blood, concentrations which approximated interpolated TU concentration in plasma (or serum) at 5 hours post-dose (60 ng/mL) and at C_{max} (300 ng/mL) in a subset of subjects from Study CLAR-09007. Table A-2-3 presents the TU concentrations measured in the serum and plasma isolated from the plain and NaF/EDTA tubes, respectively.

Table A-2-3: TU Concentrations in Serum and Plasma Isolated from Blood in Plain and NaF/EDTA Tubes After Addition of 60 or 300 mg TU per mL of Blood

Tube Type	Plain				NaF-EDTA							
Temperature	Room Temperature				Room Temperature				On Ice			
TU spiked into blood (ng/mL)	60	60	300	300	60	60	300	300	60	60	300	300
Time (minutes)	30	60	30	60	30	60	30	60	30	60	30	60
N	18	18	18	18	18	18	18	18	18	18	18	18
Concentration of TU measured in matrix (ng/mL)	Serum				NaF-EDTA Plasma							
Mean	82	83	415	422	69	71	353	357	75	76	379	382
Standard deviation	7.2	7.3	30	34	5.3	4.6	30	28	13	9.7	56	52
Median	82	81	414	419	69	71	353	356	73	73	379	364

EDTA = ethylenediaminetetraacetic acid; NaF = sodium fluoride, TU= testosterone undecanoate

Reviewer's Comment: *The TU concentrations measured in the serum and plasma were greater than the concentration of TU spiked into the whole blood. The Sponsor provided the following explanation:*

"In these experiments, a stock solution of TU in methanol was added to whole blood to a final concentration of 1% volume TU stock solution to volume whole blood (v/v). The amount of TU added assumed that the TU would be equally distributed throughout the whole blood volume. Because whole blood is not a homogeneous solution (e.g., part of the volume is fluid and the other part is cellular with the intracellular space not necessarily accessible to a solute due to the cell membrane), some solutes cannot access the entire blood volume (e.g., they are excluded or partially

excluded from intracellular compartments). TU has an 11-carbon hydrophobic tail which limits its ability to enter cells. Thus, in the in vitro experiments, the volume of distribution of TU in whole blood is < 100% of the blood volume. Since the volume of distribution is smaller than the entire blood volume, the concentration in the accessible volume is greater than the calculated spiked concentration. As a result, the TU concentrations in the serum or plasma isolated from the blood were higher than the predicted concentration at 5 hours post-dose (C_5) and C_{max}."

It appears that this observation does not affect the validity of the study as all calculations from this study were performed with measured TU concentrations.

Table A-2-4 summarizes the extent of T formation in each of the test conditions studied. For blood incubated at room temperature in either plain or NaF/EDTA tubes, longer incubation times resulted in greater increases in concentrations of T, meaning with a longer incubation time more of the TU was converted to T. There was not a substantial difference in T concentration with incubation time for the blood collected in NaF/EDTA tubes that were kept on ice. The extent of conversion at 60 minutes was somewhat less than double that during the first 30 minutes for both types of tubes incubated at room temperature (Table A-2-4). The extent of conversion during the second 30-minute incubation interval (30 minutes to 60 minutes) ranged between 40% and 85% of the extent of conversion during the first 30 minutes of incubation in the different tubes and incubation conditions. The decrease with time was greater in the NaF/EDTA tube kept on ice, than in either tube type kept at room temperature. This reduced rate of TU to T conversion might be due to the change (reduction) in esterase activity as the blood-sample cools from body temperature (37°C) to the incubation temperature, decreasing catalytic activity with time, or due to reductions in TU concentrations with elapsed incubation time.

The extent of conversion also depended substantially on the concentration of TU in the sample collection tube, with greater extents of conversion occurring at the higher TU concentration (Table A-2-4). The type of blood collection tube into which the TU was added was also a contributing factor, with the most conversion occurring in the plain tube at room temperature and less occurring in the NaF/EDTA tube held at room temperature. Temperature also was an important factor in the extent of TU to T conversion with a greater increase in T concentration in the NaF/EDTA tubes incubated at room temperature than those incubated on ice, with the least conversion occurring in the NaF/EDTA tube held on ice (Table A-2-4). This suggests that the decrease in incubation temperature from room temperature to on ice is a more important factor than the NaF inhibition of non-specific esterases in the reduction of TU to T conversion.

Table A-2-4: Comparison of TU to T Conversion Rate in Various Tube Types

Condition Tube Type (matrix), Temperature, TU	TU to T Conversion 0 to 30 minutes ΔT ng/dL/30 minutes	TU to T Conversion 30 to 60 minutes ΔT ng/dL/30 minutes	ΔT/ΔT Ratio 0 to 30 minutes/ 30 to 60 minutes
Plain (serum) at RT, 60 ng/mL TU	63.40	35.70	0.791
Plain (serum) at RT, 300 ng/mL TU	232.95	181.43	0.785
NaF-EDTA (plasma) at RT, 60 ng/mL TU	39.49	29.08	0.846
NaF-EDTA (plasma) at RT, 300 ng/mL TU	188.73	127.38	0.673
NaF-EDTA (plasma) on ice, 60 ng/mL TU	10.49	4.73	0.649
NaF-EDTA (plasma) on ice, 300 ng/mL TU	52.13	16.76	0.402

ΔT = change in testosterone concentration; EDTA = ethylenediaminetetraacetic acid; NaF = sodium fluoride; RT = room temperature; T = testosterone; TU = testosterone undecanoate

Reviewer's Comment: *The far-right column in Table A-2-4 should read as "ΔT/ΔT Ratio 30 to 60 mins/0 to 30 mins."*

The extent of TU to T conversion observed in different types of tubes at different incubation conditions (i.e., temperature and TU concentrations) are as summarized in Table A-2-5**.** This shows that the TU to T conversion depends on temperature, type of test tube (whether esterase inhibitor is present or not), and TU concentration.

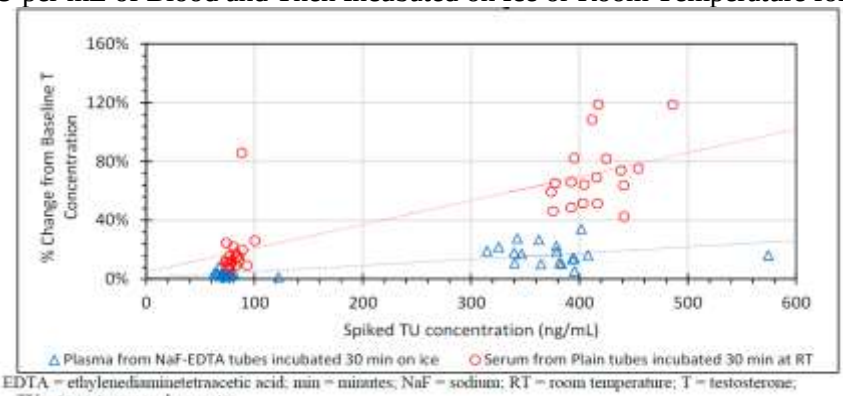
Table A-2-5: Extent of TU to T Conversion in Serum From Plain Tubes or Plasma From NaF/EDTA Tubes After Addition of 60 or 300 ng/mL TU and Incubated for 30 Minutes at Room Temperature or on Ice

Condition Tube (matrix), Temperature	TU 60 ng/mL		TU 300 ng/mL	
	Mean ΔT (ng/dL)	% of Initial TU	Mean ΔT (ng/dL)	% of Initial TU
Plain (serum), RT	63.40	1.21	232.95	0.88
NaF-EDTA (plasma), RT	39.49	0.90	188.73	0.84
NaF-EDTA (plasma), on ice	10.49	0.22	52.13	0.22

ΔT = change in testosterone concentration; EDTA = ethylenediaminetetraacetic acid; NaF = sodium fluoride; RT = room temperature; TU = testosterone undecanoate

Figure A-2-1 shows the 2 regression relationships as a combined graph and visually demonstrates the greater TU to T conversion in plain tubes at room temperature compared to the NaF/EDTA tubes on ice.

Figure A-2-1: Individual Data and Regressions for Percent Change From Baseline T Concentration in Plasma from NaF/EDTA Tube or Serum from Plain Tube After Addition of 60 or 300 ng TU per mL of Blood and Then Incubated on Ice or Room Temperature for 30 Minutes



EDTA = ethylenediaminetetraacetic acid; min = minutes; NaF = sodium; RT = room temperature; T = testosterone; TU = testosterone undecanoate

Conclusions:

Longer incubation time, increased incubation temperature, and increased TU concentration all increase the extent of conversion. The rate of TU to T *ex vivo* conversion is slowed by collection of the blood into tubes containing NaF/EDTA. However, lowering of the incubation temperature from room temperature to "on ice" results in an even greater slowing of the rate of conversion. It is noted that the results in this *in vitro* spiking study show an apparently higher rate of TU to T conversion compared to the *in vivo* study CLAR-18019.

4.1.3 Correlation Study between Two Laboratories/Methods (CLAR-18020)

Title: Cross-Validation of T Assay in Human Serum and NaF/EDTA Plasma Matrices Between Two Bioanalytical Laboratories

Primary Objective:
To cross-validate T assays using human serum collected in plain tubes and human plasma collected in NaF/EDTA tubes between two bioanalytical laboratories. Two bioanalytical laboratories performed study sample analyses: [redacted] (currently known as [redacted] and referred to as [redacted] in this report) and [redacted] A cross-validation was to be performed to compare the results from both labs, for both biological matrices.

Reviewer Comments: *These two laboratories performed T bioanalysis which supported clinical trials for this NDA. However, only one laboratory [redacted]) performed all the T bioanalysis that supported the pivotal Phase 3 trial CLAR-15012.*

Bioanalytical Study Centers: [redacted]

Study Design:
Twenty (20) serum samples and 20 NaF/EDTA plasma samples from 40 adult males were obtained commercially, and then each sample was divided into two aliquots (one for each lab). Each of the 40 samples was then analyzed for endogenous T in duplicate by the two bioanalytical labs, [redacted] and [redacted] using validated LC-MS/MS methods. After both laboratories had completed their analysis, the results were compared.

Primary Endpoint:
Confirmation of reproducible results of T concentrations obtained from LC-MS/MS methods from identical samples and run on two different matrices (serum and plasma) at two different labs is established when the coefficient of determination (r^2) is ≥ 0.9800.

Bioanalytical Methods:
The description of the LC-MS/MS method used at [redacted] can be found in Section 4.1.1 (Study CLAR-18019) of this review.

The following is a description of a LC-MS/MS method at the [redacted]

T was extracted from plasma by LLE. The extracted samples were dried under a stream of nitrogen, the residue was reconstituted. Reconstituted sample extracts were analyzed using a Shimadzu HPLC System equipped with an Applied Biosystems Sciex API 5500 triple quadrupole mass spectrometer. Chromatographic separation was performed on a Thermo Hypersil, 100 x 1.0 mm, 3 µm-column for T using gradient elution. Positive ions generated from the electrospray ion source were detected using the MRM mode. Quantitation was performed using a weighted linear regression (1/concentration^2) of the determined peak area ratios for T and T-d_2 (IS). The LC-MS/MS method was developed and validated with the dynamic range of 2-2,000 ng/dL for total T. Calibration standards and QC samples for T were prepared in serum collected in plain tubes or human NaF/Na_2EDTA plasma.

A summary of method validation parameters from methods used at the two bioanalytical laboratories are presented in Table A-3-1.

Table A-3-1: Validation Parameters for T Methods Performed at Two Bioanalytical Laboratories

Parameter	Human NaF-EDTA Plasma		Human Serum	
	(b) (4)			
Calibration Range	10.0 to 3000 ng/dL (100.00 to 30000.00 pg/mL) LLOQ at 10 ng/dL	2.0 to 2000 ng/dL LLOQ at 2.0 ng/dL	6.0 to 1200 ng/dL (60.00 to 12000.00 pg/mL) LLOQ at 6 ng/dL	2.0 to 2000 ng/dL LLOQ at 2.0 ng/dL
Selectivity	No significant interference observed in 6 out of 6 tested matrices for the internal standard. Tested matrices included one hyperlipemic matrix and one 5% hemolysis matrix	**Interference from:** Blank Matrix: No T measured Other steroids: <LLOQ, no interference Tubes: <7% CV Drugs: < 2ng/dL **Matrix Effect:** T (recovery %): 89.7% D2T (recovery %): 88.9%	No significant interference observed in 8 out of 8 tested matrices for the internal standard. Tested matrices included one hyperlipemic matrix and one 5% hemolysis matrix	**Interference from:** Blank Matrix: No T measured Other steroids: <LLOQ, no interference Tubes: <7% CV Drugs: < 2ng/dL **Matrix Effect:** T (recovery %): 87.3 ± 6.3% D2T (recovery %): 79.6 ± 8.4%
Between Run Accuracy & Precision	**Biases:** -4.25 to -1.16% CV: 4.70 to 8.52%	**Biases:** -5.4 to +11%[a] **CV:** 7.9% to 11.9%[b]	**Biases:** -7.16 to -1.91% **CV:** 4.25 to 7.89%	**Biases:** -6.5 to +7%[c] **CV:** 6.2 to 9.9%[d]
Within Run Accuracy & Precision	**Biases:** -7.18 to -0.56% **CV:** 0.76 to 1.21%	**Biases:** -15 to +16.5%[e] **CV:** 1.4 to 1.9%[f]	**Biases:** -5.16 to -1.18% **CV:** 0.90 to 1.54%	**Biases:** -19.1 to +16.2%[g] **CV:** <2.0% to <4.0%[h]

[a] Accuracy: QC1 (6.6 ng/dL): 94.8%, QC2 (152 ng/dL): 100%, QC3 (502 ng/dL): 102%, QC4 (902 ng/dL): 111%, QC5 (1502 ng/dL) 107%
[b] Precision: QC1 (6.6 ng/dL): 11.9%, QC2 (152 ng/dL): 7.9%, QC3 (502 ng/dL): 8.3%, QC4 (902 ng/dL) : 9.3%, QC5 (1502 ng/dL) : 8.7%
[c] Accuracy: QC1 (6.2 ng/dL): 93.5%, QC2 (12.4 ng/dL): 107%, QC3 (512 ng/dL): 102.5%, QC4 (912)ng/dL): 99.3%, QC5 (1512 ng/dL) 94.7%
[d] Precision: QC1 (6.2 ng/dL): 9.9%, QC2 (12.4 ng/dL): 8.5%, QC3 (137 ng/dL): 6.6%, QC4 (512 ng/dL) : 6.2%, QC5 (912 ng/dL) : 7.9%, QC6 (1512 ng/dL): 7.2%
[e] Accuracy: QC1 (6.6 ng/dL): 85% - 109.8%, QC2 (152 ng/dL):90.8% - 105.9%, QC3 (502 ng/dL): 92% - 107.8%, QC4 (902 ng/dL):109.6% - 115.3%, QC5 (1502 ng/dL): 99.2% - 116.5%
[f] Precision: QC2 (152 ng/dL): 1.9 %, QC3 (502 ng/dL) : 1.4%, QC4 (902 ng/dL) : 1.7%
[g] Accuracy: QC1 (6.2 ng/dL): 80.9 - 107.3%, QC2 (12.4 ng/dL):103.9 - 112.7%, QC3 (512 ng/dL): 96.4 - 116.2%, QC4 (912)ng/dL): 93.0 - 109.8%, QC5 (1512 ng/dL): 89.9 - 104.4%
[h] Precision: QC2 (12.4 ng/dL): < 4.0 %, QC4 (512 ng/dL) : < 2.9%, QC5 (912 ng/dL) : < 2.0%
[i] Final Bioanalytical Report: A Phase 3, Randomized, Active-Controlled, Open-Label Study of the Safety and Efficacy of Oral Testosterone Undecanoate (TU) in Hypogonadal Men
[j] Validation of a High Performance Liquid Chromatographic Method Using Tandem Mass Spectrometry Detection and Automated Extraction for the Determination of Testosterone (60 to 12000 pg/mL) in Human Serum
[k] Bioanalytical Report: (b) (4)

Reviewer's Comment: *The bioanalytical methods for T are in compliance with the Agency's Bioanalytical Method Validation Guidance and are found to be acceptable.*

All data points fell on or very close to the linear regression lines (Figure A-3-1 plot of serum T concentrations; Figure A-3-2 plot of the NaF/EDTA plasma T concentrations). The correlation of the T concentrations of the 20 serum samples from the 2 labs was very high with a correlation coefficient of r=0.995 (r^2=0.989). The correlation of the T concentrations of the 20 NaF/EDTA plasma samples from the two labs was also very high as evidenced by a correlation coefficient of r=0.997 (r^2=0.994). This confirms that the T assays in both labs yielded essentially identical results.

Figure A-3-1: Linear Regression of T Concentrations Measured in Serum

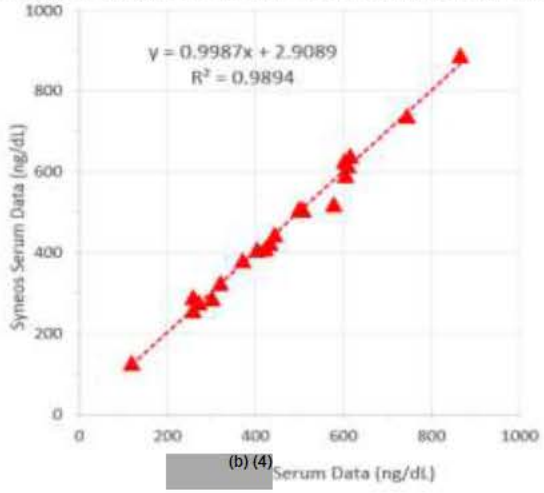


Table A-3-2: Correlation of Serum T Concentration Measured at [(b) (4)] and [(b) (4)] Laboratories

	Bioanalysis Laboratory	
Statistic	[(b) (4)]	
N	20	20
Mean (ng/dL)	463.94	461.65
SD (ng/dL)	184.30	183.56
Coefficient of determination (r^2)	0.9894	
Correlation coefficient (r)	0.9947	

Figure A-3-2: Linear Regression of T Concentrations Measured in NaF/EDTA Plasma

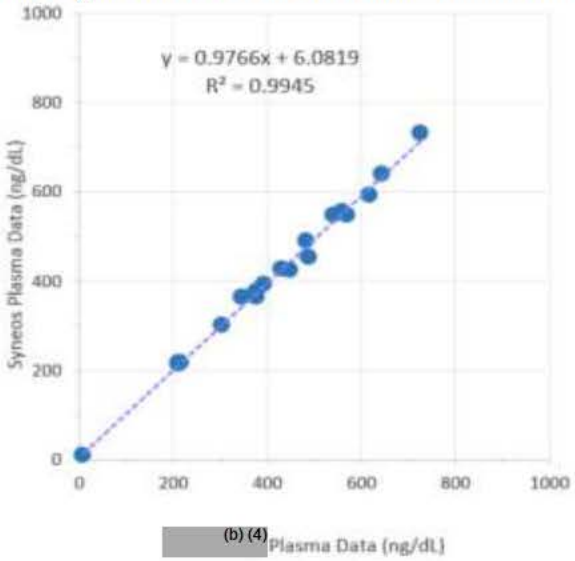


Table A-3-3: Correlation of Serum T Concentration Measured at [(b) (4)] and [(b) (4)] Laboratories

	Bioanalysis Laboratory	
Statistic	[(b) (4)]	
N	20	20
Mean (ng/dL)	412.60	416.27
SD (ng/dL)	170.16	173.75
Coefficient of determination (r^2)	0.9945	
Correlation coefficient (r)	0.9972	

Conclusions:

In this study, 20 serum samples and 20 NaF/EDTA samples were assayed in each laboratory using their validated LC-MS/MS methods. Correlation between the 20 serum samples and 20 NaF/EDTA plasma samples demonstrated an r^2=0.989 and 0.994, respectively. T values measured by LC-MS/MS in either serum or NaF/EDTA plasma matrix by either [(b) (4)] or [(b) (4)] yield essentially identical results.

4.1.4 TU to T ex vivo Conversion Study Following Andriol® Administration (CLAR-18016)

Reviewer's Comment: *The Sponsor conducted Study CLAR-18016 to follow up on the discussion at the January 9-10, 2018 Bone, Reproductive, and Urologic Drugs Advisory Committee (BRUDAC) meetings. The study report was submitted on February 27, 2018 and reviewed prior to the current review cycle. Reference is made to Dr. Chongwoo Yu's Clinical Pharmacology review dated June 29, 2018 under NDA 206089 (SDN: 055) in DARRTS. A summary from the referenced review is listed below.*

It should be noted that this study has the following limitations:

- *There were no assessments for NaF/EDTA tubes at room temperature.*
- *There was no t=0 sample collected for NaF/EDTA tubes.*
- *This study did not use JATENZO (used ANDRIOL instead).*

It should be noted that a new study (CLAR-18019; Section 4.1.1 of this review) was conducted to addressing these limitations.

4.1.5 TU Cross-reactivity Study (CLAR-18018)

Title: Assessment of the Cross-reactivity of TU with T in Commonly Used Immunoassays

Objective: To determine whether TU cross-reacts with T in several FDA-approved, commercially-available immunoassays

Study Design:
TU was dissolved in methanol (final concentration 1 mg/mL) and allowed to stand shaking overnight to ensure TU is completely dissolved. TU (in small amounts of methanol) was added to 20 mL charcoal-stripped serum and 20 mL pooled human male serum to attain the final concentration of TU at 0, 5, 10, 20, 40, 80, 160, and 320 ng/mL (Table A-5-1). 1.0 ml aliquots of the serum were prepared in plastic tubes and tightly capped before freezing. Tubes were labeled with barcodes without indication of the concentration of TU in the tube.

Duplicate tubes for T measurements were sent packed in dry ice with a manifest of the samples to:

- [redacted] (b) (4) using Siemens Centaur Siemens ADVIA Centaur Testosterone II (TSTII)
- [redacted] (b) (4) using Beckman Dxl ACCESS Testosterone
- [redacted] (b) (4) using Abbott ARCHITECT 2nd Generation Testosterone
- [redacted] (b) (4) using Roche Elecsys Testosterone II
- [redacted] (b) (4) using LC-MS/MS

Serum TU Concentration Measurements:
Table A-5-1 showed the measured TU concentrations in the charcoal stripped and male serum samples that were spiked with known concentrations of TU. The results showed that the amount measured in the serum accurately reflected what was added to the serum (0 to 320 ng/mL) with an average difference of 5%.

Table A-5-1: Serum TU (ng/mL) Measured in Serum Spiked with TU

	Serum TU measure ng/ml					
TU added (ng/ml)	Charcoal stripped	Charcoal Stripped	Male Serum	Male Serum	Average	% Difference
0	<2	<2	<2	<2	0.00	0.00
5	3.7	3.76	5.66	6.32	4.86	-2.80
10	10.4	9.61	10.3	11.8	10.53	5.28
20	21.4	21.3	25.8	21.7	22.55	12.75
40	45.5	43.7	48.3	46.9	46.10	15.25
80	85.3	87.9	98.3	79	87.63	9.53
160	152	166	170	170	164.50	2.81
320	290	332	321	308	312.75	-2.27

Serum T Concentration Measurements:
Table A-5-2 showed the serum T data measured by different immunoassays listed by each method. The results showed that the QC samples for each of the T immunoassays were within range (± 15%) of the spiked QC samples (shown in green in table) sent to each laboratory indicating the reproducibility of T results across immunoassays except for the very low T concentration (6 ng/dL) and high T concentration of 1,500 ng/dL. Charcoal stripped serum spiked with increasing

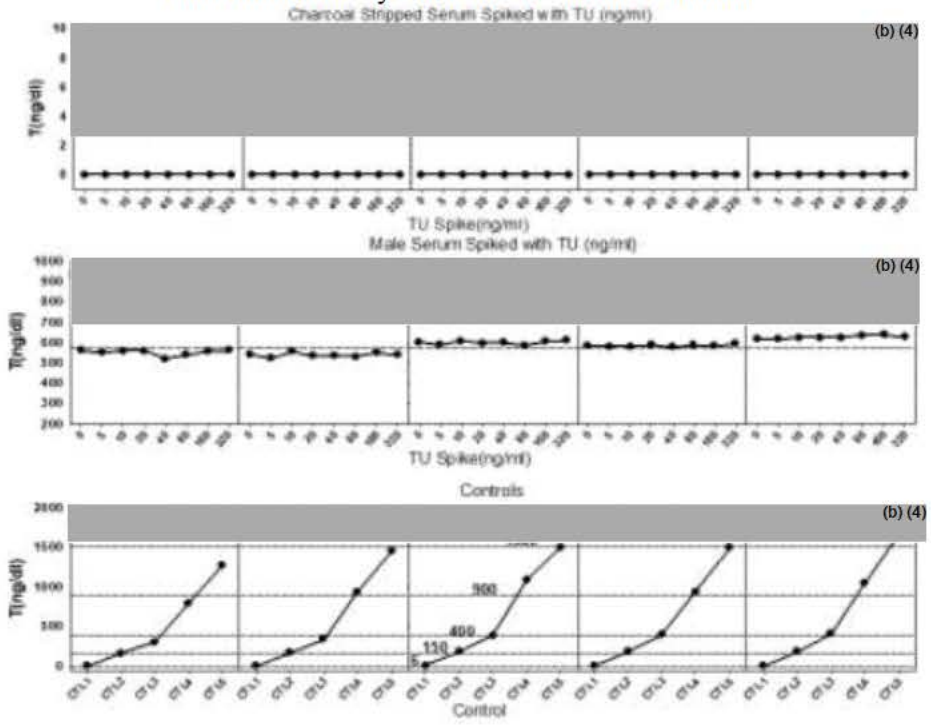
concentrations of TU showed no detectable concentrations of T (all samples were below LLOQ of each assay). Male serum sample spiked with TU showed no change in serum T concentration after spiking with increasing concentration of TU.

Table A-5-2: Serum TU (ng/mL) Measured in Serum Spiked with TU

				Serum T ng/dL				(b) (4)
Sapmple	T ng/dL added or measured prior to shipping	TU ng/mL Spike	Tubes					
Control 1	6	0	1	<10	<10	6.8 (113%)	<2.5	<2
Control 2	150	0	1	164 (109%)	175 (117%)	187 (125%)	185 (123%)	187 (125%)
Control 3	400	0	1	308 (77%)	344 (86%)	392 (98%)	395 (99%)	411 (103%)
Control 4	900	0	1	796 (88%)	939 (104%)	1091 (121%)	941 (105%)	1050 (117%)
Control 5	1500	0	1	1275 (83%)	1451 (97%)	>1500	1496 (100%)	1660 (111%)
% of Control				89.30%	101%	114%	107%	114%
Charcoal		0	1	<10	<10	<4.3	<2.5	<2
Charcoal		0	2	<10	<10	<4.3	<2.5	<2
Charcoal		5	1	<10	<10	<4.3	<2.5	<2
Charcoal		5	2	<10	<10	<4.3	<2.5	<2
Charcoal		10	1	<10	<10	<4.3	<2.5	<2
Charcoal		10	2	<10	<10	<4.3	<2.5	<2
Charcoal		20	1	<10	<10	<4.3	<2.5	<2
Charcoal		20	2	<10	<10	<4.3	<2.5	<2
Charcoal		40	1	<10	<10	<4.3	<2.5	<2
Charcoal		40	2	<10	<10	<4.3	<2.5	<2
Charcoal		80	1	<10	<10	<4.3	<2.5	<2
Charcoal		80	2	<10	<10	<4.3	<2.5	<2
Charcoal		160	1	<10	<10	<4.3	<2.5	<2
Charcoal		160	2	<10	<10	<4.3	<2.5	<2
Charcoal		320	1	<10	<10	<4.3	<2.5	<2
Charcoal		320	2	<10	<10	<4.3	<2.5	<2
Mean±SD	2.92±0.2			0±0	0±0	0±0	0±0	0±0
Male		0	1	574	535.83	596.5	588.1	624
Male		0	2	550	550.57	610.7	576.8	611
Male		5	1	568	526.61	593.4	579	634
Male		5	2	534	521.29	587.7	581.9	599
Male		10	1	525	557.22	611.5	578.6	632
Male		10	2	594	554.74	606.6	582.6	620
Male		20	1	555	532.09	603.6	586	616
Male		20	2	561	535.47	590.3	592.4	634
Male		40	1	518	526.97	598.1	579.8	619
Male		40	2	521	549.08	603.6	575.8	633
Male		80	1	533	522.69	586.6	588.4	641
Male		80	2	548	538.8	585.7	587.2	633
Male		160	1	523	535.32	598.1	576.2	646
Male		160	2	590	569.27	614	591.6	633
Male		320	1	563	537.62	607	594.5	628
Male		320	2	559	542.9	614.5	593.5	629
Mean±SD	569±16.7			551±23.9	539.8±13.4	600.5±9.9	584.5±6.5	627±11.8

The graphical representation of the data showed clearly that serum T concentrations were not affected by the spiking of charcoal stripped (upper panel) or male (middle panel) serum samples with 0 to 320 ng/mL of TU in any of the immunoassay methods tested. The lower panel showed the QC samples sent to each laboratory and showed good reproducibility across immunoassays (Figure A-5-1).

Figure A-5-1: Serum T Concentrations in Charcoal Stripped Serum (Upper Panel), Male Serum (Middle Panel), and QC Samples (Lower Panel) Measured in Four Immunoassays and One LC-MS/MS Method



T levels < laboratory LLOQ are shown as 0 (ng/ml)

Conclusions:
The results from the *in vitro* spiking of serum samples with increasing amounts of TU showed no cross reactivity in four different commonly used immunoassays to measure serum T.

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OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA: 206089	Submission Dates: 6/22/2017, 8/8/2017, 8/15/2017, 8/17/2017, 9/8/2017, 9/25/2017, 9/26/2017, 10/3/2017, 10/30/2017, 11/13/2017, 11/22/2017, 11/24/2017, 12/5/2017, 12/18/2017, and 12/19/2017
Proposed Brand Name	JATENZO
Generic Name	Testosterone undecanoate (TU)
Clinical Pharmacology Primary Reviewer	Chongwoo Yu, PhD
Clinical Pharmacology Secondary Reviewer	Doanh Tran, PhD
Pharmacometrics Primary Reviewer	Dhananjay Marathe, PhD
Pharmacometrics Secondary Reviewer	Jingyu Yu, PhD
OCP Signatory	Gilbert Burckart, PharmD
OCP Divisions	Division of Clinical Pharmacology 3 (DCP3) and Division of Pharmacometrics
OND Division	Division of Bone, Reproductive, and Urologic Products (DBRUP)
Sponsor	Clarus Therapeutics
Submission Type	Resubmission / 505(b)(1)
Relevant IND	IND 78104
Formulation, Strength, and Dosing Regimen	Oral soft-gel capsules; 158 mg, 198 mg, 237 mg; twice daily (BID) in the morning and in the evening with food (starting dose is 237 mg TU BID and can be titrated up to 396 mg or down to 158 mg TU BID)
Indication	Treatment of male hypogonadism (i.e., primary and hypogonadotropic hypogonadism)

Table of Contents

1 EXECUTIVE SUMMARY

The original NDA 206089 was submitted on January 3, 2014 and upon completion of review, the Division took a Complete Response (CR) action on November 3 2014. On June 22, 2017, the Sponsor submitted a 505(b)(1) New Drug Application (NDA) resubmission for JATENZO, oral testosterone undecanoate (TU), as an oral testosterone replacement therapy (TRT) in adult males for conditions associated with a deficiency or absence of endogenous testosterone (T).

JATENZO is a soft gelatin capsule containing TU for oral use only and are available in three strengths: 158 mg, 198 mg, and 237 mg. A new starting dose and dose titration scheme was proposed for JATENZO in this resubmission. The recommended starting dose of JATENZO is 237 mg of TU, taken orally twice daily (BID), once in the morning with food and once in the evening with food (i.e., not on an empty stomach). To ensure proper dosing, the Sponsor is proposing that T concentrations should be measured in plasma from a blood sample collected in a sodium fluoride (NaF)/ethylenediaminetetraacetic acid (EDTA) tube drawn 3-5 hours after the morning dose and at least 7 days after starting treatment or following dose adjustment.

The clinical development program for JATENZO encompasses 10 completed studies including three Phase 3 studies (Studies CLAR-09007, CLAR-12011, and CLAR-15012) involving dose-titration that assessed the efficacy and safety of JATENZO. In addition, Study CLAR-12010 was a 1-year safety extension of treatment available to subjects who completed Study CLAR-09007.

To support the approval of JATENZO, the Sponsor submitted 4 Clinical Pharmacology/ Biopharmaceutics/Clinical studies in this resubmission which included one Phase 3, efficacy and safety study (CLAR-15012), a food effect study (CLAR-16015), a study evaluating the sample collection methodology (CLAR-15013), and a study to establish the eugonadal T concentration range based on the Sponsor's sample collection and bioanalytical methods (CLAR-16014). All four studies used the to-be-marketed (TBM) formulation and this review will focus on these 4 post-CR studies.

For the new pivotal Phase 3 study (Study CLAR-15012), a formal consult to the Office of Study Integrity and Surveillance (OSIS) was made on June 29, 2017. However, the Division of New Drug Bioequivalence Evaluations (DNDBE) within OSIS recommended to accept the bioanalytical data without on-site inspection as (b) (4) was inspected recently and the inspection outcome was classified as No Action Indicated (NAI). Reference is made to the OSIS Memorandum issued on August 21, 2017 in DARRTS. There are no pending bioanalytical or clinical site inspection issues.

1.1 Recommendation

The Office of Clinical Pharmacology (OCP)/Division of Clinical Pharmacology 3 (DCP-3) and Division of Pharmacometrics have reviewed NDA 206089 submitted on June 22, 2017, August 8, 2017, August 15, 2017, August 17, 2017, September 8, 2017, September 25, 2017, September 26, 2017, October 3, 2017, October 30, 2017, November 13, 2017, November 22, 2017, November 24, 2017, December 5, 2017, December 18, 2017, and December 19, 2017. The overall Clinical Pharmacology information submitted to support this NDA is **not acceptable** and JATENZO is **not recommended for approval** from the Clinical Pharmacology standpoint.

The following CR deficiency is identified from the Clinical Pharmacology perspective:

1. The Sponsor took an approach of measuring total T concentrations from plasma in

NaF/EDTA tubes instead of serum in plain tubes. The Clinical Pharmacology review team notes that in the Sponsor's Phase 3 study, CLAR-15012, samples collected in tubes containing NaF/EDTA were chilled on ice for 30 minutes and then centrifuged for 20 minutes before storage or analysis and in general, higher T concentrations were observed from serum in plain tubes compared to those from plasma in NaF/EDTA tubes following oral TU administration. However, based on the limited data submitted, the extent that NaF/EDTA tubes prevents TU to T *ex vivo* conversion is unknown. Further investigation on the rate and extent of the TU to T *ex vivo* conversion during the time course of plasma sample preparation is warranted to determine whether T concentration measurements from plasma in NaF/EDTA tubes in your Phase 3 study are reliable.

In order to address the identified deficiency, the Sponsor should conduct an additional *in vivo* study to compare the total T concentrations measured from serum in plain tubes and plasma in NaF/EDTA tubes at different time points (e.g., 0, 15, 30, 60, 90, and 120-minutes post-sample collection) using different temperature conditions (e.g., room temperature or on ice) to determine the rate and extent of the TU to T *ex vivo* conversion during the time course of plasma sample preparation.

Additional Comments

1. We note that there were no drug-drug interaction (DDI) study conducted with JATENZO. Considering that JATENZO is administered as TU orally and high systemic concentration of TU is observed, the DDI potential of TU should be addressed.
2. Due to the similarities in the chemical structure of T and TU and because of the high concentration of TU relative to T in patient specimens, it is possible that commonly used T immunoassays would significantly cross-react with TU causing an overestimation of T concentration values regardless of sample type. Provide data demonstrating the rate of TU cross-reactivity with commonly-used immunoassays. If you intend to propose the clinical use of a liquid chromatography – tandem mass spectrometry (LC-MS/MS) assay, you should submit a proposal for companion diagnostics.

1.2 Post-marketing Requirements or Commitments

None.

1.3 Summary of Important Clinical Pharmacology Findings

Overall Efficacy and Safety Conclusion: The efficacy of JATENZO was demonstrated successfully in hypogonadal males with the proposed dosing regimen. However, there were 4 subjects that had a total T C_{max} of > 2,500 ng/dL. Inspection of data shows that the high concentrations from 3 out of the 4 subjects are likely spurious and due to specimen contamination. Therefore, the Clinical Pharmacology review team does not believe that the total T C_{max} profile is a safety concern for JATENZO. It should be noted that these efficacy and safety conclusions are pending satisfactory resolution of issues related to potential TU to T *ex vivo* conversion.

Primary Efficacy Endpoint Analysis

The Sponsor conducted a new pivotal Phase 3 study (Study CLAR-15012) to demonstrate the clinical efficacy and safety of JATENZO. Study CLAR-15012 was a Phase 3, open-label, multicenter study conducted in 222 adult hypogonadal men, 24-65 years (mean: 51.6 years) of age. Study participants were randomized in a 3:1 ratio to JATENZO (166 subjects) or Axiron® (comparator; 56 subjects). One hundred fifty four (154) subjects (92.8%) and 49 subjects (87.5%) randomized JATENZO and Axiron®, respectively, completed the study.

Subjects randomly assigned to JATENZO began treatment at an oral dose of 237 mg TU BID. The need for dose titration for each subject was assessed based on the total T C_{avg} over 24 hours (i.e., derived based on plasma T concentrations from blood collected in NaF/EDTA tubes) at Days 21 and 56. Dose titrations occurred at Days 35 and/or 70, if needed.

The primary efficacy analysis was conducted based on the total T C_{avg} data collected on Day 105 with the following endpoints.

- 75% or more of patients having a plasma total T C_{avg} in the normal range of 252-907 ng/dL
- Lower limit of the 95% confidence interval (CI) being 65% or higher

The primary **efficacy analysis showed a responder rate of 87.3%** (145 responders out 166 subjects; 95% CI: 81.3%-92.0%) on Day 105. Responders were defined as subjects who had a plasma total T C_{avg} in the normal range of 252-907 ng/dL on Day 105. The **study results met the pre-specified efficacy criteria** of responder rate ≥ 75% and the lower bound of the 95% CI to be ≥ 65%.

Key Pharmacokinetic (PK) Safety Endpoint Analysis

The key PK safety endpoint, total T C_{max}, had the following pre-specified criteria that were expected to be met on Day 105:

- Having < 5% of subjects with a plasma total T C_{max} in the range of 1,800-2,500 ng/dL
- No subjects with a plasma total T C_{max} of > 2,500 ng/dL
- Having a plasma total T C_{max} ≤ 1,500 ng/dL in at least 85% of subjects

Table 1 presents the number and percentage of subjects with plasma total T C_{max} in each range on Day 105.

Table 1: Number (Percentage) of Subjects by Plasma Total T C_{max} in Adjusted Criteria Ranges at Day 105 (Subjects who had Total T C_{max} at Day 105; Study CLAR-15012)

Testosterone C_{max} Adjusted Range[a], n (%)	FDA Target	Oral TU (N = 151)	Topical Axiron (N = 48)
C_{max} ≤ 1361 ng/dL	≥ 85%	125 (82.8%)	47 (97.9%)
C_{max} > 1633 - 2268 ng/dL	≤ 5%	5 (3.3%)	1 (2.1%)
C_{max} > 2268 ng/dL	0	4 (2.6%)	0

Source: Post-text Table 14.2.2.1b

Abbreviations: C_{avg} = average concentration over 24 hours; C_{max} = maximum observed concentration over 24 hours; FDA = Food and Drug Administration; TU = testosterone undecanoate

[a] The adjustment factor was the ratio of 907 ng/dL to the typical eugonadal upper limit (ie, 907/1000 = 0.907).

As shown in Table 1, the following criteria of the secondary safety endpoint, total T C_{max} at Day 105 was **not** met:

- No subjects with a total T C_{max} of > 2,500 ng/dL
- At least 85% of subjects with a total T C_{max} ≤ 1,500 ng/dL

Inspection of data for the 3 out of 4 subjects that had a total T C_{max} of > 2,500 ng/dL shows that the high concentrations are likely spurious and due to specimen contamination. Therefore, the Clinical Pharmacology review team does not believe that the total T C_{max} profile is a safety concern for JATENZO.

Office of Scientific Investigations (OSI) consult: A formal consult to the OSI was made for clinical study site inspections and there are no unresolved inspection findings related to the approvability of JATENZO. Reference is made to Dr. Roy Blay's OSI Memorandum dated January 9, 2018

under NDA 206089 in DARRTS.

Formulation:
JATENZO is a soft gelatin capsule [redacted] (b) (4) are available in three strengths: 158 mg, 198 mg, and 237 mg TU.

Dose Titration Scheme
Phase 3 study dose titration scheme: In the pivotal Phase 3 study (Study CLAR-15012), the starting dose of JATENZO was 237 mg TU BID with potential for up titration to 316 mg and 396 mg BID or down titration to 198 mg and 158 mg BID. The need for dose titration for each subject was assessed based on the total T C_{avg} over 24 hours (i.e., derived based on plasma T concentrations from blood collected in NaF/EDTA tubes) at Days 21 and 56. Dose titrations occurred at Days 35 and/or 70, if needed.

If the plasma total T concentration was below 350 ng/dL, JATENZO dose was increased up to the next dose level and if the plasma total T concentration exceeded 800 ng/dL, JATENZO dose was decreased down to the next dose level.

Dose titration scheme proposed for labeling: While dose titration in the Phase 3 study, CLAR-15012 was based on the 24-hour total T C_{avg} (using 0-24 hour sampling), the development of a dose titration algorithm based on a single blood draw sample in the day time is warranted as a practical approach in clinical practice. Accordingly, the Sponsor proposed titration based on a single sample in the 3-5 hour post-morning dose window with same thresholds of T concentration (350 and 800 ng/dL) for up-/down-titration as that applied to C_{avg} in the Phase 3 study.

Following language is proposed by the Sponsor in the product label under Section (b) (4) *Dosing and Dose Adjustment*:

[redacted] (b) (4)

To justify that the outcome of the above two titration algorithms will be similar, the Sponsor used following two-step approach: 1) A concordance analysis using observed data for specific single blood draw samples (C_x) and C_{avg} in Phase 3 Study CLAR-15012 to justify that titration decisions based on C_{4h} post-morning dose are effective in maintaining T concentrations in the eugonadal T concentration range. 2) A population PK based modeling and simulation analysis to confirm that results of titration decisions based on C_{avg} and C_{4h} are comparable to using a 2-hour window for the status sample (i.e., $C_{3\text{-}5h}$).

The Clinical Pharmacology review team noted some limitations in the Sponsor's modeling and simulation approach and focused on observed results from the study for justification of an appropriate sampling window. Based on the observed concentration-time profiles for T, correlation analysis between C_x and C_{avg} and concordance analysis for C_x and C_{avg} based titration algorithms, the Clinical Pharmacology review team made the following observations:

- The comparison of C_x at different time points and C_{avg} showed that C_{6h} values most closely mimic C_{avg} values on a population and individual level.
- There was a relatively strong correlation between C_x and C_{avg} at 4 hour and 6 hour post-morning dose, while there was relatively weaker correlation at other time points such as 0, 2, 9, and 12 hour post-morning dose.

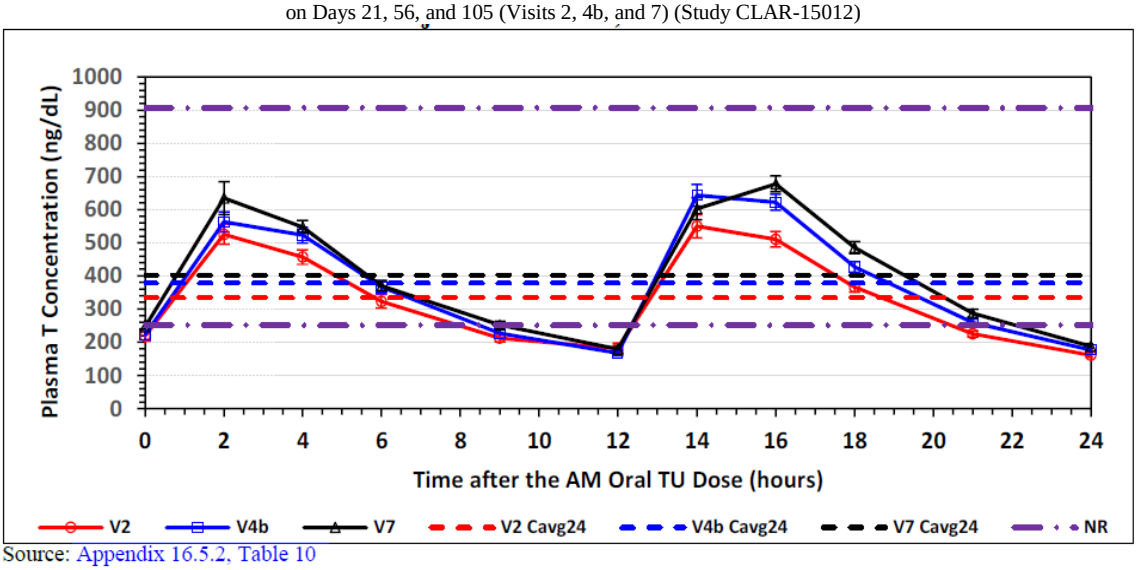
- In the concordance analysis, the numeric concordance (NC) and total concordance (TC) for both 4 h and 6 h sampling seemed reasonable (e.g., 64% and 88% for C_{4h} and 80% and 98% for C_{6h} for visit 2).
- Median T_{max} for this oral administration product is ~2 hour. So, a window of 3-5 hour is likely to have some samples that mimic C_{max} rather than C_{avg} for the same subject depending on the sampling time post-dose across different visits for the same dose. This may unduly influence titrations towards lower dose.
- On the other hand, a shallower PK profile over 4-6 hour time window means that it could likely yield less extreme measurement values and it would not be as sensitive to the sampling time for the same individual across different visits.

Based on this, the Clinical Pharmacology review team concludes that a 4-6 hour post-morning dose window for single blood draw sampling for titration decisions would be more appropriate than a 3-5 hour window proposed by the Sponsor, with titration thresholds of 350 and 800 ng/dL for up- and down-titrations. Refer to Section 2.2.8 and Section 4.2 of this review for further details regarding this issue.

Absorption

Mean concentration-time profiles for plasma total T for each of the 3 PK visits in the Phase 3, efficacy and safety study, CLAR-15012 are shown in Figure 1 for subjects administered with JATENZO. The mean concentrations include all study subjects at the particular visit; the results are not stratified by dose.

Figure 1: Mean (± SEM) Concentration-Time Profile for Plasma Total T in JATENZO-Treated Subjects on Days 21, 56, and 105 (Visits 2, 4b, and 7) (Study CLAR-15012)



Source: Appendix 16.5.2, Table 10

Abbreviations: AM = morning; C_{avg24} = time-weighted average plasma concentration morning and evening doses combined; NR = normal range; V2 = Visit 2; V4b = Visit 4b; V7 = Visit 7; SEM = standard error of the mean; T = testosterone; TU = testosterone undecanoate

Error bars indicate SEM

The mean PK parameters obtained on Day 105 (Visit 7) are summarized in Table 2. For JATENZO, these PK parameters are compiled separately for the morning and evening dosing intervals, and for the combined 24-hour interval as C_{max-am}, C_{max-pm}, C_{max24}, T_{max-am}, T_{max-pm}, AUC_{am}, AUC_{pm}, AUC_{24}, C_{avg-am}, C_{avg-pm}, and C_{avg24}. A 24-hour version of the mean T_{max} is not reported for JATENZO subjects because the T_{max} distribution of 24-hours is bimodal (i.e., one value for the morning dose and 1 value for the afternoon dose) and the mean of those 2 modes is generally a meaningless result.

Table 2: Summary of JATENZO and Axiron® Plasma Total T PK Parameters on Day 105 (Visit 7), by Treatment, for all Doses Combined (Study CLAR-15012)

Visit	PK Parameter	Units	Oral TU Subjects N	Oral TU Subjects Mean	Oral TU Subjects SD	Oral TU Subjects CV%	Topical Axiron Subjects N	Topical Axiron Subjects Mean	Topical Axiron Subjects SD	Topical Axiron Subjects CV%
Visit 7	$C_{max\text{-}am}$	ng/dL	155	773.3	584.03	75.5%				
	$C_{max\text{-}pm}$	ng/dL	151	838.4	368.55	44.0%				
	C_{max24}	ng/dL	151	1008.3	581.04	57.6%	48	664.0	319.23	48.1%
	$T_{max\text{-}am}$[a,b]	h	155	3.87[a]	(0.00, 12.08)		48	4.01[a,b]	(0.00, 24.00)	
	$T_{max\text{-}pm}$[a]	h	151	16.00[a]	(12.00, 24.02)					
	$C_{min\text{-}am}$	ng/dL	155	141.8	60.78	42.9%				
	$C_{min\text{-}pm}$	ng/dL	151	145.9	56.28	38.6%				
	C_{min24}	ng/dL	151	131.3	53.90	41.1%	48	214.7	88.15	41.1%
	AUC_{am}	ng•h/dL	155	4566.6	2066.16	45.2%				
	AUC_{pm}	ng•h/dL	151	5083.3	1661.32	32.7%				
	AUC_{24}	ng•h/dL	151	9659.1	3065.20	31.7%	48	9191.6	3152.69	34.3%
	$C_{avg\text{-}am}$	ng/dL	155	379.9	171.92	45.3%				
	$C_{avg\text{-}pm}$	ng/dL	151	424.6	139.23	32.8%				
	C_{avg24}[c]	ng/dL	151	402.5	127.72	31.7%	48	383.0	131.36	34.3%

[a] T_{max} values shown are median (range);
[b] Axiron T_{max} is relative to the AM dose since Axiron was applied just once daily, in the morning, $T_{max\text{-}am}$ and T_{max24} are interchangeable for Axiron
[c] C_{avg24} calculated after study completion using actual sample collection times
[d] C_{avg24} calculated for titration decisions as study was conducted, using nominal sample collection times (not done for Visit 7)
Source: Appendix B, Table B-1

Food Effect: The effect of food on the bioavailability (BA) of JATENZO was evaluated in Study CLAR-16015. When dosed with breakfasts containing various amounts of fat, BA among the 30 g fat, 45 g fat, or high-calorie high-fat breakfasts were comparable, but there was a food effect with the 15 g fat breakfast compared to the 30 g fat breakfast. The 15 g fat breakfast had a 25% decrease in total T exposure compared to the 30 g fat breakfast. Based on this study result, the Sponsor is proposing that JATENZO should be taken with food and not in a fasted state. Upon review of Studies CLAR-15012 and CLAR-16015, the Clinical Pharmacology review team agrees with the Sponsor's proposal.

Renal or Hepatic Impaired Patients: No studies were conducted in patients with renal or hepatic impairments.

Pediatric Use: No pediatric studies with JATENZO were conducted. The safety and efficacy of JATENZO in pediatric patients less than 18 years old have not been established. Improper use may result in acceleration of bone age and premature closure of epiphyses.

The Request for Waiver of Pediatric Studies was submitted in the original NDA 206089. The Pediatric Study Plan (PSP) was submitted to IND 78,104 on November 27, 2013, and a copy of the PSP was included in the original NDA 206089. The full pediatric waiver was granted on September 3, 2014.

Bioanalytical Methods

Plasma and serum samples were analyzed for total T and dihydrotestosterone (DHT) using validated LC-MS/MS methods. A formal consult to the OSIS was made for the bioanalytical study site (for Phase 3 study, CLAR-15012) inspection on [redacted] (b) (4) and the OSIS recommended to accept the bioanalytical data without on-site inspection as [redacted] (b) (4) was inspected recently and the inspection outcome was classified as NAI. Reference is made to the OSIS Memorandum issued on August 21, 2017 in DARRTS. There are no pending

bioanalytical site inspection issues.

The acceptance criteria and performance of the total T and DHT bioanalytical methods were in compliance with the Agency's *Bioanalytical Method Validation Guidance*. The method validation and performance of the bioanalytical methods in clinical studies are acceptable.

While the typical practice in the bioanalytical field has been to analyze T and DHT in human serum, the Sponsor took an approach of measuring total T concentrations from plasma in NaF/EDTA tubes instead of serum in plain tubes to minimize the potential TU to T *ex vivo* conversion during serum preparation from blood. In general, 14-17% higher T concentrations were observed from serum in plain tubes compared to those from plasma in NaF/EDTA tubes following oral TU administration which was consistent with literature reports of a negative bias of 11.7% (Lachance *et al*., 2015) to 20% (Wang *et al.*, 2008) when using NaF-containing tubes compared to total T concentrations measured from serum in plain tubes with no additives.

While the cause is unknown, it appears that potential contributing factors to this observed difference may include the contribution of (1) additives (i.e., NaF and/or EDTA); (2) TU to T *ex vivo* conversion; and/or (3) different sample handling and preparation procedures. It is also not known to what extent the use of NaF/EDTA tubes would inhibit TU to T *ex vivo* conversion. Further investigation on the rate and extent of the TU to T *ex vivo* conversion during the time course of plasma sample preparation is warranted in order to determine whether T concentration measurements from plasma in NaF/EDTA tubes in the Phase 3 study are reliable.

2 QUESTION BASED REVIEW

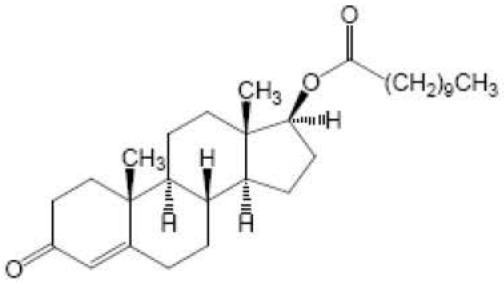
2.1 General Attributes

2.1.1 What is JATENZO and what is its active pharmacological ingredient?

JATENZO is a soft gelatin capsule [redacted] (b) (4) available in three strengths: 158 mg, 198 mg, and 237 mg TU.

TU is a fatty-acid ester prodrug of T. TU is a white to off-white yellow crystalline powder chemically described as 17β-hydroxyandrost-4-en-3-one undecanoate. The empirical formula of TU is $C_{30}H_{48}O_3$; the molecular weight is 456.7. The structural formula is presented in Figure 2.

Figure 2: Structural Formula of TU



Pharmacologically inactive ingredients in JATENZO are oleic acid, polyoxyl 40 hydrogenated castor oil (Cremophor RH 40), borage seed oil, peppermint oil, and butylated hydroxytoluene. The ingredients of the soft gelatin capsule shells are gelatin, sorbitol, glycerin, purified water, iron oxide red, FD&C Yellow #6, and titanium dioxide.

2.1.2 What is the regulatory history of JATENZO?

The original NDA 206089 was submitted on January 3, 2014 and upon completion of review, the Division took a CR action and the CR letter was issued to the Sponsor on November 3 2014.

Key issues specified in the Division's CR letter denying approval included:

- In the single-dose food effect study, the amount of fat content in meals influenced the absorption of TU, T, and DHT concentrations. Based on these data, Division stated that taking the product with food will not lead to consistent concentrations unless the fat content for every breakfast and every dinner is similar from day to day, which is not practical in the real world nor would we expect patients to always know the fat content of their meals.
- The primary efficacy endpoint in the Phase 3 study that tested the regimen proposed for marketing was narrowly met, but failed in sensitivity analyses when we attempted to account for missing data. To meet the primary efficacy endpoint, at least 75% of subjects were to achieve T C_{avg} in the normal range, and the lower bound of the corresponding 95% CI was to be at least 65%. In the Sponsor's prespecified analysis, 75.0% of subjects had C_{avg} for T in the normal range, and the lower bound of the corresponding 95% CI was 66.1%.

- In contrast, mean serum concentrations of DHT, a metabolite of T and potent androgen, were above the upper limit of the reference range. This did not appear consistent with the goal of TRT, which is to restore concentrations of T and its major metabolites to normal.
- None of the key secondary endpoints that assessed unacceptably high maximal exposures to T met the prespecified success targets.
- There were increases in blood pressure in the first Phase 3 study, with a larger blood pressure increase with JATENZO relative to the Androgel® 1% comparator. Blood pressure was also increased in the second Phase 3 study, but to a smaller degree than in the first study.
- In a toxicity study, dogs developed moderate to marked atrophy of the adrenal cortex with a possible reduction in serum cortisol, raising the possibility of adrenal insufficiency.

The Sponsor chose to address these concerns with a new randomized Phase 3 study that included an Axiron® comparator arm and a new food effect study. The new Phase 3 study included the following design features to address the previously identified Division's efficacy and safety concerns:

- A revised starting dose and titration regimen for JATENZO. Titration decisions were based on a PK parameter known as C_{avg}, which is a time-averaged T concentration based on PK sampling over 24 hours. This approach is not feasible in clinical practice so the Sponsor is proposing a single T concentration drawn several hours after the morning dose for clinical use.
- Ambulatory blood pressure monitoring to more precisely determine the effects of JATENZO on blood pressure.
- An adrenocorticotropin (ACTH) stimulation sub-study to screen for adrenal insufficiency.
- In addition to the new food effect study, the Sponsor analyzed the impact of fat content of meals on the PK results in the new Phase 3 study.

The Sponsor submitted their resubmission to NDA 206089 on June 22, 2017.

There were two advisory committee (AC) meetings held for this NDA. The first AC meeting was held on September 18, 2014 (https://wayback.archiveit.org/7993/20170404145836/https:/www.fda.gov/AdvisoryCommittees/Calendar/ucm406131.htm).
Four members voted for approval and 17 members voted against approval at the September 18, 2014 AC meeting. The Division agreed that the benefit/risk profile was not acceptable and did not approve the product due to the concerns outlined above.

The second AC meeting was held on January 9, 2018 (https://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/ReproductiveHealthDrugsAdvisoryCommittee/ucm585826.htm). The discussion topics presented by the Clinical Pharmacology team are summarized below.

Dose Titration Scheme for JATENZO
The review team's proposed time window of 4-6 hour post-morning dose for obtaining a single PK sample for titration/discontinuation based on the Sponsor's proposed thresholds of T concentration was noted to be reasonable by the panel.

The Use of NaF/EDTA Tubes for T Concentration Measurements
Committee members wanted to see more data to be convinced of the need to obtain T concentrations from plasma prepared in NaF/EDTA tubes instead of obtaining them from serum in the more

commonly used plain tubes, given that T concentrations would likely be used clinically in make decisions about dosing. There was interest in learning more about the potential cross-reactivity of TU with the immunoassays as they are commonly used to monitor patients on TRTs. Several AC panel members recommended that further investigation on the rate and extent of the TU to T *ex vivo* conversion during the time course of plasma sample preparation is warranted.

Overall Benefit/Risk Assessment of JATENZO

There was a consensus that JATENZO would likely be safe and efficacious for those with primary hypogonadism but that there is substantial concern about safety if the drug is prescribed to large numbers of men with age related hypogonadism. Committee members who voted for approval generally believed that off label risks could be mitigated through measures such as REMS programs, labeling, registries, and required practitioner education. Members who voted "No" were concerned about the scope of off-label use and its potential to cause widespread harm in terms of cardiovascular risks. Many members expressed how difficult a decision this was and how impressed they were with the need to provide another safe and effective treatment option for the men with primary hypogonadism. At the end, 9 members voted for approval and 10 members voted against approval at the January 9, 2018 AC meeting.

2.1.3 What are the relevant clinical data submitted to support the approval of JATENZO?

To support the approval of JATENZO, the Sponsor submitted 4 Clinical Pharmacology/ Biopharmaceutics/Clinical studies in this resubmission which included the following:

- CLAR-15012: Phase 3, efficacy and safety study
- CLAR-16015: Food effect study
- CLAR-15013: A study evaluating the sample collection methodology
- CLAR-16014: A study to establish the eugonadal T concentration range based on the Sponsor's sample collection and bioanalytical methods

All four studies used the TBM formulation.

In addition, the Sponsor submitted the following information:

- Draft labeling in physician labeling rule (PLR) format
- Bioanalytical study reports and method validation reports

2.2 General Clinical Pharmacology

2.2.1 What is the proposed mechanism of action?

Endogenous androgens, including T and DHT, are responsible for the normal growth and development of the male sex organs and for maintenance of secondary sex characteristics. These effects include the growth and maturation of prostate, seminal vesicles, penis, and scrotum; the development of male hair distribution, such as facial, pubic, chest, and axillary hair; laryngeal enlargement, vocal cord thickening, alterations in body musculature and fat distribution. T and DHT are necessary for the normal development of secondary sex characteristics. Male hypogonadism results from insufficient secretion of T and is characterized by low serum T concentrations. Signs/symptoms associated with male hypogonadism include erectile dysfunction and decreased sexual desire, fatigue and loss of energy, mood depression, regression of secondary sexual characteristics and osteoporosis.

Male hypogonadism has two main etiologies. Primary hypogonadism is caused by defects of the gonads, such as Klinefelter's Syndrome or Leydig cell aplasia, whereas secondary hypogonadism is the failure of the hypothalamus (or pituitary) to produce sufficient gonadotropins (i.e., follicle-stimulating hormone [FSH], luteinizing hormone [LH]).

The JATENZO formulation is designed to foster the absorption of TU via the intestinal lymphatics, thereby reducing first-pass hepatic metabolism. The androgenic activity of JATENZO occurs when the ester bond linking the T to the undecanoic acid is cleaved by endogenous non-specific esterases. Undecanoic acid is metabolized like all fatty acids via the beta-oxidation pathway.

2.2.2 What are the proposed dosing regimen and administration instructions?

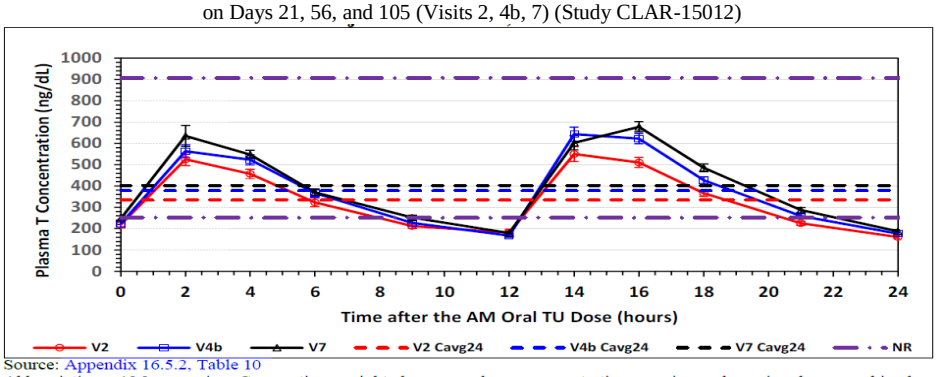
The recommended starting dose of JATENZO is 237 mg of TU, taken orally twice daily, once in the morning with food and once in the evening with food, immediately before breakfast and dinner. To ensure proper dose adjustment, T concentrations should be checked periodically.

2.2.3 What are the steady state PK parameters of total T following the administration of JATENZO?

Complete PK profiles of plasma total T on Days 21, 56, and 105 were characterized in the pivotal Phase 3 study (Study CLAR-15012) that was an open-label, multicenter study conducted in 222 adult hypogonadal men, 24-65 years (mean: 51.6 years) of age. Study participants were randomized in a 3:1 ratio to JATENZO (166 subjects) or Axiron® (56 subjects). 154 subjects (92.8%) and 49 subjects (87.5%) randomized JATENZO and Axiron®, respectively, completed the study. The starting dose was 237 mg TU BID and the dose of JATENZO was titrated based on the 24 hour plasma T C_{avg} on Days 14 and 56. The dose of JATENZO remained unchanged or was titrated up or down by Days 35 and 70, respectively. Blood samples for measurement of plasma T concentration were collected in NaF/EDTA tubes for all subjects at 30 minutes pre-dose and 0, 2, 4, 6, 9, and 12 hours post-morning dose and 2, 4, 6, 9, and 12 hours post-evening dose for the JATENZO cohort and at 30 minutes pre-dose and 0, 2, 4, 6, 9, 12, 14, 16, 18, 21, and 24 hours post-dose for the Axiron® cohort.

Mean concentration-time profiles for plasma total T for each of the 3 PK visits in the Phase 3, efficacy and safety study, CLAR-15012 are shown in Figure 3 for subjects administered with JATENZO. The mean concentrations include all study subjects at the particular visit; the results are not stratified by dose.

Figure 3: Mean (± SEM) Concentration-Time Profile for Plasma Total T in JATENZO-Treated Subjects on Days 21, 56, and 105 (Visits 2, 4b, 7) (Study CLAR-15012)



Source: Appendix 16.5.2, Table 10
Abbreviations: AM = morning; C_{avg24} = time-weighted average plasma concentration morning and evening doses combined; NR = normal range; V2 = Visit 2; V4b = Visit 4b; V7 = Visit 7; SEM = standard error of the mean; T = testosterone; TU = testosterone undecanoate
Error bars indicate SEM

The mean PK parameters obtained on Day 105 (Visit 7) are summarized in Table 3. For JATENZO, these PK parameters are compiled separately for the morning and evening dosing intervals, and for the combined 24-hour interval as $C_{max\text{-}am}$, $C_{max\text{-}pm}$, C_{max24}, $T_{max\text{-}am}$, $T_{max\text{-}pm}$, AUC_{am}, AUC_{pm}, AUC_{24}, $C_{avg\text{-}am}$, $C_{avg\text{-}pm}$, and C_{avg24}. A 24-hour version of the mean T_{max} is not reported for JATENZO subjects because the T_{max} distribution of 24-hours is bimodal (i.e., one value for the morning dose and 1 value for the afternoon dose) and the mean of those 2 modes is generally a meaningless result.

Table 3: Summary of JATENZO and Axiron® Plasma Total T PK Parameters on Day 105 (Visit 7), by Treatment, for all Doses Combined (Study CLAR-15012)

	PK		Oral TU Subjects				Topical Axiron Subjects			
Visit	Parameter	Units	N	Mean	SD	CV%	N	Mean	SD	CV%
Visit 7	$C_{max\text{-}am}$	ng/dL	155	773.3	584.03	75.5%				
	$C_{max\text{-}pm}$	ng/dL	151	838.4	368.55	44.0%				
	C_{max24}	ng/dL	151	1008.3	581.04	57.6%	48	664.0	319.23	48.1%
	$T_{max\text{-}am}$[a,b]	h	155	3.87[a]	(0.00, 12.08)		48	4.01[a,b]	(0.00, 24.00)	
	$T_{max\text{-}pm}$[a]	h	151	16.00[a]	(12.00, 24.02)					
	$C_{min\text{-}am}$	ng/dL	155	141.8	60.78	42.9%				
	$C_{min\text{-}pm}$	ng/dL	151	145.9	56.28	38.6%				
	C_{min24}	ng/dL	151	131.3	53.90	41.1%	48	214.7	88.15	41.1%
	AUC_{am}	ng•h/dL	155	4566.6	2066.16	45.2%				
	AUC_{pm}	ng•h/dL	151	5083.3	1661.32	32.7%				
	AUC_{24}	ng•h/dL	151	9659.1	3065.20	31.7%	48	9191.6	3152.69	34.3%
	$C_{avg\text{-}am}$	ng/dL	155	379.9	171.92	45.3%				
	$C_{avg\text{-}pm}$	ng/dL	151	424.6	139.23	32.8%				
	C_{avg24}[c]	ng/dL	151	402.5	127.72	31.7%	48	383.0	131.36	34.3%

[a] T_{max} values shown are median (range);
[b] Axiron T_{max} is relative to the AM dose since Axiron was applied just once daily, in the morning, $T_{max\text{-}am}$ and T_{max24} are interchangeable for Axiron
[c] C_{avg24} calculated after study completion using actual sample collection times
[d] C_{avg24} calculated for titration decisions as study was conducted, using nominal sample collection times (not done for Visit 7)
Source: Appendix B, Table B-1

2.2.4 Was there food effect observed with JATENZO and what is the proposed food intake instruction for JATENZO?

***Background*:** In the original NDA, the proposed starting dose was 200 mg T (316.6 mg TU as 2 x 158.3 mg TU capsules) BID to be administered with food (i.e., not on an empty stomach). The dose could be adjusted (up- or down-titrated) in 50 mg T increments to a maximum of 300 mg T (474.9 mg TU) BID or a minimum of 100 mg T (158.3 mg TU) BID. It should be noted that the proposed dosage regimen, options of different dose levels, and dose titration scheme in the new Phase 3 study are different from those used in the previous studies. The first food effect study (CLAR-09008) was conducted as a single dose study utilizing a higher dose of 300 mg T (474.9 mg TU as 3 x 158.3 mg TU capsules).

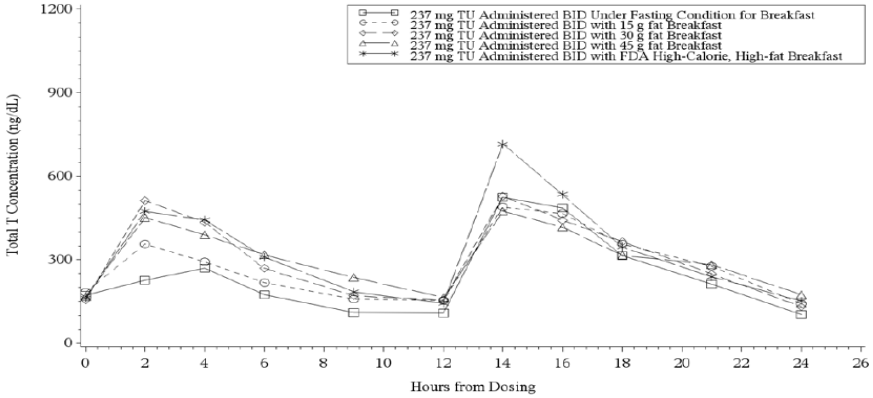
Sponsor's Investigation & Data: The Sponsor conducted a new (post-CR) open-label, randomized, 5-period crossover, food effect study (CLAR-16015) in 18 hypogonadal males to compare the effect of meals (i.e., breakfast) containing various amounts of fat on the total T exposure (C_{max} and AUC) when JATENZO (i.e., the TBM, soft gelatin capsule formulation) 237 mg was dosed immediately prior to the meal to mimic the dosing scheme used in this Phase 3 study (CLAR-15012). Reference is made to the Individual Study Review for Study CLAR-15012 for details on study design and outcome.

The study included a 14-day run-in phase, a 6-day PK phase, and a safety follow-up phase. During the 14-day run-in period, study participants received 237 mg TU orally BID immediately prior to meals. On each of the PK Phase Periods 1 through 5, the subject was orally dosed with 237 mg

TU immediately prior to the breakfast meal (or in the morning with 240 mL of water for the fasting period). Subjects were randomized to a sequence of 5 breakfast meals, 4 that varied primarily in fat content (i.e., 15 g/30 g/45 g with approximately 850 calories; and a high calorie, high-fat meal with approximately 1,000 calories, with 50% of the calories from fat) and one fasted sequence. The evening doses of 237 mg TU were taken immediately prior to dinner, all of which contained 30 g of fat. It should be noted that the 15 g, 30 g, and 45 g fat meals were meal options on PK days of the new Phase 3 study, CLAR-15012.

The post-breakfast concentration-time profiles (from 0 to 12 hours in Figure 4) following the 30 g fat, 45 g fat, and high-calorie, high-fat breakfast were similar, and the profile following dosing of JATENZO under fasted state was substantially lower. All of the dinner meals contained 30 g fat, and the concentration-time profiles for all the post-dinner meals were similar (from 12 to 24 hours in Figure 4), except when the high-calorie, high-fat breakfast was served. There was a higher arithmetic mean C_{max} during the post-dinner concentration-time curve for subjects who had a high-calorie, high-fat breakfast as compared to subjects who received lower-fat breakfasts.

Figure 4: Arithmetic Mean Plasma T Concentration-Time Profiles (Study CLAR-16015; Linear Scale; N=18)



Source: Post-text Figure 14.2.2.1.2
Abbreviations: BID = twice daily; FDA = Food and Drug Administration; PK = pharmacokinetic; T = testosterone; TU = testosterone undecanoate

The post-breakfast concentration-time PK profiles following the 30 g, 45 g, and high-calorie/high-fat breakfast were comparable while the BA of the 15 g fat breakfast was lower by about 25%.

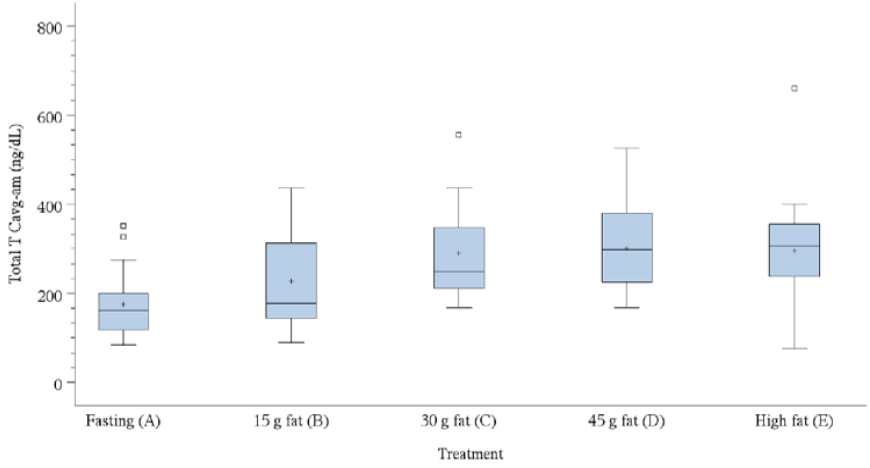
Table 4: Descriptive Statistics for Plasma Total T PK Parameters Following the Morning Dose with Different Breakfast Meal Types (Study CLAR-16015)

Pharmacokinetic Parameters	Oral TU Administered With Different Breakfast Meal Types									
	A Fasting		B 15 g Fat		C 30 g Fat		D 45 g Fat		E FDA (High Calorie, High Fat)	
	GM (GCV%)	n	GM (GCV%)	n	GM (GCV%)	n	GM (GCV%)	n	GM (GCV%)	n
$C_{max\text{-}am}$ (ng/dL)	250.7 (48.6)	18	334.7 (57.7)	18	529.7 (33.9)	18	506.0 (37.8)	18	463.4 (62.7)	18
AUC_{am} (ng•hr/dL)	1905 (45.2)	18	2428 (51.3)	18	3279 (33.6)	18	3395 (34.7)	18	3187 (52.8)	18
$T_{max\text{-}am}$ (hours)	4.000 (0.00, 4.17)	18	2.000 (0.00, 11.92)	18	2.000 (1.83, 6.00)	18	2.000 (1.97, 11.92)	18	2.000 (0.00, 6.00)	18
$C_{avg\text{-}am}$ (ng/dL)	160.0 (45.4)	18	203.7 (51.3)	18	275.1 (33.6)	18	285.1 (34.7)	18	267.3 (52.6)	18

Source: Post-text Tables 14.2.1.2.1, 14.2.1.2.2, 14.2.1.2.3, 14.2.1.2.4, and 14.2.1.2.5
Abbreviations: AM = morning; AUC_{am} = area under the concentration-time curve over the morning dosing interval; $C_{avg\text{-}am}$ = time-weighted average plasma concentration over the dosing interval following the morning dose; $C_{max\text{-}am}$ = maximum measured plasma concentration following the morning dose; FDA = Food and Drug Administration; GCV = geometric coefficient of variation; GM = geometric mean; n = number of observations used in the analysis; PK = pharmacokinetic; $T_{max\text{-}am}$ = time to reach $C_{max\text{-}am}$; TU = testosterone undecanoate
Note: $T_{max\text{-}am}$ is presented as median (minimum, maximum); AUC_{am}, $C_{max\text{-}am}$ and $C_{avg\text{-}am}$ are presented as GM and GCV%.

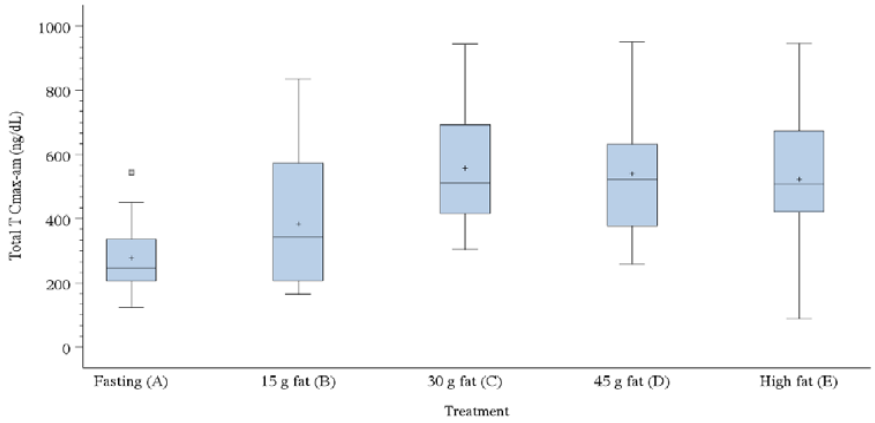
A visual examination of the variability in the PK parameters of C_{max} and AUC for T (Figures 5 and 6, respectively) shows that while there is significant variability in the presence of food and varying amount of fat content, the observed concentrations do fall within the expected range of T concentrations with treatment. Interestingly the observed variability seen with the FDA High Fat diet shows a "bias" towards lower values (excluding one outlier at approximately 650 ng/dL). However, as this diet is designed to "stress" a dosage form and not to mimic a normal diet this observation is not considered significant vis-a-vis chronic use.

Figure 5: Effect of Food on Plasma Total T $C_{avg\text{-}am}$ (Study CLAR-16015; N=18)



Treatment A: 237 mg TU Administered BID Under Fasting Condition for Breakfast
Treatment B: 237 mg TU Administered BID with 15 g fat Breakfast
Treatment C: 237 mg TU Administered BID with 30 g fat Breakfast
Treatment D: 237 mg TU Administered BID with 45 g fat Breakfast
Treatment E: 237 mg TU Administered BID with FDA High-Calorie, High-fat Breakfast
The upper and lower whiskers of the boxplot represent, respectively, the largest and smallest observed values within 1.5 × the interquartile range (IQR) from the upper and lower quartiles (Q3 and Q1). Values greater or smaller than the bounds represented by these whiskers are identified as extreme values.

Figure 6: Effect of Food on Plasma Total T $C_{max\text{-}am}$ (Study CLAR-16015; N=18)



Treatment A: 237 mg TU Administered BID Under Fasting Condition for Breakfast
Treatment B: 237 mg TU Administered BID with 15 g fat Breakfast
Treatment C: 237 mg TU Administered BID with 30 g fat Breakfast
Treatment D: 237 mg TU Administered BID with 45 g fat Breakfast
Treatment E: 237 mg TU Administered BID with FDA High-Calorie, High-fat Breakfast
The upper and lower whiskers of the boxplot represent, respectively, the largest and smallest observed values within 1.5 × the interquartile range (IQR) from the upper and lower quartiles (Q3 and Q1). Values greater or smaller than the bounds represented by these whiskers are identified as extreme values.

In the new Phase 3 study, CLAR-15012, subjects had a choice of 15 g, 30 g, or 45 g fat breakfasts and dinners at their PK visits. When subjects were asked to choose the meals for their PK visits, the selection criterion was "most similar to typical breakfast or dinner that you would eat most mornings (or evenings)." Once a subject made his meal choice, the same meal was used for all 3 PK visits (i.e., Day 21, 56, and 105). All subjects had a number of lunch options, which all had 30

g fat content and lunch composition was not incorporated into the analysis. On non-PK days during the study, subjects were not given special diet instructions regarding fat or calorie consumption for meals. Subjects were instructed to take JATENZO immediately prior to breakfast and dinner.

Out of the 105-day active treatment period, meals were not controlled for the 102 days (besides the 3 PK days). Efficacy (i.e., based on T C_{avg}) and safety (i.e., based on T C_{max}) were demonstrated for PK driven endpoints obtained on a single end of study PK visit day when meals were controlled. General safety (e.g., adverse events [AEs], and laboratory parameters) were obtained throughout the study.

Overall, the Sponsor proposes that JATENZO should be taken with food without further instructions on the fat content of meals. In general, the Clinical Pharmacology review team agrees with the conclusion of the Sponsor that as subjects cannot reliably estimate fat content in their diet that the subjects should be instructed to take the dosage form with their normal diet as was done in the Phase 3 studies.

2.2.5 How was the dose of JATENZO for the pivotal Phase 3 study determined?

The Sponsor's first Phase 3 clinical study, CLAR-09007, submitted in the original NDA, demonstrated that > 85% of subjects achieved serum T C_{avg} concentrations in the eugonadal range after 90 days of treatment; however, 13.7% (20/146) of subjects experienced maximum total T concentrations higher than desired. The Division has set targets for T C_{max} > 2,500 ng/dL at 0% of subjects and 5% of subjects with a T C_{max} of 1,800 to 2,500 ng/dL. Since the percentage of subjects with elevated C_{max} values did not align with the Division's targets for TRTs, the dose-titration algorithm was revised. PK modeling of results from Study CLAR-09007 led to the revised dosing algorithm that was used in Study CLAR-12011. At the final PK visit in Study CLAR-12011, 75.0% of the subjects had serum T C_{avg} values within the pre-specified eugonadal range for serum collected in plain tubes of 300-1,000 ng/dL. The frequency of high C_{max} values was substantially decreased. Approximately 3% of subjects had a C_{max} > 2,500 ng/dL and 6% of the subjects had a C_{max} of 1,800-2,500 ng/dL. In Study CLAR-12011, approximately 75% of the subjects' final TU dose was lower than the starting dose (316 mg TU BID); suggesting that a lower starting dose might reduce the likelihood that a subject was exposed to too high a dose prior to his first dose titration. PK modeling of the Study CLAR-12011 data, combined with the data from CLAR-09007, was used to further refine the dose-titration algorithm in the new Phase 3 study, CLAR-15012. Subjects randomly assigned to JATENZO in this study started with a dose of 237 mg TU BID, with the goal of having few subjects requiring a reduction in dose.

2.2.6 How was the efficacy and safety of JATENZO assessed and what were the results?

To address the identified CR deficiencies from the original NDA, the Sponsor conducted a new pivotal Phase 3 study (Study CLAR-15012) to demonstrate the clinical efficacy and safety of JATENZO. Study CLAR-15012 was a Phase 3, open-label, multicenter study conducted in 222 adult hypogonadal men, 24-65 years (mean: 51.6 years) of age. Study participants were randomized in a 3:1 ratio to JATENZO (166 subjects) or Axiron® (comparator; 56 subjects). One hundred fifty four (154) subjects (92.8%) and 49 subjects (87.5%) randomized JATENZO and Axiron®, respectively, completed the study.

A revised starting dose and titration regimen for JATENZO was employed in the new Phase 3 study. Subjects randomly assigned to JATENZO began treatment at an oral dose of 237 mg TU BID. The need for dose titration for each subject was assessed based on the total T C_{avg} over 24

hours (i.e., derived based on plasma T concentrations from blood collected in NaF/EDTA tubes) at Days 21 and 56. Dose titrations occurred at Days 35 and/or 70, if needed.

Overall Efficacy and Safety Conclusion: The efficacy of JATENZO was demonstrated successfully in hypogonadal males with the proposed dosing regimen. However, there were 4 subjects that had a total T C_{max} of > 2,500 ng/dL. Inspection of data shows that the high concentrations from 3 out of the 4 subjects are likely spurious and due to specimen contamination. Therefore, the Clinical Pharmacology review team does not believe that the total T C_{max} profile is a safety concern for JATENZO.

Primary Efficacy Endpoint Analysis

The primary efficacy endpoint in this study was consistent with that used in other studies for TRTs. The Sponsor needed to demonstrate that JATENZO achieves 24 hour C_{avg} for total T on Day 105 (i.e., end of treatment) within the normal eugonadal range for at least 75% of subjects and that the lower bound of the corresponding 95% CI for this point estimate is at least 65%. The primary efficacy endpoint, C_{avg}, was calculated from the AUC using the following formula and actual collection times were used in the calculation:

$$C_{avg} = AUC(0\text{-}24) / 24$$

To support the use of NaF/EDTA tubes in the new study, the Sponsor conducted a separate study (Study CLAR-16014) in 97 healthy males to derive the normal plasma T concentration range then applied that normal range to the primary efficacy endpoint in this study. The mean, calculated using natural-log transformed T concentrations, was 478 ng/dL; and the eugonadal range was determined as the exponential of the mean ±2 SDs of the population, namely 252 to 907 ng/dL. Reference is made to the Individual Study Review of Study CLAR-16014 (Section 4.1.4) in this NDA review. As shown in Table 5, the primary efficacy endpoint was achieved in this study.

Table 5: Percentage of Subjects With Total T C_{avg} Values in the Eugonadal Range on Day 105 (Visit 7) for Primary Analysis (Study CLAR-15012; Modified ITT Population)

Testosterone C_{avg} Range, n (%)	FDA Target	Oral TU (N = 166)	Topical Axiron (N = 55)
252 ng/dL ≤ C_{avg} ≤ 907 ng/dL[a]	≥ 75%	145 (87.3%)	48 (87.3%)
Lower bound 95% confidence interval	≥ 65%	81.3%	75.5%
Upper bound 95% confidence interval		92.0%	94.7%
C_{avg} mean (standard deviation) ng/dL		401.2 (140.2)	390.6 (139.9)
95% confidence interval		379.7, 422.7	352.8, 428.5

Source: Appendix 16.5.1, Table 3

Abbreviations: C_{avg} = average observed concentration over 24 hours; FDA = Food and Drug Administration; ITT = intention-to-treat; LOCF = last observation carried forward; TU = testosterone undecanoate

[a] Eugonadal range.

Note: The primary efficacy analysis treated all missing data as if the subject failed to achieve a Visit 7 plasma sample measurement in the eugonadal range unless the data were missing because of a cause not related to the study drug. For missing values not attributed to a study drug-related cause, the Visit 7 C_{avg} was imputed by LOCF and determined whether it was in the eugonadal range.

Reviewer Comment: *Modified intended-to-treat (ITT) population was used for the primary analysis and all sensitivity analyses. Modified ITT population included all subjects who actually received at least 1 dose of study drug. The 1 subject randomized to the Axiron® treatment arm who was never dosed was excluded from the Modified ITT,*

Three sensitivity analyses (LOCF, multiple imputation, imputation from baseline) were performed in addition to the primary analysis. All 3 sensitivity analyses provided an imputed T C_{avg} value for

all subjects missing Visit 7 values, regardless of reasons for discontinuation. For the JATENZO group, all 3 sensitivity analyses resulted in estimates of the percentage of subjects in the eugonadal range of 86.1% to 89.6%. Thus, the sensitivity analyses met the efficacy target of ≥ 75% of subjects with a T C_{avg} in the eugonadal range and the lower bound of the 95% CI ≥ 65% (Table 6).

Table 6: Percentage of Subjects with T C_{avg} Values in the Eugondal Range at Visit 7 for Sensitivity Analyses (Study CLAR-15012; Modified ITT Population)

Testosterone C_{avg} Range, n (%)	FDA Target	Oral TU (N = 166)	Topical Axiron (N = 55)
Last Observation Carried Forward Method			
252 ng/dL ≤ C_{avg} ≤ 907 ng/dL[a]	≥ 75%	146 (88.0%)	50 (90.9%)
Lower bound of 95% confidence interval	≥ 65%	82.0%	80.0%
C_{avg} mean (standard deviation)		401.2 (140.2)	390.6 (139.9)
95% confidence interval		379.7, 422.7	352.8, 428.5
Multiple Imputation Method			
252 ng/dL ≤ C_{avg} ≤ 907 ng/dL[a]	≥ 75%	149 (89.6%)	50 (90.6%)
Lower bound of 95% confidence interval	≥ 65%	84.6%	82.3%
C_{avg} mean (standard deviation)		403.6 (143.3)	388.3 (141.3)
95% confidence interval		381.8, 425.4	351.0, 425.7
Imputation From Baseline Method			
252 ng/dL ≤ C_{avg} ≤ 907 ng/dL[a]	≥ 75%	143 (86.1%)	45 (81.8%)
Lower bound of 95% confidence interval	≥ 65%	79.9%	69.1%
C_{avg} mean (standard deviation)		384.1 (137.4)	358.2 (142.0)
95% confidence interval		363.1, 405.2	319.8, 396.5

Source: Appendix 16.5.1, Tables 6, 8, and 10
Abbreviations: C_{avg} = average observed concentration over 24 hours; FDA = Food and Drug Administration; ITT = intention-to-treat; TU = testosterone undecanoate
[a] Eugonadal range.

In summary, the primary **efficacy analysis showed a responder rate of 87.3%** (145 responders out 166 subjects; 95% CI: 81.3%-92.0%) on Day 105. Responders were defined as subjects who had a plasma total T C_{avg} in the normal range of 252-907 ng/dL on Day 105. The **study results met the pre-specified efficacy criteria** of responder rate ≥75% and the lower bound of the 95% CI to be ≥ 65%.

Key PK Safety Endpoint Analysis

The key PK safety endpoint, total T C_{max}, had the following pre-specified criteria that were expected to be met on Day 105:

- Having < 5% of subjects with a serum total T C_{max} in the range of 1,800-2,500 ng/dL
- No subjects with a serum total T C_{max} of > 2,500 ng/dL
- Having a serum total T C_{max} ≤ 1,500 ng/dL in at least 85% of subjects

Table 7 presents the number and percentage of subjects who had total T C_{max} values at Day 105 (Visit 7) in each C_{max} category.

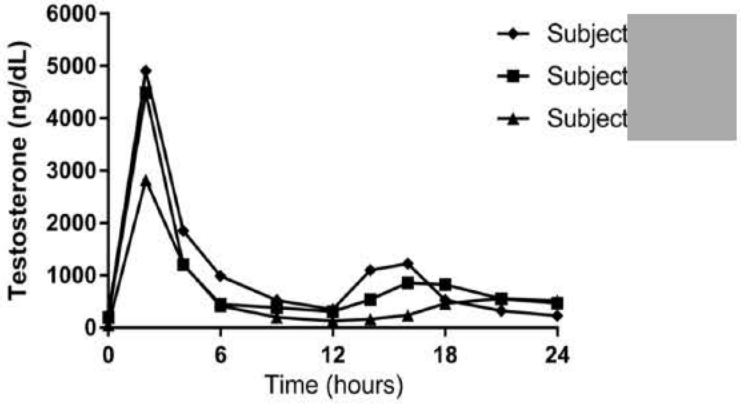
Table 7: Number (Percentage) of Subjects by Total T C_{max} Criteria Ranges at Day 105 (Subjects who had Total T C_{max} at Visit 7) (Study CLAR-15012)

Testosterone C_{max} Range, n (%)	FDA Target	Oral TU (N = 151)[a]	Topical Axiron (N = 48)
C_{max} ≤ 1500 ng/dL	≥ 85%	137 (90.7%)	47 (97.9%)
C_{max} > 1800 - 2500 ng/dL	≤ 5%	3 (2.0%)	1 (2.1%)
C_{max} > 2500 ng/dL	0	3 (2.0%)[b]	0

Source: Post-text Table 14.2.2.1
Abbreviations: C_{max} = maximum observed concentration over 24 hours; FDA = Food and Drug Administration; TU = testosterone undecanoate
[a] Eight subjects had C_{max} values > 1500 - ≤ 1800 ng/dL.
[b] All 3 subjects had C_{max} values suggestive of contamination.

Figure 7 shows the total T concentration – Time plot for JATENZO-treated subjects with total T > 2,500 ng/dL at Visit 7 (Day 105)

Figure 7: Total T Concentration – Time Plot for JATENZO-Treated Subjects with Total T C_{max} > 2500 ng/dL at Visit 7 (Study CLAR-15012; Day 105; Safety Population)



A supplemental analysis was performed in which the C_{max} criteria boundaries were adjusted for the upper limit of the eugonadal range, namely 907 ng/dL (Table 8).

Table 8: Number (Percentage) of Subjects by Total T C_{max} in Adjusted Criteria Ranges at Day 105 (Subjects who had Total T C_{max} at Visit 7) (Study CLAR-15012)

Testosterone C_{max} Adjusted Range[a], n (%)	FDA Target	Oral TU (N = 151)	Topical Axiron (N = 48)
$C_{max} \leq 1361$ ng/dL	≥ 85%	125 (82.8%)	47 (97.9%)
$C_{max} > 1633$ - 2268 ng/dL	≤ 5%	5 (3.3%)	1 (2.1%)
$C_{max} > 2268$ ng/dL	0	4 (2.6%)	0

Source: Post-text Table 14.2.2.1b
Abbreviations: C_{avg} = average concentration over 24 hours; C_{max} = maximum observed concentration over 24 hours; FDA = Food and Drug Administration; TU = testosterone undecanoate
[a] The adjustment factor was the ratio of 907 ng/dL to the typical eugonadal upper limit (ie, 907/1000 = 0.907).

The adjustment factor was the ratio of 907 ng/dL to the typical eugonadal upper limit (i.e., 907/1,000 = 0.907). Total T C_{max} over 24 hours was evaluated by estimating the proportions of JATENZO-treated subjects at Visit 7 according to the following categories: < 1,361 ng/dL (e.g., 1,500 × 0.907), > 1,633 to ≤ 2,268 ng/dL, and > 2,268 ng/dL. This *post hoc* analysis was performed to understand how the revised upper limits might affect the frequency distribution of outliers.

The observed T, DHT, and DHT/T ratios in the high C_{max} samples and the estimated T concentrations assuming high T includes contamination from exogenous T are summarized in Table 9.

Table 9: Observed T, DHT, and DHT/T Ratios in High T C_{max} Samples, and Estimated T Concentrations Assuming High T Includes Contamination from Exogenous T (Study CLAR-15012)

	Observed Values at Visit 7 for Subjects With High Testosterone C_{max} Samples					Estimated 2 Hour Testosterone Concentrations	
	2 h	2 h	2 h	4 h	14 h	Estimate from 4 h DHT/T	Estimate from 14 h DHT/T
Subject	T ng/dL	DHT ng/dL	DHT/T mole ratio	DHT/T mole ratio	DHT/T mole ratio	T ng/dL	T ng/dL
(b) (6)	4905	297.2	0.0602	0.1665	0.1625	1773	1817
	4485	198.3	0.0439	0.1378	0.0993	1429	1984
	2824	152.9	0.0538	0.1301	0.2305	1167	659

Source: Listing 16.2.6.2.2.1; Appendix 16.5.2, Table 5
Abbreviations: C_{max} = maximum observed concentration over 24 hours; DHT = dihydrotestosterone; T = testosterone

Reviewer's Comment: *The Sponsor states that there are several common features in these three patients with a total T C_{max} > 2,500 ng/dL indicating contamination of samples with T:*

- *The DHT/T molar ratios were all between 0.0439 and 0.0602 values that are less than half the DHT/T ratio (0.1484) of the other JATENZO-treated subjects in the 2-hour post dose sample. This is consistent with contamination with T, which would be expected to increase the T concentration but not affect the DHT concentration.*
- *An intra-subject comparison of the 2-hour DHT/T values for these 3 subjects to the other 9 post-dose samples collected at Visit 7 confirmed the 2-hour values were also atypically low for those subjects, being less than half the DHT/T ratio of any of the other 9 post-dose samples.*
- *The estimated T concentrations, assumed to approximate the pre-contamination plasma T concentrations for the 3 subjects, are all < 2,500 ng/dL (last 2 columns of Table 9); all 3 cases result in concentration-time profiles for Visit 7 consistent with the generally expected oral TU profile shape, and are consistent with the previous PK patterns observed in these 3 subjects at Visit 2 and Visit 4b.*
- *All three subjects were at the same clinical site and underwent PK sampling on the same day and at the same time.*
- *A subject receiving Axiron® (Subject* (b) (6) *was having PK sampling at the same time as JATENZO-treated subjects,* (b) (6)
- *All other concentrations for the 3 subjects, during both the morning and evening dosing intervals, were < 1,500 ng/dL, except that Subject* (b) (6) *had a concentration of 1,855 ng/dL 4 hours following the morning JATENZO dose.*

When these C_{max} outlier thresholds were adjusted downwards to account for the new lower T reference range proposed by the Sponsor, an analysis of outliers yielded one additional patient with a serum T concentration > 2,268 ng/dL (which corresponds to the revised 2,500 ng/dL threshold). No explanation could be determined for this patient's result.

Table 10 summarizes the comparison of Total T C_{max} profile of JATENZO with other approved T gel products.

Table 10: Comparison of Total T C_{max} Profile of JATENZO to Other Approved T gel Products

Product	C_{max} < 1500 ng/dL N (%)	1800 ng/dL < C_{max} ≤ 2,500 ng/dL N (%)	C_{max} > 2,500 ng/dL N (%)	Average C_{avg} (ng/dL)	Average C_{max} (ng/dL)
JATENZO[a] (Day 105)	125/151 (82.8)	5/151 (3.3)	4/151 (2.6)	403	1008
Androgel 1.62% (Day 112)	159/179 (88.8)	10/179 (5.6)	2/179 (1.1)	561	845
Testim (Day 90)	191/199 (96.0)	4/199 (2)	0/199 (0)	612	897
Axiron (Day 120)	128/135 (94.8)	4/135 (3)	1/135 (0.7)	480	792
Fortesta (Day 90)	122/129 (94.6)	2/129 (1.5)	0/129 (0)	440	528
Natesto (Day 90)	58/69 (84.1)	1/69 (1.5)	0/69 (0)	421	1044

[a] As JATENZO T concentrations were measured in plasma using NaF/EDTA tubes, the following adjusted T C_{max} ranges were used:
C_{max} ≤ 1,361 ng/dL; C_{max} > 1,633-2,268 ng/dL; C_{max} > 2268 ng/dL

Reviewer's Comment: *It should be noted that while other products in Table 10 are T gels administered once daily, Natesto® has a TID dosage regimen. JATENZO (BID dosage regimen) appears to have comparable total T C_{avg} and C_{max} values with Natesto®.*

Table 11 summarizes the plasma DHT PK parameters at Day 105 (Visit 7) by treatment following JATENZO or Axiron® treatments.

Table 11: Summary of Plasma DHT PK Parameters at Day 105 (Visit 7) by Treatment Following JATENZO or Axiron® Treatments

Visit	PK Parameter	Units	Oral TU, All Doses				Topical Axiron, All Doses			
			N	Mean	SD	CV%	N	Mean	SD	CV%
Visit 1	DHT	ng/dL	164	15.53	8.871	57.1%	54	13.86	5.957	43.0%
	DHT/T	mol ratio	164	0.08240	0.053935	65.5%	54	0.08231	0.067902	82.5%
Visit 7	C_{avg24}	ng/dL	152	73.25	30.088	41.1%	48	73.76	30.858	41.8%
	AUC_{24}	ng•h/dL	152	1757.9	722.11	41.1%	48	1770.2	740.58	41.8%
	C_{max24}	ng/dL	152	117.1	46.03	39.3%	48	97.97	39.154	40.0%
	$T_{max\text{-}am}$ [a,b]	h	155	4.00	(0.00, 12.08)		48	4.01	(0.00, 24.00)	
	$T_{max\text{-}pm}$ [a]	h	152	16.13	(12.00, 24.13)					
	DHT/T	mol ratio	151	0.1822	0.05138	28.2%	48	0.1941	0.06392	32.9%

Source: Appendix 16.5.2, Table 6

Abbreviations: AM = morning; AUC_{24} = area under the concentration-time curve morning and evening doses combined; C_{avg24} = time-weighted average plasma concentration morning and evening doses combined; C_{max24} = maximum observed concentration morning and evening doses combined; $C_{max\text{-}am}$ = time-weighted average concentration over the daytime dosing interval following the AM dose; $C_{max\text{-}pm}$ = time-weighted average concentration over the daytime dosing interval following the PM dose; CV = coefficient of variation; DHT/T = dihydrotestosterone/testosterone ratio; PK = pharmacokinetic; SD = standard deviation; $T_{max\text{-}am}/T_{max\text{-}pm}$ = time to $C_{max\text{-}am}/C_{max\text{-}pm}$; TU = testosterone undecanoate

[a] T_{max} values shown are median (range).

[b] Topical Axiron T_{max} is relative to the morning dose since it was applied just once daily, in the morning.

Reviewer's Comment: *Mean plasma DHT concentrations and DHT/T ratios for the JATENZO- and Axiron®-treated subjects were comparable and within the normal reference range of 0.05-0.33 (Wang et al., 2000; Diver et al., 2003).*

Overall Assessment on the Plasma Total T C_{max} at Day 105

As shown in Table 7 above, the following criteria of the secondary safety endpoint, total T C_{max} at Day 105 was **not** met:

- No subjects with a total T C_{max} of > 2,500 ng/dL
- At least 85% of subjects with a total T $C_{max} \leq$ 1,500 ng/dL

Inspection of data for the 3 out of 4 subjects that had a total T C_{max} of > 2,500 ng/dL shows that the high concentrations are likely spurious and due to specimen contamination. Therefore, the Clinical Pharmacology review team does not believe that the total T C_{max} profile is a safety concern for JATENZO.

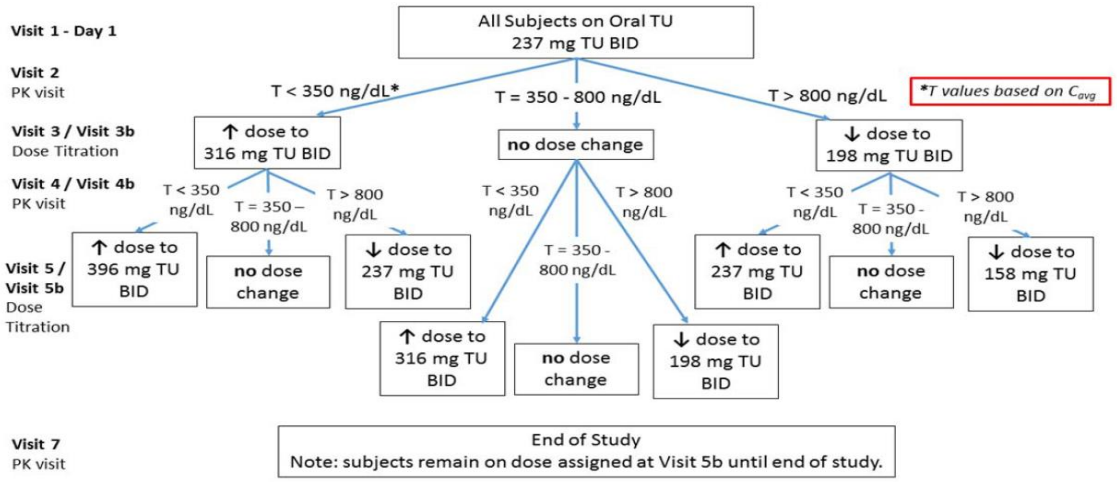
OSI consult: A formal consult to the OSI was made for clinical study site inspections and there are no unresolved inspection findings related to the approvability of JATENZO. Reference is made to Dr. Roy Blay's OSI Memorandum dated January 9, 2018 under NDA 206089 in DARRTS.

2.2.7 What dose titration scheme did the Sponsor use in the pivotal Phase 3 study?

In the pivotal Phase 3 study, CLAR-15012, the need for dose titration for each subject was assessed based on the total T C_{avg} over 24 hours (i.e., derived based on plasma T concentrations from blood

collected in NaF/EDTA coated tubes) on Days 21 and 56. Dose titrations occurred on Days 35 and/or 70, if needed. The dose titration scheme for JATENZO are illustrated in Figures 8. The Sponsor reports that the titration boundaries of 350-800 ng/dL were based on PK modeling and simulation using T concentration data collected during the Sponsor's studies (CLAR-09007 and CLAR-12011).

Figure 8: JATENZO Dose Titration Scheme



Abbreviations: BID = twice daily; C_{avg} = average concentration; PK = pharmacokinetic; T = testosterone; TU = testosterone undecanoate; ↑ = increase; ↓ = decrease

2.2.8 What dose titration scheme is the Sponsor proposing for labeling and is it acceptable?

The Sponsor proposed the following language in the product label under Section (b) (4) *Dosing and Dose Adjustment*:

(b) (4)

The proposed dose titration scheme is outlined in Table 12 below.

Table 12: Sponsor's Proposed JATENZO Dose Titration Scheme

Plasma Testosterone Value Drawn 3-5 hours After Dose	Current JATENZO Dose (mg, BID)	New JATENZO Dose (mg, BID)
<350 ng/dL	158	198
	198	237
	237	316
	316	396
350 – 800 ng/dL	No Dose Change	
>800 ng/dL	396	316
	316	237
	237	198
	198	158
	158	Discontinue Treatment

In the pivotal Phase 3 study, CLAR-15012, the starting dose of JATENZO was 237 mg TU BID with potential for up titration to 316 mg and 396 mg BID or down titration to 198 mg and 158 mg

BID. In the study, the titrations were based on 24-hour total T C_{avg} (0-24 hour sampling) with thresholds of 350 and 800 ng/dL for up- and down-titration corresponding to measurements at two visits (Visit 2 on Day 21, Visit 4b on Day 56). The Sponsor stated that a more practical approach in clinical practice would be to base the titration decision on the T concentration measured in a single blood sample drawn at a time convenient for patients and health care systems (e.g., daytime hours). Accordingly, the Sponsor proposed titration based on a single sample (C_x) in the 3-5 hour post-morning dose window with same thresholds of T concentration (350 and 800 ng/dL).

To justify that the outcome of the above two titration algorithms will be similar, the Sponsor used following two-step approach: 1) A concordance analysis using observed data for specific single blood draw samples (C_x) and C_{avg} in Phase 3 Study CLAR-15012 to justify that titration decisions based on C_{4h} post-morning dose are effective in maintaining T concentrations in the eugonadal T concentration range; 2) A population PK based modeling and simulation analysis to confirm that titration decisions based on C_{4h} are effective in maintaining T concentrations in the eugonadal T concentration range and avoid high C_{max} values and sample collection time had some flexibility from practical standpoint in that the results of using a single-time status sample (C_{4h}) was comparable to using a 2-hour window for the status sample (i.e., $C_{3\text{-}5h}$).

However, the Clinical Pharmacology review team noted some limitations in the Sponsor's modeling and simulation approach (refer to Section 4.2 of this review) and focused on observed results from the study for justification of an appropriate sampling window. Evidence from following data/analyses were used by the review team for the conclusion of appropriateness of titration algorithm for labeling: 1) observed concentration-time profiles for T; 2) correlation analysis between C_x and C_{avg}; and 3) concordance analysis for C_x and C_{avg} based titration algorithms.

In the concordance analysis, the following evaluations were proposed by the Sponsor to evaluate concordance between the C_x and C_{avg} based titration algorithms (refer to Section 4.2 for details):

- **Numeric concordance:** Subjects will have same up/down-titration using the two algorithms (C_{avg} or C_x based)
- **Effective concordance:** Subjects may have different titration using C_x compared to C_{avg}, but the study outcome (subjects in eugonadal range of 252-907 ng/dL) will not be altered
- **Total concordance:** Sum of numeric and effective concordance

Based on the observed concentration-time profiles for T, correlation analysis between C_x and C_{avg} and concordance analysis for C_x and C_{avg} based titration algorithms, the review team made the following observations:

1. The comparison of C_x at different time points and C_{avg} shows that C_{6h} values most closely mimic C_{avg} values on a population level (Refer to time points in red curve for T conc.-time profile and red dotted line for C_{avg} for Visit 2 in Figure 3 as an example) and on an individual level (data not shown).
2. There was a relatively strong correlation between C_x and C_{avg} at 4 hour and 6 hour post-morning dose, while there was relatively weaker correlation at other time points such as 0, 2, 9, and 12 h post-morning dose (Table 13).

Table 13: Correlation between Morning PK Samples and 24-hour C_{avg} for Visit 2 and Visit 4b (Study CLAR-15012)

Post-Dose Sample (hour)	Correlation Between Observed (Cx) and Average (C_{avg}) Concentration	
	Visit 2 (R^2)	Visit 4b (R^2)
0	0.28	0.33
2	0.40	0.49
4	0.76	0.75
6	0.64	0.64
9	0.44	0.50
12	0.21	0.42

C_{avg}= Average concentration; Cx= Single sample collected at time x; R^2= Coefficient of determination.

Source: Sponsor's study report

3. The numeric concordance and total concordance for both 4 hour and 6 hour post-morning dose sampling was reasonable (e.g., 64% and 88% for C_{4h} and 80% and 98% for C_{6h} for Visit 2; Refer to Table 14 below and refer to Section 4.2 for details of components in effective concordance).

Table 14: Comparison of concordance for three Single Draw sampling (C_{2h}: sample at 2 hour post-dose; C_{4h}: sample at 4 hour post-dose; C_{6h}: sample at 6 hour post-dose) and C_{avg} Based Titration at Visit 2 and Visit 4b (Study CLAR-15012)

	Numeric Concordance	**Effective Concordance in Different Cells**			**Total Concordance = Numeric + Effective**
		Cell I	**Cell II**	**Cell III**	
Visit 2					
C_{2h}	**46.9%**	12.7%	5.4%	14.5%	**79.5%**
C_{4h}	**63.9%**	18.1%	0.0%	6.0%	**88.0%**
C_{6h}	**80.0%**	4.2%	10.9%	3.0%	**98.1%**
Visit 4b					
C_{2h}	**45.0%**	15.4%	3.7%	18.5%	**82.6%**
C_{4h}	**58.6%**	22.2%	0.0%	12.3%	**93.1%**
C_{6h}	**72.2%**	9.9%	10.5%	3.1%	**95.7%**

Source: Adapted from Sponsor's analysis

4. Median T_{max} for this oral administration product is ~2 hour post-dose. So, a window of 3-5 hour post-dose is likely to have some samples that mimic C_{max} rather than C_{avg} for the same subject depending on the sampling time post-dose across different visits for the same dose. This may unduly influence titrations towards lower dose.
5. On the other hand, a shallower PK profile over 4-6 hour post-dose time window means that it could likely yield less extreme measurement values and it would not be as sensitive to the sampling time for the same individual across different visits.

Based on this, from the labeling perspective, the Clinical Pharmacology review team concludes that a 4-6 hour post-morning dose window for single blood draw sampling for titration decisions would be more appropriate than a 3-5 hour window proposed by the Sponsor, with titration thresholds of 350 and 800 ng/dL for up- and down-titrations.

Refer to Section 4.2 for further details regarding this issue.

2.3 Intrinsic Factors

2.3.1 Was there any age effect observed in the efficacy and safety of JATENZO?

There have not been sufficient numbers of geriatric patients involved in controlled clinical studies utilizing JATENZO to determine whether efficacy in those over 65 years of age differs from younger subjects. No patients over 65 years of age were enrolled in the Phase 3 study, CLAR-15012. Additionally, there is insufficient long-term safety data in geriatric patients utilizing JATENZO to assess the potential incremental risk of cardiovascular disease and prostate cancer.

2.3.2 Did the Sponsor conduct any pediatric studies during the development of JATENZO?

No pediatric studies with JATENZO were conducted. The safety and efficacy of JATENZO in pediatric patients less than 18 years old have not been established. Improper use may result in acceleration of bone age and premature closure of epiphyses.

The Request for Waiver of Pediatric Studies was submitted in the original NDA 206089. The PSP was submitted to IND 78,104 on November 27, 2013, and a copy of the PSP was included in the original NDA 206089. The full pediatric waiver was granted on September 3, 2014.

2.3.3 Did the Sponsor conduct PK studies in population with renal or hepatic impairment?

No. The Sponsor did not conduct any studies in patients with renal or hepatic impairments. No additional information is available in the labeling of topical drugs in the same drug class (i.e., Testim®, AndroGel®, or Axiron®) regarding this aspect.

2.3.4 Did baseline body weight have impact on the responder rate (i.e., efficacy)?

No. In the pivotal Phase 3 study (Study CLAR-15012), the Sponsor performed a *post-hoc* analysis of the primary endpoint by weight subgroups (≤ 100 kg and > 100 kg). In both the JATENZO and Axiron® groups, a slightly higher percentage of subjects who weighed ≤ 100 kg had T C_{avg} values in the eugonadal range (89.2% and 90.3%, respectively) compared with subjects who weighed > 100 kg (85.5% and 83.3%, respectively). In the JATENZO group, the mean (± SD) dosage strength of the last dose of study drug was higher for subjects who weighed > 100 kg compared with those who weighed ≤ 100 kg; however, in the Axiron® group, the mean (± SD) dosage strength of the last dose of study drug was comparable between the weight subgroups. For subjects weighing > 100 kg in the JATENZO group, both the estimated percentage of subjects (85.5%) and the lower bound of the 95% CI (76.1%) met the FDA target of ≥ 75% and ≥ 65%, respectively.

Table 15: Percentage of Subjects with T C_{avg} Values in the Eugonadal Range at Visit 7 for Primary Analysis by Weight (Study CLAR-15012; Modified ITT Population)

		Oral TU (N = 166)		Topical Axiron (N = 55)	
Testosterone C_{avg} Range, n (%)	**FDA Target**	**≤ 100 kg (N = 83)**	**> 100 kg (N = 83)**	**≤ 100 kg (N = 31)**	**> 100 kg (N = 24)**
252 ng/dL ≤ C_{avg} ≤ 907 ng/dL[a]	≥ 75%	74 (89.2%)	71 (85.5%)	28 (90.3%)	20 (83.3%)
Lower bound 95% CI	≥ 65%	80.4%	76.1%	74.2%	62.6%
Upper bound 95% CI		94.9%	92.3%	98.0%	95.3%
Last dose of study drug (mg)					
Mean (SD)		298.1 (64.5)	348.9 (58.4)	79.4 (21.3)	78.8 (19.4)
95% CI		284.1, 312.2	336.2, 361.7	71.5, 87.2	70.6, 86.9

Source: Appendix 16.5.1, Tables 11 and 12

Abbreviations: C_{avg} = average observed concentration over 24 hours; CI = confidence interval; FDA = Food and Drug Administration; ITT = intention-to-treat; LOCF = last observation carried forward; SD = standard deviation; TU = testosterone undecanoate

[a] Eugonadal range.

Note: The primary efficacy analysis treated all Visit 7 missing data as if the subject failed to achieve a Visit 7 plasma sample measurement in the eugonadal range unless the data were missing because of a cause not related to the study drug. For missing values not attributed to a study drug-related cause, the Visit 7 C_{avg} was imputed by LOCF and determined whether it was in the eugonadal range.

2.4 Extrinsic Factors

2.4.1 Did the Sponsor conduct any DDI studies?

No DDI studies were conducted with JATENZO. The following information is available in the labeling of topical drugs in the same drug class (e.g., Testim®, AndroGel®, or Axiron®): Changes in insulin sensitivity or glycemic control may occur in patients treated with androgens. In diabetic patients, the metabolic effects of androgens may decrease blood glucose and, therefore, may necessitate a decrease in the dose of anti-diabetic medication. Changes in anticoagulant activity may be seen with androgens. Therefore, more frequent monitoring of International Normalized Ratio (INR) and prothrombin time is recommended in patients taking warfarin, especially at the initiation and termination of androgen therapy. The concurrent use of T with corticosteroids may result in increased fluid retention and requires monitoring particularly in patients with cardiac, renal, or hepatic disease.

Considering that JATENZO is administered as TU orally and high systemic concentration of TU is observed, the DDI potential of TU should be addressed.

Reviewer Comment: *It should be noted that while TU concentrations were not measured in the new Phase 3 study, CLAR-15012, higher TU concentrations compared to total T concentrations were observed in Studies 16015 (food effect study) and 15013 (blood collection methodology evaluation study) when both TU and T concentrations were measured. Reference is made to Sections 4.1.2 and 4.1.3 of this review for details.*

2.5 General Biopharmaceutics

2.5.1 What is the quantitative composition of the drug products used in the clinical studys of this application?

JATENZO is a soft gelatin capsule (b) (4) and are available in three strengths: 158 mg, 198 mg, and 237 mg TU. It should be noted that only the 158 mg and 237 mg strengths were used in the original NDA and the 198 mg strength was additionally developed and used in the post-CR studies.

Table 16: Composition of JATENZO

Ingredient	Amount (mg) per 198 mg capsule	Function
Formulation		
Testosterone Undecanoate	197.88[1]	Active Ingredient
Oleic Acid NF, EP	(b) (4)	
Borage Seed Oil[2]		
Butylated Hydroxytoluene NF, EP (BHT)		
Peppermint Oil NF, FCC		
Polyoxyl 40 Hydrogenated Castor Oil NF (Cremophor RH40)		
Total Fill Weight		
Soft Gelatin Capsule Shell:[3]		
(b) (4)		
Gelatin (b) (4) NF		
Sorbitol (b) (4)		
Glycerin (b) (4)		
Purified Water USP, EP		
Titanium Dioxide USP, EP		
Filled Gelatin Capsule Imprinting:		
Red (b) (4) Ink[3,5]		
(b) (4)		

Ingredient	Amount (mg) 100 mg capsule	Amount (mg) 150 mg capsule	Function
Formulation			
Testosterone Undecanoate	158.30[1]	237.46[2]	Active Ingredient
Oleic Acid NF, EP	(b) (4)		
Borage Seed Oil[3]			
Butylated Hydroxytoluene NF, EP (BHT)			
Peppermint Oil NF, FCC			
Polyoxyl 40 Hydrogenated Castor Oil NF (Cremophor RH40)			
Total Fill Weight			
Soft Gelatin Capsule Shell:[4]			
(b) (4)			
Gelatin (b) (4) NF			
Sorbitol (b) (4)			
Glycerin (b) (4)			
Purified Water USP, EP			
Iron Oxide Red NF			
FD&C Yellow No. 6			
Titanium Dioxide USP, EP			
Filled Gelatin Capsule Imprinting:			
White (b) (4) Ink[4,6]			
(b) (4)			

Reviewer's Comment: *It should be noted that the 100 mg and 150 mg T capsules refer to the 158 mg and 198 mg TU capsules. All 4 post-CR studies were conducted using the TBM formulation.*

2.6 Bioanalytical Methods

2.6.1 Did the Sponsor use validated bioanalytical methods to generate the study data?

Yes. Human blood sample were collected into plain (red-top) tubes and tubes that contained NaF/EDTA. Serum was prepared from samples collected in plain tubes which were held at room temperature for 30 minutes and then centrifuged for 20 minutes. Plasma was prepared from samples collected in tubes containing NaF/EDTA were chilled for 30 minutes on ice and centrifuged for 20 minutes. Serum and plasma samples were transferred in aliquot storage tubes and frozen at -20ºC and then shipped for analysis.

The two bioanalytical laboratories used for bioanalysis were (b) (4) (serum in plain tubes) and (b) (4) (plasma in NaF/EDTA tubes). Bioanalysis for total T and DHT used in the primary efficacy analysis was conducted at (b) (4)

Bioanalysis for Serum in Plain Tubes

The LC-MS/MS method was developed and validated with the dynamic range of 0.02-20 ng/mL (2-2,000 ng/dL) for total T. Accuracy and precision of the calibration standards and QC samples for total T from serum in plain tubes during sample analysis were within the pre-specified acceptance range per the Agency's *Bioanalytical Method Validation Guidance*. Long-term storage stability for total T in human plasma at -20°C was established for 3 years. Incurred sample reanalysis (ISR) results confirmed the reproducibility of the bioanalytical method.

Bioanalysis for Plasma in NaF/EDTA Tubes

The LC-MS/MS method was developed and validated with the dynamic range of 0.1-30 ng/mL (10-3,000 ng/dL) and 0.05-5 ng/mL (5-500 ng/dL) for total T and DHT, respectively. Accuracy and precision of the calibration standards and QC samples for total T and DHT from plasma in NaF/EDTA tubes during sample analysis were within the pre-specified acceptance range per the Agency's *Bioanalytical Method Validation Guidance*. Long-term storage stability for total T and DHT in human plasma at -80°C was established for 246 days. ISR results confirmed the reproducibility of the bioanalytical method.

OSIS Inspection of the Bioanalytical Site

For the new pivotal Phase 3 study (Study CLAR-15012), the Clinical Pharmacology review team made a formal consult to the OSIS on June 29, 2017. However, the DNDBE within the OSIS recommended to accept the bioanalytical data without on-site inspection as (b) (4) was inspected recently (dates not specified) and the inspection outcome was classified as NAI. Reference is made to the OSIS Memorandum issued on August 21, 2017 in DARRTS.

It should be noted that on February 26, 2014, the Clinical Pharmacology review team requested an inspection on the bioanalytical site (b) (4) (b) (4) that conducted the bioanalysis of Phase 3 studies, CLAR-12011 and CLAR-09007 during the original NDA review cycle. Following inspections, the OSIS concluded that the clinical and bioanalytical data from (b) (4) are acceptable for further Agency review. Reference is made to the OSIS Memorandum issued on August 8, 2014 in DARRTS.

Reviewer's Comment: *The acceptance criteria and performance of the total T and DHT bioanalytical methods were in compliance with the Agency's Bioanalytical Method Validation Guidance. In summary, the method validation and performance of the bioanalytical methods in clinical studies are acceptable and there are no unresolved bioanalytical issues related to the approvability of JATENZO.*

2.6.2 Why did the Sponsor's approach of measuring total T concentrations from plasma in NaF/EDTA tubes instead of serum in plain tubes?

Esters such as TU may be hydrolyzed, into steroid and the fatty acid side chain moieties due to non-specific esterases in blood during blood collection and processing (Wang *et al*., 2008; Lachance *et al*., 2015).

While the typical practice in the bioanalytical field has been to analyze T and DHT from human serum in plain tubes, the Sponsor took an approach of measuring total T concentrations from plasma in NaF/EDTA tubes to minimize the potential TU to T *ex vivo* conversion during preparation of serum from blood. This potential TU to T *ex vivo* conversion may lead to overestimation of the circulating T concentration in the patient. The Sponsor has proposed that using NaF/EDTA plasma will stabilize TU in the specimen and that this specimen type should be used for T monitoring (i.e., dose titration) in patients taking TU.

2.6.3 Is measuring total T concentrations in NaF/EDTA tubes critical for the safe and effective use of JATENZO?

In order to determine their sample collection method and select the type of tubes, the Sponsor conducted Study CLAR-15013 which was an open-label, single oral TU dose study in 8 hypogonadal men. Each study participant received a single oral dose of 316 mg TU (i.e., equivalent to 200 mg T) in the form of 2 soft gel capsules each containing 158 mg TU. The oral TU dose was administered immediately prior to a standardized breakfast meal comprised of 800-1,000 calories and containing approximately 30 g of fat (~25-30% of calories as fat). Subjects were asked to consume the entire breakfast meal in no more than 30 minutes. Concentrations of T were measure in serum samples collected from whole blood after the whole blood samples sat at room temperature for 30 minutes after being spiked with 1 of 5 TU concentrations (i.e., 0, 30, 100, 300, or 1,000 ng/mL). The collected serum samples were stored at -20°C until analyzed for T. The mean (SD) for the T concentrations at the 5 spiked TU concentrations are summarized in Table 17 in units of ng/dL.

Table 17: Mean (SD) Total T Concentrations at the 5 Spiked TU Concentrations (Study CLAR-15013; N=4)

Conventional Units	
Theoretical TU Concentration	Observed Serum T ng/dL (N=4)
ng/mL	Mean ± SD (CV)
0	26.04±12.396 (47.6%)
30	48.92±10.261 (21.0%)
100	89.49±9.719 (10.9%)
300	242.0±30.32 (12.5%)
1000	578.5±133.11 (23.0%)

The spiking of the whole blood with between 30 ng/mL and 1,000 ng/mL of TU increased the measured mean serum T concentration to between 49 ng/dL and 579 ng/dL within that 30-minute time span. The extent of increase in serum T concentration associated with the bioconversion of TU increased as the spiked TU concentration increased. The Sponsor believes that further increases in T due to *ex vivo* conversion from TU would be expected to occur if the blood sample sat on the bench top for a longer time. The Sponsor concluded that TU conversion to DHT appears to be minimal to nonexistent at all concentrations of TU spiking tested. This *in vitro* assessment was not performed in plasma collected using NaF/EDTA blood collection tubes. However, the Sponsor conducted an *in vivo* PK assessment described below.

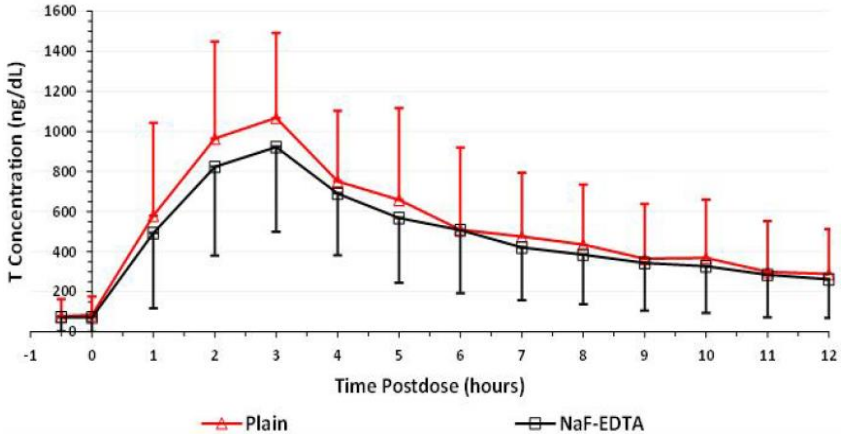
For the *in vivo* PK assessments from the same study, concentrations of total T were analyzed at 14 timepoints over a 12.5-hour period starting 0.5-hour pre-dose to 12-hours post-dose. PK was assessed comparing the following test tubes and matrix:

- ***Plain (Red Top) Tubes (Serum)***: Blood collected in these tubes was kept at room temperature for 30 minutes then centrifuged at 4°C for 20 minutes at > 1,000 g. Serum was separated promptly after centrifugation and was stored at -20ºC until analysis.
- ***NaF (Light Gray Top) Tubes (Serum)***: Blood collected in these tubes was kept on ice for 30 minutes then centrifuged at 4°C for 20 minutes at > 1,000 g. Serum was separated promptly after centrifugation and was stored at -20ºC until analysis.
- ***NaF + Oxalate (Gray Top) Tubes (Plasma)*:** Blood collected in these tubes was kept on ice for 30 minutes then centrifuged at 4°C for 20 minutes at > 1,000 g. Plasma was separated promptly after centrifugation and was stored at -20ºC prior to analysis.
- ***NaF + EDTA (Gray Top) Tubes (Plasma)*:** Blood collected in these tubes was kept on ice for 30 minutes then centrifuged at 4ºC for 20 minutes at > 1,000 g. Plasma was separated promptly after centrifugation and was stored at -20ºC prior to analysis.

The following was observed by the Sponsor:

- Following a single oral dose of 316 mg TU, mean T concentrations from samples in plain tubes without any additives to inhibit non-specific esterases or prevent clotting were higher compared to the other 3 NaF-containing test tubes. The mean T concentrations obtained from samples collected in the 3 different types of NaF-containing test tubes were similar.
- There was a high inter-subject variability observed in the PK measurements regardless of the type of test tube used (Figure 9).

Figure 9: Mean (SD) Concentration-Time Profiles for T Following a Single 316 mg Oral TU Dose, for Plain and for NaF/EDTA Collection Tubes (Study CLAR-15013; N=8)



- Greater differences between tube types were observed when circulating T concentrations were higher compared to when T concentrations were lower.
- The geometric mean T C_{max} and C_{avg} (and AUC[0-12]) values from the 3 types of NaF-containing test tubes were 18-26% less and 11-16% less, respectively, than that of samples from the plain tube.
- The NaF/EDTA tube, which contains the lowest NaF concentration of the 3 NaF-containing tubes evaluated, showed the smallest systematic difference (i.e., mean of 8.6% difference between T concentrations in samples obtained from the NaF/EDTA test tubes and the red-topped plain serum tube. The higher the NaF concentration, the greater was the decrease in mean T concentration.
- The Sponsor believes that the extent of *ex vivo* conversion from TU to T can vary from subject to subject, most likely because of genetic and environmental factors that might affect the circulating concentrations of non-specific esterases and their intrinsic activity. Both time and sample temperature are factors likely to impact the extent of de-esterification. The non-specific activity would be expected to be greater when samples are near body temperature (just after sample collection) and least when cooled down to -20°C or -80°C.
- There was no consistent pattern of differences in DHT concentrations measured between samples collected in plain tubes and in NaF/EDTA tubes.
- Mean TU concentrations (Table A-3-4 in Section 4.1.3) determined in samples collected in plain tubes were nearly the same as for the other 3 types of NaF-containing tubes except for the time period of 2-6 hours post-dose (i.e., samples from NaF-containing tubes having a mean of 11-14% lower TU concentration compared to those from plain tubes).

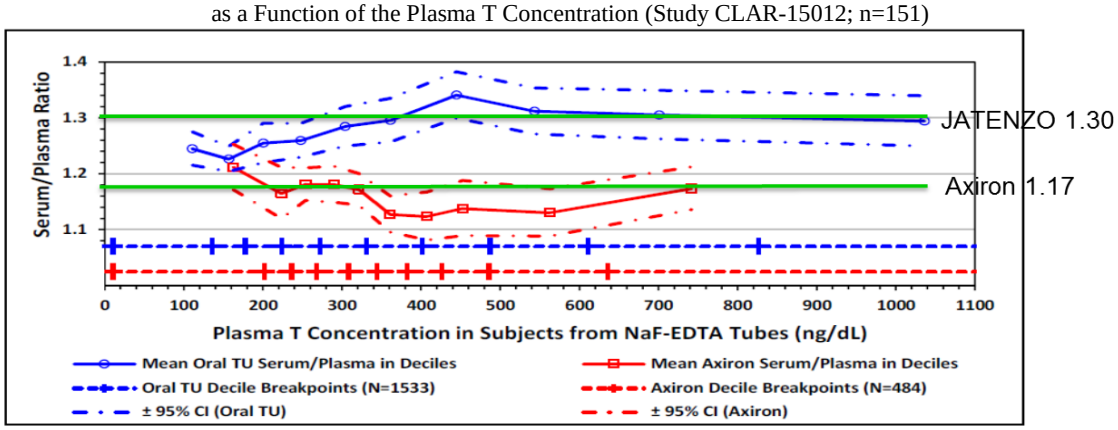
Reviewer's Comment: *It should be noted that sample handling time and temperature appears to affect the extent of TU to T ex vivo conversion. While serum collected in red-topped tubes were held at room temperature for 30 minutes following collection to allow clotting (i.e., standard practice), NaF-containing tubes were held on ice immediately following collection. The Sponsor did not submit data comparing different types of tubes at the same temperature (i.e., room temperature) or other sample handling time besides 30 minutes. It was reported that temperature also has an effect on the TU to T ex vivo conversion when comparing T concentrations obtained from samples prepared at room temperature and 4ºC as samples prepared at room temperature showed a higher conversion rate than those prepared at 4ºC (Lachance et al., 2015).*

It appears that the ex vivo conversion of TU to T continues over time in the blood collected in plain tubes (source of the serum) when no enzyme inhibitors are present, and the addition of an esterase inhibitor, namely NaF, minimizes the hydrolysis of TU to T.

In clinical studies conducted during the Sponsor's drug development, a mean of 14-17% higher T concentrations were observed from serum in plain tubes compared to those from plasma in NaF/EDTA tubes following oral TU administration. This was consistent with literature reports of a negative bias of 11.7% (Lachance *et al.*, 2015) to 20% (Wang *et al.*, 2008) for total T concentrations when using NaF-containing tubes compared to total T concentrations measured from serum in plain tubes with no additives.

Figure 10 shows the ratios of serum total T concentrations (in plain tubes) to plasma total T concentrations (in NaF/EDTA tubes) when plotted against the plasma T concentration measured in the NaF/EDTA sample collection tubes from Phase 3 study, CLAR-15012.

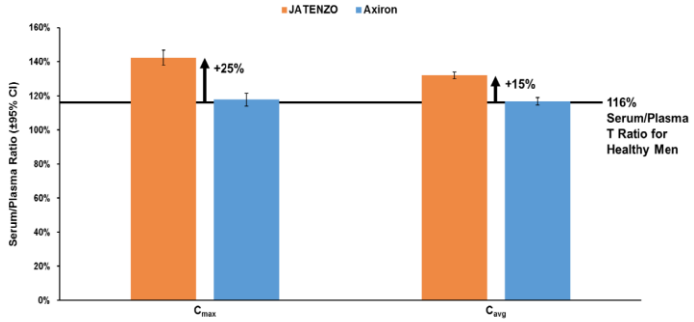
Figure 10: Ratio of Serum Testosterone Concentration in Plain Tubes to Plasma T Concentration in NaF/EDTA Tubes as a Function of the Plasma T Concentration (Study CLAR-15012; n=151)



Notes: Mean Serum/Plasma ratio within a decile plotted at the median plasma T for the decile; 95% CI for each bin estimated using the Student's t-distribution; All samples collected over the 24 hours following the AM dose were included which had both assay results greater than the LLOQ of the plasma assay (10 ng/dL), except for 2 instances of outlier ratios (Serum/Plasma ratio >7)

Figure 10 illustrates the comparison of bias analysis between non-TU containing Axiron®-treated subjects and JATENZO (oral TU). As Axiron®-treated subjects did not have TU in their circulation, the mean 17% difference between serum and plasma T concentrations appears to be related to an additive effect (i.e., NaF/EDTA) rather than a TU-treatment related effect (e.g., TU to T *ex vivo* conversion).

Figure 11: Impact on C_{max} and C_{avg} When Total T Concentration is Measured from Serum in Plain Tubes vs. from Plasma in NaF/EDTA Tubes (Study CLAR-15012; N=151)



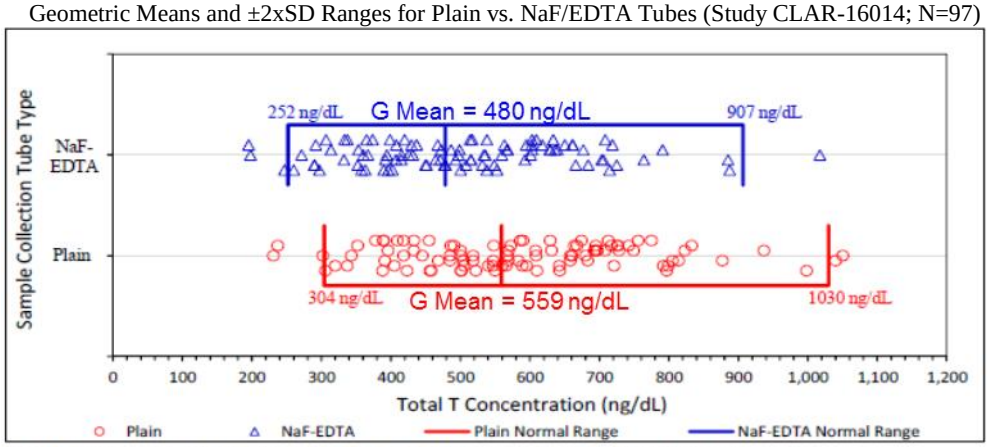
Abbreviations: C_{avg} = average testosterone concentration; CI = confidence interval; C_{max} = maximum testosterone concentration; EDTA = ethylenediaminetetraacetic acid; NaF = sodium fluoride; T = testosterone

When comparing total T C_{max} and C_{avg} in serum and NaF/EDTA plasma samples collected from patients at the final PK visit was performed, JATENZO-treated patients had total T C_{max} serum/plasma ratios that were approximately 25% higher and C_{avg} ratios that are approximately 15% higher than those from Axiron®-treated patients (Figure 11). The Axiron®-treated patients had no TU in their circulation, so they act as a control, but have a ratio of 116% because of the effect that collecting the blood in NaF/EDTA tubes (i.e., additive [NaF and/or EDTA] effect) has on the measured T concentrations compared to plain tubes.

Reviewer's Comment: *The results from this large collection of serum and plasma samples shows that the differences are not negligible and can potentially affect titration decisions in subjects treated with JATENZO. If the analyte of interest has a stability issue like this case, using plasma may have an advantage over serum, as plasma samples can be processed very quickly followed by sample analysis or storage.*

In addition, the Sponsor conducted a phlebotomy study (CLAR-16014) to compare the total T concentrations when blood is drawn into plain tubes vs. NaF/EDTA tubes from healthy men. This study was conducted in 97 healthy males (age: 19-40 years). Blood samples were drawn into serum plain (red-top) tubes and NaF/EDTA (gray-top) tubes from each subject. When blood was collected into serum tubes and processed, serum was obtained and when blood was collected into NaF/EDTA tubes and processed, plasma was obtained. The blood collection occurred under fasted state (no food for at least 3 hours) between 6 and 10 am.

Figure 12: Distributions of Total T Measurement Results:
Geometric Means and ±2xSD Ranges for Plain vs. NaF/EDTA Tubes (Study CLAR-16014; N=97)



Note 1: Data points are distributed in the vertical dimension only to facilitate visualization
Note 2: Vertical lines identify the geometric mean and ±2 x SD (for log-transformed data) from the geometric mean

The following was observed by the Sponsor:

- When comparing the 2 different types of tube after log transformation, the mean total T concentration (95% CI) from the NaF/EDTA tubes was 85.8% (84.4-87.3%), i.e., 14.2% less, than that obtained from the plain tubes. The use of NaF/EDTA tubes for blood samples also resulted in lower values for DHT concentrations and DHT/T ratios.
- The lower and upper bounds of the normal ranges were calculated as the exponentiated values of the mean plus and minus two standard deviations (SDs) after log-transformation of the concentration. The observed normal T concentration range was 304-1,030 ng/dL in serum from blood samples collected in plain tubes and 252-907 ng/dL in plasma from blood samples collected in NaF/EDTA tubes (Figure 12).

- The observed normal T concentration range for the serum tubes was comparable to the widely used range of 300-1,000 ng/dL.

Reviewer's Comment: *This reference range study was performed using healthy males (i.e., not treated with oral TU) to measure endogenous T. Therefore, the observed mean negative bias of 14.2% for total T concentrations measured from plasma in NaF/EDTA tubes compared to those from serum in plain tubes indicate that there is a non-drug (i.e., oral TU) related additive effect (i.e., NaF and/or EDTA effect) when measuring total T concentrations from plasma in NaF/EDTA tubes as TU was not administered in this study*.

The issue of whether NaF/EDTA tubes are critical for the safe and effective use of JATENZO was discussed at the January 9, 2018 Bone, Reproductive, and Urologic Drugs Advisory Committee (BRUDAC) Meeting (East Hyattsville, MD). Committee members wanted to see more data to be convinced of the need to obtain T concentrations from plasma prepared in NaF/EDTA tubes instead of obtaining them from serum in the more commonly used plain tubes, given that T concentrations would likely be used clinically in make decisions about dosing. It was noted that although the NaF-containing tubes are available in most labs, physicians who order the test, phlebotomists, and clinical labs prefer the simplicity of using serum as they can perform multiple tests on the same sample. As well, ordering practitioners could easily be confused about the details and could have difficulty interpreting the results. There was interest in learning more about the potential cross-reactivity of TU with the immunoassays as they are commonly used to monitor patients on TRTs. Several AC panel members recommended that further investigation on the rate and extent of the TU to T ex vivo conversion during the time course of plasma sample preparation is warranted.

Reviewer's Comment: *Immunoassays are commonly used to monitor patients on TRT. Due to the similarities in the chemical structure of T and TU, it is possible that commonly used T immunoassays would significantly cross-react with TU, causing an overestimation of T concentrations regardless of sample type. Because of the high concentration of TU relative to T in patient specimens, the immunoassay cross-reactivity could cause clinically significant inaccurate T concentration measurements in patients taking TU. Data demonstrating the rate of TU cross-reactivity with commonly-used T immunoassays are warranted. Reference is made to the Clinical Laboratory Standards Institute's document EP07-A2, Interference Testing in Clinical Chemistry (https://clsi.org/standards/products/method-evaluation/documents/ep07/) for guidelines.*

Based on the AC meeting outcome, the Clinical Pharmacology review team sent the following comment to the Sponsor on February 2, 2018:
"***At the teleconference call on January 25, 2018, you mentioned your plans to conduct a study to assess ex vivo conversion of TU to T over various timepoints after blood draw in subjects dosed with JATENZO. We recommend that you submit the protocol for FDA review prior to initiating the study.***"

Reviewer's Comment: *While the cause is unknown, it appears that potential contributing factors to this observed difference may include the contribution of (1) additives, NaF and/or EDTA; (2) TU to T ex vivo conversion; and/or (3) different sample handling and preparation procedures. It is also not known to what extent the use of NaF/EDTA tubes would inhibit TU to T ex vivo conversion. Further investigation on the rate and extent of the TU to T ex vivo conversion during the time course of plasma sample preparation is warranted in order to determine whether T concentration measurements from plasma in NaF/EDTA tubes in the Phase 3 study are reliable.*

In order to address this deficiency, the Sponsor should conduct an additional in vivo study to compare the total T concentrations measured from serum in plain tubes and plasma in NaF/EDTA

tubes at different time points (e.g., 0, 15, 30, 60, 90, and 120 minutes post-sample collection) using different temperature conditions (e.g., room temperature or on ice) to determine the rate and extent of the TU to T ex vivo conversion during the time course of plasma sample preparation. For instance, a comparison of the following samples after oral administration of JATENZO should be included in the Sponsor's in vivo assessment:

- *Total T concentrations from plasma in NaF/EDTA tubes at 0 (processed immediately after blood collection), 15, 30, 60, 90, and 120 minutes post-sample collection at room temperature*
- *Total T concentrations from plasma in NaF/EDTA tubes at 0 (processed immediately after blood collection), 15, 30, 60, 90, and 120 minutes post-sample collection on ice*
- *Total T concentrations from plasma in tubes without an esterase inhibitor at 0 (processed immediately after blood collection), 15, 30, 60, 90, and 120 minutes post-sample collection at room temperature*
- *Total T concentrations from serum in plain tubes at 30, 60, 90, and 120 minutes post-sample collection at room temperature*

3 PROPOSED PRODUCT LABEL

The following Clinical Pharmacology related parts of the Sponsor's proposed label were submitted in this NDA. Please note that Sections illustrated below does not necessarily reflect the entire corresponding Section of the product label.

Reviewer's Comment: *It has been decided by the multi-disciplinary review team that a formal labeling review will not be conducted during this review cycle. Therefore, the labeling language presented below is* ***solely*** *from the Sponsor's proposed product label.*

Highlights

(b) (4)

3 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/ TS) immediately following this page

4 APPENDICES

4.1 Individual Study Reviews

4.1.1 Phase 3, Efficacy and Safety Study (CLAR-15012)

Title: A Phase 3, Randomized, Active-controlled, Open-label Study of the Safety and Efficacy of Oral TU in Hypogonadal Men

Primary Objective: To determine the efficacy and safety of JATENZO in adult hypogonadal males

Clinical Study Centers: Multiple Centers in U.S.
Clinical Study Period: March 14, 2016 – November 2, 2016

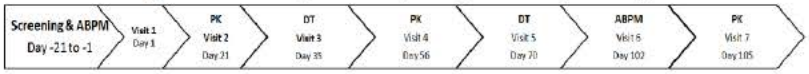
Bioanalytical Study Center: (b) (4)

Bioanalysis Period: June 28, 2016 – November 24, 2016 (b) (4)
March 16, 2016 – January 4, 2017 (b) (4)

Study Design, Treatments, and Drug Administration:
This was a Phase 3, open-label, multicenter study conducted in 222 adult hypogonadal men, 24-65 years (mean: 51.6 years) of age, inclusive with two fasting morning (taken between 6 am and 10 am) serum total T concentrations < 300 ng/dL, approximately 7 days apart. Study participants were randomized in a 3:1 ratio to JATENZO (166 subjects) or Axiron® (56 subjects). 154 subjects (92.8%) and 49 subjects (87.5%) randomized JATENZO and Axiron®, respectively, completed the study.

The study included a 21-day screening phase, two titration phases, two 35-day maintenance phases, and an end-of-study visit (Visit 7). Subjects randomly assigned to JATENZO began treatment at an oral dose of 237 mg TU BID. Subjects who were randomly assigned to Axiron® began treatment at a dose of 60 mg QD in the morning. Axiron® was applied to the axilla only, preferably at the same time each morning, to clean, dry, intact skin. After applying Axiron®, the subject was instructed to allow the application site to dry completely before dressing.

Figure A-1-1: Original Study Design for Subject Progress



Abbreviations: ABPM = automated blood pressure monitor; DT = dose titration; PK = pharmacokinetic

Food intake: Subjects were offered a number of meal choices during confinement; 6 breakfast meal options and 6 dinner meal options. Each of the 6 meal choices included 2 with 15 g fat, 2 with 30 g fat, and 2 with 45 g fat. Without disclosing the nutritional content of the various meal options, subjects were asked to select the meal that most reflected what they would typically eat for breakfast and dinner. Once the subject chose his meal preference, he remained on that meal plan at subsequent PK visits. All lunch options had 30 g of fat. Throughout the study, subjects were encouraged to consume the entire meal; however, study center staff weighed and recorded the weight of unconsumed food from prepared breakfast and dinner meals. For subjects randomly assigned to JATENZO, study drug was administered in the morning and evening (approximately

12 hours apart), immediately before breakfast and dinner. On days when PK samples were obtained, subjects were advised to consume the entire breakfast and dinner meals within 20 minutes after taking JATENZO.

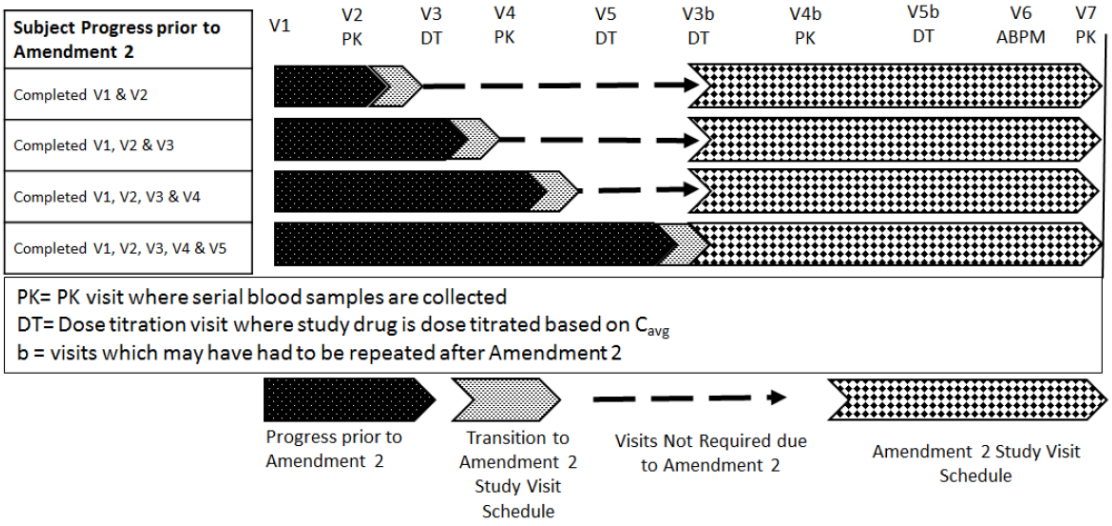
PK sampling: The PK visit confinement periods began at least 1 hour before the morning dose and continued through collection of a blood sample 24 hours after the morning dose, for a total of approximately 26 hours. During confinement, subjects had meals provided, underwent dosing, and had blood samples collected. Blood sampling for total T and DHT PK characterization took place according to the pre-defined sampling schedule (see the *PK Sampling and Characterization* section below for details).

Bioanalytical laboratory issue and amendment: Early in this open-label study, the Sponsor noted that subjects randomized to Axiron® were having their T dose increased in a manner that was inconsistent with the Axiron® product label. The Axiron® product label (Table 4 in Section 14.1 of the label) indicated that, after the first dose titration (Day 60), 78% of the subjects (105/135) remained at the starting dose of 60 mg QD and 21% (29/135) required an increase in dose to 90 mg QD. At that time, 36% (10/28) of the Axiron® subjects in this current study (CLAR-15012) remained on the starting dose of 60 mg QD and 64% (18/28) had undergone dose escalation to 90 mg QD. This difference between the product label and the current study, despite using the same dose-titration algorithm as used in the Axiron® pivotal Phase 3 study, suggested a potential issue with the plasma T assay at (b) (4) upon which the dose-titration decisions were made. Accordingly, the Sponsor requested that (b) (4) re-analyze some of the retained PK samples. At the time of the request, about 114 subjects (total from both treatment groups) had completed at least the first dose-titration visit. The re-analysis results were substantially different (> 20%) from the initial analysis in > 33% of the samples, thus the Sponsor believed it was confirming the suspicion that there was a problem with the plasma T assay. Detail information can be found in the *Bioanalytical Methods* Section of this individual study review.

Typically, such re-analysis referred to as ISR is performed when all the analyses are complete, but it was decided to perform the re-analysis part-way through the study. Since the ISR conducted on June 20, 2016 at (b) (4) did not meet the standards described in the FDA *Bioanalytical Method Validation* Guidance, the T concentrations measured from the NaF-plasma PK samples were determined to be unreliable by the Sponsor and all titration decisions based on the analysis results were under suspect. Therefore, the Sponsor made the decision to re-analyze all NaF-plasma PK Visit 2 samples (first PK visit) at (b) (4). The assay used at (b) (4) to measure T in NaF-plasma samples is a LC-MS/MS method, which had been fully validated, including passing ISR.

Modification to the study design and plan (Amendment 2.0) was necessary to allow subjects to be informed of the decision and to extend their study treatment during the re-analysis of the collected samples with the validated method to ensure that study drug titration was based on reliable C_{avg} results. This change most significantly impacted subjects who had completed the first dose adjustment visit (Visit 3). These subjects had the samples that were collected at Visit 2 re-analyzed and the T C_{avg} re-calculated. These subjects repeated Visit 3 (designated as Visit 3b) in which their JATENZO or Axiron® dose was titrated based on the C_{avg} calculated using the (b) (4) analysis results. After Visit 3b, subjects proceeded through the subsequent study visits as described in the original protocol. Between the time that the assay issue was identified and Visit 3b, subjects remained on study medication at the dose level assigned prior to identification of the assay problem.

Figure A-1-2: Subject Progress Through Study After Amendment 2.0



Abbreviations: ABPM = automated blood pressure monitor; C_{avg} = average concentration; DT = dose titration; PK = pharmacokinetic; V = visit; b = repeat visits after Amendment 2.0

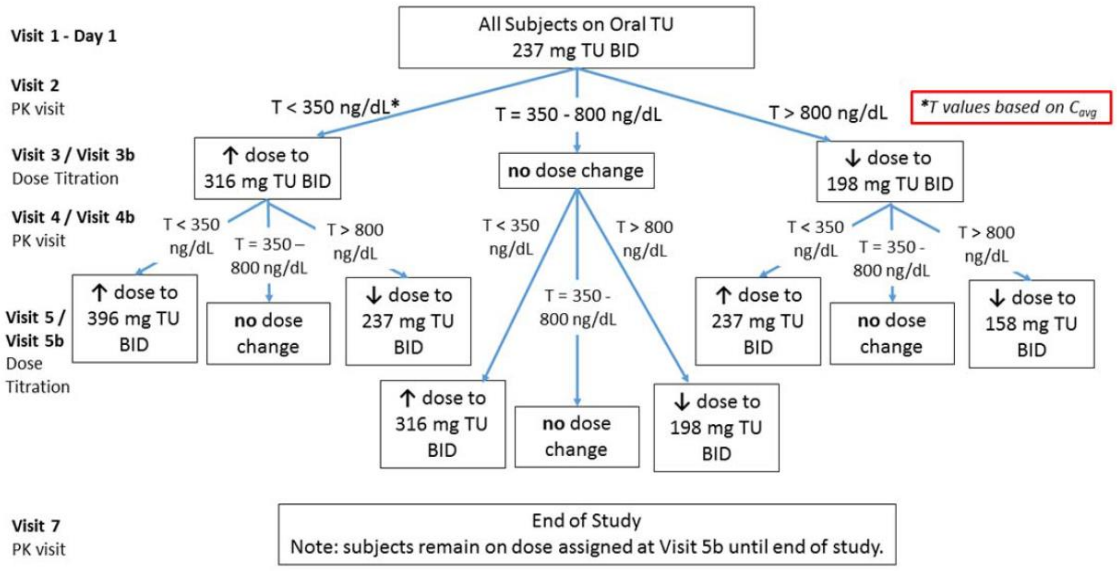
Figure A-1-2 depicts the impact of the need to re-assay Visit 2 PK samples and Amendment 2.0 on the movement of subjects during the approximately 3-week transition period. During the transition period, subjects continued to take their assigned study drug at their current dose level (dose level assigned at the most recent clinic visit). It also shows that subjects who had progressed past Visit 3 needed to repeat Visit 3 (Visit 3b) and any subsequent scheduled visits that they had completed. No subjects had completed Visit 6 at the time the assay issue was recognized, so no subjects repeated either Visit 6 or Visit 7. The changes depicted in Figure A-1-2 are the same for subjects randomized to JATENZO as well as Axiron®.

Throughout this review, Visits 3, 4, and 5, which occurred prior to Amendment 2.0, are designated Visit 3 or V3, Visit 4 or V4, and Visit 5 or V5. If these visits occurred after Amendment 2.0, they are designated with a 'b' suffix, namely Visit 3b (V3b), Visit 4b (V4b) and Visit 5b (V5b). The assessments that occurred at the 'b' visits were the same as the non 'b' visits.

The Sponsor believes that there was no need to wash subjects out prior to the restart of the study, since the subjects had entered the study with confirmed low T values and symptoms consistent with hypogonadism, and as long as TRT dosing duration is long enough to allow T steady state to be reached, any T exposure prior to valid PK visits is irrelevant.

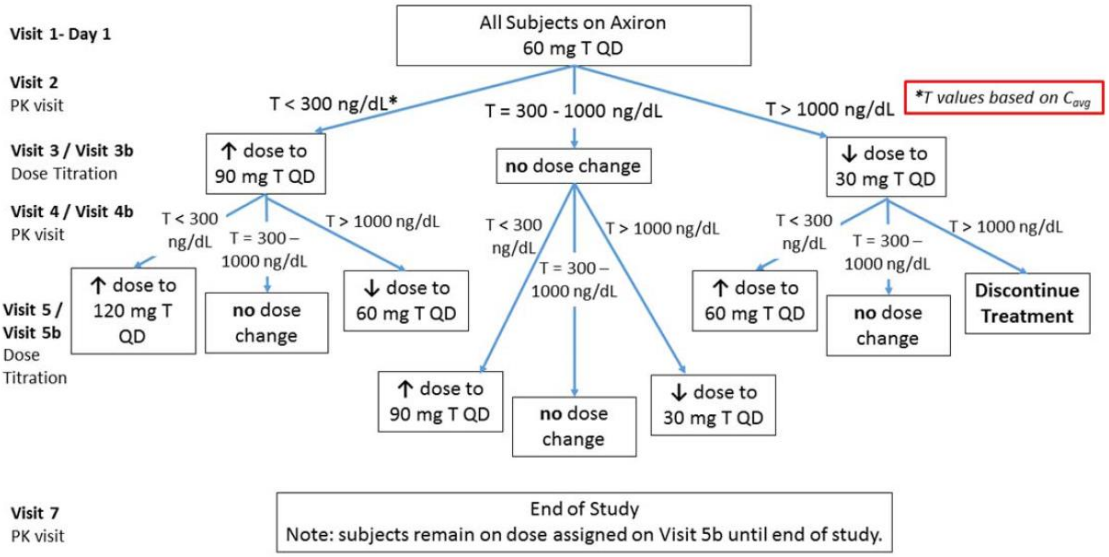
Dose Titration:
For both cohorts, the need for dose titration for each subject was based on the total T C_{avg} over 24 hours (i.e., derived based on plasma T concentrations from blood collected in NaF/EDTA coated tubes) at Visit 2, Visit 4 (depending on the subject's progress prior to Amendment 2.0), and Visit 4b. Dose titrations occurred at Visit 3b and/or Visit 5b, if needed. Depending on the subject's progress prior to Amendment 2.0, dose titrations also might have occurred at Visit 3 and/or Visit 5. The dose titration scheme for JATENZO and Axiron® are illustrated in Figures A-1-3 and A-1-4. The Sponsor reports that the titration boundaries of 350-800 ng/dL were based on PK modeling and simulation using T concentration data collected during the Sponsor's studies (CLAR-09007 and CLAR-12011). It should be noted that the titration boundaries of 300-1,000 ng/dL were used for Axiron® based on the clinical development of Axiron®.

Figure A-1-3: JATENZO Dose Titration Scheme



Abbreviations: BID = twice daily; C_{avg} = average concentration; PK = pharmacokinetic; T = testosterone; TU = testosterone undecanoate; ↑ = increase; ↓ = decrease

Figure A-1-4: Axiron® Dose Titration Scheme



Abbreviations: C_{avg} = average concentration; PK = pharmacokinetic; QD = daily; T = testosterone; ↑ = increase; ↓ = decrease

Inclusion Criteria:

- Male between 18-65 years of age
- Had two morning (i.e., between 6 am and 10 am) serum total T concentrations < 300 ng/dL, at least 7 days apart

Exclusion Criteria:

- Received oral, topical (e.g., gel or patch), intranasal, or buccal T therapy within the previous 2 weeks, intramuscular T injection of short-acting duration (e.g., T enanthate, T cypionate) within the previous 4 weeks, intramuscular T injection of long-acting duration (e.g., Aveed®) within the previous 20 weeks, or T implantable pellets (Testopel®) within the previous 6 months.
- Received oral TU in a previous Clarus-sponsored investigational study.
- Had significant intercurrent disease of any type; in particular, liver, kidney, uncontrolled or poorly controlled heart disease, including hypertension, congestive heart failure or coronary heart disease, or psychiatric illness, including severe depression.
- Had a recent (within 2 years) history of stroke, transient ischemic attack, or acute coronary event.
- At screening,
  - if the subject was not on antihypertensives, regardless of age, and had a mean of the triplicate assessment of systolic blood pressure > 150 mm Hg and/or diastolic blood pressure > 90 mm Hg;
  - if the subject was on antihypertensives and < 60 years of age, and had a mean of the triplicate assessment of systolic blood pressure > 140 mm Hg and/or diastolic blood pressure > 90 mm Hg; or
  - if the subject was on antihypertensives and > 60 years of age, and had a mean of the triplicate assessment of systolic blood pressure > 150 mm Hg and/or diastolic blood pressure > 90 mm Hg.
- Had recent (within 2 years) history of angina or stent (coronary or carotid) placement.
- Had untreated, severe obstructive sleep apnea.
- Had clinically significant abnormal laboratory values, including serum transaminases > 2 × upper limit of normal (ULN), serum bilirubin > 1.5 × ULN, or serum creatinine > 1.5 × ULN.
- Had a hematocrit value of < 35% or > 48%.
- Had a history of polycythemia, either idiopathic or associated with TRT treatment.
- Was a diabetic subject with a glycosylated hemoglobin > 8.5%.
- Had a BMI ≥ 38 kg/m^2.
- If receiving the following medications:
  - Had been on stable doses of lipid-lowering medication for < 3 months (Note: subject was expected to remain on a stable dose of lipid-lowering medication(s) throughout the study);
  - Had been on stable doses of oral medication for diabetes for < 2 months;
  - Had been on stable doses of antihypertensive medication for < 3 months; or
  - Had been on stable doses of anticonvulsant therapy for < 3 months.
- Had an abnormal prostate digital rectal examination (palpable nodules), elevated PSA (serum PSA > 4.0 ng/mL), I-PSS > 19 points at screening, and/or history of, or current or suspected, prostate cancer.
- Had a history of, or current or suspected, breast cancer.
- Had a history of abnormal bleeding tendencies or thrombophlebitis unrelated to venipuncture or intravenous cannulation within the previous 2 years.
- Used dietary supplements such as saw palmetto or phytoestrogens and any dietary supplements that may have increased total testosterone, such as androstenedione or dehydroepiandrosterone within the previous 4 weeks.
- Had known malabsorption syndrome and/or current treatment with oral lipase inhibitors (e.g., orlistat [Xenical®]) and/or bile acid-binding resins (e.g., cholestyramine [Questran®], colestipol [Colestid®]).

- Inability to refrain from smoking during the confinement periods as required by the individual study center.
- Had history of abuse of alcohol or any drug substance within the previous 2 years.
- Poor compliance or unlikely to keep clinic appointments.
- Had received any drug as part of another research study within 30 days of initial dose administration in this study.
- Donated blood (≥ 500 mL) within the 12-week period before the initial study drug dose.
- Current use of the following groups of drugs that affect T concentrations, T metabolism, or concentrations of T metabolites, namely antiandrogens, 5-alpha-reductase inhibitors (e.g., dutasteride, finasteride), estrogens, long-acting opioid analgesics (e.g., methadone hydrochloride, buprenorphine hydrochloride) or human growth hormone.

Removal of Subjects from the Study:
Subjects may have stopped study drug for any of the following reasons:

- Subject request.
- Use of non-permitted concurrent therapy as assessed by the medical monitor and Sponsor.
- Two hematocrit results taken within approximately 5 days of each other were > 54%.
- Repeat mean systolic/diastolic blood pressure (taken on a separate day) was > 180/100 mm Hg and the subject was compliant with antihypertensive medication and the antihypertensive medication was taken on the days that the blood pressure was assessed. Antihypertensive therapy could have been increased, changed or additional therapy added to prevent discontinuing a subject from the study for this reason.
- Non-compliance with the study drug or study schedule.
- Lost to follow-up.
- Occurrence of adverse events not compatible with the continuation of subject participation in the study, in the Investigator's opinion, or unacceptable to the subject to continue.
- Investigator request.
- Significant intercurrent illness.
- Sponsor request.
- Subject-reported treatment failure.

Subjects had the right to withdraw from the study at any time for any reason, without the need to justify their decision. However, the Investigator had to record the reason for the subject's withdrawal, if possible.

Prior and Concomitant Medications:
Medication use (prescription or over-the-counter, including vitamins and herbal supplements) from 6 months before study drug administration through the end of the study was recorded on the concomitant medication electronic case report form (eCRF), including the name, dose, route, frequency of dosing, and reason for use. Subjects were asked about their treatment history for hypogonadism and the start and stop dates for their most recent TRT. In addition, start dates for the use of any medications for hypertension, diabetes, and lipid lowering taken > 3 months within screening were recorded in the eCRF.

Changes in any concomitant drug specifically designed for lipid modification was not allowed during the study. Subjects taking prescribed antihypertensives should have been taking medications on the day of the Screening Visit with sips of water; the medication should have been noted as a prior medication. Any increase in the dose of the antihypertensive medication or any need to add new antihypertensive medications were recorded, and were considered an adverse event and recorded in the eCRF.

Prohibited Medications and Other Restrictions:
Subjects must have remained off all forms of T except for study drug throughout the entire study. Use of dietary supplements such as saw palmetto or phytoestrogens, as well as any dietary supplements that may have affected total T concentrations, such as androstenedione or dehydroepiandrosterone during the study was not permitted. Use of the following groups of drugs that affect T concentrations, T metabolism, or concentrations of T metabolites, namely antiandrogens, 5-alpha-reductase inhibitors (e.g., dutasteride, finasteride), estrogens, long-acting opioid analgesics (e.g., methadone hydrochloride, buprenorphine hydrochloride), or human growth hormone were not permitted during the study.

Subjects were asked to refrain from consuming grapefruit, grapefruit juice, or grapefruit supplements while on study drug. Subjects were asked to observe the smoking restrictions in place at the clinical facility during confinement.

Treatment Compliance:
Compliance with JATENZO was assessed by capsule counts and Axiron® was assessed by weighing the returned Axiron® bottles. The compliance rate is calculated as the total amount of study drug actually used divided by the total amount of expected to be used. The compliance rate is expected to be between 80% and 120%.

PK Sampling and Characterization:
At screening, the total T concentration must have been < 300 ng/dL based on serum samples collected in plain tubes obtained between 6 am and 10 am on 2 separate days (approximately 7 days apart). A NaF-plasma sample for determination of baseline total T was collected pre-dose in a NaF/EDTA tube between 6 am and 10 am at Visit 1 Day 1.

In addition, at Visit 2, Visit 4b, and Visit 7, 24-hour serial blood samples were collected in NaF/EDTA tubes for all subjects at 30 minutes pre-dose and 0, 2, 4, 6, 9, and 12 hours post-morning dose and 2, 4, 6, 9, and 12 hours post-evening dose for the JATENZO cohort and at 30 minutes pre-dose and 0, 2, 4, 6, 9, 12, 14, 16, 18, 21, and 24 hours post-dose for the Axiron® cohort.

Visit 4 PK samples from subjects who had progressed past Visit 4 prior to Amendment 2.0 were only assayed using the plasma T assay from (b) (4) that potentially had an issue, so the results were not included as part of the efficacy analysis.

The Visit 2 and Visit 4b samples assayed at (b) (4) were used to determine the total T C_{avg} values for the 2 dose-titration decisions prior to the final PK visit (Visit 7).

The concentrations of total T and DHT collected at Visit 2, Visit 4b, and Visit 7 were analyzed to derive the PK parameters of C_{max}, T_{max}, area under the plasma concentration-time curve (AUC) and C_{avg} for both the morning and evening dosing intervals (JATENZO only), as well as the entire 24-hour period (JATENZO and Axiron®).

Sample Size Determination:
At least 135 hypogonadal subjects randomized to JATENZO treatment were planned to be enrolled at multiple study centers. The Sponsor reports that the sample size of 135 was based on the following considerations and assumptions:

- If 135 subjects were enrolled, approximately 120 subjects were expected to complete Visit 7;

- The FDA requires that at least 75% of the subjects treated with Oral TU achieve a C_{avg} within the normal range of values for total T and that the lower end of the 95% CI for the proportion must be above 65%;
- Modeling the Phase 3 PK data, but simulating to reflect the current protocol (e.g., dose titration based on C_{avg}, 3 dosage strengths available, 2 titration opportunities, and titration boundaries of 350-800 ng/dL), led to the prediction that 89% (95% CI: 82%, 95%) of subjects would be titrated into the eugonadal range without an excessive number of C_{max} outliers. Given the conditions of the study, the actual proportion of subjects whose C_{avg} normalized was predicted to be 86%;
- If all subjects completed the study and the true percentage in the eugonadal range at Visit 7 was 86%, a sample size of 120 would give over 99% power to show that the observed proportion is above 75% and that the lower end of the 95% CI is above 65%;
- Assuming approximately 12% of treated subjects withdraw before Visit 7, and a multiple imputation method that projects the missing data as if the subject were to continue on oral TU, the effective probability of success would be approximately 85%. A sample size of 120 subjects would still give over 99% power that the observed proportion would be above 75% and the lower end of the 95% CI would be above 65%;
- If the true proportion of being in the eugonadal range is only 80%, the power to show a 75% or greater proportion with a lower end of the CI above 65% would be nearly 90%;
- If the observed percentage in the eugonadal range is 75%, then the lower end of the 95% CI would be 75% - 1.96 × (75% × 25%/120)1/2 = 67%, which would satisfy the requirement of being above 65%.

The study included an Axiron® treatment group as a comparator treatment for safety. Forty-five (45) subjects were to be randomly assigned to receive Axiron®. This sample size was based on the numbers required for the ambulatory blood pressure monitoring (ABPM) assessment. ABPM was performed during the study to evaluate blood pressure changes, a surrogate of cardiovascular risk. The daytime systolic blood pressure was the blood pressure measure upon which the power calculations were performed, because changes in systolic blood pressure are the best predictor of cardiovascular risk in an older age population (Pickering, 2003). Based on the planned sample size of at least 45 hypogonadal subjects enrolled into the Axiron® arm, approximately 39 were expected to complete through Visit 7. This number was based on the following considerations:

- Assuming approximately 12% of treated subjects withdraw before completing the ABPM measurements at Visit 6, and approximately 10% of the ABPM measures are not interpretable, then enrolling 45 subjects on Axiron® and 135 subjects on JATENZO would result in analyzable data on approximately 35 subjects on Axiron® and 105 subjects on JATENZO;
- Review of the ABPM literature showed that the SD of systolic blood pressure is roughly 8 mm Hg, with a correlation over 3 months of 0.71 (Palatini, 1994);
- A systolic blood pressure change > 4.9 mm Hg was considered clinically significant (Verdecchia, 2010).

A study with ABPM data on 35 subjects on Axiron® and 105 subjects on JATENZO (i.e., the original recruitment targets) had more than 85% power to rule out a baseline-corrected $\leq$ 4.9 mm Hg systolic blood pressure increase in the JATENZO group relative to the Axiron® group, assuming that the 2 formulations had equal effects on systolic blood pressure.

Efficacy and Safety Variables and Assessments

The primary efficacy endpoint: The number and percentage of subjects with a plasma total T C_{avg} within the normal range of $\geq$ 252 ng/dL and $\leq$ 907 ng/dL on Day 105 (Visit 7).

The primary efficacy endpoint, C_{avg}, was calculated from the AUC using the following formula:

$$C_{avg} = AUC(0\text{-}24) / 24$$

Actual collection times were used in the calculation. The study was considered to have met its efficacy criteria if the percentage was ≥ 75% and the lower bound of the 95% CI was ≥ 65%.

The analysis of the primary efficacy endpoint was performed according to the rules outlined in Table A-1-1 using the ITT Population (i.e., all subjects who actually received at least 1 dose of study drug). In this analysis, subjects who dropped out prior to Visit 7 due to a possible treatment-related cause, such as an adverse event, were counted as treatment failures, while subjects who dropped out for other causes (e.g., site closure not related to study conduct) had their T C_{avg} imputed using last observation carried forward (LOCF).

Table A-1-1: Primary Efficacy Analysis Rules in Study CLAR-15012

Reason for Stopping Oral TU Prior to Visit 7	**Analysis**
Died before Visit 7 measurement	For efficacy analysis subject: Included in denominator Defined as failure in the numerator For calculation of testosterone C_{avg}: Used LOCF to insert a value for the subject, so his value was part of the calculation of the mean testosterone C_{avg}.
Experienced an adverse event that led to stopping Oral TU	For efficacy analysis subject: Included in denominator Defined as failure in the numerator For calculation of testosterone C_{avg}: Used LOCF to insert a value for the subject, so his value was part of the calculation of the mean testosterone C_{avg}.
Did not tolerate TU or reported it was not effective (eg, subject said the product was not effective for him)	For efficacy analysis subject: Included in denominator Defined as failure in the numerator For calculation of testosterone C_{avg}: Used LOCF to assess whether subject was in the eugonadal range.
Moved from area, withdrew consent without indicating that it was related to the therapy, was lost to follow-up, or did not have a measurement at Visit 7	For efficacy analysis subject: Used LOCF to assess whether subject was in the eugonadal range. For calculation of testosterone C_{avg}: Used LOCF value for the calculation of the mean testosterone C_{avg}.

Abbreviations: C_{avg} = average concentration; LOCF = last observation carried forward; TU = testosterone undecanoate

Reviewer's Comment: *In response of the Division's request, the Sponsor conducted a dedicated study to determine the normal (i.e., eugonadal) T concentration range based on the Sponsor's proposed blood sample collection and bioanalytical methods. In this study, T concentrations measured in blood collected in plain (red top) tubes and NaF/EDTA tubes in the morning were compared in 97 healthy males aged 18-40 years old. When blood was collected into plain tubes and processed, serum was obtained; when blood was collected into NaF/EDTA tubes and processed, plasma was obtained. Both serum and plasma samples were analyzed using a LC-MS/MS method. A normal T range was established based on the mean ± 2 SD. Based on the serum*

T concentrations from the 97 men, the derived normal range (304 to 1,030 ng/dL) was comparable to the commonly used 300-1,000 ng/dL. The equivalent normal T range in the plasma collected in NaF/EDTA tubes were 252-907 ng/dL, and was used for assessing the efficacy in the current study. Reference is made to Section 4.1.4 for the details of Study CLAR-16014.

Key PK Safety Endpoint:
The key PK safety endpoint, total T C_{max}, had the following criteria that were expected to be met on Day 105 (Visit 7):

- Having < 5% of subjects with a plasma total T C_{max} in the range of 1,800-2,500 ng/dL
- No subjects with a plasma total T C_{max} of > 2,500 ng/dL
- Having a plasma total T $C_{max} \leq$ 1,500 ng/dL in at least 85% of subjects

Reviewer's Comment: *The Sponsor states that in the FDA background document for the September 17, 2014 public meeting of the Drug Safety and Risk Management Advisory Committee indicated that the C_{max} outlier criteria are independent of the upper limit for C_{avg} used in the primary efficacy analysis. A supplementary analysis was performed in which the C_{max} criteria boundaries were adjusted for the upper limit of C_{avg}, namely 907 ng/dL. T C_{max} over 24 hours was evaluated by estimating the proportions of Oral TU-treated subjects at Visit 7 according to the following categories: < 1,361 ng/dL, > 1,633 to ≤ 2,268 ng/dL, and > 2,268 ng/dL (e.g., 1,500, 1,800, or 2,500 ng/dL × 0.907).*

Other Secondary efficacy/safety variables:

- Psychosexual Daily Questionnaire (PDQ) to assess the subject's sexual function and mood changes
- Concentrations of DHT (i.e., Visits 2, 4b, and 7) and E2 (i.e., Visit 7)
- Adverse events
- Vital signs including office cuff, ABPM, and International Prostate Symptom Score (IPSS)
- Physical examinations
- Laboratory evaluations (e.g., clinical chemistry, hematology, hematocrit, HDL cholesterol, and PSA)
- Cosyntropin stimulation test

Other Safety Assessments:
Other safety variables included assessment of adverse events (AEs), vital signs (including office cuff and ABPM), physical examinations, and laboratory evaluations (e.g., clinical chemistry and hematology, particularly hematocrit, HDL cholesterol, and prostate-specific antigen [PSA]). Prostate symptoms were assessed using the I-PSS.

Subjects with clinically significant symptoms or abnormal physical findings were followed until the abnormal finding resolved or until further care was no longer required. Any abnormal clinical laboratory results were followed by the Investigator to resolution, whenever possible.

The schedule of procedures of this study is presented in Tables A-1-2 and A-1-3 below.

Table A-1-2: Schedule of Assessments – Main Study and Cosyntropin Stimulation Test Sub-study
(Study CLAR-15012; Planned prior to Amendment 2.0)

Activity	Screening			Treatment/Maintenance								
	Screen 1	Screen 2	Screen 3	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	
Study Days	Day -21 to Day-3	~7 Days After Screen 1	Day -2 (±1 Day)	Day 1[a]	Day 21 (±3 days)	Day 35 (±2 days)	Day 56 (±3 days)	Day 70 (±2 days)	Day 102 (±2 days)	Day 105 (±3 days)	Day 106	Early Withdrawal
Informed consent signed	X											
Inclusion/exclusion	X	X	X									
Medical history review	X											
Review of prior and concomitant medications	X	X	X	X	X	X	X	X	X	X		X
Physical with DRE[b]		X								X		X
Brief physical[b]					X		X					
Weight and height	X											
Adverse event assessment		X		X	X	X	X	X	X	X		X
Vital signs (sitting BP and HR in triplicate)	X			X	X		X			X		X
Randomization number				X								
Sample collection												
Abbreviated safety laboratory tests (fasting)[c]				X								
Complete safety laboratory tests (fasting)[d]		X					X			X		X
Urine dipstick		X										
Total T between 6:00 and 10:00 AM	X	X										
SHBG, albumin, LH, and FSH (predose)				X	SHBG only					X		
PSA		X								X		X
Predose total T, DHT, estradiol between 6:00 and 10:00 AM				X[e]								
Serial sampling (24 hour over-night stay) total T, DHT, estradiol[f]					X		X			X		
Saliva for T[g]					X		X			X		

Activity	Screening			Treatment/Maintenance								
	Screen 1	Screen 2	Screen 3	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	
Study Days	Day -21 to Day-3	~7 Days After Screen 1	Day -2 (±1 Day)	Day 1[a]	Day 21 (±3 days)	Day 35 (±2 days)	Day 56 (±3 days)	Day 70 (±2 days)	Day 102 (±2 days)	Day 105 (±3 days)	Day 106	Early Withdrawal
Sample collection (cont.)												
Predose exploratory serum sample for ApoA1 assessment, cholesterol efflux analysis, and hepcidin[h]				X						X		
Dose titration (based on 24-hour T C_{avg})						X		X				
I-PSS	X									X		X
Dispense PDQ[i]		X						X				
Collect PDQ				X						X		
24-hour ABPM assessment[j]			X						X			X[k]
Study drug administration				X	X	X	X	X		X		
Study drug accountability					X	X	X	X		X		X
Study drug dispensed				X	X	X	X	X				
Cosyntropin stimulation test substudy – only												
Cosyntropin stimulation test[l]				X							X	

ABPM = ambulatory blood pressure monitor; ApoA1 = apolipoprotein A-1; BP = blood pressure; C_{avg} = average concentration; DHT = dihydrotestosterone; DRE = digital rectal examination; EDTA = ethylenediaminetetraacetic acid; FSH = follicle-stimulating hormone; HR = heart rate; I-PSS = International Prostate Symptom Score; LH = luteinizing hormone; NaF = sodium fluoride; PDQ = Psychosexual Daily Questionnaire; PSA = prostate-specific antigen; SHBG = sex hormone binding globulin; T = testosterone; TU = testosterone undecanoate

[a] Visit 1 was to have occurred between 6:00 and 10:00 AM.

[b] A complete physical examination included, at minimum, an examination of head/eyes/ears/nose/throat, a DRE of the prostate, breast and testicular exams. An abbreviated physical examination included, at minimum, examination of head/eyes/ears/nose/throat. On those visits where PSA was collected, the PSA was to have been collected before the DRE.

[c] Subjects were to be reminded to fast from food but to take all concomitant medications before the study visit. Chemistry panel (sodium, potassium, chloride, bicarbonate, glucose, calcium), lipids (total cholesterol, high-density lipoprotein, low-density, triglycerides), complete blood count.

[d] Chemistry panel (sodium, potassium, chloride, bicarbonate, glucose, calcium), alanine aminotransferase, aspartate transaminase, alkaline phosphatase, bilirubin, creatinine, lipids (total cholesterol, high-density lipoprotein, low-density lipoprotein, triglycerides), albumin, complete blood count.

[e] Blood samples for total T, DHT, and estradiol: Subjects had 1 Plain tube (for serum) and 1 NaF-EDTA-containing tube (for plasma) collected.

[f] Blood samples for total T, DHT, and estradiol: Subjects had 1 Plain tube (for serum) and 1 NaF-EDTA-containing tube (for plasma) collected. Subjects in the Oral TU treatment group: blood samples were collected -30 minutes and 0, 2, 4, 6, 9, and 12 hours after AM dose and 2, 4, 6, 9, and 12 hours after PM dose. Subjects in the Topical Axiron treatment group: blood samples were collected -30 minutes and 0, 2, 4, 6, 9, 12, 14, 16, 18, 21, and 24 hours after AM dose. Estradiol was not assayed in the Visit 2 or Visit 4 samples.

[g] Saliva was collected into clean sterile cups 4 hours after the AM dose, frozen immediately and samples stored at −20 °C. The subject was to have avoided food for 1 hour before saliva collection and was not to have brushed or flossed his teeth 30 minutes before collecting saliva. Saliva samples were stored for possible future analysis.

[h] Samples were collected, frozen, and stored for potential future analysis to address questions related to lipid-related analyses and/or hematocrit changes, and/or other changes observed with testosterone replacement therapy.

[i] The PDQ was dispensed as paper booklets at Screen 2 and Visit 5b. Subjects were instructed to complete the questionnaire for 7 consecutive days before Visit 1 and Visit 7.

[j] Ambulatory BP monitor was placed on subject at Screen 3 and again at Visit 6. The subject returned the monitor to the study center the following day and study center determined whether a minimum number of readings for a valid ABPM interpretation was seen, if not, the subject was asked to repeat the 24-hour ABPM (unscheduled visit).

[k] 24-hour ABPM at early withdrawal, if feasible.

[l] A subset of subjects participated in the cosyntropin stimulation test at selected study centers. A separate informed consent was signed. Subjects were injected with 0.25 mg cosyntropin and blood samples for cortisol assay were collected immediately before the injection, as well as 30 and 60 minutes after the injection at each visit. At Visit 1, the cosyntropin stimulation test was conducted before administration of study drug. At Visit 8, subjects remained at the study center after the last 24-hour serial blood sample had been obtained before beginning the cosyntropin stimulation test.

Table A-1-3: Schedule of Assessments (Study CLAR-15012; After Amendment 2.0)

Activity	Visit 3b (Repeat Titration Visit 3)	Visit 4b (Repeat Serial PK Visit 4)	Visit 5b (Repeat Titration Visit 5)	Visit 6	Visit 7	Visit 8	Early Withdrawal
Amended informed consent signed	X						
Review of prior and concomitant medications	X	X	X	X	X		X
Physical examination with DRE					X		X
Brief physical examination		X					
Adverse event assessment	X	X	X	X	X		X
Vital signs (sitting blood pressure and heart rate in triplicate)		X			X		X
Sample collection							
Complete safety laboratory tests (fasting)		X			X		X
SHBG, albumin, LH, and FSH (predose)		X			X		
PSA					X		X
Serial sampling (24 hour over-night stay) total T, DHT, estradiol		X[a]			X		
Saliva for T		X			X		
Predose exploratory serum sample for ApoA1 assessment, cholesterol efflux analysis, and hepcidin					X		
Dose titration (based on 24-hour T C_{avg})	X		X				
I-PSS					X		X
Dispense PDQ			X				
Collect PDQ					X		
24-hour ABPM assessment				X			X
Study drug administration	X	X	X		X		
Study drug accountability	X	X	X		X		X
Study drug dispensed	X	X	X				
Cosyntropin stimulation test substudy – only							
Cosyntropin stimulation test						X	

ApoA1 = apolipoprotein A-1; C_{avg} = average concentration; DHT = dihydrotestosterone; DRE = digital rectal examination; FSH = follicle-stimulating hormone; I-PSS = International Prostate Symptom Score; LH = luteinizing hormone; PDQ = Psychosexual Daily Questionnaire; PK = pharmacokinetic; PSA = prostate-specific antigen; SHBG = sex hormone binding globulin; T = testosterone

[a] Estradiol was not assayed in the Visit 4b samples.

Bioanalytical Methods:
Human blood sample were collected into plain (red-top) tubes and tubes that contained NaF/EDTA. Samples collected in plain tubes were held at room temperature for 30 minutes and then centrifuged for 20 minutes. Samples collected in tubes containing NaF/EDTA were chilled for 30 minutes on ice and centrifuged for 20 minutes. Samples were transferred in aliquot storage tubes and frozen at -20ºC and then shipped for analysis.

The two bioanalytical laboratories used for this study were [redacted] (b) (4) (serum in plain tubes) and [redacted] (b) (4) (plasma in NaF/EDTA tubes). Bioanalysis for total T and DHT used in the primary efficacy analysis was conducted at [redacted] (b) (4)

Bioanalysis for Serum in Plain Tubes
For screening, when men have not been administered oral TU, samples can be collected in plain tubes which do not contain the esterase inhibitor NaF. Serum T concentrations were measured using a LC-MS/MS method at the [redacted] (b) (4) For this study, eligibility was based in part on serum T concentrations measured at two consecutive visits.

T was extracted from plasma by liquid-liquid extraction (LLE). The extracted samples were dried under a stream of nitrogen, the residue was reconstituted.

Reconstituted sample extracts were analyzed using a Shimadzu HPLC System equipped with an Applied Biosystems Sciex API 5500 triple quadrupole mass spectrometer. Chromatographic separation was performed on an Thermo Hypersil, 100 x 1.0 mm, 3 µm-column for T using gradient elution. Positive ions generated from the electrospray ion source were detected using the MRM mode. Quantitation was performed using a weighted linear regression ($1/concentration^2$) of the determined peak area ratios for T and T-d_2 (IS). The LC-MS/MS method was developed and validated with the dynamic range of 0.02-20 ng/mL (2-2,000 ng/dL) for total T. Calibration standards and QC samples for T were prepared in serum collected in plain tubes.

The nominal concentrations for the T quality controls (QCs) were as follows:

- QC1: 6.2 ng/dL
- QC2: 12.4 ng/dL
- QC3: 512 ng/dL
- QC4: 912 ng/dL
- QC5: 1512 ng/dL

Accuracy and precision of the calibration standards and QC samples for total T from serum in plain tubes during sample analysis were within the pre-specified acceptance range per the Agency's *Bioanalytical Method Validation Guidance*.

Long-term storage stability for total T in human plasma at -20°C was established for 3 years.

Stability (i.e., accuracy of ≤ 15%) of total T in human serum was confirmed for 10 freeze/thaw cycles, respectively.

After 24 hours in human serum on the bench-top at room temperature (25ºC), the % REs of the replicate analyses of total T QC samples were always ≤ 15%.

ISR was conducted on 193 samples (5.9%) for total T, out of a total of 3,268 study samples. For total T, 169 out of 193 ISR samples (87.6%) were within ± 20% of the original results. These ISR results confirmed the reproducibility of the bioanalytical method.

Bioanalysis for Plasma in NaF/EDTA Tubes

T and DHT were extracted from plasma by LLE. The extracted samples were dried under a stream of nitrogen, the residue was reconstituted.

Reconstituted sample extracts were analyzed using a Waters UPLC System equipped with an Applied Biosystems Sciex API 5000 triple quadrupole mass spectrometer. Chromatographic separation was performed on an ACE Excel 2 C18-PFP, 100 x 3.0 mm, 2 µm-column for T and DHT using gradient elution. Positive ions generated from the electrospray ion source were detected using the multiple reaction monitoring (MRM) mode. Quantitation was performed using a weighted linear regression ($1/concentration^2$) of the determined peak area ratios for T, DHT, T-d_3 (IS), and DHT-d_4 (IS). The LC-MS/MS method was developed and validated with the dynamic range of 0.1-30 ng/mL (10-3,000 ng/dL) and 0.05-5 ng/mL (5-500 ng/L) for total T and DHT, respectively.

Calibration standards and QC samples for T and DHT were prepared in human NaF/Na_2EDTA plasma. The endogenous concentration of the analyte in unstripped human NaF/Na_2EDTA plasma was determined using 6 zero standard unstripped samples which are blank unstripped samples containing the ISs. This measured concentration (i.e., average of the six samples) was then added to the spiked amounts to obtain the final nominal concentrations of QC1, QC2, QC3, and QC4 prepared in that unstripped matrix. The nominal concentrations for the T QCs were as follows:

- QC1: 357.6; 364.5; 366.3; and 417.7 pg/mL
- QC2: 15,157.6; 15,164.5; 15,166.3; and 15,217.7 pg/mL
- QC3: 22,657.6; 22,664.5; 22,666.3; and 22,717.7 pg/mL
- QC4: 2,557.6, 2,564.5, 2,566.3, and 2,617.7 pg/mL

The nominal concentrations for the DHT QCs were as follows:

- QC1: 140.6 pg/mL
- QC2: 440.6 pg/mL
- QC3: 2,540.6 pg/mL
- QC4: 3,790.6 pg/mL

Accuracy of the calibration standards and QC samples during sample analysis was expressed as percent difference from theoretical concentration (i.e., % RE). For NaF/Na_2EDTA plasma total T, the %RE ranged from -1.8% to 1.2% for the 8 calibration standards in the range of 0.1-30 ng/mL and -8.0% to 2.9% for QC1, QC2, QC3, and QC4. For NaF/Na_2EDTA serum DHT, the % RE ranged from -0.9% to 0.7% for the 8 calibration standards in the range of 0.05-5 ng/mL and -6.5% to 4.7% for QC1, QC2, QC3, and QC4.

Precision of the calibration standards and QC samples during sample analysis was expressed as the percent % CV. For NaF/Na_2EDTA plasma total T, the % CV ranged from 1.8% to 6.3% for the 8 calibration standards in the range of 0.1-30 ng/mL and 2.3% to 5.4% for QC1, QC2, QC3, and QC4. For NaF/Na_2EDTA plasma DHT, the % CV ranged from 2.0% to 4.9% for the 8 calibration standards in the range of 0.05-5 ng/dL and 2.5% to 8.8% for QC1, QC2, QC3, and QC4.

Long-term storage stability for both T and DHT in human plasma at -80°C was established for 246 days.

Stability (i.e., accuracy of ≤ 15%) of both T and DHT in human NaF/Na_2EDTA plasma was confirmed for 4 freeze/thaw cycles.

After 23 hours and 55 minutes in human NaF/Na_2EDTA plasma on the bench-top at room temperature, the % REs of the replicate analyses of T and DHT QC samples were always ≤ 15%.

ISR was conducted on 459 samples (6.2%) for total T and 446 samples (5.6%) for DHT out of a total of 7,934 study samples. For total T, 445 out of 459 ISR samples (96.9%) were within ± 20% of the original results. For DHT, 427 out of 446 ISR samples (95.7%) were within ± 20% of the original results. These ISR results confirmed the reproducibility of the bioanalytical method.

OSIS Inspection of the bioanalytical study site: The Clinical Pharmacology review team requested an inspection on bioanalytical study site on (b) (4) However, the DNDBE within the OSIS recommended to accept the bioanalytical data without on-site inspection as (b) (4) was inspected recently (dates not specified) and the inspection outcome was classified as No Action Indicated (NAI). Reference is made to the OSIS Memorandum issued on August 21, 2017 in DARRTS.

It should be noted that on February 26, 2014, the Clinical Pharmacology review team requested an inspection on the bioanalytical site (i.e., (b) (4) (b) (4) that conducted the bioanalysis of Phase 3 studies, CLAR-12011 and CLAR-09007 during the original NDA review cycle. Following inspections, the OSIS concluded that the clinical and bioanalytical data from (b) (4) are acceptable for further Agency review. Reference is made to the OSIS Memorandum issued on August 8, 2014 in DARRTS.

Reviewer's Comment: *The acceptance criteria and performance of the total T and DHT bioanalytical methods are in compliance with the Agency's Bioanalytical Method Validation Guidance. In summary, the method validation and performance of the bioanalytical methods in clinical studies are acceptable and there are no unresolved bioanalytical issues related to the approvability of JATENZO.*

The Sponsor conducted an investigation comparing the total T concentration measurements from plasma in NaF/EDTA tubes and serum in plain tubes. Reference is made to the "Plasma Total T PK" section of this individual study review.

Bioanalysis for E2, E2 concentrations were measured in serum samples isolated from whole blood drawn into plain blood collection tubes collected at Visit 1 and Visit 7. E2 was analyzed using a validated LC-MS/MS method at the (b) (4) for this study. The dynamic range was 2 pg/mL (0.2 ng/dL) – 2,000 pg/mL (200 ng/dL). Precision (%CV) ranged 4.23% - 12.48%, while the accuracy ranged 92.85% - 103.7%. It was demonstrated that 80.2% of the ISR results were acceptable.

Reviewer's Comment: *While concentrations of E2 were also measured, it should be noted that this review is focused on T and DHT concentrations that are relevant to the primary and secondary endpoints. However, the method validation and performance of the bioanalytical method for E2 was reviewed and considered acceptable.*

Disposition of Subjects:

Of the 537 screened subjects from multiple study centers in the U.S., 222 were eligible to be enrolled into the study. The most common reason for screening failure was subjects who did not meet inclusion criteria for diagnosis of hypogonadism, primarily due to screening serum T concentrations $\geq$ 300 ng/dL (183 subjects), unable to commit to appointment schedule or compliance with study procedures (29 subjects), and elevated hematocrit values (23 subjects).

The remaining 222 subjects were randomized in a 3:1 ratio to JATENZO (166 subjects) or Axiron® (56 subjects); all but 1 subject randomized to Axiron® received at least 1 dose of study drug. The proportions of subjects who completed the study were similar between the treatment groups (JATENZO: 92.8%; Axiron®: 87.5%). The most common reason for early discontinuation from the study was subject request in the JATENZO group (3.0%) and subject request and "other" in the Axiron® group (5.4% each). Adverse events led to early discontinuation from the study in 4 (2.4%) JATENZO subjects and 1 (1.8%) Axiron® subject. A summary of subject disposition is presented by treatment group for the ITT Population in Table A-1-5.

Table A-1-5: Overall Subject Disposition by Treatment Group – ITT Population

Number of Subjects (%)	Oral TU	Topical Axiron
Subjects Randomized	166	56
Subjects Treated (Modified ITT)	166	55
Subjects Who Completed Study	154 (92.8)	49 (87.5)
Subjects Who Discontinued Early from the Study	12 (7.2)	7 (12.5)
Reasons for Early Discontinuation		
Subject Request	5 (3.0)	3 (5.4)
Subject no longer able to commit to study procedures (eg, due to work)	3	1
Subject moved out of state	1	1
Subject felt he was under dosed	0	1
Spouse requested subject withdrawal due to his general health problems	1	0
Adverse Events	4 (2.4)	1 (1.8)
Lost to Follow-up	2 (1.2)	0
Non-compliance with Study Drug or Procedure	1 (0.6)	0
Other[a]	0	3 (5.4)

Source: Post-text Table 14.1.1.2.1
Abbreviations: ITT = intention-to-treat; PSA = prostate-specific antigen; TU = testosterone undecanoate
[a] Other reasons included: subject had high PSA prestudy, was not eligible, and subsequently withdrew; subject withdrew consent after realizing he was randomized to Topical Axiron instead of Oral TU; and site closure not related to study conduct.
Note: Percentages were calculated from the total number of randomized subjects per treatment group.

Data Sets Analyzed:
The analysis populations used in this study are described as follows:

- ITT Population: All subjects who were randomized to either JANTENZO or Axiron®.
- Modified ITT Population: All subjects who actually received at least 1 dose of study drug. The Modified ITT Population was used for the primary analysis and all sensitivity analyses.
- Safety Population: All subjects randomly assigned into the study who took at least 1 dose of study drug (identical to the Modified ITT Population). This population was used to analyze all safety endpoints, with the exception of the ABPM-measured blood pressures.
- PK Population: All subjects in the study who had at least 1 evaluable PK profile (calculable C_{max} and 24-hour C_{avg}) and no significant protocol deviation. A Completers Population was also defined as all subjects in the PK Population who had an evaluable total testosterone C_{avg} at Visit 7.
- ABPM Population: All subjects who had ABPM measurements and had interpretable results at both the pre-dose visit (Screen 3) baseline and Visit 6.
- Cosyntropin Stimulation Test Sub-study Population: All subjects who participated in this sub-study and had interpretable results at both baseline (Visit 1 Day 1) and Visit 8. The analysis only included subjects who had normal results at baseline.

Table A-1-6: Summary of Data Sets Analyzed (All Randomized Subjects)

Population, n (%)	Oral TU (N=166)	Topical Axiron (N=56)
ITT (all randomized subjects)	166 (100.0)	56 (100.0)
Modified ITT (≥1 study drug dose)	166 (100.0)	55 (98.2)
PK (at least one evaluable PK profile)	166 (100.0)	55 (98.2)
Safety (all randomized and ≥1 study drug dose)	166 (100.0)	55 (98.2)
ABPM	135 (81,3)	45 (80.4)
Cosyntropin Sub study	24 (14.5)	8 (14.3)

Reviewer's Comment: *All subjects randomized in the study were included in the ITT Population. The 1 subject randomized to the Axiron® treatment arm who was never dosed was excluded from the Modified ITT, Safety, and PK Populations.*

Approximately 80% of the subjects in both treatment groups had ABPM measurements with interpretable results at Screening and Visit 6 and were included in the ABPM Population.

Approximately 30 subjects (15 subjects randomly assigned to JATENZO and 15 subjects to Axiron®) were planned to participate in the cosyntropin stimulation sub-study; however, the numbers of subject enrolled were consistent with the 3:1 randomization ratio used in the study (24 JATENZO and 8 Axiron®).

Demographics of Subjects:

The mean age of subjects was 51.6 (range: 24-65) years old for the JATENZO group and 53.4 (range: 31-65) years for the Axiron® group. The majority of subjects were Caucasian (80.1% in the JATENZO group; 75.0% in the Axiron® group). The mean BMI was 31.8 (range: 17-38) kg/m^2 for the JATENZO group and 30.9 (range: 17-38) kg/m^2 for the Axiron® group. Demographics are summarized in Table A-1-7.

Table A-1-7: Demographics of ITT Population

Characteristic	Oral TU (N = 166)	Topical Axiron (N = 56)
Age (years)		
Mean (SD)	51.6 (9.08)	53.4 (7.86)
Median	53.0	53.0
Minimum, Maximum	24, 65	31, 65
Race, n (%)		
American Indian or Alaska Native	0	1 (1.8)
Asian	3 (1.8)	2 (3.6)
Black or African American	29 (17.5)	11 (19.6)
White	133 (80.1)	42 (75.0)
Other	1 (0.6)	0
Ethnicity, n (%)		
Hispanic or Latino	25 (15.1)	15 (26.8)
Not Hispanic or Latino	141 (84.9)	41 (73.2)
Height (cm)		
Mean (SD)	178.4 (6.81)	178.4 (7.61)
Median	179.0	177.8
Minimum, Maximum	159, 194	163, 193
Weight (kg)		
Mean (SD)	101.4 (15.75)	98.2 (14.24)
Median	100.1	97.5
Minimum, Maximum	50, 136	64, 131
BMI (kg/m^2)*		
Mean (SD)	31.8 (4.16)	30.9 (4.13)
Median	32.2	30.6
Minimum, Maximum	17, 38	21, 38
BMI Categories, n (%)		
Under Weight: < 18.50 (kg/m^2)	1 (0.6)	0
Normal Weight: 18.50-24.99 (kg/m^2)	7 (4.2)	4 (7.1)
Overweight: 25.00-29.99 (kg/m^2)	50 (30.1)	20 (35.7)
Obese: ≥ 30.00 (kg/m^2)	108 (65.1)	32 (57.1)

Source: Post-text Table 14.1.3.1.1

Abbreviations: BMI = body mass index; ITT = intention-to-treat; SD = standard deviation; TU = testosterone undecanoate

Protocol Deviations:
Violations of enrollment criteria were reported for 4 (2.4%) JATENZO subjects including hematocrit value > 48% (2 subjects), inadequate washout of prior testosterone medication (1 subject), and HbA1c test not performed for a diabetic subject (1 subject). Violations of enrollment criteria were reported for 2 (3.6%) Axiron® subjects including participation in the cosyntropin substudy despite having a pituitary adenoma (1 subject) and enrollment after Amendment 1.0 without documented hypogonadism signs and symptoms (1 subject).

There were no protocol deviations of significance related to PSA, blood lipids, or vital signs. The reported protocol deviations are not expected to affect study conclusions.

Treatment Compliance Results:
Mean and median percent compliance during the study was comparable between the two treatment groups (Table A-1-8). The proportion of subjects who were 80% to 120% compliant with their dosing regimen throughout the study was 91.0% in the JATENZO group and 85.5% in the Axiron® group.

Table A-1-8: Summary of Treatment Compliance (Safety Population)

Characteristic	Oral TU (N = 166)	Topical Axiron (N = 55)
Percent Compliance with Study Drug	n = 162	n = 55
Mean (SD)	96.6 (11.06)	94.3 (15.33)
Median	98.1	93.3
Minimum, Maximum	42, 154	43, 136
Proportions of Subjects by Compliance Category, n (%)		
< 80% Compliance	8 (4.8)	4 (7.3)
≥ 80% to ≤ 120% Compliance	151 (91.0)	47 (85.5)
> 120% Compliance	3 (1.8)	4 (7.3)
Unknown	4	0

Source: Post-text Table 14.1.5.1.1
Abbreviations: SD = standard deviation; TU = testosterone undecanoate

Compliance was unable to be determined for 4 JATENZO subjects (i.e., Subjects (b) (6)) as they failed to return at least 1 of the study drug bottles dispensed and the site was unable to provide any additional information regarding these missing bottles.

The 3 subjects in the JATENZO group that had a compliance rate > 120% are listed below:

- Subject (b) (6): He did not return a bottle of JATENZO at Visit 7, which had been dispensed at Visit 5b. Because it was assumed that he consumed all 120 capsules in the bottle during his 8-day period between V5b and Visit 7 (the subject prematurely discontinued from the study), when he only needed to consume 16 capsules, his calculated compliance for this period was 750% and his overall compliance was 126.5%.
- Subject (b) (6): He had an overall compliance rate of 97.6% but had a compliance rate of 142.9% between Visit 5b and 7. did not return at least one study drug bottle (that accounts for 240 capsules while he was expected to take 168 capsules during that period) to the site at the end of the study. Documentation reported that this unit has been discarded by the subject. For compliance purposes, the assumption was made that all study drug from the discarded unit has been consumed by the subject and therefore, resulted in a compliance rate of 142.9% for the period between Visit 5b and 7.
- Subject (b) (6) He had an overall compliance of 153.5% (this subject took 433 capsules while he was expected to take only 282 capsules during the study). This subject was over-complaint at every visit, resulting in high overall compliance.

Concomitant Medication Results:

Concomitant medication use was reported by 88% of subjects in the JATENZO group and 78.2% of subjects in the Axiron® group. The most commonly used mediations in both treatment groups were lipid-modifying agents (JATENZO group: 40.4%; Axiron® group: 43.6%). A summary of concomitant medications used by ≥ 5% of subjects in either treatment group is presented in Table A-1-9.

Table A-1-9: Concomitant Medications Used by ≥ 5% of Subjects in Either Treatment Group (Safety Population)

ATC Level 2 Preferred Term,[a] n (%)	Oral TU (N = 166)	Topical Axiron (N = 55)
Subjects who received any concomitant medication	146 (88.0)	43 (78.2)
Lipid Modifying Agents, Plain	67 (40.4)	24 (43.6)
Fish Oil	23 (13.9)	5 (9.1)
Simvastatin	20 (12.0)	5 (9.1)
Atorvastatin	12 (7.2)	9 (16.4)
Ezetimibe	2 (1.2)	3 (5.5)
Anti-inflammatory and Anti-rheumatic Products	40 (24.1)	12 (21.8)
Ibuprofen	21 (12.7)	7 (12.7)
Blood Glucose Lowering Drugs, Excluding Insulins	39 (23.5)	12 (21.8)
Metformin	31 (18.7)	9 (16.4)
Glipizide	6 (3.6)	3 (5.5)
Sitagliptin Phosphate	1 (0.6)	4 (7.3)
ACE Inhibitors, Plain	40 (24.1)	10 (18.2)
Lisinopril	35 (21.1)	9 (16.4)
Anti-thrombotic Agents	42 (25.3)	8 (14.5)
Acetylsalicyclic Acid	40 (24.1)	8 (14.5)
Drugs for Peptic Ulcer and Gastro-oesophageal Reflux Disease	33 (19.9)	10 (18.2)
Omeprazole	16 (9.6)	6 (10.9)
Angiotensin II Antagonists, Plain	29 (17.5)	9 (16.4)
Losartan	18 (10.8)	3 (5.5)
Losartan Potassium	1 (0.6)	3 (5.5)
Antidepressants	26 (15.7)	9 (16.4)
Trazodone	4 (2.4)	5 (9.1)
Selective Calcium Channel Blockers with Mainly Vascular Effects	22 (13.3)	8 (14.5)
Amlodipine	15 (9.0)	7 (12.7)
Low-Ceiling Diuretics, Thiazides	21 (12.7)	8 (14.5)
Hydrochlorothiazide	21 (12.7)	8 (14.5)
Vitamin A and D, Including Combinations of the Two	23 (13.9)	5 (9.1)
Colecalciferol	11 (6.6)	3 (5.5)
Vitamin D NOS	12 (7.2)	2 (3.6)
Other Vitamin Products, Combinations	20 (12.0)	7 (12.7)
Vitamins NOS	19 (11.4)	7 (12.7)
Other Analgesics and Anti-pyretics	19 (11.4)	7 (12.7)
Paracetamol	10 (6.0)	4 (7.3)
Beta Blocking Agents	23 (13.9)	2 (3.6)
Metroprolol	12 (7.2)	1 (1.8)
Antihistamines for Systemic Use	16 (9.6)	8 (14.5)
Loratadine	8 (4.8)	3 (5.5)
Cetirizine Hydrochloride	3 (1.8)	3 (5.5)
Other Urologicals, Including Anti-spasmodics	17 (10.2)	5 (9.1)
Tadalafil	8 (4.8)	3 (5.5)
Ascorbic Acid (Vitamin C), Including Combinations	11 (6.6)	1 (1.8)
Ascorbic Acid	11 (6.6)	1 (1.8)
Vitamin B12 and Folic Acid	7 (4.2)	5 (9.1)
Vitamin B12 NOS	7 (4.2)	3 (5.5)
Beta-Lactam Anti-bacterials, Penicillins	4 (2.4)	5 (9.1)
Amoxicillin	1 (0.6)	4 (7.3)

Source: Post-text Table 14.1.4.2
Abbreviations: ATC = anatomical therapeutic chemical; NOS = not otherwise specified; TU = testosterone undecanoate
[a] WHO DRUG Version September 2012 was used for coding.
Note: Concomitant medications were defined as those that either: (1) started prior to the first dose of study medication and stopped after the first dose of study medication, (2) started prior to the first dose of study medication and were ongoing, or (3) started after the first dose of study medication.

OSI inspection of the clinical study sites:
The Clinical review team requested inspections on clinical study sites on September 20, 2017. As a result, the following 3 clinical study sites were inspected during October 16 - November 27, 2017 and the inspection report was issued on January 9, 2018. The 3 clinical study sites inspected are listed together with the inspection results in Table A-1-10 below. These 3 clinical study sites were chosen for inspection because each of these investigators enrolled a relatively large number of subjects. A copy of the OSI inspection report can be found in DARRTS under NDA 206089.

Table A-1-10: Summary of Clinical Study Sites that were Inspected

Site #/ Name of CI/ Address	Protocol #/ # of Subjects (screened)	Inspection Dates	Classification
Site #109 Laurence Belkoff, M.D. Urologic Consultants of SE PA 1 Presidential Blvd Suite 100 Bala Cynwd, PA 19004-1015	CLAR-15012 Subjects: 30	20-27 Nov 2017	NAI
Site #104 Gregory Flippo, M.D. Alabama Clinical Therapeutics 52 Medical Park East Drive, Suite 202 Birmingham, AL 35235	CLAR-15012 Subjects: 32	23-26 Oct 2017	NAI
Site #122 Charles White, M.D. Coastal Clinical Research Inc. 100 Memorial Hospital Drive Annex Building, Suite 3B Mobile, Ala 36608-1185	CLAR-15012 Subjects: 31	16-19 Oct 2017	NAI

NAI: No deviations from regulations

Based on the results of these inspections, the OSI inspector concluded that the study appears to have been conducted adequately and recommended that data generated from these sites to be accepted for further FDA review for this NDA.

Dose Selection for the starting dose

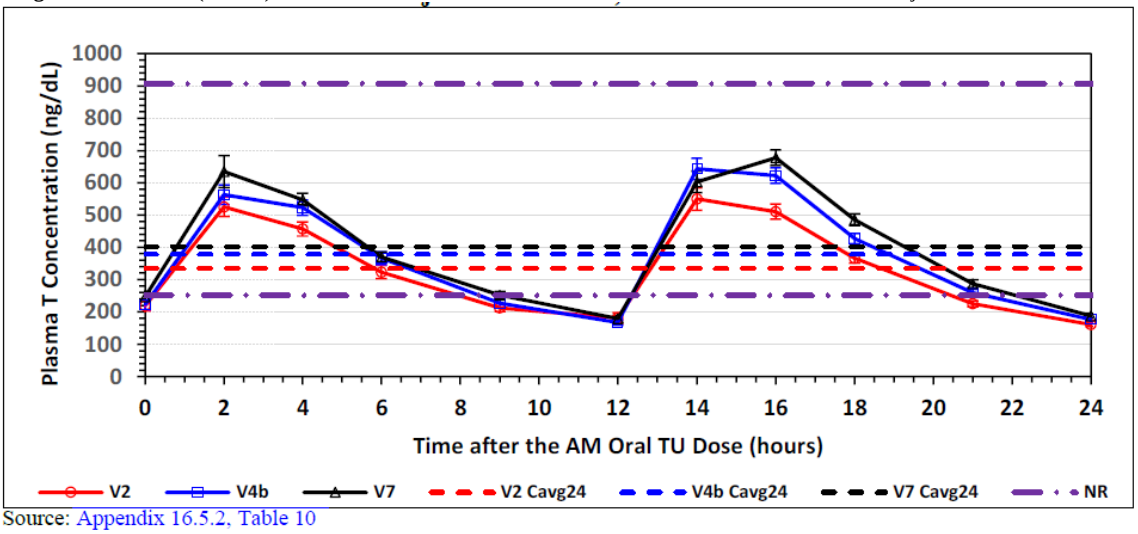
The Sponsor's first Phase 3 clinical study, CLAR-09007, submitted in the original NDA, demonstrated that > 85% of subjects achieved serum T C_{avg} concentrations in the eugonadal range after 90 days of treatment; however, 13.7% (20/146) of subjects experienced maximum total T concentrations higher than desired. The Division has set targets for T C_{max} > 2,500 ng/dL at 0% of subjects and 5% of subjects with a T C_{max} of 1,800 to 2,500 ng/dL. Since the percentage of subjects with elevated C_{max} values did not align with the Division's targets for TRTs, the dose-titration algorithm was revised. PK modeling of results from Study CLAR-09007 led to the revised dosing algorithm that was used in Study CLAR-12011. At the final PK visit in Study CLAR-12011, 75.0% of the subjects had serum T C_{avg} values within the pre-specified eugonadal range for serum collected in plain tubes of 300-1,000 ng/dL. The frequency of high C_{max} values was substantially decreased. Approximately 3% of subjects had a C_{max} > 2,500 ng/dL and 6% of the subjects had a C_{max} of 1,800-2,500 ng/dL. In Study CLAR-12011, approximately 75% of the subjects' final TU dose was lower than the starting dose (316 mg TU BID); suggesting that a lower starting dose might reduce the likelihood that a subject was exposed to too high a dose prior to his first dose titration. PK modeling of the Study CLAR-12011 data, combined with the data from CLAR-09007, was used to further refine the dose-titration algorithm in this study. Subjects randomly assigned to JATENZO in this study started with a dose of 237 mg TU BID, with the goal of having few subjects requiring a reduction in dose. The titration schemes employed in previous Sponsor's studies provided an effective means of controlling C_{avg} concentrations by adjusting the administered dose based on the total T concentration in a single status - indicating blood sample collected after dosing. The time point for the T sample upon which titration decisions were made was changed from the 4 to 6-hour window after dosing in Study CLAR-09007 to a 3 to 5-hour window after dosing in Study CLAR-12011. In this study, CLAR-15012, the need for dose titration was based on a subject's total T C_{avg} determined from serial PK samples obtained over a 24-hour period. Using the C_{avg} from samples obtained over a 24-hour period as the determinant for titration ensured a more complete characterization of the subject's T concentration, and was consistent with the method used in the Axiron® clinical program and formed the basis for approval.

The Axiron® starting dose of 60 mg of T QD is the starting dose recommended on the Axiron® product label. The use of 24-hour T C_{avg} to guide dose titration is consistent with what was used in the clinical study described in the Product label of Axiron®.

Plasma Total T PK

Mean concentration-time profiles for plasma total T for each of the 3 PK visits are shown in Figure A-1-5 for JATENZO subjects. The mean concentrations include all study subjects at the particular visit; the results are not stratified by dose. The average dose of JATENZO progressively increased during the titration process (237 mg TU at Visit 2, to 287.2 mg at Visit 4b, to 325.1 mg at Visit 7) and the increases in the mean concentration-time profiles for the 3 different visits were consistent with the increases in the mean dose.

Figure A-1-5: Mean (± SEM) Concentration-Time Profile for Plasma Total T in JATENZO-Treated Subjects at Visits 2, 4b, and 7



Source: Appendix 16.5.2, Table 10

Abbreviations: AM = morning; C_{avg24} = time-weighted average plasma concentration morning and evening doses combined; NR = normal range; V2 = Visit 2; V4b = Visit 4b; V7 = Visit 7; SEM = standard error of the mean; T = testosterone; TU = testosterone undecanoate

Error bars indicate SEM

The mean C_{max}, T_{max}, AUC, and C_{avg} values for each of the PK observation periods are summarized in Table A-1-11. For JATENZO, these PK parameters are compiled separately for the morning and evening dosing intervals, and for the combined 24-hour interval as $C_{max\text{-}am}$, $C_{max\text{-}pm}$, C_{max24}, $T_{max\text{-}am}$, $T_{max\text{-}pm}$, AUC_{am}, AUC_{pm}, AUC_{24}, $C_{avg\text{-}am}$, $C_{avg\text{-}pm}$ and C_{avg24}. A 24-hour version of the mean T_{max} is not reported for JATENZO subjects because the T_{max} distribution of 24-hours is bimodal (i.e., one value for the morning dose and 1 value for the afternoon dose) and the mean of those 2 modes is generally a meaningless result. The Sponsor stated that only the 24-hour PK parameters are reported for Axiron® subjects because Axiron® was applied once daily in the morning. Table A-1-11 shows that when the results of all subjects at a particular PK visit were combined for the summary statistics, regardless of the dose of oral TU they received, the mean C_{max24} for JATENZO ranged from 803.4 ng/dL (Visit 2) to 1,008.3 ng/dL (Visit 7) and occurred at median times of approximately 2-4 hours following the morning dose, and approximately 4 hours following the evening dose. The mean C_{avg24} values ranged from 334.7 ng/dL (Visit 2) to 402.5 ng/dL (Visit 7) and were approximately 40% of the C_{max24} concentration at the same PK visit. The PK parameters generally had CVs in the 30%-60% range. The CV for C_{avg24} decreased as the PK visits progressed through the study (46.6% to 37.7% to 31.7%), as would be expected since the titration process was designed to titrate downwards subjects with high C_{avg24} values, and titrate upwards subjects with

low C_{avg24} values, thus progressively narrowing the distribution of C_{avg24} values with each titration step.

As is apparent from Table A-1-11, the mean value for C_{max24} is generally greater than the mean value for either C_{max-am} or C_{max-pm}. This is a direct result of the C_{max24} for each subject being defined as the larger of the morning or evening values for that subject. Thus, the population mean for C_{max24} tends to be composed of the upper portions of the distributions of C_{max-am} and C_{max-pm}, resulting in a higher mean for that new distribution than characterizes either of the distributions contributing a portion of its members. C_{max24} would only be similar to C_{max-am} (or to C_{max-pm}) if the morning dose (or the evening dose) consistently has the higher C_{max} value.

Table A-1-11: Summary of JATENZO and Axiron® Plasma Total T PK Parameters by Visit, by Treatment, for all Doses Combined

			Oral TU Subjects				Topical Axiron Subjects			
Visit	PK Parameter	Units	N	Mean	SD	CV%	N	Mean	SD	CV%
Visit 2	C_{max-am}	ng/dL	166	649.8	424.38	65.3%				
	C_{max-pm}	ng/dL	166	678.1	427.51	63.0%				
	C_{max24}	ng/dL	166	803.4	470.24	58.5%	55	523.7	283.06	54.1%
	T_{max-am}[a,b]	h	166	2.07[a]	(0.00, 12.15)		55	5.97[a,b]	(0.00, 24.00)	
	T_{max-pm}[a]	h	166	15.88[a]	(11.93, 24.00)					
	C_{min-am}	ng/dL	166	129.0	74.05	57.4%				
	C_{min-pm}	ng/dL	166	128.8	63.43	49.2%				
	C_{min24}	ng/dL	166	114.9	60.70	52.8%	55	187.6	85.43	45.5%
	AUC_{am}	ng•h/dL	166	3907.9	2079.20	53.2%				
	AUC_{pm}	ng•h/dL	166	4120.1	2070.58	50.3%				
	AUC_{24}	ng•h/dL	166	8028.0	3749.71	46.7%	55	7885.4	3231.10	41.0%
	C_{avg-am}	ng/dL	166	324.2	171.21	52.8%				
	C_{avg-pm}	ng/dL	166	344.8	173.80	50.4%				
	C_{avg24}[c]	ng/dL	166	334.5	156.24	46.7%	55	328.6	134.63	41.0%
	C_{avg24}[d]	ng/dL	166	334.7	156.14	46.6%	55	328.6	134.69	41.0%
Visit 4b	C_{max-am}	ng/dL	161	691.0	395.99	57.3%				
	C_{max-pm}	ng/dL	160	789.2	388.13	49.2%				
	C_{max24}	ng/dL	160	909.0	411.63	45.3%	51	671.0	312.09	46.5%
	T_{max-am}[a,b]	h	161	2.07[a]	(0.00, 12.08)		51	3.98[a,b]	(0.00, 24.00)	
	T_{max-pm}[a]	h	160	15.88[a]	(12.05, 24.08)					
	C_{min-am}	ng/dL	161	138.5	68.99	49.8%				
	C_{min-pm}	ng/dL	160	140.9	67.69	48.0%				
	C_{min24}	ng/dL	160	127.7	61.18	47.9%	51	220.5	77.83	35.3%
	AUC_{am}	ng•h/dL	161	4246.7	2140.63	50.4%				
	AUC_{pm}	ng•h/dL	160	4802.2	1795.81	37.4%				
	AUC_{24}	ng•h/dL	160	9064.8	3419.47	37.7%	51	9663.8	3409.60	35.3%
	C_{avg-am}	ng/dL	161	353.2	177.86	50.4%				
	C_{avg-pm}	ng/dL	160	401.0	150.26	37.5%				
	C_{avg24}[c]	ng/dL	160	377.7	142.48	37.7%	51	402.7	142.07	35.3%
	C_{avg24}[d]	ng/dL	161	377.1	142.30	37.7%	51	402.8	142.07	35.3%

[a] T_{max} values shown are median (range);
[b] Axiron T_{max} is relative to the AM dose since Axiron was applied just once daily, in the morning, T_{max-am} and T_{max24} are interchangeable for Axiron
[c] C_{avg24} calculated after study completion using actual sample collection times
[d] C_{avg24} calculated for titration decisions as study was conducted, using nominal sample collection times
Source: Appendix B, Table B-1 and Table B-2

Visit	PK Parameter	Units	Oral TU Subjects N	Mean	SD	CV%	Topical Axiron Subjects N	Mean	SD	CV%
Visit 7	$C_{max\text{-}am}$	ng/dL	155	773.3	584.03	75.5%				
	$C_{max\text{-}pm}$	ng/dL	151	838.4	368.55	44.0%				
	C_{max24}	ng/dL	151	1008.3	581.04	57.6%	48	664.0	319.23	48.1%
	$T_{max\text{-}am}$ [a,b]	h	155	3.87[a]	(0.00, 12.08)		48	4.01[a,b]	(0.00, 24.00)	
	$T_{max\text{-}pm}$ [a]	h	151	16.00[a]	(12.00, 24.02)					
	$C_{min\text{-}am}$	ng/dL	155	141.8	60.78	42.9%				
	$C_{min\text{-}pm}$	ng/dL	151	145.9	56.28	38.6%				
	C_{min24}	ng/dL	151	131.3	53.90	41.1%	48	214.7	88.15	41.1%
	AUC_{am}	ng•h/dL	155	4566.6	2066.16	45.2%				
	AUC_{pm}	ng•h/dL	151	5083.3	1661.32	32.7%				
	AUC_{24}	ng•h/dL	151	9659.1	3065.20	31.7%	48	9191.6	3152.69	34.3%
	$C_{avg\text{-}am}$	ng/dL	155	379.9	171.92	45.3%				
	$C_{avg\text{-}pm}$	ng/dL	151	424.6	139.23	32.8%				
	C_{avg24} [c]	ng/dL	151	402.5	127.72	31.7%	48	383.0	131.36	34.3%

[a] T_{max} values shown are median (range);
[b] Axiron T_{max} is relative to the AM dose since Axiron was applied just once daily, in the morning, $T_{max\text{-}am}$ and T_{max24} are interchangeable for Axiron
[c] C_{avg24} calculated after study completion using actual sample collection times
[d] C_{avg24} calculated for titration decisions as study was conducted, using nominal sample collection times (not done for Visit 7)
Source: Appendix B, Table B-1

An alternative summary of the mean values of these PK parameters is provided in Table A-1-12 for JATENZO.

Table A-1-12: Mean Plasma Total T PK Parameters in JATENZO-Treated Subjects by Dose of TU, by PK Visit

Oral TU Dose mg TU	PK Visit x	N	Mean Plasma Total T PK Parameters with Twice Daily Dosing of Oral TU: $C_{max\text{-}am}$ ng/dL	$C_{max\text{-}pm}$ ng/dL	C_{max24} ng/dL	$T_{max\text{-}am}$ h	$T_{max\text{-}pm}$ h	$C_{min\text{-}am}$ ng/dL	$C_{min\text{-}pm}$ ng/dL	C_{min24} ng/dL	AUC_{am} ng•h/dL	AUC_{pm} ng•h/dL	AUC_{24} ng•h/dL	$C_{avg\text{-}am}$ ng/dL	$C_{avg\text{-}pm}$ ng/dL	C_{avg24} ng/dL
			Mean	Mean	Mean	Median	Median	Mean	Mean	Mean	Mean	Mean	Mean	Mean	Mean	Mean
			(SD)	(SD)	(SD)	Min	Min	(SD)	(SD)	(SD)	(SD)	(SD)	(SD)	(SD)	(SD)	(SD)
			CV%	CV%	CV%	Max	Max	CV%	CV%	CV%	CV%	CV%	CV%	CV%	CV%	CV%
158	Visit 7	1	4905.19	1220.87	4905.19	2.00	16.03	241.4	228.5	228.5	18329.5	7613.0	25942.6	1523.2	636.2	1080.9
			NE	NE	NE	2.00	16.03	NE	NE	NE	NE	NE	NE	NE	NE	NE
			NE	NE	NE	2.00	16.03	NE	NE	NE	NE	NE	NE	NE	NE	NE
198	Visit 4b	4	1081.5	1191.2	1243.2	2.04	15.03	228.2	239.7	228.2	6283.1	7175.3	13458.4	520.0	603.3	560.8
			(726.64)	(619.93)	(616.48)	2.00	14.03	(149.93)	(138.28)	(149.93)	(3743.56)	(2298.25)	(6029.20)	(313.14)	(189.37)	(251.22)
			67.2%	52.0%	49.6%	4.00	16.03	65.7%	57.7%	65.7%	59.6%	32.0%	44.8%	60.2%	31.4%	44.8%
198	Visit 7	2	953.6	1021.2	1139.6	2.98	13.99	131.0	180.6	131.0	5659.0	6661.2	12320.2	470.6	556.3	513.3
			(52.47)	(377.98)	(210.57)	2.00	13.95	(55.0)	(15.13)	(55.0)	(87.95)	(1395.17)	(1307.23)	(7.78)	(117.05)	(54.47)
			5.5%	37.0%	18.5%	3.97	14.03	42.0%	8.4%	42.0%	1.6%	20.9%	10.6%	1.7%	21.0%	10.6%
237	Visit 2	166	649.8	678.1	803.4	2.07	15.88	129.0	128.8	114.9	3907.9	4120.1	8028.0	324.2	344.8	334.5
			(424.38)	(427.51)	(470.24)	0.00	11.93	(74.05)	(63.43)	(60.70)	(2079.20)	(2070.58)	(3749.71)	(171.21)	(173.80)	(156.24)
			65.3%	63.0%	58.5%	12.15	24.00	57.4%	49.2%	52.8%	53.2%	50.3%	46.7%	52.8%	50.4%	46.7%
237	Visit 4b	53	827.2	913.3	1071.6	2.02	16.00	160.4	166.6	147.3	5158.7	5542.7	10701.4	428.9	463.0	445.9
			(401.03)	(461.85)	(433.83)	0.00	13.92	(68.37)	(70.91)	(58.74)	(2340.23)	(1900.99)	(3597.80)	(194.40)	(158.90)	(149.91)
			48.5%	50.6%	40.5%	9.00	24.00	42.6%	42.6%	39.9%	45.4%	34.3%	33.6%	45.3%	34.3%	33.6%
237	Visit 7	40	848.8	925.5	1085.8	2.00	16.00	158.0	166.0	147.9	5004.3	5645.8	10645.8	416.2	471.6	443.6
			(478.82)	(429.30)	(519.30)	0.00	13.88	(75.87)	(70.55)	(73.33)	(1923.27)	(1825.62)	(2937.83)	(160.01)	(152.81)	(122.41)
			56.4%	46.4%	47.8%	9.02	21.03	48.0%	42.5%	49.6%	38.4%	32.3%	27.6%	38.4%	32.4%	27.6%

NE = Not evaluable
Source: Appendix B, Table B-3

Oral TU Dose mg TU	PK Visit x	N	Mean Plasma Total T PK Parameters with Twice Daily Dosing of Oral TU: $C_{max\text{-}am}$ ng/dL	$C_{max\text{-}pm}$ ng/dL	C_{max24} ng/dL	$T_{max\text{-}am}$ h	$T_{max\text{-}pm}$ h	$C_{min\text{-}am}$ ng/dL	$C_{min\text{-}pm}$ ng/dL	C_{min24} ng/dL	AUC_{am} ng•h/dL	AUC_{pm} ng•h/dL	AUC_{24} ng•h/dL	$C_{avg\text{-}am}$ ng/dL	$C_{avg\text{-}pm}$ ng/dL	C_{avg24} ng/dL
			Mean	Mean	Mean	Median	Median	Mean	Mean	Mean	Mean	Mean	Mean	Mean	Mean	Mean
			(SD)	(SD)	(SD)	Min	Min	(SD)	(SD)	(SD)	(SD)	(SD)	(SD)	(SD)	(SD)	(SD)
			CV%	CV%	CV%	Max	Max	CV%	CV%	CV%	CV%	CV%	CV%	CV%	CV%	CV%
316	Visit 4b	104	606.6	709.7	812.3	3.83	14.08	123.9	123.9	113.8	3703.5	4329.0	8052.0	308.3	361.3	335.5
			(352.63)	(306.69)	(359.79)	0.00	12.05	(60.04)	(54.74)	(51.20)	(1748.74)	(1515.77)	(2715.54)	(145.37)	(126.78)	(113.15)
			58.1%	43.2%	44.3%	12.08	24.08	48.4%	44.2%	45.0%	47.2%	35.0%	33.7%	47.2%	35.1%	33.7%
316	Visit 7	50	778.7	827.0	983.2	3.96	16.00	144.7	144.3	131.9	4497.7	5065.2	9553.4	374.5	422.5	398.1
			(630.50)	(320.55)	(601.85)	1.83	12.00	(65.90)	(54.51)	(49.69)	(2007.68)	(1522.46)	(2964.23)	(167.34)	(127.22)	(123.51)
			81.0%	38.8%	61.2%	12.00	24.00	45.6%	37.8%	37.7%	44.6%	30.1%	31.0%	44.7%	30.1%	31.0%
396	Visit 7	62	647.7	778.6	909.0	3.84	16.00	127.8	131.7	118.3	4082.5	4637.7	8743.9	339.4	387.8	364.3
			(307.31)	(358.09)	(341.65)	1.85	12.08	(39.54)	(42.37)	(36.69)	(1289.42)	(1532.11)	(2216.23)	(107.24)	(129.07)	(92.34)
			47.4%	46.0%	37.6%	12.08	24.02	30.9%	32.2%	31.0%	31.6%	33.0%	25.3%	31.6%	33.3%	25.3%

NE = Not evaluable
Source: Appendix B, Table B-3

In these tables the mean values for C_{max}, T_{max}, AUC, and C_{avg} parameters are sorted by the dose of JATENZO received on each of the PK visits. Some caution in interpretation is required since the population of subjects at each dose is progressively narrowed as the PK visits go from Visit 2 to Visit 4b, and Visit 7, such that by Visit 7 subjects with high T clearance rates or low bioavailability were likely to be preferentially distributed to the higher doses, and subjects with low T clearance rates or high BA were likely to be preferentially distributed to the lower doses. This progressive narrowing of the population is the reason that the mean values for C_{max}, AUC or C_{avg} tend to increase as one compares Visit 2 and Visit 4b at the same dose, or Visit 4b and Visit 7 at the same dose.

The number of JATENZO subjects in the 158 mg and 198 mg BID TU dose groups were too small ($n \leq 2$) to have meaningful confidence in their mean values. In addition to the above mean PK parameter summary tables, a third summary table from the same data set is provided that summarizes the mean PK parameters with the study subjects grouped according to their final titrated dose on Visit 7. The table can be used to understand how the T PK parameters in those subjects changed over the 3 PK visits in concert with changes in the JATENZO (Table A-1-13) doses between the PK visits.

Table A-1-13: Mean Plasma Total T PK Parameters in JATENZO-Treated Subjects Grouped by Final Titrated Dose

Visit 7 Final Titrated Oral TU Dose mg TU	Mean Oral TU Dose on PK Visit x mg TU	N	Mean Plasma Total T PK Parameters with Twice Daily Dosing of Oral TU													
			$C_{max\text{-}am}$ ng/dL	$C_{max\text{-}pm}$ ng/dL	C_{max24} ng/dL	$T_{max\text{-}am}$ h	$T_{max\text{-}pm}$ h	$C_{min\text{-}am}$ ng/dL	$C_{min\text{-}pm}$ ng/dL	C_{min24} ng/dL	AUC_{am} ng•h/dL	AUC_{pm} ng•h/dL	AUC_{24} ng•h/dL	$C_{avg\text{-}am}$ ng/dL	$C_{avg\text{-}pm}$ ng/dL	C_{avg24} ng/dL
			Mean (SD) CV%	Mean (SD) CV%	Mean (SD) CV%	Median Min Max	Median Min Max	Mean (SD) CV%	Mean (SD) CV%	Mean (SD) CV%	Mean (SD) CV%	Mean (SD) CV%	Mean (SD) CV%	Mean (SD) CV%	Mean (SD) CV%	Mean (SD) CV%
Visit 7 158	Visit 2 237.00	1	952.8	2028.2	2028.2	0.00	14.13	492.9	325.7	325.7	8514.8	11495.2	20010.0	701.8	968.7	833.8
			NE	NE	NE	0.00	14.13	NE	NE	NE	NE	NE	NE	NE	NE	NE
			NE	NE	NE	0.00	14.13	NE	NE	NE	NE	NE	NE	NE	NE	NE
Visit 7 158	Visit 4b 198.00	1	2008.4	2095.3	2095.3	2.00	14.03	445.2	445.2	445.2	11358.9	10267.5	21626.4	943.9	858.0	901.1
			NE	NE	NE	2.00	14.03	NE	NE	NE	NE	NE	NE	NE	NE	NE
			NE	NE	NE	2.00	14.03	NE	NE	NE	NE	NE	NE	NE	NE	NE
Visit 7 158	Visit 7 158.00	1	4905.2	1220.9	4905.2	2.00	16.03	241.4	228.5	228.5	18329.5	7613.0	25942.5	1523.2	636.2	1080.9
			NE	NE	NE	2.00	16.03	NE	NE	NE	NE	NE	NE	NE	NE	NE
			NE	NE	NE	2.00	16.03	NE	NE	NE	NE	NE	NE	NE	NE	NE
Visit 7 198	Visit 2 237.00	2	2158.2	2397.5	2612.0	1.99	13.98	288.1	305.1	288.1	10899.3	12423.1	23322.4	904.5	1039.3	971.8
			(107.98)	(837.13)	(533.75)	1.98	13.93	(20.98)	(3.08)	(20.98)	(18.75)	(3987.37)	(3968.62)	(.21)	(331.62)	(165.36)
			5.0%	34.9%	20.4%	2.00	14.03	7.3%	1.0%	7.3%	0.2%	32.1%	17.0%	0.0%	31.9%	17.0%
Visit 7 198	Visit 4b 198.00	2	969.1	968.6	1072.7	2.04	16.00	183.6	184.3	183.6	5263.0	6724.8	11987.8	433.6	568.4	499.5
			(454.69)	(160.99)	(308.19)	2.00	14.03	(9.77)	(8.81)	(9.77)	(2232.31)	(1037.67)	(3269.99)	(190.78)	(77.61)	(136.25)
			46.9%	16.6%	28.7%	2.08	16.03	5.3%	4.8%	5.3%	42.4%	15.4%	27.3%	44.0%	13.7%	27.3%
Visit 7 198	Visit 7 198.00	2	953.6	1021.2	1139.6	2.98	13.99	131.0	180.6	131.0	5659.0	6661.2	12320.2	470.6	556.3	513.3
			(52.47)	(377.98)	(210.57)	2.00	13.95	(55.0)	(15.13)	(55.0)	(87.95)	(1395.17)	(1307.23)	(7.78)	(117.05)	(54.47)
			5.5%	37.0%	18.5%	3.97	14.03	42.0%	8.4%	42.0%	1.6%	20.9%	10.6%	1.7%	21.0%	10.6%

NE = Not evaluable
Source: Appendix B, Table B-5

Visit 7 Final Titrated Oral TU Dose mg TU	Mean Oral TU Dose on PK Visit x mg TU	N	Mean Plasma Total T PK Parameters with Twice Daily Dosing of Oral TU													
			$C_{max\text{-}am}$ ng/dL	$C_{max\text{-}pm}$ ng/dL	C_{max24} ng/dL	$T_{max\text{-}am}$ h	$T_{max\text{-}pm}$ h	$C_{min\text{-}am}$ ng/dL	$C_{min\text{-}pm}$ ng/dL	C_{min24} ng/dL	AUC_{am} ng•h/dL	AUC_{pm} ng•h/dL	AUC_{24} ng•h/dL	$C_{avg\text{-}am}$ ng/dL	$C_{avg\text{-}pm}$ ng/dL	C_{avg24} ng/dL
			Mean (SD) CV%	Mean (SD) CV%	Mean (SD) CV%	Median Min Max	Median Min Max	Mean (SD) CV%	Mean (SD) CV%	Mean (SD) CV%	Mean (SD) CV%	Mean (SD) CV%	Mean (SD) CV%	Mean (SD) CV%	Mean (SD) CV%	Mean (SD) CV%
Visit 7	Visit 2	40	1017.8	1010.4	1221.3	2.03	14.15	179.0	175.1	158.0	5865.5	5889.6	11755.1	485.5	493.5	489.8
237	237.00		(477.34)	(441.62)	(460.64)	0.00	12.00	(77.72)	(65.72)	(65.51)	(1891.36)	(1921.31)	(2793.62)	(152.30)	(161.39)	(116.40)
			46.9%	43.7%	37.7%	12.15	24.00	43.4%	37.5%	41.5%	32.2%	32.6%	23.8%	31.4%	32.7%	23.8%
Visit 7	Visit 4b	40	871.1	961.2	1148.1	2.02	16.00	172.1	178.1	156.6	5385.8	5798.5	11184.4	448.0	484.1	466.0
237	236.03		(362.64)	(439.30)	(387.51)	0.00	13.90	(68.86)	(69.32)	(57.29)	(1919.46)	(1489.01)	(2342.84)	(159.69)	(124.40)	(97.62)
			41.6%	45.7%	33.8%	9.00	24.00	40.0%	38.9%	36.6%	35.6%	25.7%	20.9%	35.6%	25.7%	20.9%
Visit 7	Visit 7	40	848.8	925.5	1085.8	2.00	16.00	158.0	166.0	147.9	5004.3	5645.8	10645.8	416.2	471.6	443.6
237	237.00		(478.82)	(429.30)	(519.30)	0.00	13.88	(75.87)	(70.55)	(73.33)	(1923.27)	(1825.62)	(2937.83)	(160.01)	(152.81)	(122.41)
			56.4%	46.4%	47.8%	9.02	21.03	48.0%	42.5%	49.6%	38.4%	32.3%	27.6%	38.4%	32.4%	27.6%
Visit 7	Visit 2	50	591.6	618.3	743.2	2.03	14.18	119.8	119.9	106.7	3552.4	3798.3	7350.6	295.1	317.8	306.3
316	237.00		(243.27)	(263.61)	(258.43)	0.00	11.93	(59.97)	(52.57)	(47.12)	(1192.03)	(994.12)	(1535.14)	(99.22)	(84.12)	(63.96)
			41.1%	42.6%	34.8%	9.00	24.00	50.1%	43.9%	44.1%	33.6%	26.2%	20.9%	33.6%	26.5%	20.9%
Visit 7	Visit 4b	50	776.6	834.1	990.4	2.05	14.13	148.1	148.3	136.6	4616.7	5152.6	9769.2	384.2	430.2	407.1
316	298.62		(403.13)	(329.19)	(393.68)	0.00	12.05	(72.25)	(60.16)	(59.75)	(1977.55)	(1469.80)	(2708.04)	(164.32)	(123.01)	(112.83)
			51.9%	39.5%	39.7%	9.00	21.15	48.8%	40.6%	43.7%	42.8%	28.5%	27.7%	42.8%	28.6%	27.7%
Visit 7	Visit 7	50	778.7	827.0	983.2	3.96	16.00	144.7	144.3	131.9	4497.7	5065.2	9553.4	374.5	422.5	398.1
316	316		(630.50)	(320.55)	(601.85)	1.83	12.00	(65.90)	(54.51)	(49.69)	(2007.68)	(1522.46)	(2964.23)	(167.34)	(127.22)	(123.51)
			81.0%	38.8%	61.2%	12.00	24.00	45.6%	37.8%	37.7%	44.6%	30.1%	31.0%	44.7%	30.1%	31.0%

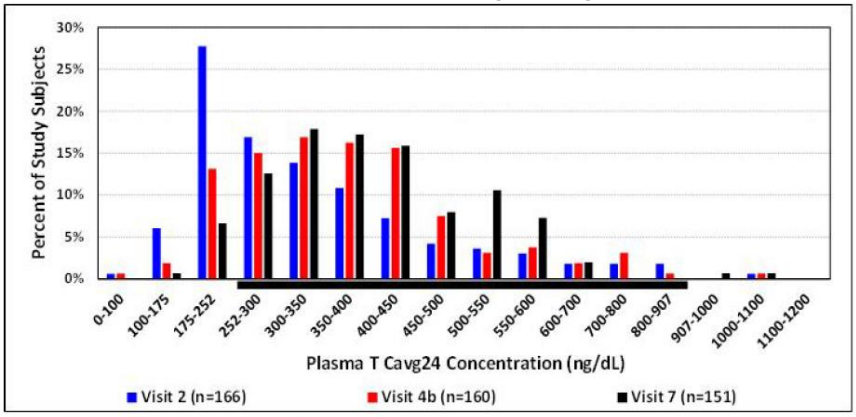
NE = Not evaluable
Source: Appendix B, Table B-5

Visit 7 Final Titrated Oral TU Dose mg TU	Mean Oral TU Dose on PK Visit x mg TU	N	Mean Plasma Total T PK Parameters with Twice Daily Dosing of Oral TU													
			$C_{max\text{-}am}$ ng/dL	$C_{max\text{-}pm}$ ng/dL	C_{max24} ng/dL	$T_{max\text{-}am}$ h	$T_{max\text{-}pm}$ h	$C_{min\text{-}am}$ ng/dL	$C_{min\text{-}pm}$ ng/dL	C_{min24} ng/dL	AUC_{am} ng•h/dL	AUC_{pm} ng•h/dL	AUC_{24} ng•h/dL	$C_{avg\text{-}am}$ ng/dL	$C_{avg\text{-}pm}$ ng/dL	C_{avg24} ng/dL
			Mean (SD) CV%	Mean (SD) CV%	Mean (SD) CV%	Median Min Max	Median Min Max	Mean (SD) CV%	Mean (SD) CV%	Mean (SD) CV%	Mean (SD) CV%	Mean (SD) CV%	Mean (SD) CV%	Mean (SD) CV%	Mean (SD) CV%	Mean (SD) CV%
Visit 7	Visit 2	62	404.2	463.6	522.5	3.96	15.98	97.5	99.1	87.9	2591.1	2953.9	5545.1	215.3	247.0	231.0
396	237.00		(161.47)	(190.23)	(183.45)	0.00	13.85	(35.55)	(33.82)	(30.04)	(723.50)	(936.90)	(1278.32)	(59.94)	(78.34)	(53.26)
			39.9%	41.0%	35.1%	12.08	21.02	36.5%	34.1%	34.2%	27.9%	31.7%	23.1%	27.8%	31.7%	23.1%
Visit 7	Visit 4b	62	451.2	581.5	636.4	3.89	15.90	101.7	102.9	93.0	2865.5	3564.1	6448.7	238.5	297.5	268.7
396	316.00		(194.21)	(219.95)	(212.33)	0.00	13.87	(33.35)	(38.14)	(29.96)	(888.11)	(1073.83)	(1396.81)	(74.03)	(89.90)	(58.20)
			43.0%	37.8%	33.4%	12.08	24.08	32.8%	37.0%	32.2%	31.0%	30.1%	21.7%	31.0%	30.2%	21.7%
Visit 7	Visit 7	62	647.7	778.6	909.0	3.84	16.00	127.8	131.7	118.3	4082.5	4637.7	8743.9	339.4	387.8	364.3
396	396.00		(307.31)	(358.09)	(341.65)	1.85	12.08	(39.54)	(42.37)	(36.69)	(1289.42)	(1532.11)	(2216.23)	(107.24)	(129.07)	(92.34)
			47.4%	46.0%	37.6%	12.08	24.02	30.9%	32.2%	31.0%	31.6%	33.0%	25.3%	31.6%	33.3%	25.3%

NE = Not evaluable
Source: Appendix B, Table B-5

The frequency distributions of the C_{avg24} for total T at the 3 PK visits relative to the total T eugonadal range (heavy black line along the x-axis) is presented in Figure A-1-6. By Visit 7, of the 155 JATENZO subjects still in the study, 138 (89.0%) were within the plasma total T normal range for eugonadal men for NaF/EDTA plasma (252-907 ng/dL), 11 (7.1%) were below the normal range, 2 (1.3%) were above the normal range and 4 (2.6%) were not evaluable for Visit 7 (3 because a missing assay value was potentially C_{max}, and 1 because multiple sequential assay results were missing).

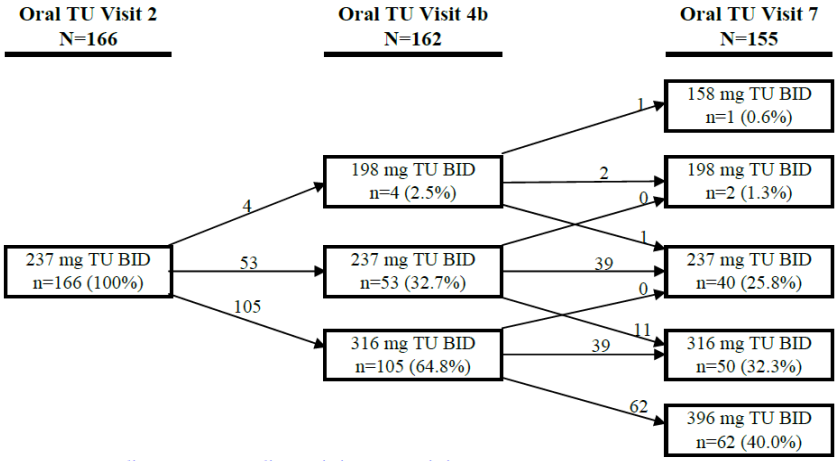
Figure A-1-6: Distributions of JATENZO C_{avg24} Values for Plasma Total T on Visit 2, Visit 4b and Visit 7 Relative to the Total T Normal Range for Eugonadal Men



Source: Listing 16.2.6.2.5; Appendix 16.5.2, Figure 2
Abbreviations: C_{avg24} = time-weighted average plasma concentration morning and evening doses combined; EDTA = ethylenediaminetetraacetic acid; NaF = sodium fluoride; T = testosterone; TU = testosterone undecanoate
Note: Plasma testosterone normal range = 252 to 907 ng/dL (heavy black line along the x-axis) for samples collected in NaF-EDTA tubes

As shown in Figure A-1-7, these Visit 7 results for JATENZO were obtained by 39 subjects not requiring dose adjustment, 52 subjects undergoing 1 dose adjustment, and 64 subjects undergoing 2 dose adjustments; 11 subjects had early terminated from the study prior to Visit 7.

Figure A-1-7: Summary of Titration Steps and Number of Subjects at Each JATENZO Dose



Source: Appendix 16.5.2, Appendix C, Listing C-1 – Listing C-3
Abbreviations: BID = twice daily; TU = testosterone undecanoate

Comparison of Total T Concentration Measurements from Plasma in NaF/EDTA Tubes and Serum in Plain Tubes

TU, a prodrug of T, is metabolized by non-specific esterases in blood to T (Andriol® [TU] capsules product monograph, Health Canada, 2012; Yin *et al*., 2011). Typical practice in the bioanalytical field has been to analyze T and DHT in human serum. To minimize the potential TU to T *ex vivo* conversion during preparation of serum from blood, the Sponsor took an approach of measuring total T concentrations from plasma in NaF/EDTA tubes instead of serum in plain tubes. NaF is an esterase inhibitor while EDTA is an anticoagulant used for plasma sample preparation.

During this study, an additional set of blood samples was collected from each study subject in plain (red top) tubes in addition to blood samples collected in NaF/EDTA tubes at the final PK visit,

Visit 7. The serum T concentrations from these samples in the plain red top tubes were analyzed at the [redacted] (b) (4) The total T concentrations obtained from serum in plain tubes from Visit 7 were compared to the plasma total T concentrations obtained from the blood collected in the NaF/EDTA tubes at Visit 7 (from the same subject).

Table A-1-14 shows the results of the JATENZO and Axiron® serum/plasma ratio distribution analysis with a comparison of serum/plasma ratios between JATENZO and Axiron®-treated subjects.

Table A-1-14: JATENZO and Axiron® serum/plasma ratio distribution analysis

Oral TU vs. Axiron Plasma / Serum Distribution Analysis: Data for Deciles Plot of Geometric Mean at the Median													
	Bin Start ng/dL	Bin End ng/dL	Median T ng/dL	Count #	Transformed Ln(Serum/Plasma) Mean(ln's)	SD(ln's)	μ-95%CI	μ+95%CI	Untransformed Serum/Plasma Gmean ng/dL	LCB ng/dL	UCB ng/dL	% in Bin %	Cum % in Bins %
Oral TU 1	10.01	135.24	110.5	153	0.2191	0.1507	0.1950	0.2431	1.2449	1.2153	1.2753	9.98%	9.98%
Oral TU 2	135.24	177.44	156.6	153	0.2039	0.1156	0.1854	0.2224	1.2262	1.2037	1.2490	9.98%	19.96%
Oral TU 3	177.44	223.10	200.2	154	0.2269	0.1770	0.1987	0.2551	1.2547	1.2198	1.2906	10.05%	30.01%
Oral TU 4	223.10	272.10	247.4	153	0.2308	0.1517	0.2065	0.2550	1.2596	1.2294	1.2905	9.98%	39.99%
Oral TU 5	272.10	331.00	303.9	153	0.2506	0.1711	0.2232	0.2779	1.2848	1.2501	1.3204	9.98%	49.97%
Oral TU 6	331.00	401.20	360.9	154	0.2591	0.1894	0.2289	0.2892	1.2957	1.2572	1.3354	10.05%	60.01%
Oral TU 7	401.20	487.00	444.5	153	0.2932	0.1934	0.2623	0.3241	1.3407	1.2999	1.3828	9.98%	69.99%
Oral TU 8	487.00	611.00	543.2	153	0.2714	0.1964	0.2400	0.3027	1.3117	1.2712	1.3535	9.98%	79.97%
Oral TU 9	611.00	826.00	701.1	154	0.2664	0.2090	0.2331	0.2996	1.3052	1.2625	1.3494	10.05%	90.02%
Oral TU 10	826.00	4906.00	1036.2	153	0.2579	0.2169	0.2232	0.2925	1.2942	1.2501	1.3398	9.98%	100.00%
Oral TU Overall	10.01	4906.00	331.00	1533	0.2479	0.1809	0.2389	0.2570	1.2814	1.2698	1.2930	100.00%	100.00%
Axiron 1	10.01	202.00	162.4	48	0.1920	0.1155	0.1584	0.2255	1.2116	1.1716	1.2529	9.92%	9.92%
Axiron 2	202.00	236.00	222.9	48	0.1526	0.1348	0.1135	0.1917	1.1649	1.1201	1.2113	9.92%	19.83%
Axiron 3	236.00	268.00	253.8	49	0.1665	0.0856	0.1419	0.1910	1.1811	1.1524	1.2105	10.12%	29.96%
Axiron 4	268.00	308.00	289.8	48	0.1660	0.0933	0.1389	0.1931	1.1805	1.1490	1.2129	9.92%	39.88%
Axiron 5	308.00	344.00	320.8	49	0.1586	0.0845	0.1344	0.1829	1.1719	1.1438	1.2007	10.12%	50.00%
Axiron 6	344.00	381.50	360.6	48	0.1201	0.0990	0.0913	0.1488	1.1276	1.0956	1.1604	9.92%	59.92%
Axiron 7	381.50	426.50	407.3	49	0.1165	0.1333	0.0782	0.1547	1.1235	1.0813	1.1674	10.12%	70.04%
Axiron 8	426.50	485.50	452.4	48	0.1290	0.1491	0.0857	0.1723	1.1377	1.0895	1.1881	9.92%	79.96%
Axiron 9	485.50	635.50	562.8	49	0.1225	0.1304	0.0850	0.1600	1.1303	1.0888	1.1735	10.12%	90.08%
Axiron 10	635.50	1958.50	741.9	48	0.1599	0.1120	0.1274	0.1925	1.1734	1.1359	1.2122	9.92%	100.00%
Axiron Overall	10.01	1958.50	343.5	484	0.1483	0.1171	0.1378	0.1588	1.1599	1.1478	1.1721	100.00%	100.00%

Note 1: Plasma/Serum concentrations from Visit 7 (plasma from inVentiv bioanalysis, serum from [redacted] (b) (4) analysis) arranged so as to plot geometric mean of plasma/serum ratio of samples within the decile (y-axis) vs. median of plasma Total T concentration of samples within the decile (x-axis)
Note 2: Assay results <10 ng/dL in either assay not included in the analysis. Outlier samples differing by more than 7-fold (P/S ratio >7 or <1/7, n=2 of 1535) not included in the analysis.

Table A-1-15 summarizes the descriptive statistics for the T concentration measurement results for the populations of post-dose samples collected from subjects receiving JATENZO and receiving Axiron® in this study. T concentrations below 10 ng/dL (n=5; the greater LLOQ of the two different assays [for serum and plasma]), or T concentrations that differed between serum vs. plasma by more than a factor of 7 (n=2) were not included in the analysis.

Table A-1-15: Descriptive Statistics for Serum/Plasma Ratios (Study CLAR-15012; N=151)

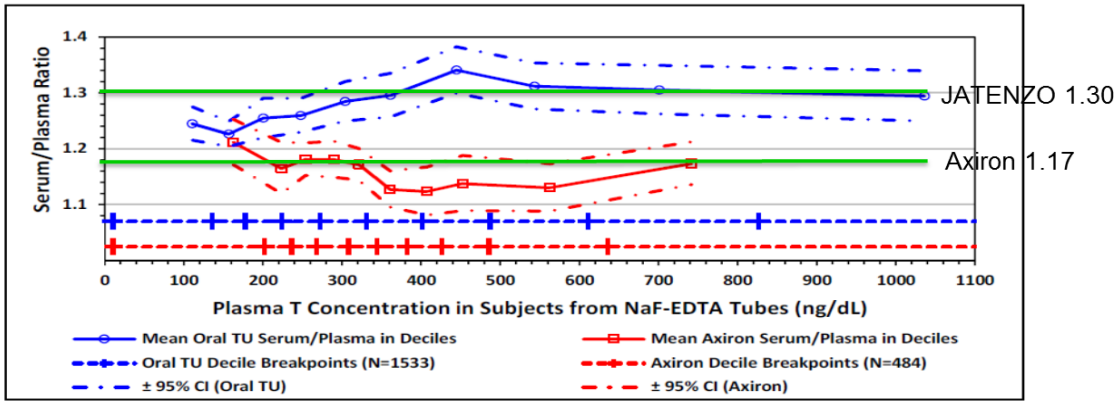
Descriptive Statistics for Serum/Plasma T Ratios (without log transformation)								
Treatment	Count (n)	Arith Mean	SD (CV%)	Median	Min	Max	Arith LB 95%CI	Arith UB 95%CI
Oral TU	1533	1.3026	0.2526 (19.4%)	1.2611	0.3023	4.0577	1.2900	1.3153
Axiron	484	1.1674	0.1287 (11.0%)	1.1783	0.5883	1.7504	1.1559	1.1789
Descriptive Statistics for Serum/Plasma T Ratios (following ln transformation)								
Treatment	Count (n)	Mean (ln)	SD (ln)	Gmean	Gmean LB 90%CI	Gmean UB 90%CI	Gmean LB 95%CI	Gmean UB 95%CI
Oral TU	1533	0.2479	0.1809	1.2814	1.2716	1.2911	1.2698	1.2930
Axiron	484	0.1483	0.1171	1.1599	1.1497	1.1701	1.1478	1.1721

The Sponsor states that a systematic bias between the 2 assays is an expected result if deliberate precautions are not taken to inhibit the continuing enzymatic conversion of TU to T *ex vivo* due to

non-specific esterase activity in a plain (red top) sample collection tube. Not only are concentrations of circulating T increased as the circulating TU concentrations increase due to the *in vivo* conversion of TU to T (i.e., desired conversion of prodrug to active moiety), but the Sponsor also believes that the T concentration continues to increase after the blood sample has been collected due to the *ex vivo* conversion of TU to T (i.e., undesirable conversion).

The ratios of serum total T concentrations (in plain tubes) to plasma total T concentrations (in NaF/EDTA tubes) when plotted against the plasma T concentration measured in the NaF/EDTA sample collection tubes, are shown in Figure A-1-8.

Figure A-1-8: Ratio of Serum Testosterone Concentration in Plain Tubes to Plasma T Concentration in NaF/EDTA Tubes as a Function of the Plasma T Concentration



Notes: Mean Serum/Plasma ratio within a decile plotted at the median plasma T for the decile; 95% CI for each bin estimated using the Student's t-distribution; All samples collected over the 24 hours following the AM dose were included which had both assay results greater than the LLOQ of the plasma assay (10 ng/dL), except for 2 instances of outlier ratios (Serum/Plasma ratio >7)

Concentration measurement results were divided into deciles based on the plasma total T concentration; the mean serum/plasma ratio for the samples within a decile were plotted at the median plasma T associated with the decile.

Reviewer's Comment: *Figure A-1-8 illustrates the comparison of bias analysis between non-TU containing Axiron®-treated subjects and JATENZO (oral TU). As Axiron®-treated subjects did not have TU in their circulation, the mean 17% difference between serum and plasma T concentrations appears to be related to an additive effect (i.e., NaF/EDTA) rather than a TU-treatment related effect (e.g., TU to T ex vivo conversion).*

It should be noted that this is consistent with literature reports stating that the use of NaF-containing test tubes introduces a negative bias of 11.7% (Lachance et al., 2015) to 20% (Wang et al., 2008) when compared to total T concentrations measured from serum in plain tubes with no additives. In addition, there was a mean of 14.2% negative bias for total T concentrations observed from plasma in NaF/EDTA tubes compared to those from serum in plain tubes in Study CLAR-16014. Reference is made to the Individual Study Review for Study CLAR-16014 for details.

The results from this large collection of serum and plasma samples shows that the differences are not negligible and can potentially affect titration decisions in subjects treated with JATENZO. The main difference between plasma and serum is that no anticoagulants are used in the collection of serum and all the fibrinogen and associated proteins are removed through the clotting process. Therefore, serum always contains less protein material than plasma, leading to a cleaner sample. However, if the analyte of interest has a stability issue like this case, using plasma may have an

advantage over serum, as plasma samples can be processed very quickly followed by sample analysis or storage.

It should be noted that sample handling time and temperature appears to affect the TU to T ex vivo conversion. When whole blood sample was fortified with different concentrations of TU, the T concentration increased over time and depended on the TU concentration used to fortify the samples, showing that TU degrades into T in whole blood during clotting and serum harvesting. In addition, it was reported that temperature also has an effect on the TU to T ex vivo conversion when comparing T concentrations obtained from samples prepared at room temperature and 4ºC as samples prepared at room temperature showed a higher conversion rate than those prepared at 4ºC (Lachance et al., 2015).

The TU concentration-dependent increase of T concentrations was also observed in the Sponsor's own study, CLAR-15013. Reference is made to the individual study review of Study CLAR-15013 for details of the study design and outcome.

Primary Efficacy Evaluation Results:
The primary efficacy endpoint in this study was consistent with that used in other studys for TRTs. The Sponsor needed to demonstrate that JATENZO achieves 24 hour C_{avg} for total T at Visit 7 (i.e., end of treatment) within the normal eugonadal range for at least 75% of subjects and that the lower bound of the corresponding 95% CI for this point estimate is at least 65%.

To support the use of NaF/EDTA tubes in the new study, the Sponsor conducted a separate study (Study CLAR-16014) in 97 healthy males to derive the normal plasma T concentration range then applied that normal range to the primary efficacy endpoint in this study. The mean, calculated using natural-log transformed T concentrations, was 478 ng/dL; and the eugonadal range was determined as the exponential of the mean ±2 SDs of the population, namely 252 to 907 ng/dL. Reference is made to the Individual Study Review of Study CLAR-16014 in this NDA review.

As shown in Table A-1-16, the primary efficacy endpoint was achieved in this study.

Table A-1-16: Percentage of Subjects With Testosterone Cavg Values in the Eugonadal Range at Visit 7 for Primary Analysis (Modified ITT Population)

Testosterone C_{avg} Range, n (%)	FDA Target	Oral TU (N = 166)	Topical Axiron (N = 55)
252 ng/dL ≤ C_{avg} ≤ 907 ng/dL[a]	≥ 75%	145 (87.3%)	48 (87.3%)
Lower bound 95% confidence interval	≥ 65%	81.3%	75.5%
Upper bound 95% confidence interval		92.0%	94.7%
C_{avg} mean (standard deviation) ng/dL		401.2 (140.2)	390.6 (139.9)
95% confidence interval		379.7, 422.7	352.8, 428.5

Source: Appendix 16.5.1, Table 3
Abbreviations: C_{avg} = average observed concentration over 24 hours; FDA = Food and Drug Administration; ITT = intention-to-treat; LOCF = last observation carried forward; TU = testosterone undecanoate
[a] Eugonadal range.
Note: The primary efficacy analysis treated all missing data as if the subject failed to achieve a Visit 7 plasma sample measurement in the eugonadal range unless the data were missing because of a cause not related to the study drug. For missing values not attributed to a study drug-related cause, the Visit 7 C_{avg} was imputed by LOCF and determined whether it was in the eugonadal range.

Reviewer's Comment: *For missing values not attributed to a study drug-related cause, the Visit 7 C_{avg} was imputed by LOCF, and then determined whether it was in the eugonadal range.*

Three sensitivity analyses (LOCF, multiple imputation, imputation from baseline) were performed in addition to the primary analysis. All 3 sensitivity analyses provided an imputed T C_{avg} value for all subjects missing Visit 7 values, regardless of reasons for discontinuation. For the JATENZO group, all 3 sensitivity analyses resulted in estimates of the percentage of subjects in the eugonadal range of 86.1% to 89.6%. Thus, the sensitivity analyses met the efficacy target of ≥ 75% of subjects with a T C_{avg} in the eugonadal range and the lower bound of the 95% CI ≥ 65% (Table A-1-17).

Table A-1-17: Percentage of Subjects with T C_{avg} Values in the Eugondal Range at Visit 7 for Sensitivity Analyses (Modified ITT Population)

Testosterone C_{avg} Range, n (%)	FDA Target	Oral TU (N = 166)	Topical Axiron (N = 55)
Last Observation Carried Forward Method			
252 ng/dL ≤ C_{avg} ≤ 907 ng/dL[a]	≥ 75%	146 (88.0%)	50 (90.9%)
Lower bound of 95% confidence interval	≥ 65%	82.0%	80.0%
C_{avg} mean (standard deviation)		401.2 (140.2)	390.6 (139.9)
95% confidence interval		379.7, 422.7	352.8, 428.5
Multiple Imputation Method			
252 ng/dL ≤ C_{avg} ≤ 907 ng/dL[a]	≥ 75%	149 (89.6%)	50 (90.6%)
Lower bound of 95% confidence interval	≥ 65%	84.6%	82.3%
C_{avg} mean (standard deviation)		403.6 (143.3)	388.3 (141.3)
95% confidence interval		381.8, 425.4	351.0, 425.7
Imputation From Baseline Method			
252 ng/dL ≤ C_{avg} ≤ 907 ng/dL[a]	≥ 75%	143 (86.1%)	45 (81.8%)
Lower bound of 95% confidence interval	≥ 65%	79.9%	69.1%
C_{avg} mean (standard deviation)		384.1 (137.4)	358.2 (142.0)
95% confidence interval		363.1, 405.2	319.8, 396.5

Source: Appendix 16.5.1, Tables 6, 8, and 10
Abbreviations: C_{avg} = average observed concentration over 24 hours; FDA = Food and Drug Administration; ITT = intention-to-treat; TU = testosterone undecanoate
[a] Eugonadal range.

The Sponsor performed a *post-hoc* analysis of the primary endpoint by weight subgroups (≤ 100 kg and > 100 kg). In both the JATENZO and Axiron® groups, a slightly higher percentage of subjects who weighed ≤ 100 kg had T C_{avg} values in the eugonadal range (89.2% and 90.3%, respectively) compared with subjects who weighed > 100 kg (85.5% and 83.3%, respectively). In the JATENZO group, the mean (± SD) dosage strength of the last dose of study drug was higher for subjects who weighed > 100 kg compared with those who weighed ≤ 100 kg; however, in the Axiron® group, the mean (± SD) dosage strength of the last dose of study drug was comparable between the weight subgroups. For subjects weighing > 100 kg in the JATENZO group, both the estimated percentage of subjects (85.5%) and the lower bound of the 95% CI (76.1%) met the FDA target of ≥ 75% and ≥ 65%, respectively.

Table A-1-18: Percentage of Subjects with T C_{avg} Values in the Eugonadal Range at Visit 7 for Primary Analysis by Weight (Modified ITT Population)

		Oral TU (N = 166)		Topical Axiron (N = 55)	
Testosterone C_{avg} Range, n (%)	FDA Target	≤ 100 kg (N = 83)	> 100 kg (N = 83)	≤ 100 kg (N = 31)	> 100 kg (N = 24)
252 ng/dL ≤ C_{avg} ≤ 907 ng/dL[a]	≥ 75%	74 (89.2%)	71 (85.5%)	28 (90.3%)	20 (83.3%)
Lower bound 95% CI	≥ 65%	80.4%	76.1%	74.2%	62.6%
Upper bound 95% CI		94.9%	92.3%	98.0%	95.3%
Last dose of study drug (mg)					
Mean (SD)		298.1 (64.5)	348.9 (58.4)	79.4 (21.3)	78.8 (19.4)
95% CI		284.1, 312.2	336.2, 361.7	71.5, 87.2	70.6, 86.9

Source: Appendix 16.5.1, Tables 11 and 12
Abbreviations: C_{avg} = average observed concentration over 24 hours; CI = confidence interval; FDA = Food and Drug Administration; ITT = intention-to-treat; LOCF = last observation carried forward; SD = standard deviation; TU = testosterone undecanoate
[a] Eugonadal range.
Note: The primary efficacy analysis treated all Visit 7 missing data as if the subject failed to achieve a Visit 7 plasma sample measurement in the eugonadal range unless the data were missing because of a cause not related to the study drug. For missing values not attributed to a study drug-related cause, the Visit 7 C_{avg} was imputed by LOCF and determined whether it was in the eugonadal range.

Safety Evaluation Results:

Key PK Safety Endpoint (Plasma total T C_{max} on Day 105): The following criteria were expected to be met for the critical secondary safety endpoint, total T C_{max} on Day 105:

- No subjects with a total T C_{max} of > 2,500 ng/dL
- Less than 5% of subjects with a total T C_{max} in the range of 1,800-2,500 ng/dL
- At least 85% of subjects with a total T $C_{max} \leq$ 1,500 ng/dL

Table A-1-19 presents the number and percentage of subjects who had total T C_{max} values at Day 105 (Visit 7) in each C_{max} category.

Table A-1-19: Number (Percentage) of Subjects by Total T C_{max} Criteria Ranges at Day 105 (Subjects who had Total T C_{max} at Visit 7)

Testosterone C_{max} Range, n (%)	FDA Target	Oral TU (N = 151)[a]	Topical Axiron (N = 48)
$C_{max} \leq$ 1500 ng/dL	≥ 85%	137 (90.7%)	47 (97.9%)
C_{max} > 1800 - 2500 ng/dL	≤ 5%	3 (2.0%)	1 (2.1%)
C_{max} > 2500 ng/dL	0	3 (2.0%)[b]	0

Source: Post-text Table 14.2.2.1

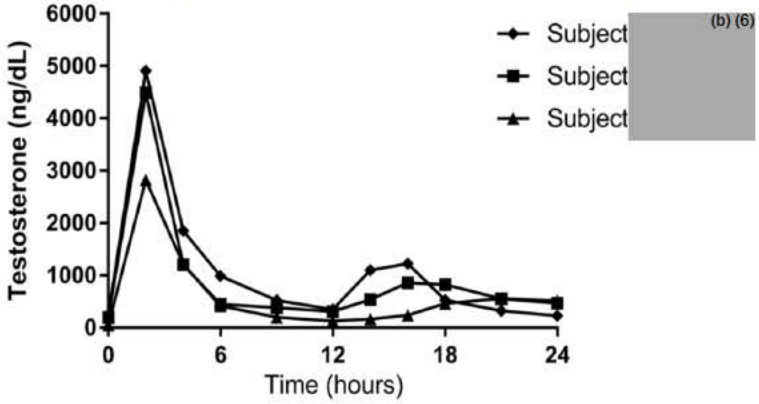
Abbreviations: C_{max} = maximum observed concentration over 24 hours; FDA = Food and Drug Administration; TU = testosterone undecanoate

[a] Eight subjects had C_{max} values > 1500 - ≤ 1800 ng/dL.

[b] All 3 subjects had C_{max} values suggestive of contamination.

Figure A-1-9 shows the total T concentration – Time plot for JATENZO-treated subjects with total T > 2,500 ng/dL at Visit 7 (Day 105)

Figure A-1-9: Total T Concentration – Time Plot for JATENZO-Treated Subjects with Total T C_{max} > 2,500 ng/dL at Visit 7 (Day 105; Safety Population)



A supplemental analysis was performed in which the C_{max} criteria boundaries were adjusted for the upper limit of the eugonadal range, namely 907 ng/dL (Table A-1-20).

Table A-1-20: Number (Percentage) of Subjects by Total T C_{max} in Adjusted Criteria Ranges at Day 105 (Subjects who had Total T C_{max} at Visit 7)

Testosterone C_{max} Adjusted Range[a], n (%)	FDA Target	Oral TU (N = 151)	Topical Axiron (N = 48)
$C_{max} \leq$ 1361 ng/dL	≥ 85%	125 (82.8%)	47 (97.9%)
C_{max} > 1633 - 2268 ng/dL	≤ 5%	5 (3.3%)	1 (2.1%)
C_{max} > 2268 ng/dL	0	4 (2.6%)	0

Source: Post-text Table 14.2.2.1b

Abbreviations: C_{avg} = average concentration over 24 hours; C_{max} = maximum observed concentration over 24 hours; FDA = Food and Drug Administration; TU = testosterone undecanoate

[a] The adjustment factor was the ratio of 907 ng/dL to the typical eugonadal upper limit (ie, 907/1000 = 0.907).

The adjustment factor was the ratio of 907 ng/dL to the typical eugonadal upper limit (i.e., 907/1,000 = 0.907). Total T C_{max} over 24 hours was evaluated by estimating the proportions of JATENZO-treated subjects at Visit 7 according to the following categories: < 1,361 ng/dL (e.g., 1,500 × 0.907), > 1,633 to ≤ 2,268 ng/dL, and > 2,268 ng/dL. This *post hoc* analysis was performed to understand how revised upper limits might affect the frequency distribution of outliers.

Reviewer's Comment: *Although 3 JATENZO-treated subjects had single, transient total T C_{max} values > 2,500 ng/dL, inspection of their data shows that the high concentrations are likely spurious and due to specimen contamination.*

Table A-1-21: Observed T, DHT, and DHT/T Ratios in High T C_{max} Samples, and Estimated T Concentrations Assuming High T Includes Contamination from Exogenous T

	Observed Values at Visit 7 for Subjects With High Testosterone C_{max} Samples					Estimated 2 Hour Testosterone Concentrations	
	2 h	2 h	2 h	4 h	14 h	Estimate from 4 h DHT/T	Estimate from 14 h DHT/T
Subject	T ng/dL	DHT ng/dL	DHT/T mole ratio	DHT/T mole ratio	DHT/T mole ratio	T ng/dL	T ng/dL
(b) (6)	4905	297.2	0.0602	0.1665	0.1625	1773	1817
	4485	198.3	0.0439	0.1378	0.0993	1429	1984
	2824	152.9	0.0538	0.1301	0.2305	1167	659

Source: Listing 16.2.6.2.2.1; Appendix 16.5.2, Table 5
Abbreviations: C_{max} = maximum observed concentration over 24 hours; DHT = dihydrotestosterone; T = testosterone

The Sponsor states that there are several common features in these three patients with a total T C_{max} > 2,500 ng/dL indicating contamination of samples with T:

- *The DHT/T molar ratios were all between 0.0439 and 0.0602 values that are less than half the DHT/T ratio (0.1484) of the other JATENZO-treated subjects in the 2-hour post dose sample. This is consistent with contamination with T, which would be expected to increase the T concentration but not affect the DHT concentration.*
- *An intra-subject comparison of the 2-hour DHT/T values for these 3 subjects to the other 9 post-dose samples collected at Visit 7 confirmed the 2-hour values were also atypically low for those subjects, being less than half the DHT/T ratio of any of the other 9 post-dose samples.*
- *The estimated T concentrations, assumed to approximate the pre-contamination plasma T concentrations for the 3 subjects, are all < 2,500 ng/dL (last 2 columns of Table A-1-21); all 3 cases result in concentration-time profiles for Visit 7 consistent with the generally expected oral TU profile shape, and are consistent with the previous PK patterns observed in these 3 subjects at Visit 2 and Visit 4b.*
- *All three subjects were at the same clinical site and underwent PK sampling on the same day and at the same time.*
- *A subject receiving Axiron® (Subject (b) (6) was having PK sampling at the same time as JATENZO-treated subjects, (b) (6) and (b) (6)*
- *All other concentrations for the 3 subjects, during both the morning and evening dosing intervals, were < 1,500 ng/dL, except that Subject (b) (6) had a concentration of 1,855 ng/dL 4 hours following the morning JATENZO dose.*

When these C_{max} outlier thresholds were adjusted downwards to account for the new lower T reference range proposed by the Sponsor, an analysis of outliers yielded one additional patient with a serum T concentration > 2,268 ng/dL (which corresponds to the revised 2,500 ng/dL threshold). No explanation could be determined for this patient's result.

Overall assessment on the serum total T C_{max} at Day 105

In summary, the following criteria of the secondary safety endpoint, total T C_{max} at Day 105 was not met:

- No subjects with a total T C_{max} of > 2,500 ng/dL

When using the adjusted threshold of 1361 ng/dL (for plasma in NaF/EDTA tubes) instead of 1500 ng/dL, the following T C_{max} criteria was not met as well:

- At least 85% of subjects with a total T $C_{max} \leq$ 1,500 ng/dL

Reviewer's Comment: *While 3 out of the 4 subjects had a total T C_{max} of > 2,500 ng/dL, inspection of their data shows that the high concentrations are likely spurious and due to specimen contamination. Therefore, the Clinical Pharmacology review team does not believe that the total T C_{max} profile is a safety concern for JATENZO.*

Table A-1-22: Comparison of Total T C_{max} Profile of JATENZO to Other Approved T gel Products

Product	C_{max} < 1,500 ng/dL N (%)	1,800 ng/dL < C_{max} ≤ 2,500 ng/dL N (%)	C_{max} > 2,500 ng/dL N (%)	Average C_{avg} (ng/dL)	Average C_{max} (ng/dL)
JATENZO[a] (Day 105)	125/151 (82.8)	5/151 (3.3)	4/151 (2.6)	403	1008
Androgel 1.62% (Day 112)	159/179 (88.8)	10/179 (5.6)	2/179 (1.1)	561	845
Testim (Day 90)	191/199 (96.0)	4/199 (2)	0/199 (0)	612	897
Axiron (Day 120)	128/135 (94.8)	4/135 (3)	1/135 (0.7)	480	792
Fortesta (Day 90)	122/129 (94.6)	2/129 (1.5)	0/129 (0)	440	528
Natesto (Day 90)	58/69 (84.1)	1/69 (1.5)	0/69 (0)	421	1044

[a] As JATENZO T concentrations were measured in plasma using NaF/EDTA tubes, the following adjusted T C_{max} ranges were used:
$C_{max} \leq$ 1361 ng/dL
C_{max} > 1633-2268 ng/dL
C_{max} > 2268 ng/dL

Reviewer's Comment: *It should be noted that while other products in Table A-1-22 are T gels administered once daily, Natesto® has a TID dosage regimen. JATENZO (BID dosage regimen) appears to have comparable total T C_{avg} and C_{max} values with Natesto®.*

DHT PK Parameters and DHT/T Ratios

Table A-1-23 summarizes the plasma DHT PK parameters at Day 105 (Visit 7) by treatment following JATENZO or Axiron® treatments.

Table A-1-23: Summary of Plasma DHT PK Parameters at Day 105 (Visit 7) by Treatment Following JATENZO or Axiron® Treatments

Visit	PK Parameter	Units	Oral TU, All Doses				Topical Axiron, All Doses			
			N	Mean	SD	CV%	N	Mean	SD	CV%
Visit 1	DHT	ng/dL	164	15.53	8.871	57.1%	54	13.86	5.957	43.0%
	DHT/T	mol ratio	164	0.08240	0.053935	65.5%	54	0.08231	0.067902	82.5%
Visit 7	C_{avg24}	ng/dL	152	73.25	30.088	41.1%	48	73.76	30.858	41.8%
	AUC_{24}	ng•h/dL	152	1757.9	722.11	41.1%	48	1770.2	740.58	41.8%
	C_{max24}	ng/dL	152	117.1	46.03	39.3%	48	97.97	39.154	40.0%
	$T_{max\text{-}am}$ [a,b]	h	155	4.00	(0.00, 12.08)		48	4.01	(0.00, 24.00)	
	$T_{max\text{-}pm}$ [a]	h	152	16.13	(12.00, 24.13)					
	DHT/T	mol ratio	151	0.1822	0.05138	28.2%	48	0.1941	0.06392	32.9%

Source: Appendix 16.5.2, Table 6

Abbreviations: AM = morning; AUC_{24} = area under the concentration-time curve morning and evening doses combined; C_{avg24} = time-weighted average plasma concentration morning and evening doses combined; C_{max24} = maximum observed concentration morning and evening doses combined; $C_{max\text{-}am}$ = time-weighted average concentration over the daytime dosing interval following the AM dose; $C_{max\text{-}pm}$ = time-weighted average concentration over the daytime dosing interval following the PM dose; CV = coefficient of variation; DHT/T = dihydrotestosterone/testosterone ratio; PK = pharmacokinetic; SD = standard deviation; $T_{max\text{-}am}/T_{max\text{-}pm}$ = time to $C_{max\text{-}am}/C_{max\text{-}pm}$; TU = testosterone undecanoate

[a] T_{max} values shown are median (range).

[b] Topical Axiron T_{max} is relative to the morning dose since it was applied just once daily, in the morning.

Reviewer's Comment: *Mean plasma DHT concentrations and DHT/T ratios for the JATENZO- and Axiron®-treated subjects were comparable and within the normal reference range of 0.05-0.33 (Wang et al., 2000; Diver et al., 2003).*

Other Hormones

Findings regarding other hormones are summarized below:

- Estradiol concentrations increased in both treatment groups, with similar mean concentrations observed at Visit 7.
- Mean serum sex hormone binding globulin (SHBG) concentrations in JATENZO- and Axiron®-treated subjects were within the normal range both before start of treatment and after approximately 3 to 4 months of TRT.
- Consistent with expected hormonal feedback at the hypothalamic/pituitary level in subjects receiving TRT, similar reductions in mean serum FSH and LH concentrations were observed in both JATENZO- and Axiron®-treated subjects.

Other Safety Findings

Other safety findings are summarized below. References is made to Dr. Roger Wiederhorn's Clinical review for details of these findings:

- No deaths occurred. There were 2 serious adverse events (SAEs) reported in JATENZO-treated subjects: intestinal obstruction and periumbilical abscess. Neither of these were considered drug-related. Among Axiron® subjects, there was one SAE, a perforated appendix.
- The major safety risk identified for JATENZO is blood pressure elevation, as illustrated by a mean daytime systolic blood pressure increase of 5 mm Hg for JATENZO vs. 0.1 mm Hg for Axiron®.
- Eight (4.8%) JATENZO-treated subjects had hematocrit > 54% while Axiron®-treated subjects had none.
- There were small mean changes in serum lipids, modestly less favorable for JATENZO compared to Axiron®.
- Adrenal gland findings in nonclinical studies and results from cosyntropin stimulation testing in CLAR-15012 need further human investigation. This investigation could be conducted post-marketing.

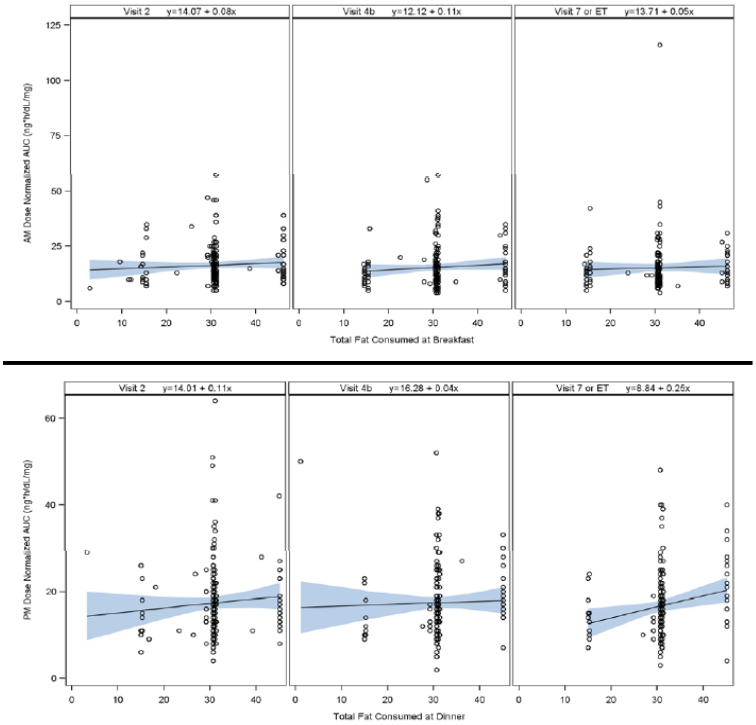
- One JATENZO-treated subject experienced a myocardial infarction (MI) two weeks after his last dose of JATENZO. The relationship between MI and JATENZO in this case is unknown.
- Four (2.4%) JATENZO-treated subjects experienced AEs that led to premature discontinuation including: axillary rash (n=1), panic attack (n=1), and headache (n=2). One Axiron subject (1.8%) discontinued due to an AE.
- Commonly reported AEs revealed an excess of gastrointestinal disorders: JATENZO (12%) vs. Axiron® (0.0%), probably related to route of administration. Headache was reported as an AE in 7 (4.8%) JATENZO-treated subjects vs. 1 (1.8%) Axiron®-treated subject.
- In three of the 7 JATENZO-treated subjects who reported headache, increased blood pressure was reported sometime prior to the headache event.

Food Effect:

In this study (CLAR-15012), subjects had a choice of 15 g, 30 g, or 45 g fat breakfasts and dinners at their PK visits. When subjects were asked to choose the meals for their PK visits, the selection criterion was "most similar to typical breakfast or dinner that you would eat most mornings (or evenings)." Once a subject made his meal choice, the same meal was used for all 3 PK visits (i.e., Visit 2, Visit 4b, and Visit 7). All subjects had a number of lunch options, which all had 30 g fat content and lunch composition was not incorporated into the analysis. On non-PK days during the study, subjects were not given special diet instructions regarding fat or calorie consumption for meals. Subjects were instructed to take JATENZO immediately prior to breakfast and dinner.

Based on regression analysis, the Sponsor believes that no clinically important trends in dose-normalized AUC versus meal fat content were noted during the morning and evening dosing intervals (Figure A-1-10).

Figure A-1-10: Regression Analysis of Dose-Normalized AUC for Plasma Total T Concentration Versus Meal Fat Content by Study Visit (Study CLAR-15012)



Out of the 105-day active treatment period in this study, meals were not controlled for 102 days (besides the 3 PK days). Efficacy (i.e., based on T C_{avg}) and safety (i.e., based on T C_{max}) were demonstrated for PK driven endpoints obtained on a single, end of study PK visit day (i.e., Day 105) when meals were controlled. General safety (e.g., AEs, and laboratory parameters) were obtained throughout the study.

The Sponsor states that there was no meaningful difference in dose-normalized T C_{avg} and C_{max} among the different meal types, and that dose titration will not be significantly affected by meal fat composition.

The Sponsor proposes that JATENZO should be taken with food without further instructions on the fat content of meals.

Conclusion:
The primary efficacy endpoint was met. However, the following criteria of the secondary safety endpoint, total T C_{max} at Day 105 was not met:

- No subjects with a total T C_{max} of > 2,500 ng/dL

When using the adjusted threshold of 1,361 ng/dL (for plasma in NaF/EDTA tubes) instead of 1,500 ng/dL, the following T C_{max} criteria was not met as well:

- At least 85% of subjects with a total T $C_{max} \leq$ 1,500 ng/dL

While 3 out of the 4 subjects had a total T C_{max} of > 2,500 ng/dL, inspection of their data shows that the high concentrations are likely spurious and due to specimen contamination. Therefore, the Clinical Pharmacology review team does not believe that the total T C_{max} profile is a safety concern for JATENZO.

The Clinical Pharmacology review team concludes that Sponsor's approach of using total concordance (including effective concordance) is reasonable. The review team also concludes that a 4-6-hour post-dose window for dose titration evaluation appears to be more optimal than a 3-5 hour post-dose window proposed by the Sponsor.

Total T concentrations obtained from plasma in NaF/EDTA tubes were lower compared to when measuring total T concentrations measure from serum collected in plain tubes (red top) from same subjects. Potential contributing factors may be additive (e.g., NaF and/or EDTA) effect, TU to T *ex vivo* conversion, or different sample handling conditions/procedures. The Clinical Pharmacology review team concludes that additional investigation on the rate and extent of the TU to T *ex vivo* conversion during the time course of plasma sample preparation is warranted prior to JATENZO's approval.

4.1.2 Food Effect Study (CLAR-16015)

Title: A Phase 2 Study of the Effect of Meals with Various Amounts of Fat Given Immediately After Dosing on the Pharmacokinetics of an Oral Testosterone Undecanoate in Hypogonadal Men

Primary Objectives:

- To compare the effect of meals (breakfast) containing various amounts of fat on the PK parameters of JATENZO at a dose of 237 mg TU (the highest strength capsule being developed).
- Maximum morning exposure ($C_{max\text{-}am}$) and total morning exposure (area under the concentration-time curve over the AM dosing interval [AUC_{am}], time-weighted average plasma concentration over the dosing interval following the AM dose [$C_{avg\text{-}am}$]) of total T after consuming various lower and higher fat content breakfasts and fasting versus 30 g fat for breakfast

Clinical Study Center: (b) (4)

Clinical Study Period: October 17, 2016 – January 23, 2017

Bioanalytical Study Center: (b) (4)
Bioanalysis Period: January 30 – February 7, 2017

Study Design, Treatments, and Drug Administration:
This was a Phase 2, multicenter, repeat-dose, food-effect study conducted in 18 males. Subjects were randomized to a sequence of meals that varied primarily in fat content. The study included up to a 28-day Screening Phase (Screen 1 and Screen 2 visits), a 14-day Run-In Phase, a 6-day PK Phase, and a Safety Follow-Up Phase (phone contact or clinic visit 5 to 7 days after the last dose of JATENZO). Throughout the Run-In (14 days) and the PK Phases, subjects were dosed with 237 mg JATENZO BID (i.e., the highest strength in development and the starting dose for the Phase 3 study, CLAR-15012).

The 14-day Run-In Phase was designed to suppress each subject's endogenous T production while allowing JATENZO to reach steady-state. After the 14-day Run-In Phase, subjects were confined in the clinic for approximately 6 consecutive days for evaluations and serial blood draws in the 5-period crossover PK Phase. Subjects presented at the clinic in the evening of Day 14 of the Run-In Phase prior to dinner and were dosed with JATENZO immediately prior to a dinner meal. Subjects remained in the clinic until collection of the 24-hour serial sample following the morning dosing in Period 5 of the PK Phase. On each of the PK Phase Periods 1 through 5, the subject was dosed immediately prior to the breakfast meal (or in the morning with 240 mL of water for the fasting period).

There were a total of 4 fed breakfast types, in addition to fasting. Three of the 4 fed breakfast types contained approximately 850 calories (including 15 g fat, 30 g fat, or 45 g fat), and the fourth fed breakfast type was a high-calorie, high-fat meal (approximately 1000 calories, with 50% of the calories from fat) consistent with the *Guidance for Industry on Food-Effect Bioavailability and Fed Bioequivalence Studies*. Notably, the 15 g, 30 g, and 45 g fat meals were meal options that were incorporated into Phase 3 study, CLAR-15012.

Subjects were randomized to a sequence of the 5 defined meal plans (including fasting for breakfast) that were administered on PK Phase Periods 1 through 5 (Days 1 to 5). The 5 meal plans provided during the PK Phase were as follows:

Meal Plan A (Fasting)

- Overnight fast (≥ 10 hours)
- Dose JATENZO with 240 mL of water
- Fast additional 4 hours
- Lunch 30 g fat
- Dose JATENZO immediately prior to dinner
- Dinner 30 g fat

Meal Plan B (15 g fat)

- Overnight fast (≥ 10 hours)
- Dose JATENZO immediately prior to breakfast
- Breakfast 15 g fat
- Lunch 30 g fat
- Dose JATENZO immediately prior to dinner
- Dinner 30 g fat

Meal Plan C (30 g fat)

- Overnight fast (≥ 10 hours)
- Dose JATENZO immediately prior to breakfast
- Breakfast 30 g fat
- Lunch 30 g fat\
- Dose JATENZO immediately prior to dinner
- Dinner 30 g fat

Meal Plan D (45 g fat)

- Overnight fast (≥ 10 hours)
- Dose Oral TU immediately prior to breakfast
- Breakfast 45 g fat
- Lunch 30 g fat
- Dose Oral TU immediately prior to dinner
- Dinner 30 g fat

Meal Plan E (FDA high-calorie, high-fat)

- Overnight fast (≥ 10 hours)
- Dose Oral TU immediately prior to breakfast
- Breakfast FDA high-calorie, high-fat meal (≈1000 calories, 50% of calories as fat)
- Lunch 30 g fat
- Dose Oral TU immediately prior to dinner
- Dinner 30 g fat

The confinement for the PK Phase began on Run-In Day 14 immediately prior to the evening dose and meal, and continued through PK Phase Period 5, which ended with the collection of a blood sample 24 hours after the Period 5 morning dose, for a total of approximately 135 hours. During the PK Phase, subjects were to consume their entire breakfast and dinner meals and study drug was administered in the morning and evening (approximately 12 hours apart) immediately before breakfast and dinner.

For all subjects, serial blood samples were collected as follows: 0 (pre-morning dose), 2, 4, 6, 9, 12, 14, 16, 18, 21, and 24 hours after the morning dose. Blood sample collection was performed

within ±10 minutes of the scheduled time points (with the exception of the 0-hour time point which was collected no more than 5 minutes before JATENZO dose administration in each PK Phase Period). Subjects were released from the clinic following the 24-hour blood draw of Period 5 and designated end of study activities of the PK Phase, which occurred in the morning after the fifth PK Phase study period.

Inclusion Criteria:
Subjects were required to meet the following criteria in order to be eligible for the study:

- Men 18 to 65 years of age, inclusive, with a clinical diagnosis of hypogonadism (signs/symptoms consistent with hypogonadism for T-naive subjects and history of signs/symptoms for subjects who had received prior treatment) as well as serum T concentrations consistent with hypogonadism as defined by 2 total T concentrations of < 300 ng/dL (between 6 and 10 am drawn on 2 separate days approximately 7 [± 2] days apart).
- Adequate venous access in the left or right arm to allow collection of a number of blood samples via a venous cannula.
- Naive to androgen-replacement therapy or washed out of prior androgen-replacement therapies; that is, was willing to cease current T treatment or was not currently taking T treatment. Subjects were to remain off all forms of T, except for dispensed study drug, throughout the entire study.
- Subjects on replacement therapy for hypopituitarism or multiple endocrine deficiencies must have been on stable doses of thyroid hormone and adrenal replacement hormones for at least 14 days before Screen 1.
- Had voluntarily given written informed consent to participate in this study.

Exclusion Criteria:
Subjects meeting any of the following criteria were not eligible for participation in this study:

- Received oral, topical (e.g., gel or patch), intranasal, or buccal T therapy within the previous 2 weeks, intramuscular T injection of short-acting duration (e.g., T enanthate, T cypionate) within the previous 4 weeks, intramuscular T injection of long-acting duration (e.g., Aveed®) within the previous 20 weeks, or T implantable pellets (Testopel®) within the previous 6 months.
- Had an intercurrent disease deemed clinically significant, in the opinion of the Investigator, of any type; in particular, liver, kidney, uncontrolled or poorly controlled heart disease, including hypertension, congestive heart failure or coronary heart disease, or psychiatric illness, including severe depression.
- Had a recent (within 2 years) history of stroke, transient ischemic attack, or acute coronary event.
- Had a mean of the triplicate assessment of systolic blood pressure > 150 mm Hg and/or diastolic blood pressure > 90 mm Hg at screening (if prescribed antihypertensives, subject should have taken medications on the day of the screening visit with a sip of water). Subjects < 60 years of age and prescribed antihypertensives were excluded if the mean of the triplicate assessment of systolic blood pressure was > 140 mm Hg and/or diastolic blood pressure > 90 mm Hg at screening.
- Had recent (within 2 years) history of angina or stent (coronary or carotid) placement.
- Had untreated, severe obstructive sleep apnea.
- Had clinically significant abnormal laboratory values, including serum transaminases > 2 × upper limit of normal (ULN), serum bilirubin > 1.5 × ULN and serum creatinine > 1.5 × ULN.
- Had a hematocrit value of < 35% or > 48%.

- Had a history of polycythemia, either idiopathic or associated with TRT.
- Was a diabetic with a glycosylated hemoglobin > 8.5%.
- Had a BMI ≥ 38 kg/m^2.
- Had been on stable doses of antihypertensive medication for < 3 months.
- Had an abnormal prostate by digital rectal examination (palpable nodules), elevated prostate-specific antigen (PSA; serum > 4.0 ng/mL), International Prostate Symptom Score (I-PSS) > 19 points at screening, and/or history of, or current or suspected, prostate cancer.
- Had a history of, or current or suspected, breast cancer.
- Had a history of abnormal bleeding tendencies or thrombophlebitis unrelated to venipuncture or intravenous cannulation within the previous 2 years.
- Used dietary supplements such as saw palmetto or phytoestrogens and any dietary supplements that may have increased total T, such as androstenedione or dehydroepiandrosterone within the previous 4 weeks.
- Had known malabsorption syndrome and/or current treatment with oral lipase inhibitors (eg, orlistat [Xenical®]) and/or bile acid-binding resins (e.g., cholestyramine [Questran®], colestipol [Colestid®]) or treatments that promote gastric emptying (e.g., metoclopramide [Reglan®]).
- Inability to observe all rules and smoking restrictions in place at the study site during confinement.
- Had history of abuse of alcohol or any drug substance within the previous 2 years.
- Poor compliance or unlikely to keep clinic appointments and remain for the entire confinement period.
- Had received any drug as part of another research study within 30 days of initial dose administration in this study.
- Donated blood (≥ 500 mL) within the 12-week period before the initial dose administration in this study.
- Currently used the following groups of drugs that affect T concentrations, T metabolism, or concentrations of T metabolites, namely antiandrogens, 5-alpha-reductase inhibitors (e.g., dutasteride, finasteride), estrogens, long-acting opioid analgesics (eg, methadone hydrochloride, buprenorphine hydrochloride) or human growth hormone.
- Unwilling or unable to follow the dietary requirements for this study.

Prior and Concomitant Medications

If any medication or nutritional supplement was taken, the name, dose, route, frequency of dosing, and reason for use was recorded on the concomitant medication page in the CRF. Subjects were asked about their treatment history for hypogonadism and the start and stop dates for their most recent TRT. In addition, start dates for the use of any antihypertensive medications taken less than 3 months before screening were recorded in the CRF. Subjects taking antihypertensive medications had to be on a stable dose for at least 3 months prior to screening.

PK Endpoints:

Pharmacokinetic endpoints included:

- Area under the concentration-time curve for the morning (AUC_{am}), evening (AUC_{pm}), and combined morning and evening dosing intervals (AUC_{24})
- Maximum measured plasma concentration for the morning ($C_{max\text{-}am}$), evening ($C_{max\text{-}pm}$), and combined morning and evening dosing intervals ($C_{max\text{-}24}$)
- Time-weighted average plasma concentration for the morning dosing interval ($C_{avg\text{-}am}$), evening dosing interval ($C_{avg\text{-}pm}$), and combined morning and evening dosing interval ($C_{avg\text{-}24}$)

- Time to maximum measured plasma concentration morning ($T_{max\text{-}am}$) and evening ($T_{max\text{-}pm}$) dosing intervals

Safety Endpoints:
The safety profile was assessed by recording adverse events, measuring vital signs, performing physical examinations, and performing laboratory evaluations (clinical chemistry and hematology).

Study Flow Chart
The study flow chart is shown in Table A-2-1.

Table A-2-1: Schedule of Assessment

	Screening Phase		Treatment Phase							Safety Follow-Up Phase
	Screen 1	Screen 2	14 (± 2) Day Run-In Phase		PK Phase					Phone or Clinic Visit[a]
Activity	Day -28 to -21	~7 (± 2) Days Post Screen 1	Dosing Day 1	Dosing Day 14	Period 1/ Day 1 Dosing Day 15	Period 2/ Day 2 Dosing Day 16	Period 3/ Day 3 Dosing Day 17	Period 4/ Day 4 Dosing Day 18	Period 5[b]/ Day 5-6 Dosing Day 19	5 to 7 Days After Last Dose
Informed consent	X									
Inclusion/exclusion review	X	X	X							
Medical history review	X									
Prior & concomitant medications	X	X	X	X	X	X	X	X	X	X
Physical examination with DRE		X								X[c]
Brief physical examination			X						X[b]	
Weight, height, and body mass index	X									
Adverse event assessment		X	X	X	X	X	X	X	X	X
Vital signs (including triplicate sitting blood pressure and heart rate)	X		X		X	X	X	X	X	X[c]
Complete safety labs (fasting)	X		X		X				X[d]	X[c]
Urine dipstick	X									
Serum total T (6 to 10 AM)	X	X								
PSA	X								X[d]	
Study Meal Administration			X[e]	X[e]	X	X	X	X	X	
Predose total T/DHT (6 to 10 AM)			X[f]							
Serial PK samples total T/DHT/TU					X[g]	X[g]	X[g]	X[g]	X[g]	
I-PSS	X									
Dispense study drug and provide dosing instructions			X							
In clinic study drug administered			X[e]	X[e]	X	X	X	X	X	
Study drug accountability				X	X	X	X	X	X	

Abbreviations: AM = morning; DHT = dihydrotestosterone; DRE = digital rectal examination; EDTA = ethylenediaminetetraacetic acid; I-PSS = International Prostate Symptom Score; NaF = sodium fluoride; PK = pharmacokinetic; PM = evening; PSA = prostate-specific antigen; T = testosterone; TU = testosterone undecanoate

[a] A visit performed by telephone was acceptable if follow-up for safety issues (ie, abnormal lab result or adverse event) was not needed.
[b] Subjects were discharged from clinic the morning of Day 6 after brief physical examination. No study drug was administered after PK Phase Period 5.
[c] Sample collected or procedure completed if abnormal at PK Phase Period 5 or required as follow-up for a safety concern.
[d] PK Phase Period 5 sample drawn at the 24-hour post AM dose time point.
[e] During Run-In Phase, subjects took AM dose on Day 1 and PM dose on Day 14 in the clinic with meals provided. Study drug was dispensed from the bottle on Dosing Day 1. Subjects took study drug immediately prior to the protocol-defined meal provided in the clinic. Drug accountability was performed after the PM dose on Day 14.
[f] Both serum (red top) and plasma (gray top with NaF-EDTA) samples for T/DHT were collected.
[g] Blood samples for total T: 4 NaF-EDTA-containing tubes (for plasma) were collected at 0 (pre-AM dose), 2, 4, 6, 9, 12, 14, 16, 18, 21, and 24 hours after AM dose. The 24-hour PK sample for Day 1, 2, 3, and 4 also served as the 0 (predose) PK sample for Day 2, 3, 4, and 5, respectively. Samples following the AM dose were to have been drawn within 10 minutes of the nominal time relative to the AM dose taken in each period.

Bioanalytical Methods:
T and DHT were extracted from plasma by LLE. The extracted samples were dried under a stream of nitrogen, the residue was reconstituted.

Reconstituted sample extracts were analyzed using a Waters UPLC System equipped with an Applied Biosystems Sciex API 5000 triple quadrupole mass spectrometer. Chromatographic separation was performed on an ACE Excel 2 C18-PFP, 100 x 3.0 mm, 2 µm-column for T and DHT using gradient elution. Positive ions generated from the electrospray ion source were detected using the MRM mode. Quantitation was performed using a weighted linear regression ($1/concentration^2$) of the determined peak area ratios for T, DHT, T-d_3 (IS), and DHT-d_4 (IS). The LC-MS/MS method was developed and validated with the dynamic range of 0.1-30 ng/mL (10-3,000 ng/dL) and 0.05-5 ng/mL (5-500 ng/L) for total T and DHT, respectively.

Calibration standards and QC samples for T and DHT were prepared in human NaF/Na_2EDTA plasma. The endogenous concentration of the analyte in unstripped human NaF/Na_2EDTA plasma was determined using 6 zero standard unstripped samples which are blank unstripped samples containing

the ISs. This measured concentration (i.e., average of the six samples) was then added to the spiked amounts to obtain the final nominal concentrations of QC1, QC2, QC3, and QC4 prepared in that unstripped matrix. The nominal concentrations for the T QCs were as follows:

- QC1: 357.6 pg/mL
- QC2: 15,157.6 pg/mL
- QC3: 22,657.6 pg/mL
- QC4: 2,557.6 pg/mL

The nominal concentrations for the DHT QCs were as follows:

- QC1: 140.6 pg/mL
- QC2: 440.6 pg/mL
- QC3: 2,540.6 pg/mL
- QC4: 3,790.6 pg/mL

Accuracy of the calibration standards and QC samples during sample analysis was expressed as percent difference from theoretical concentration (i.e., % RE). For NaF/Na_2EDTA plasma total T, the %RE ranged from -2.8% to 3.1% for the 8 calibration standards in the range of 0.1-30 ng/mL and -4.1% to 2.5% for QC1, QC2, QC3, and QC4. For NaF/Na_2EDTA plasma DHT, the % RE ranged from -1.2% to 2.3% for the 8 calibration standards in the range of 0.05-5 ng/mL and -5.4% to 1.1% for QC1, QC2, QC3, and QC4.

Precision of the calibration standards and QC samples during sample analysis was expressed as the percent % CV. For NaF/Na_2EDTA plasma total T, the % CV ranged from 1.4% to 4.6% for the 8 calibration standards in the range of 0.1-30 ng/mL and 2.2% to 4.3% for QC1, QC2, QC3, and QC4. For NaF/Na_2EDTA plasma DHT, the % CV ranged from 1.8% to 4.9% for the 8 calibration standards in the range of 0.05-5 ng/dL and 3.0% to 5.2% for QC1, QC2, QC3, and QC4.

Long-term storage stability for both T and DHT in human plasma at -80°C was established for 246 days.

Stability (i.e., accuracy of $\leq$ 15%) of both T and DHT in human NaF/Na_2EDTA plasma was confirmed for 4 freeze/thaw cycles.

After 23 hours and 55 minutes in human NaF/Na_2EDTA plasma on the bench-top at room temperature, the % REs of the replicate analyses of T and DHT QC samples were always $\leq$ 15%.

ISR was conducted on 188 samples (20.1%) for both total T and DHT out of a total of 936 study samples. For total T, 186 out of 188 ISR samples (98.9%) were within ± 20% of the original results. For DHT, 171 out of 188 ISR samples (91.0%) were within ± 20% of the original results. These ISR results confirmed the reproducibility of the bioanalytical method.

Reviewer's Comment: *The acceptance criteria and performance of the total T and DHT bioanalytical methods were in compliance with the Agency's Bioanalytical Method Validation Guidance and are found to be acceptable.*

PK Evaluation and Statistical Methods:
The primary PK endpoint of interest was the total T exposure (maximum and cumulative) over the dosing interval following the morning doses of TU for each specific PK period. The analogous PK parameters (AUC_{pm}, $C_{max\text{-}pm}$, $T_{max\text{-}pm}$, and $C_{avg\text{-}pm}$) for total T were calculated following the evening dose of JATENZO, and the analogous PK parameters ($C_{max\text{-}24}$, AUC_{24}, and $C_{avg\text{-}24}$) for the combined 24-hour period (following both the morning and evening doses of TU for each specific PK period).

In addition, the morning dose, evening dose, and full day PK parameters including maximum concentration (C_{max}), time to C_{max} (T_{max}), and AUC were calculated for DHT and TU following the doses of TU for each PK period. Note that T_{max} was not calculated for the full day.

An analysis of variance (ANOVA) was performed on the natural log (ln) transformed $C_{max\text{-}am}$, AUC_{am}, and $C_{avg\text{-}am}$. Each ANOVA included calculation of meal type least-squares means (LSMs) and the difference between meal type LSMs. The point estimate and 90% CI for the LSM mean difference in ln transformed PK parameters $C_{max\text{-}am}$, AUC_{am}, and $C_{avg\text{-}am}$ were exponentiated to obtain estimates for ratios of geometric LSMs on the original scale. No food effect was concluded for a contrasted meal type if the 90% CI about the ratio of geometric LSMs of $C_{max\text{-}am}$ and AUC_{am} for that contrast were totally within the 0.80 to 1.25 interval.

Safety Analyses
All AEs occurring during the study were coded using the Medical Dictionary for Regulatory Activities (MedDRA®), Version 15.1. An AE was considered treatment-emergent if it began or worsened in severity after the first dose of study drug. The number and percentage of subjects with TEAEs were tabulated by system organ class and preferred term. Summaries of the number of subjects with TEAEs were provided by severity and by relationship to study drug. The incidences of TEAEs, serious TEAEs, TEAEs resulting in discontinuation from study drug, and TEAEs resulting in death were summarized.

For all chemistry and hematology safety laboratory values (including PSA results) that are numeric, descriptive statistics were presented for each laboratory test by assessment time point. All out-of-range values for serum chemistry, hematology, and urinalysis were listed by subject. Descriptive statistics were provided for blood pressure and heart rate at each assessment time point, including change from baseline. The mean of the triplicate values was used in the calculation of the summary statistics.

Sample Size Determination:
No formal sample size calculations were performed for this study. Approximately 20 hypogonadal subjects were to be enrolled at 2 to 3 study centers, with the expectation that approximately 16 subjects would complete the PK Phase.

Reviewer's Comment: *Eighteen (18) males completed the study. The Clinical Pharmacology review team considers this to be sufficient to provide adequate data.*

Disposition of Subjects and Subject Demographics
A total of 18 subjects were enrolled and randomized. The age of subjects ranged from 28 to 65 years, with a mean of 46.2 years (Table A-2-2). Most of the male subjects were White (83%), with an ethnicity that was Hispanic or Latino (67%). Mean BMI was 30.7 kg/m^2.

Table A-2-2: Study Subject Demographics

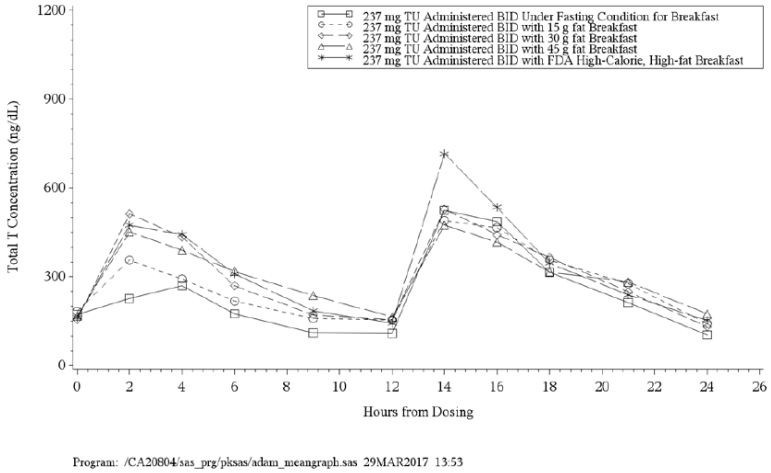
Characteristic	Oral TU (N = 18)
Age (years)	
Mean (SD)	46.2 (11.12)
Median	49.0
Minimum, Maximum	28, 65
Gender, n (%)	
Male	18 (100%)
Race, n (%)	
Black or African American	3 (17%)
White	15 (83%)
Ethnicity, n (%)	
Hispanic or Latino	12 (67%)
Not Hispanic or Latino	6 (33%)
Height (cm)	
Mean (SD)	174.2 (7.71)
Median	174.0
Minimum, Maximum	161, 195
Weight (kg)	
Mean (SD)	93.38 (16.841)
Median	90.15
Minimum, Maximum	63.0, 142.3
Body mass index (kg/m^2)	
Mean (SD)	30.694 (4.4945)
Median	29.900
Minimum, Maximum	20.80, 37.60
I-PSS (Questions 1 through 7)	
Mean (SD)	3.222 (4.1523)
Median	2.000
Minimum, Maximum	0.00, 16.00
I-PSS Quality of Life (Question 8)	
Mean (SD)	1.000 (1.2367)
Median	0.500
Minimum, Maximum	0.00, 3.00
Prostate specific antigen, (µg/L)	
Mean (SD)	0.771 (0.8651)
Median	0.540
Minimum, Maximum	0.10, 3.71
Serum testosterone at screening, (ng/dL)[a]	
Mean (SD)	109.697 (85.9786)
Median	75.725
Minimum, Maximum	12.20, 255.00

Source: Post-text Table 14.1.3
Abbreviations: I-PSS = International Prostate Symptom Score; SD = standard deviation; TU = testosterone undecanoate
[a] Total testosterone was measured twice at screening for each subject and the screening values averaged. For study inclusion, both serum testosterone levels had to be < 300 ng/dL.

Protocol Deviations:
All but 1 of the subjects met the study eligibility criteria. Subject (b) (6) was enrolled with a screening hematocrit value of 49%, which exceeded the limit of the exclusion criterion regarding hematocrit (> 48%). The Investigator notified the Sponsor of the deviation, and both agreed that this posed no risk to the subject and that the 49% value was within the normal range for the local laboratory. In addition, the subject's hematocrit value prior to initiating dosing in the Run-In Phase was 45%. All subsequent hematocrit values obtained during the study or during follow-up were ≤ 47%.

PK Results:
Total T PK
The post-breakfast concentration-time profiles (from 0 to 12 hours in Figure A-2-1) following the 30 g fat, 45 g fat, and high-calorie, high-fat breakfast were similar, and the profile following dosing of JATENZO under fasted state was substantially lower. All of the dinner meals contained 30 g fat, and the concentration-time profiles for all the post-dinner meals were similar (from 12 to 24 hours in Figure A-2-1), except when the high-calorie, high-fat breakfast was served. There was a higher arithmetic mean C_{max} during the post-dinner concentration-time curve for subjects who had a high-calorie, high-fat breakfast as compared to subjects who received lower-fat breakfasts.

Figure A-2-1: Arithmetic Mean Plasma T Concentration-Time Profiles (Linear Scale; N=18)



Source: Post-text Figure 14.2.2.1.2
Abbreviations: BID = twice daily; FDA = Food and Drug Administration; PK = pharmacokinetic; T = testosterone; TU = testosterone undecanoate

Plasma total T PK parameters following different breakfast meal types are summarized for the PK Evaluable Population in Table A-2-3.

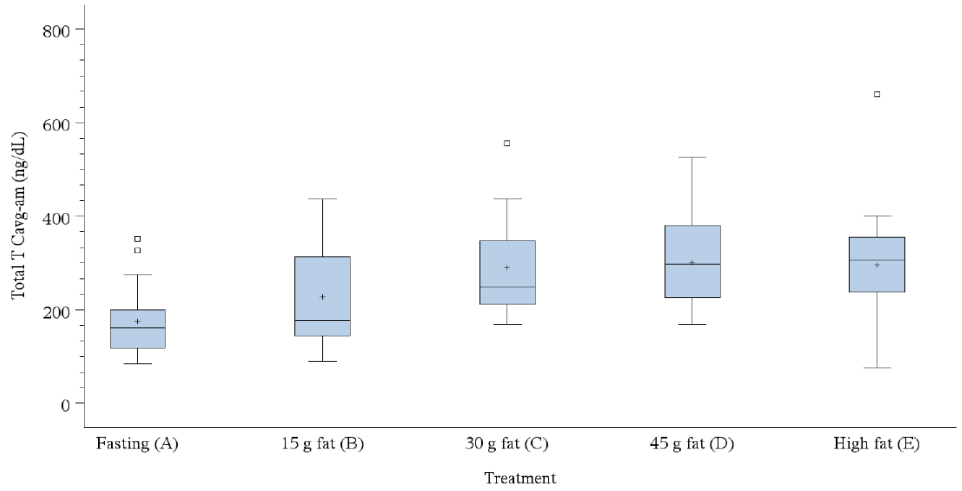
Table A-2-3: Descriptive Statistics for Plasma Total T PK Parameters Following the Morning Dose with Different Breakfast Meal Types

Pharmacokinetic Parameters	Oral TU Administered With Different Breakfast Meal Types									
	A Fasting		B 15 g Fat		C 30 g Fat		D 45 g Fat		E FDA (High Calorie, High Fat)	
	GM (GCV%)	n	GM (GCV%)	n	GM (GCV%)	n	GM (GCV%)	n	GM (GCV%)	n
$C_{max\text{-}am}$ (ng/dL)	250.7 (48.6)	18	334.7 (57.7)	18	529.7 (33.9)	18	506.0 (37.8)	18	463.4 (62.7)	18
AUC_{am} (ng•hr/dL)	1905 (45.2)	18	2428 (51.3)	18	3279 (33.6)	18	3395 (34.7)	18	3187 (52.8)	18
$T_{max\text{-}am}$ (hours)	4.000 (0.00, 4.17)	18	2.000 (0.00, 11.92)	18	2.000 (1.83, 6.00)	18	2.000 (1.97, 11.92)	18	2.000 (0.00, 6.00)	18
$C_{avg\text{-}am}$ (ng/dL)	160.0 (45.4)	18	203.7 (51.3)	18	275.1 (33.6)	18	285.1 (34.7)	18	267.3 (52.6)	18

Source: Post-text Tables 14.2.1.2.1, 14.2.1.2.2, 14.2.1.2.3, 14.2.1.2.4, and 14.2.1.2.5
Abbreviations: AM = morning; AUC_{am} = area under the concentration-time curve over the morning dosing interval; $C_{avg\text{-}am}$ = time-weighted average plasma concentration over the dosing interval following the morning dose; $C_{max\text{-}am}$ = maximum measured plasma concentration following the morning dose; FDA = Food and Drug Administration; GCV = geometric coefficient of variation; GM = geometric mean; n = number of observations used in the analysis; PK = pharmacokinetic; $T_{max\text{-}am}$ = time to reach $C_{max\text{-}am}$; TU = testosterone undecanoate
Note: $T_{max\text{-}am}$ is presented as median (minimum, maximum); AUC_{am}, $C_{max\text{-}am}$ and $C_{avg\text{-}am}$ are presented as GM and GCV%.

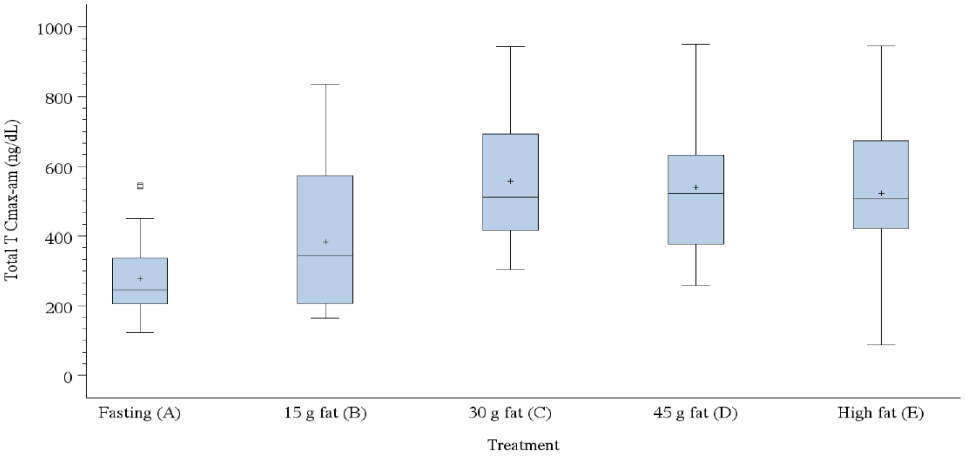
The post-breakfast concentration-time PK profiles following the 30 g, 45 g, and high-calorie/high-fat breakfast were comparable while the bioavailability of the 15 g fat breakfast was lower by about 25%.

Figure A-2-2: Effect of Food on Plasma Total T $C_{avg\text{-}am}$ (N=18)



Treatment A: 237 mg TU Administered BID Under Fasting Condition for Breakfast
Treatment B: 237 mg TU Administered BID with 15 g fat Breakfast
Treatment C: 237 mg TU Administered BID with 30 g fat Breakfast
Treatment D: 237 mg TU Administered BID with 45 g fat Breakfast
Treatment E: 237 mg TU Administered BID with FDA High-Calorie, High-fat Breakfast
The upper and lower whiskers of the boxplot represent, respectively, the largest and smallest observed values within 1.5 × the interquartile range (IQR) from the upper and lower quartiles (Q3 and Q1). Values greater or smaller than the bounds represented by these whiskers are identified as extreme values.

Figure A-2-3: Effect of Food on Plasma Total T $C_{max\text{-}am}$ (Study CLAR-16015; N=18)



Treatment A: 237 mg TU Administered BID Under Fasting Condition for Breakfast
Treatment B: 237 mg TU Administered BID with 15 g fat Breakfast
Treatment C: 237 mg TU Administered BID with 30 g fat Breakfast
Treatment D: 237 mg TU Administered BID with 45 g fat Breakfast
Treatment E: 237 mg TU Administered BID with FDA High-Calorie, High-fat Breakfast
The upper and lower whiskers of the boxplot represent, respectively, the largest and smallest observed values within 1.5 × the interquartile range (IQR) from the upper and lower quartiles (Q3 and Q1). Values greater or smaller than the bounds represented by these whiskers are identified as extreme values.

A visual examination of the variability in the PK parameters of C_{max} and AUC for T (Figures A-2-2 and A-2-3, respectively) shows that while there is significant variability in the presence of food and varying amount of fat content, that the observed concentrations do fall within the expected range of T concentrations with treatment.

Plasma total T PK parameters following the evening dosing interval and over 24 hours (i.e., combined morning and evening dosing intervals) are summarized by breakfast meal types for the PK evaluable population in Table A-2-4.

Table A-2-4: Summary of Plasma Total T PK Parameters Following the Evening Dose and Over the Combined 24 Hours of a Morning and an Evening Dose (PK Evaluable Population)

Pharmacokinetic Parameters	Oral TU Administered With Different Meal Types									
	A Fasting		B 15 g Fat		C 30 g Fat		D 45 g Fat		E FDA (High Calorie, High Fat)	
	GM (GCV%)	n	GM (GCV%)	n	GM (GCV%)	n	GM (GCV%)	n	GM (GCV%)	n
Evening										
$C_{max\text{-}pm}$ (ng/dL)	522.5 (50.6)	18	544.3 (47.4)	18	555.0 (38.8)	18	517.0 (36.4)	18	693.3 (50.3)	18
AUC_{pm} (ng•hr/dL)	3507 (42.5)	18	3759 (41.4)	18	3820 (31.8)	18	3641 (34.9)	18	4218 (37.7)	18
$T_{max\text{-}pm}$ (hours)	14.000 (13.92, 21.00)	18	14.000 (14.00, 21.00)	18	14.000 (13.83, 18.00)	18	15.040 (14.00, 21.00)	18	14.000 (14.00, 18.00)	18
$C_{avg\text{-}pm}$ (ng/dL)	290.0 (42.4)	18	311.1 (41.3)	18	315.9 (31.9)	18	301.1 (35.0)	18	347.7 (37.7)	18
24 hour										
$C_{max\text{-}24}$ (ng/dL)	522.5 (50.6)	18	549.4 (47.6)	18	666.5 (28.4)	18	572.4 (34.6)	18	737.3 (46.6)	18
AUC_{24} (ng•hr/dL)	5475 (39.8)	18	6270 (41.3)	18	7187 (27.6)	18	7078 (32.7)	18	7518 (38.7)	18
$C_{avg\text{-}24}$ (ng/dL)	228.2 (39.8)	18	261.2 (41.3)	18	299.3 (27.7)	18	294.9 (32.7)	18	312.5 (38.7)	18

The quantitative impact of food on the exposure following the morning dose did not carry-over into the evening dosing interval.

TU PK

Plasma TU PK parameters following different breakfast and dinner meal types and over 24 hours (i.e., combined morning and evening dosing intervals) are summarized by breakfast meal types for the PK evaluable population in Table A-2-5.

Table A-2-5: Summary of Plasma TU PK Parameters Following Different Breakfast and Dinner Meal Types and Over the Combined 24 Hours of a Morning and an Evening Dose (PK Evaluable Population)

Pharmacokinetic Parameters	Oral TU Administered With Different Meal Types									
	A Fasting		B 15 g Fat		C 30 g Fat		D 45 g Fat		E FDA (High Calorie, High Fat)	
	GM (GCV%)	n	GM (GCV%)	n	GM (GCV%)	n	GM (GCV%)	n	GM (GCV%)	n
Morning										
$C_{max\text{-}am}$ (ng/mL)	42.03 (89.1)	18	114.3 (79.1)	18	256.8 (67.0)	18	245.8 (68.7)	18	197.9 (186.8)	18
AUC_{am} (ng•hr/mL)	149.2 (72.8)	18	356.4 (70.3)	18	793.6 (52.2)	18	840.8 (75.9)	18	642.7 (199.9)	18
$T_{max\text{-}am}$ (hr)	4.000 (1.98, 6.00)	18	2.000 (2.00, 11.92)	18	2.000 (1.83, 4.00)	18	2.000 (2.00, 9.00)	18	2.000 (1.83, 6.00)	18
Evening										
$C_{max\text{-}pm}$ (ng/mL)	249.4 (69.4)	18	303.1 (72.8)	18	302.0 (45.1)	18	247.6 (59.9)	18	365.8 (56.8)	18
AUC_{pm} (ng•hr/mL)	787.1 (54.2)	18	1003 (49.3)	18	980.4 (40.7)	18	891.7 (41.6)	18	1060 (33.8)	18
$T_{max\text{-}pm}$ (hr)	14.000 (13.92, 21.00)	18	14.000 (14.00, 21.00)	18	14.000 (13.83, 18.00)	18	14.000 (14.00, 21.00)	18	14.000 (14.00, 16.17)	18
24 hour										
$C_{max\text{-}24}$ (ng/mL)	249.4 (69.4)	18	303.1 (72.8)	18	370.3 (41.3)	18	324.0 (54.1)	18	438.4 (43.9)	18
AUC_{24} (ng•hr/mL)	955.3 (52.2)	18	1404 (45.9)	18	1842 (31.0)	18	1791 (50.3)	18	1924 (40.1)	18

Safety Results:

Safety findings include the following:

- Five subjects reported at least 1 TEAE during the study. No serious TEAEs or TEAEs leading to discontinuation were reported. All TEAEs were mild or moderate in severity.
- One TEAE (i.e., gastroenteritis) was considered by the Investigator to be possibly drug-related. The event of gastroenteritis began on Day 1 of the Run-In Phase, was of mild intensity, and resolved on Day 3. No action was taken.
- Mean changes from baseline in clinical laboratory values were small and not clinically important.
- A small mean increase (i.e., 2.3 mm Hg) from baseline in systolic blood pressure was observed on PK Phase Day 1, but mean decreases of -0.5 to -4.1 mm Hg were observed on subsequent days. A mean increase (i.e., 5.7 mm Hg) from baseline in diastolic blood pressure was observed on PK Phase Day 1.

- Mean increases from baseline in heart rate (i.e., 4.2 to 10.6 bpm) were observed on PK Phase Days 1 through 6.
- One subject developed prostatitis, which manifested as out-of-range PSA values during the study that were considered clinically significant by the Investigator. The subject had abnormal urinalysis findings and elevated white blood cell counts, as well as adverse events of dysuria, prostatic specific antigen increased, white blood cell count increased, prostatomegaly, pollakiuria, and pyrexia during the Follow-Up Phase. He was treated with ciprofloxacin.

Conclusions:
Subjects had lower T exposure during the fasting and 15 g fat meal periods relative to the 30 g or higher fat meals. The Sponsor proposes that JATENZO should be taken with food without further instructions on the fat content of meals.

In general, the Clinical Pharmacology review team agrees with the conclusion of the Sponsor that as subjects cannot reliably estimate fat content in their diet that the subjects should be instructed to take the dosage form with their normal diet as was done in the Phase 3 studies.

4.1.3 Evaluation of Blood Collection Methodology Study (CLAR-15013)

Title: Evaluation of Blood Collection Methodology Following Administration of a Single Dose of an Oral TU Formulation in Hypogonadal Men

Primary Objective:
The primary objective of the study was to evaluate the effects of blood collection tubes on T, DHT, TU, and DHTU concentrations in blood samples collected after oral administration of a single oral dose of TU in 8 hypogonadal men.

Secondary Objective:
A secondary objective was to evaluate whether *in vitro* spiking of whole blood samples with TU, followed by a short period of bench top storage, does or does not, predict *ex vivo* conversion of TU to T in the Plain (red-top) blood collection tubes.

Clinical Study Center: (b) (4) (b) (4)

Clinical Study Period: December 29, 2015 – February 18, 2016

Bioanalytical Study Center: (b) (4) (b) (4)

Bioanalysis Period: January 4, 2016 – March 30, 2016

Study Design, Treatments, and Drug Administration:
In vitro PK After Spiking Whole Blood with TU
Concentrations of T were analyzed in serum samples collected from whole blood after the whole blood samples sat at room temperature for 30 minutes after being spiked at 1 of 5 TU concentrations (0, 30, 100, 300, or 1000 ng/mL). The collected serum samples were stored at -20 °C until assayed for T.

In vivo PK Study
This was an open-label, single oral TU dose study conducted in 8 hypogonadal men at a single study site. Each study participant received a single oral dose of 316 mg TU in the form of 2 soft gelatin capsules each containing 158 mg TU. The oral TU dose was administered immediately prior to a standardized breakfast meal comprised of 800 to 1,000 calories and containing approximately 30 g of fat (~25 to 30% of calories as fat). Subjects were asked to consume the entire breakfast meal in no more than 30 minutes.

For the *in vivo* PK assessments, concentrations of total T were analyzed at 14 timepoints over a 12.5-hour period starting 0.5-hour pre-dose to 12-hours post-dose. PK was assessed comparing the following test tubes and matrix:

- ***Plain (Red Top) Tubes (Serum)***: Blood collected in these tubes was kept at room temperature for 30 minutes then centrifuged at 4°C for 20 minutes at > 1,000 g. Serum was separated promptly after centrifugation and was stored at -20ºC until analysis.
- ***NaF (Light Gray Top) Tubes (Serum)***: Blood collected in these tubes was kept on ice for 30 minutes then centrifuged at 4°C for 20 minutes at > 1,000 g. Serum was separated promptly after centrifugation and was stored at -20ºC until analysis.
- ***NaF + Oxalate (Gray Top) Tubes (Plasma)*:** Blood collected in these tubes was kept on ice for 30 minutes then centrifuged at 4°C for 20 minutes at > 1,000 g. Plasma was separated promptly after centrifugation and was stored at -20ºC prior to analysis.

- ***NaF + EDTA (Gray Top) Tubes (Plasma)*:** Blood collected in these tubes was kept on ice for 30 minutes then centrifuged at 4ºC for 20 minutes at > 1,000 g. Plasma was separated promptly after centrifugation and was stored at -20ºC prior to analysis.

Blood Sample Collection: Blood samples were collected 30 minutes prior to oral TU administration and at 0 (pre-dose), and 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, and 12 hour post-dose.

Subjects were confined at the study site from approximately 1 hour prior to dosing until after collection of the 12-hour post-dose blood sample. Seven days later, subjects were contacted by phone to ascertain if any adverse events had occurred following discharge from the study site.

Inclusion Criteria:
Subjects were required to meet all of the following criteria in order to be eligible for the study:

- Males, 18 to 65 years of age, inclusive, with a diagnosis of hypogonadism and a screening total serum T of < 300 ng/dL. If serum T obtained at screening was ≥ 300 ng/dL but < 350 ng/dL, then the serum T could have been repeated once, and if the repeat serum T was < 300 ng/dL, then the subject met the inclusion criteria.
- Naïve to androgen-replacement therapy or willing to temporarily cease current T treatment (topical or short-acting injectable) in order to participate in the study. Subjects had to remain off all forms of T except for study medication throughout the entire study (screening through Visit 1).
- Voluntarily gave written informed consent to participate in this study

Exclusion Criteria:
Subjects who met any of the following criteria were not eligible for participation in this study:

- Significant intercurrent disease of any type, in particular liver, kidney, or heart disease, uncontrolled diabetes mellitus, or psychiatric illness (subjects with treated hyperlipidemia were not excluded provided they had been stable on lipid-lowering medication).
- Abnormal prostate digital rectal examination, elevated prostate-specific antigen (PSA; serum > 4 ng/mL), American Urological Association/International Prostate Symptom Score ≥ 15 points, and/or history of prostate cancer. (Note: Subjects with a PSA > 4 ng/mL were to be referred to a urologist.)
- BMI less than 18 kg/m^2 or greater than 37 kg/m^2.
- Serum transaminases > 2 times upper limit of normal or serum bilirubin > 2.0 mg/dL.
- History of severe or multiple allergies, or severe adverse drug reaction. A known hypersensitivity to lidocaine or all surgical dressings that could have been used in the study procedures.
- History of abnormal bleeding tendencies or thrombophlebitis unrelated to venipuncture or intravenous cannulation.
- Oral, topical (i.e., gel or patch) or buccal T therapy within the previous 2 weeks, or intramuscular T injection of T-propionate, T-cypionate or T-enanthate within the previous 4 weeks.
- Parenteral TU therapy within the past 6 months.
- Use of dietary supplements that could have increased serum T, such as androstenedione or dehydroepiandrosterone, within the previous 4 weeks.
- Known malabsorption syndrome and/or current treatment with oral lipase inhibitors [e.g., orlistat (Xenical)], bile acid-binding resins [e.g., cholestyramine (Questran), colestipol (Colestid)], fibric acid derivatives [e.g., clofibrate (Atromid-S), gemfibrozil (Lopid)], and probucol (Lorelco).

- Smokers who were unable to refrain from smoking during the confinement period required in this study.
- History of, or current evidence of, abuse of alcohol or any drug substance.

Prior and Concomitant Medications
Prior and concomitant medications were documented on the eCRF, including name, dose, route, frequency of dosing and reason for use. Subjects were to abstain from all forms of T replacement except for study medication throughout the entire study, as well as any dietary supplements that could have increased serum T such as androstenedione or DHEA.

All subjects continued receiving prior medications during the study, with the exception of TRT. The most common concomitant medications included medications for treatment of hypertension, diabetes, gastroesophageal reflux disease, and dyslipidemia. All concomitant medications taken during the study were considered by the investigator to be not clinically significant for exclusion from the study.

PK Endpoints:
The primary PK endpoints were concentrations of T, DHT, TU, and DHTU in serum or plasma as analyzed after collection in the various sample collection tubes. The secondary PK endpoints were concentrations of T, DHT, TU, and DHTU in serum as assayed after the *in vitro* spiking of known quantities of TU to whole blood collected prior to oral dosing.

Exploratory endpoints included the PK parameters of peak concentration (C_{max}), time post-dose of time when peak concentration is reached (T_{max}), and area under the concentration-time profile from time 0 to 12 hours (AUC_{12}) as calculated from concentration results in samples collected using the various sample collection tubes.

Safety Endpoints:
Vital signs and monitoring of adverse events.

Study Flow charts
The study flow charts are shown in Table A-3-1.

Table A-3-1: Schedule of Assessment

	Screening	Visit 1														Follow Up
	Day -21 to -1	Day 1														Day 7 (± 2)
		-30 min	0	1 hr	2 hr	3 hr	4 hr	5 hr	6 hr	7 hr	8 hr	9 hr	10 hr	11 hr	12 hr	
Sign informed consent form	+															
Medical history	+															
Review of prior/concomitant medications	+															
Adverse events	+	+[1]	+												+	
Vital signs (blood pressure in triplicate, heart rate)	+	+[1]													+	
Weight and height	+															
Serum total T between 6:00 and 10:00 AM	+															
Clinical laboratory tests	+[2]															
AUA/IPSS	+															
Physical examination with digital rectal exam	+[2]															
Brief physical examination		+[1]														
Update of concomitant medications		+[1]														
T, TU, DHT, DHTU in Plain tube, NaF + EDTA tube, & NaF + Oxalate tube[3]		+	+[4,5]	+	+	+	+[4]	+	+	+	+	+	+[4]	+	+	
T, TU, DHT, DHTU in 1 NaF tube			+		+	+		+		+						
Sex hormone binding globulin		+														
Sample for *in vitro* spiking experiment		+														
Meal			+[4]				+[4]						+[4]			
Dose oral TU			+[5,6]													
Saliva		+[7]				+[7]			+[7]							
Phone call for adverse event follow up																+

1. These activities occurred prior to the -30 minute blood draw.
2. Samples for screening clinical laboratory tests (see Section 9.5.4.5) were obtained prior to performing digital rectal exam.
3. One Plain tube, 1 NaF + Oxalate tube, and 2 NaF + EDTA tubes were drawn at each time point.
4. Blood drawn prior to meal.
5. Blood drawn prior to dosing oral TU.
6. Oral TU dosed immediately prior to meal.
7. Mouth was rinsed with water 15 minutes before sample collection. Saliva was allowed to collect in mouth and then spit into sterile cup. About 5 mL of saliva were collected. The saliva collection occurred immediately following the blood collection.

Bioanalytical Methods:
Serum and plasma total T concentrations were analyzed using a LC-MS/MS method at the [redacted] (b) (4)

T and DHT were extracted from plasma by LLE. The extracted samples were dried under a stream of nitrogen, the residue was reconstituted.

Reconstituted sample extracts were analyzed using a Shimadzu HPLC System equipped with an Applied Biosystems Sciex API 5500 triple quadrupole mass spectrometer. Chromatographic separation was performed on an Thermo Hypersil, 100 x 1.0 mm, 3 µm-column for T and DHT using gradient elution. Positive ions generated from the electrospray ion source were detected using the MRM mode. Quantitation was performed using a weighted linear regression ($1/concentration^2$) of the determined peak area ratios for T, DHT, T-d_2 (IS), and DHT-d_3 (IS). The LC-MS/MS method was developed and validated with the dynamic range of 0.02-20 ng/mL (2-2,000 ng/dL) and 0.02-10 ng/mL (2-1000 ng/dL) for total T and DHT, respectively.

Calibration standards and QC samples for T and DHT were prepared in serum collected in plain tubes or human NaF/Na_2EDTA plasma.

The nominal concentrations for the T QCs were as follows:

- QC1: 6.2 ng/dL (serum) / 6.6 ng/dL (plasma)
- QC2: 12.4 ng/dL (serum) / 152 ng/dL (plasma)
- QC3: 512 ng/dL (serum) / 502 ng/dL (plasma)
- QC4: 912 ng/dL (serum) / 902 ng/dL (plasma)
- QC5: 1512 ng/dL (serum) / 1502 ng/dL (plasma)

The nominal concentrations for the DHT QCs were as follows:

- QC1: 6.0 ng/dL (serum) / 6.0 ng/dL (plasma)
- QC2: 12.0 ng/dL (serum) / 12.0 ng/dL (plasma)
- QC3: 90 ng/dL (serum) / 92 ng/dL (plasma)
- QC4: 280 ng/dL (serum) / 282 ng/dL (plasma)
- QC5: 750 ng/dL (serum) / 752 ng/dL (plasma)

Accuracy and precision of the calibration standards and QC samples for both T and DHT from serum in plain tubes and plasma in NaF-containing tubes during sample analysis were within the pre-specified acceptance range per the Agency's *Bioanalytical Method Validation Guidance*.

Long-term storage stability for both T and DHT in human serum and plasma at -20°C was established for 3 years.

Stability (i.e., accuracy of ≤ 15%) of total T and DHT in human serum and plasma was confirmed for 6 and 10 freeze/thaw cycles, respectively.

After 24 hours in human serum and plasma on the bench-top at room temperature (25ºC), the % REs of the replicate analyses of T and DHT QC samples were always ≤ 15%.

ISR was conducted on 21 samples (4.4%) and 20 samples (4.2%) for total T and DHT, respectively, out of a total of 477 study samples. For total T, 20 out of 21 ISR samples (95.2%) were within ±

20% of the original results. For DHT, 16 out of 20 ISR samples (80.0%) were within ± 20% of the original results. These ISR results confirmed the reproducibility of the bioanalytical method.

Reviewer's Comment: *It should be noted that the ISR sample size is less than the recommended 7% per the Agency's Bioanalytical Method Validation Guidance. However, ISR results support the reproducibility of the bioanalytical method and there are no concerns on the performance of the method based on the data submitted. Otherwise, the acceptance criteria and performance of the total T and DHT bioanalytical methods were in compliance with the Agency's Bioanalytical Method Validation Guidance and are found to be acceptable.*

While this review focused on T and DHT, TU, and DHTU were also analyzed in this study. The bioanalytical methods for TU and DHTU are also in compliance with the Agency's Bioanalytical Method Validation Guidance and are found to be acceptable.

PK Evaluation and Statistical Methods:
Descriptive statistics were calculated for serum or plasma T, DHT, TU, and DHTU concentrations determined from the collected blood samples. Three approaches were used to compare T, DHT, TU, and DHTU concentrations between commercially available sample collection tube types. First, the concentration-times profiles for the analyte in each of the sample collection tube types were compared to see if there was a consistent pattern of higher or lower concentrations in some collection tube types. Second, linear regressions were conducted to provide 2-way comparisons between the Plain tubes and each of the other 3 types of collection tubes. Third, Bland-Altman plots (difference plots) were constructed comparing concentration results from each of the NaF-containing tubes to the concentration results from the Plain tubes. Descriptive statistics were used to summarize the *in vitro* results by nominal spiked concentration.

All subjects dosed with study drug were included in the Safety Analysis Population. All subjects with concentration results from at least the Plain collection tube and 1 other sample collection tube for a majority of the scheduled sample collection times, and who did not have any major protocol deviations that affected the interpretation of their PK result were included in the PK Analysis Population.

Safety Evaluation:
Data were listed by individual subject, except for screening laboratory results, which were provided in individual laboratory reports. Where applicable, continuous data were summarized using descriptive statistics. Categorical data were described using frequencies and percentages. AEs were coded using the MedDRA, Version 1.1 and summarized by system organ class and preferred term.

Disposition of Subjects:
Of the 10 subjects screened, 8 hypogonadal men were enrolled, received study drug, and completed the study.

Subject Demographics:
Mean (SD) age of the safety analysis population was 47.3 (11.6) years. Overall, 7 (87.5%) subjects were White and 1 (12.5%) subject was Asian; 4 of the 8 subjects were Hispanic or Latino (50%). Mean (SD) BMI measured at screening was 30.0 (7.1) kg/m^2.

Table A-3-2: Study Subject Demographics

		Total
Total Number of Subjects		8
Age (years)	Mean (SD)	47.3 (11.60)
	Median	45.5
	Minimum, Maximum	31, 64
Gender	Male, n (%)	8 (100.0)
Ethnicity	Hispanic or Latino, n (%)	4 (50.0)
	Not Hispanic or Latino, n (%)	4 (50.0)
Race	White, n (%)	7 (87.5)
	Asian, n (%)	1 (12.5)
Height (cm)	Mean (SD)	174.8 (9.13)
	Median	175.5
	Minimum, Maximum	162, 188
Weight (kg)	Mean (SD)	90.84 (20.55)
	Median	93.7
	Minimum, Maximum	63.1, 117.3
Body mass index (kg/m^2)	Mean (SD)	29.98 (7.119)
	Median	31.1
	Minimum, Maximum	18.1, 36.8
Screening Testosterone (ng/dL)	Mean (SD)	71.01 (56.570)
	Median	51.0
	Minimum, Maximum	15.6, 185
Screening AUA/IPSS	Mean (SD)	6.4 (3.66)
	Median	6
	Minimum, Maximum	1, 14

Source: End of Text Table 14.1.2, Table 14.3.3.1, and Table 14.3.4; Listing 16.2.3 and Listing 16.2.7; Appendix 16.5, Listing 3.
Abbreviations: AUA/IPSS=American Urological Association/International Prostate Symptom Score; SD=standard deviation

Protocol Deviations:
Subject 10 requested a delayed start of the study. The site accommodated the subject and allowed dosing to begin on Day 1 in the afternoon and serial PK samples were obtained at time points relative to the subject's dose time per the protocol. Meals were provided at the times relative to his dose according to the protocol. All other protocol deviations were minor and did not interfere with subject evaluations.

PK Results:
In vitro Serum T Concentrations After Spiking Whole Blood with TU
The mean (SD) for the T concentrations at the 5 spiked TU concentrations are summarized in Table A-3-3 in units of ng/dL.

Table A-3-3: Mean (SD) Total T Concentrations at the 5 Spiked TU Concentrations (N=4)

Conventional Units	
Theoretical TU Concentration	Observed Serum T ng/dL (N=4)
ng/mL	Mean ± SD (CV)
0	26.04±12.396 (47.6%)
30	48.92±10.261 (21.0%)
100	89.49±9.719 (10.9%)
300	242.0±30.32 (12.5%)
1000	578.5±133.11 (23.0%)

The subjects' endogenous T concentrations were augmented by the *in vitro* addition of TU to the whole blood as the blood sample sat on the bench top for 30 minutes at room temperature. The mean endogenous concentration of T was approximately 26 ng/dL (range: 8-36 ng/dL). The

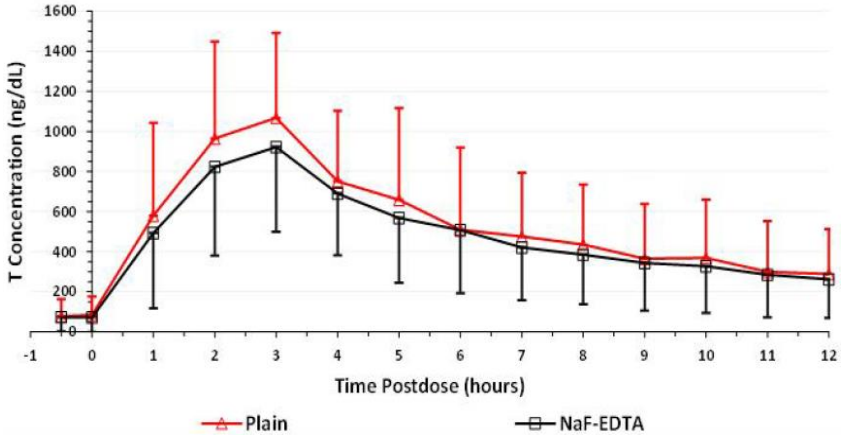
spiking of the whole blood with between 30 ng/mL and 1,000 ng/mL of TU increased the analyzed mean serum T concentration to between 49 ng/dL and 579 ng/dL within that 30-minute time span. The extent of increase in serum T concentration associated with the bioconversion of TU increased as the spiked TU concentration increased. The Sponsor believes that further increases in T concentrations due to *ex vivo* TU conversion would be expected to occur if the blood sample sat on the bench top for longer than 30 minutes. The Sponsor states that TU conversion to T, or related molecules does not materially decrease the amount of TU detected in serum harvested from blood samples sitting for up to 30 minutes at room temperature to allow clot formation. The Sponsor also concludes that TU conversion to DHT appears to be minimal to nonexistent at all levels of TU spiking tested. This *in vitro* assessment was not performed in plasma collected using NaF/EDTA blood collection tubes. However, the Sponsor conducted an *in vivo* PK assessment described below.

In vivo PK Results

The following was observed:

- Following a single oral dose of 316 mg TU, mean T concentrations from samples in plain tubes without any additives to inhibit non-specific esterases or prevent clotting were higher compared to the other 3 NaF-containing test tubes. The mean T concentrations obtained from samples collected in the 3 different types of NaF-containing test tubes were similar.
- There was a high inter-subject variability observed in the PK measurements regardless of the type of test tube used (Figure A-3-1).

Figure A-3-1: Mean (SD) Concentration-Time Profiles for T Following a Single 316 mg Oral TU Dose, for Plain and for NaF + EDTA Collection Tubes (N=8)



- Greater differences between tube types were observed when circulating T concentrations were higher compared to when T concentrations were lower.
- The geometric mean T C_{max} and C_{avg} (and AUC[0-12]) values from the 3 types of NaF-containing test tubes were 18-26% less and 11-16% less, respectively, than that of samples from the plain tube.
- The NaF/EDTA tube, which contains the lowest NaF concentration of the 3 NaF-containing tubes evaluated, showed the smallest systematic difference (i.e., mean of 8.6% difference between T concentrations in samples obtained from the NaF/EDTA test tubes and the red-topped plain serum tube. The higher the NaF concentration, the greater was the decrease in mean T concentration.
- The Sponsor believes that the extent of *ex vivo* conversion from TU to T can vary from subject to subject, most likely because of genetic and environmental factors that might affect the circulating concentrations of non-specific esterases and their intrinsic activity.

Both time and sample temperature are factors likely to impact the extent of de-esterification. The non-specific activity would be expected to be greater when samples are near body temperature (just after sample collection) and least when cooled down to -20°C or -80°C.

- There was no consistent pattern of differences in DHT concentrations measured between samples collected in plain tubes and in NaF/EDTA tubes.
- Mean TU concentrations (Table A-3-4) determined in samples collected in plain tubes were nearly the same as for the other 3 types of NaF-containing tubes except for the time period of 2-6 hours post-dose (i.e., samples from NaF-containing tubes having a mean of 11-14% lower TU concentration compared to those from plain tubes).

Reviewer's Comment: *It should be noted that sample handling time and temperature appears to affect the TU to T ex vivo conversion. While serum collected in red-topped tubes were held at room temperature for 30 minutes following collection to allow clotting (i.e., standard practice), NaF-containing tubes were held on ice immediately following collection. The Sponsor did not submit data comparing different types of tubes at the same temperature (i.e., room temperature) or other sample handling time besides 30 minutes. It was reported that temperature also has an effect on the TU to T ex vivo conversion when comparing T concentrations obtained from samples prepared at room temperature and 4ºC as samples prepared at room temperature showed a higher conversion rate than those prepared at 4ºC (Lachance et al., 2015).*

Table A-3-4: Mean ± SD of TU Concentrations (ng/mL) in Various Sample Collection Tube Types Following a Single 316 mg Oral TU Dose

Sample Time	Plain Mean ± SD	NaF + EDTA Mean ± SD	NaF + Oxalate Mean ± SD	NaF[a] Mean ± SD
-0.5 h	0.0 ± 0.00	0.0 ± 0.00	0.0 ± 0.00	ND ± ND
0 h	0.0 ± 0.00	0.0 ± 0.00	0.0 ± 0.00	0.0 ± 0.00
1 h	100.3 ± 91.13	100.9 ± 93.69	94.1 ± 86.22	ND ± ND
2 h	329.9 ± 172.94	324.1 ± 176.72	305.2 ± 158.85	320.3 ± 174.29
3 h	170.2 ± 76.42	155.0 ± 81.58	151.4 ± 82.30	140.7 ± 75.07
4 h	97.6 ± 111.99	81.9 ± 84.98	85.9 ± 99.89	ND ± ND
5 h	68.1 ± 114.04	53.6 ± 81.95	57.4 ± 96.87	59.5 ± 99.16
6 h	36.8 ± 58.27	32.3 ± 49.97	45.1 ± 87.80	ND ± ND
7 h	10.2 ± 14.58	9.3 ± 13.18	8.6 ± 12.56	9.9 ± 15.24
8 h	8.8 ± 19.52	7.2 ± 15.85	7.4 ± 16.00	ND ± ND
9 h	13.9 ± 35.74	11.1 ± 28.16	10.6 ± 26.32	ND ± ND
10 h	14.6 ± 36.19	11.2 ± 27.34	14.3 ± 35.52	ND ± ND
11 h	12.1 ± 28.32	9.0 ± 21.41	10.2 ± 23.98	ND ± ND
12 h	4.1 ± 5.74	5.5 ± 8.18	4.1 ± 7.85	ND ± ND

[a] Samples were collected in NaF tubes only at 0 (predose) and 2, 3, 5 and 7 hours postdose
ND=Not done

Safety Results:
No treatment emergent adverse events were reported by any subject during the study. No subject died or experienced a treatment-emergent adverse event that was serious or led to study discontinuation. No clinically significant changes in vital signs were observed in subjects dosed in this study.

Conclusions:
In the *in vitro* assessment, an increase of serum T concentrations was observed as the concentrations of spiked TU increased. TU to DHT conversion was not observed.

In the *in vivo* PK assessment, higher T concentrations were observed from serum in plain tubes compared to plasma in NaF/EDTA tubes obtained from the same subjects. There was a higher

difference between the two types of samples around the T_{max} where T concentrations were higher than other timepoints.

Factors such as temperature, time, esterase inhibitor (e.g., NaF) concentration, genetic, and environmental factors can potentially affect the non-specific esterase activity and contribute to the TU to T *ex vivo* conversion that could be one of the causes for the different T concentrations observed between serum in plain tubes and plasma in NaF/EDTA tubes.

Based on the results of this study, the Sponsor took an approach of measuring total T and DHT concentrations from plasma in NaF/EDTA tubes instead of serum in plain tubes for the new clinical studies including the pivotal Phase 3, efficacy and safety study.

4.1.4 Eugonadal T Concentration Range Establishment Study (CLAR-16014)

Title: Phlebotomy Study to Compare T concentrations when Blood is Collected into Plain and NaF/EDTA Tubes from Healthy Men

Primary Objectives:
The primary objectives of the study were:

- To compare the T concentrations measured in blood collected into Plain (red-top) and NaF/EDTA tubes.
- To establish a normal range for plasma obtained from blood collected in tubes containing NaF/EDTA.

Clinical Study Center: (b) (4)
Clinical Study Period: August 18, 2016 – September 30, 2016

Bioanalytical Study Center: (b) (4)

Bioanalysis Period: October 14, 2016 – October 17, 2016 (b) (4)
October 14, 2016 – October 24, 2016 (b) (4)

Study Design:
This study was a bioanalytical study that had no drug administered to the participants. Blood was collected from 97 healthy young males aged 18 to 40 years. Blood samples were drawn into Plain (red-top) and NaF/EDTA tubes. When blood was collected into Plain tubes and processed, serum was obtained. When blood was collected into NaF/EDTA tubes, the EDTA prevented coagulation, and so after processing, plasma was obtained. The serum/plasma was analyzed by validated LC-MS/MS methods for T and DHT concentrations. The blood collection was performed under the supervision of a single investigator at 2 locations in the U.S. Subjects were screened to confirm that they were generally healthy, and then, assuming no exclusionary issues were identified, the blood samples were collected. The blood collection occurred in the fasted state (no food for at least 3 hours) between 6 and 10 am. The screening and blood draw could have occurred at a single visit or across 2 visits up to 7 days apart, to accommodate the subject and/or site's convenience.

This was a bioanalytical study. Samples were collected in the morning to reflect clinical practice for T monitoring because of the diurnal changes of T. The young healthy male population with no history suggestive of abnormalities of the hypothalamic-pituitary-testicular axis was selected to yield T concentrations spanning the eugonadal (normal) range.

Inclusion Criteria:
Subjects were required to meet the following criteria in order to be eligible for the study:

- Healthy male 18 to 40 years of age, inclusive, and legally able to give informed consent, as applicable by law
- Adequate venous access in the left or right arm to allow collection of the blood samples
- Voluntarily provided written informed consent to participate in this study

Exclusion Criteria:
Subjects who met any of the following criteria were not eligible for participation in this study:

- Chronic medical condition requiring treatment, including human immunodeficiency virus, hepatitis C, hypertension, asthma, diabetes, skin conditions such as eczema or psoriasis,

heart disease, liver disease or kidney disease and deemed clinically significant in the opinion of the Investigator

- History of testicular removal, testicular injury, or absence of testicle(s)
- Past use of TRT or other androgen supplements (e.g., dehydroepiandrosterone)
- Use of chronic medications or supplements, except multivitamins, over previous 6 months
- Frequent use (> 3 doses/week) of an as-needed medication, including Tylenol and nonsteroidal anti-inflammatory drugs (eg, within the last 1 month)
- History of recreational drug use within past 3 months
- Recent use (within past 4 weeks) of an opioid or tramadol
- Alcohol use > 10 drinks per week within the past 6 months on average
- BMI $\geq$ 30 kg/m^2
- History of abuse of alcohol or any drug substance within the previous 2 years
- Received any drug as part of another research study within 30 days
- Donated blood ($\geq$ 500 mL) within the 12-week period prior to screening

Concomitant Medications
Subjects were excluded from study participation if they used any chronic medications or supplements, with the exception of multivitamins in the previous 6 months and during the study period.

Criteria for Evaluation:
This was not an efficacy study. T and DHT concentrations were measured in serum and plasma isolated from blood drawn into Plain (red-top) and NaF/EDTA tubes, respectively. The concentrations obtained from serum and plasma were compared. Based on the differences observed between the two methods of sample collection, a normal range for total T for plasma samples collected in tubes containing NaF/EDTA was established.

Safety Endpoints:
As no drugs were administered, no AEs were captured.

Study Flow charts
The study flow charts are shown in Table A-4-1.

Table A-4-1: Schedule of Assessment

Activity	Screening Period Visit 1: Day -7[a]	Phlebotomy Period Visit 2: Day 1[a]
Sign informed consent	X	
Assess inclusion/exclusion criteria	X	X[b]
Medical history review	X	X[b]
Review of prior and concomitant medications	X	X[b]
Weight and height (calculate body mass index)	X	
Vital signs (body temperature, sitting blood pressure, and heart rate)	X	
Sample collection		
Two Plain (red-top) tubes		X
Four NaF-EDTA tubes		X

EDTA = ethylenediaminetetraacetic acid; NaF = sodium fluoride
a Screening Visit was within 7 days prior to Phlebotomy Visit; however, the Screening Visit and the Phlebotomy Visit could have been performed on the same day.
b Did not need to be repeated if Screening Visit and the Phlebotomy Visit were performed on the same day.

Bioanalytical Methods:
For T and DHT bioanalysis, human blood sample were collected into plain (red-top) tubes and tubes that contained NaF/EDTA. Samples collected in plain tubes were held at room temperature

for 30 minutes and then centrifuged for 20 minutes. Samples collected in tubes containing NaF/EDTA were chilled for 30 minutes on ice and centrifuged for 20 minutes. Samples were transferred in aliquot storage tubes and frozen at -20ºC and then shipped for analysis.

The two bioanalytical laboratories were used for this study were [redacted] (b) (4) (serum in plain tubes) and [redacted] (b) (4) (plasma in NaF/EDTA tubes).

Bioanalysis for Serum in Plain Tubes

Serum T concentrations were analyzed using a LC-MS/MS method at the [redacted] (b) (4)

T and DHT were extracted from plasma by LLE. The extracted samples were dried under a stream of nitrogen, the residue was reconstituted.

Reconstituted sample extracts were analyzed using a Shimadzu HPLC System equipped with an Applied Biosystems Sciex API 5500 triple quadrupole mass spectrometer. Chromatographic separation was performed on an Thermo Hypersil, 100 x 1.0 mm, 3 µm-column for T and DHT using gradient elution. Positive ions generated from the electrospray ion source were detected using the MRM mode. Quantitation was performed using a weighted linear regression ($1/concentration^2$) of the determined peak area ratios for T, DHT, T-d_2 (IS), and DHT-d_3 (IS). The LC-MS/MS method was developed and validated with the dynamic range of 0.02-20 ng/mL (2-2,000 ng/dL) and 0.02-10 ng/mL (2-1,000 ng/dL) for total T and DHT, respectively.

Calibration standards and QC samples for T and DHT were prepared in serum collected in plain tubes or human NaF/Na_2EDTA plasma.

The nominal concentrations for the T QCs were as follows:

- QC1: 6.2 ng/dL
- QC2: 12.4 ng/dL
- QC3: 512 ng/dL
- QC4: 912 ng/dL
- QC5: 1512 ng/dL

The nominal concentrations for the DHT QCs were as follows:

- QC1: 6.0 ng/dL
- QC2: 12.0 ng/dL
- QC3: 92 ng/dL
- QC4: 282 ng/dL
- QC5: 752 ng/dL

Accuracy and precision of the calibration standards and QC samples for both T and DHT from serum in plain tubes and plasma in NaF-containing tubes during sample analysis were within the pre-specified acceptance range per the Agency's *Bioanalytical Method Validation Guidance*.

Long-term storage stability for both T and DHT in human plasma at -20°C was established for 3 years.

Stability (i.e., accuracy of ≤ 15%) of total T and DHT in human serum and plasma was confirmed for 10 freeze/thaw cycles, respectively.

After 24 hours in human serum and plasma on the bench-top at room temperature (25ºC), the % REs of the replicate analyses of T and DHT QC samples were always ≤ 15%.

ISR was conducted on 20 samples (20.6%) for both total T and DHT, out of a total of 97 study samples. For both total T and DHT, 18 out of 20 ISR samples (90.0%) were within ± 20% of the original results. These ISR results confirmed the reproducibility of the bioanalytical method.

Bioanalysis for Plasma in NaF/EDTA Tubes

T and DHT were extracted from plasma by LLE. The extracted samples were dried under a stream of nitrogen, the residue was reconstituted.

Reconstituted sample extracts were analyzed using a Waters UPLC System equipped with an Applied Biosystems Sciex API 5000 triple quadrupole mass spectrometer. Chromatographic separation was performed on an ACE Excel 2 C18-PFP, 100 x 3.0 mm, 2 µm-column for T and DHT using gradient elution. Positive ions generated from the electrospray ion source were detected using the multiple reaction monitoring (MRM) mode. Quantitation was performed using a weighted linear regression ($1/concentration^2$) of the determined peak area ratios for T, DHT, T-d_3 (internal standard [IS]), and DHT-d_4 (IS). The LC-MS/MS method was developed and validated with the dynamic range of 0.1-30 ng/mL (10-3,000 ng/dL) and 0.05-5 ng/mL (5-500 ng/L) for total T and DHT, respectively.

Calibration standards and QC samples for T and DHT were prepared in human NaF/Na_2EDTA plasma. The endogenous concentration of the analyte in unstripped human NaF/Na_2EDTA plasma was determined using 6 zero standard unstripped samples which are blank unstripped samples containing the ISs. This measured concentration (i.e., average of the six samples) was then added to the spiked amounts to obtain the final nominal concentrations of QC1, QC2, QC3, and QC4 prepared in that unstripped matrix. The nominal concentrations for the T QCs were as follows:

- QC1: 357.6 pg/mL
- QC2: 15,157.6 pg/mL
- QC3: 22,657.6 pg/mL
- QC4: 2,557.6 pg/mL

The nominal concentrations for the DHT QCs were as follows:

- QC1: 140.6 pg/mL
- QC2: 440.6 pg/mL
- QC3: 2,540.6 pg/mL
- QC4: 3,790.6 pg/mL

Accuracy of the calibration standards and QC samples during sample analysis was expressed as percent difference from theoretical concentration (i.e., % RE). For NaF/Na_2EDTA plasma total T, the %RE ranged from -2.5% to 2.8% for the 8 calibration standards in the range of 0.1-30 ng/mL and -3.4% to 3.1% for QC1, QC2, QC3, and QC4. For NaF/Na_2EDTA serum DHT, the % RE ranged from -1.4% to 1.6% for the 8 calibration standards in the range of 0.05-5 ng/mL and -3.1% to 4.3% for QC1, QC2, QC3, and QC4.

Precision of the calibration standards and QC samples during sample analysis was expressed as the percent % CV. For NaF/Na_2EDTA plasma total T, the % CV ranged from 0.5% to 13.1% for the 8 calibration standards in the range of 0.1-30 ng/mL and 1.6% to 4.6% for QC1, QC2, QC3, and QC4. For NaF/Na_2EDTA plasma DHT, the % CV ranged from 0.4% to 4.4% for the 8 calibration standards in the range of 0.05-5 ng/dL and 1.2% to 5.8% for QC1, QC2, QC3, and QC4.

Long-term storage stability for both T and DHT in human plasma at -80°C was established for 246 days.

Stability (i.e., accuracy of ≤ 15%) of both T and DHT in human NaF/Na_2EDTA plasma was confirmed for 4 freeze/thaw cycles.

After 23 hours and 35 minutes in human NaF/Na_2EDTA plasma on the bench-top at room temperature, the % REs of the replicate analyses of T and DHT QC samples were always ≤ 15%.

ISR was conducted on 50 samples (51.5%) for both total T and DHT out of a total of 97 study samples. All ISR results (100%) were within ± 20% of the original results. These ISR results confirmed the reproducibility of the bioanalytical method.

Reviewer's Comment: *The acceptance criteria and performance of the total T and DHT bioanalytical methods for both serum and plasma were in compliance with the Agency's Bioanalytical Method Validation Guidance. In summary, the method validation and performance of the bioanalytical methods in clinical studies are acceptable and there are no unresolved bioanalytical issues related to the approvability of JATENZO.*

Primary Endpoint Evaluation and Statistical Methods:
For establishing the eugondal T concentration range, it was calculated as the exponentiated values of the mean - 2 x SD and mean +2 x SD after log-transformation of the concentrations.

For the comparison between T and DHT concentrations obtained from serum and plasma, a 1-tailed paired data t-test was used to compare the T and DHT concentrations measured in the blood collection tubes. A 95% upper confidence limit was calculated to estimate high end values above 10% difference between tubes.

Safety Evaluation:
Observed values at baseline include vital sign measurements, including systolic blood pressure, diastolic blood pressure, heart rate, height, weight, and BMI.

Disposition of Subjects:
A total of 97 subjects were enrolled and completed the study

Subject Demographics:
Mean (SD) age of the analysis population was 28.0 (5.82) years. Overall, 79 (81.4%) subjects were White and 9 (9.3%) subject were Black or African-American; 7 (7.2%) subjects were Asian. Five subjects were Hispanic or Latino (5.2%). Mean (SD) BMI measured at screening was 25.1 (2.64) kg/m^2.

A summary of demographics and baseline characteristics for the safety analysis population is presented in Table A-4-2.

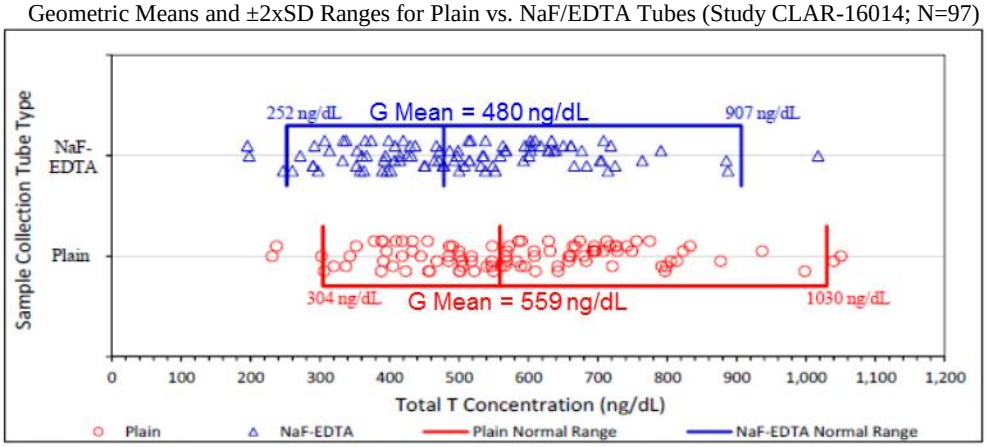
Table A-4-2: Study Subject Demographics

		Total
Total Number of Subjects		97
Age (Years)	Mean (SD)	28.0 (5.82)
	Median	27.0
	Min, Max	19, 40
Gender	Male, n (%)	97 (100.0)
Ethnicity	Hispanic or Latino, n (%)	5 (5.2)
	Not Hispanic or Latino, n (%)	92 (94.8)
Race	White, n (%)	79 (81.4)
	Black or African American, n (%)	9 (9.3)
	Asian, n (%)	7 (7.2)
	Hawaiian or Other Pacific Islander, n (%)	1 (1.0)
	American Indian or Alaskan Native, n (%)	0 (0.0)
	Other, n (%)	1 (1.0)
Height (cm)	Mean (SD)	177.4 (7.53)
	Median	177.3
	Min, Max	161.5, 208.3
Weight (kg)	Mean (SD)	79.3 (11.27)
	Median	77.1
	Min, Max	52.3, 120.2
BMI (kg/m^2)	Mean (SD)	25.1 (2.64)
	Median	25.5
	Min, Max	18.1, 29.9

Protocol Deviations:
There were minimal protocol deviations in sample handling but none of these deviations were significant enough to affect the outcome of the study.

Study Result Summary:
Total T Normal Concentration Range: Total T concentrations measured from the plasma samples in NaF/EDTA sample collection tubes were lower, by approximately 14.2% on average, than the T concentrations determined in the serum samples derived from the plain sample collection tubes. The geometric mean of the total T concentration analyzed in plasma isolated from blood collected in NaF/EDTA tubes was 478 ng/dL and for serum from blood collected in plain tubes was 559 ng/dL. When analyzed total T concentrations from the 2 tube types were compared after log transformation, the mean (95% CI) for the NaF/EDTA tube value as a percent of the plain tube value was 85.8% (84.4%, 87.3%). When the total T concentration distributions from the 2 sample collection tube types were assessed to establish the "normal range" for total T, the observed normal range from the plain sample collection tube type was 304 ng/dL to 1030 ng/dL, and the observed normal range for the NaF/EDTA tube type was 252 ng/dL to 907 ng/dL (Figure A-4-1).

Figure A-4-1: Distributions of Total T Measurement Results:
Geometric Means and ±2xSD Ranges for Plain vs. NaF/EDTA Tubes (Study CLAR-16014; N=97)



Note 1: Data points are distributed in the vertical dimension only to facilitate visualization
Note 2: Vertical lines identify the geometric mean and ±2 x SD (for log-transformed data) from the geometric mean

Reviewer's Comment: *In general, T concentrations obtained from serum in plain tubes were higher than those obtained from plasma in NaF/EDTA tubes with a mean difference of 14.2%. The potential cause of the observed difference in T concentrations may be either an additive (NaF/EDTA) effect and/or the different sample handling/preparation of different matrix at different labs.*

DHT Normal Concentration Range: DHT concentrations determined in the plasma samples derived from the NaF/EDTA sample collection tubes were statistically less, by approximately 28% on average, than the DHT concentrations determined in the serum samples derived from the Plain sample collection tubes. The geometric mean of the DHT concentration as analyzed in plasma isolated from blood collected in NaF/EDTA tubes was 29.2 ng/dL and for plain tubes was 40.8 ng/dL, respectively. When analyzed DHT concentrations from the 2 tube types were compared after log transformation, the mean (95% CI) for the NaF/EDTA tube value as a percent of the plain tube value was 71.5% (69.2%, 73.9%). The observed DHT normal range from the plain sample collection tube type was 18.4 ng/dL to 90.7 ng/dL, and the observed normal range for the NaF/EDTA tube type was 13.1 ng/dL to 65.0 ng/dL.

DHT/T Ratio: The DHT/T ratio was determined after converting the total T and DHT concentrations in each sample from units of ng/dL to units of nmol/L. DHT/T ratios determined from the DHT and T concentrations in the plasma samples derived from the NaF/EDTA sample collection tubes were statistically less, by approximately 16% on average, than the DHT/T ratios determined from the analyte concentrations in the serum samples derived from the Plain sample collection tubes. The geometric mean of the DHT/T ratio in plasma isolated from blood samples collected in NaF/EDTA tubes was 0.0604. When DHT/T ratios from the 2 tube types were compared after log transformation, the mean (95% CI) for the NaF/EDTA tube value as a percent of the plain tube value was 83.3% (81.3%, 85.4%). The observed DHT/T normal range from the plain sample collection tube type was 0.0430 to 0.1220, and the observed normal range for the NaF/EDTA tube type was 0.0365 to 0.0993.

Safety Results:
No investigational product was administered. Therefore, AEs were not collected and no clinical laboratory evaluations were performed.

Conclusions:
When comparing the 2 different types of tube after log transformation, the mean total T concentration (95% CI) from the NaF/EDTA tubes was 85.8% (84.4-87.3%), i.e., 14.2% less, than that obtained from the plain tubes. The use of NaF/EDTA tubes for blood samples also resulted in lower values for DHT concentrations and DHT/T ratios.

The lower and upper bounds of the normal ranges were calculated as the exponentiated values of the mean plus and minus two SDs after log-transformation of the concentration. The observed normal T concentration range was 304-1,030 ng/dL in serum from blood samples collected in plain tubes and 252-907 ng/dL in plasma from blood samples collected in NaF/EDTA tubes. The observed normal T concentration range for the serum tubes was comparable to the widely used range of 300-1,000 ng/dL.

4.2 Analysis for Determination of Appropriate Dose Titration Algorithm

In the pivotal Phase 3 Study CLAR-15012, the starting dose of JATENZO was 237 mg TU BID with potential for up titration to 316 mg and 396 mg BID or down titration to 198 mg and 158 mg BID. In the study the titrations were based on 24-hour total T C_{avg} (0-24 h sampling) with thresholds of 350 and 800 ng/dL for up- and down-titration corresponding to measurements at two visits (Visit 2 on Day 21, Visit 4b on Day 56). The Sponsor stated that a more practical approach in clinical practice would be to base the titration decision on the T concentration measured in a single blood sample drawn at a time convenient for patients and health care systems (e.g., daytime hours). Accordingly, the Sponsor proposed titration based on a single sample (C_x) in the 3-5 h post-morning dose window with same thresholds of T concentration (350 and 800 ng/dL).

To justify that the outcome of the above two titration algorithms will be similar, the Sponsor used following two-step approach:
1. **A concordance analysis** using observed data for specific single blood draw samples (C_x) and C_{avg} in Phase 3 study, CLAR-15012 to justify that titration decisions based on C_{4h} post-morning dose are effective in maintaining T concentrations in the eugonadal T concentration range.
2. **A population PK based modeling and simulation analysis** to confirm that titration decisions based on C_{4h} are effective in maintaining T concentrations in the eugonadal T concentration range and avoid high C_{max} values and sample collection time had some flexibility from practical standpoint in that the results of using a single-time status sample (C_{4h}) was comparable to using a 2-hour window for the status sample (i.e., $C_{3\text{-}5h}$).

The Clinical Pharmacology review team noted that there are possible limitations in the Sponsor's modeling and simulation analysis:
1. The Sponsor's population PK model had very high residual error and inter-occasion variability, and
2. With the simulations, the distribution of C_{avg} (bins of < 350, 350-800, and > 800 ng/dL) generated at first and second titration visits in the simulated study were quite different from the actual observed results in the Phase 3 study (CLAR-15012).

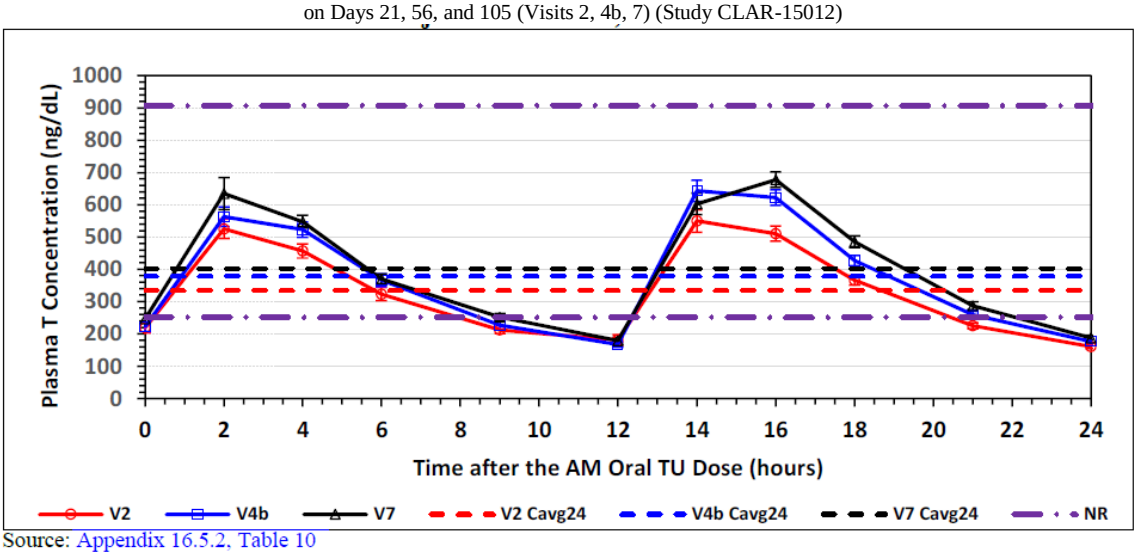
Thus, the Clinical Pharmacology review team focused on observed results from the study for justification of an appropriate sampling window for single sample based titration decisions.

Evidence from following data/analyses were used by the Clinical Pharmacology review team for the conclusion of appropriateness of titration algorithm for labeling:

i) Observed concentration-time profiles for T,
ii) Correlation analysis between C_x and C_{avg}, and
iii) Concordance analysis for C_x and C_{avg} based titration algorithms.

Observed concentration-time profiles for T:
The comparison of C_x at different time points and C_{avg} from observed data in Phase 3 Study CLAR-15012 shows that C_{6h} values most closely mimic C_{avg} values on a population level (e.g., refer to time points in red curve for T conc.-time profile and red dotted line for C_{avg} for Visit 2 in Figure A-5-1 below) and on an individual level (data not shown).

Figure A-5-1: Mean (± SEM) Concentration-Time Profile for Plasma Total T in JATENZO-Treated Subjects on Days 21, 56, and 105 (Visits 2, 4b, 7) (Study CLAR-15012)



Source: Appendix 16.5.2, Table 10

Abbreviations: AM = morning; C_{avg24} = time-weighted average plasma concentration morning and evening doses combined; NR = normal range; V2 = Visit 2; V4b = Visit 4b; V7 = Visit 7; SEM = standard error of the mean; T = testosterone; TU = testosterone undecanoate

Error bars indicate SEM

Correlation analysis between C_x and C_{avg}:

In the Phase 3 Study CLAR-15012, the post-morning dose samples for T were collected at 0, 2, 4, 6, 9, and 12 hours post-dose. As per the sponsor, the 4-hour post-dose sample (C_{4h}) was selected for further evaluation as the status sample, because C_{4h} had the highest correlation with C_{avg} with an r^2 of 0.76 and 0.75 at Visits 2 and 4b, respectively.

Overall, the data shows that there was a relatively strong correlation between C_x and C_{avg} at 4 h and 6 h, while there was relatively weaker correlation at other time points such as 0, 2, 9, and 12 h post-morning dose (Table A-5-1).

Table A-5-1: Correlation between Morning PK Samples and 24-hour C_{avg} for Visit 2 and Visit 4b (Study CLAR-15012)

Post-Dose Sample (hour)	Correlation Between Observed (Cx) and Average (C_{avg}) Concentration	
	Visit 2 (R^2)	Visit 4b (R^2)
0	0.28	0.33
2	0.40	0.49
4	0.76	0.75
6	0.64	0.64
9	0.44	0.50
12	0.21	0.42

C_{avg}= Average concentration; Cx= Single sample collected at time x; R^2= Coefficient of determination.

Concordance analysis for C_x and C_{avg} based titration algorithms:

In the concordance analysis, the following evaluations were proposed by the Sponsor to evaluate concordance between the C_x and C_{avg} based titration algorithms:

- **Numeric concordance:** Subjects will have same up/down-titration using the two algorithms (C_{avg} or C_x based)
- **Effective concordance:** Subjects may have different titration using C_x compared to C_{avg}, but the study outcome (subjects in eugonadal range of 252-907 ng/dL) will not be altered
- **Total concordance:** Sum of numeric and effective concordance

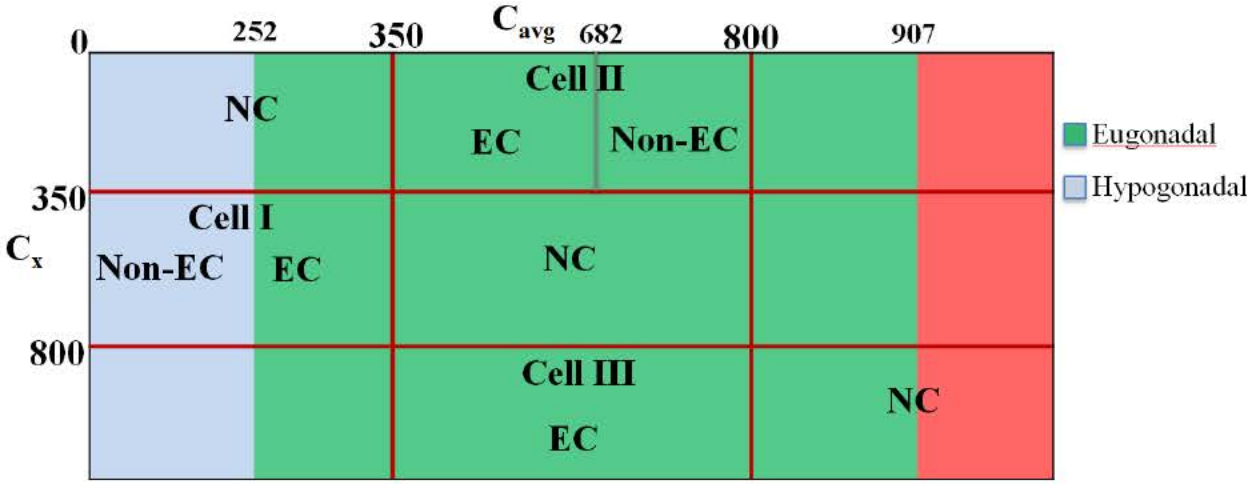
A concordance table is shown in Table A-5-2 and illustrated further on a continuum of T concentration in Figure A-5-2. This compares the outcome of titration decisions based on C_{avg} with titration decisions that would have been made if C_x was used alone.

Table A-5-2: Numeric Concordance (NC) and Criteria for Sponsor's Effective Concordance (EC)

		C_{avg}		
Titration boundaries		**< 350 ng/dL**	**350 to 800 ng/dL**	**> 800 ng/dL**
C_x	**< 350 ng/dL**	Numeric concordance	**Cell II** Effective concordance when $C_{avg} \leq 682$ ng/dL	Discordant
	350 to 800 ng/dL	**Cell I** (Effective concordance when $C_{avg} \geq 252$ ng/dL)	Numeric concordance	Discordant[b]
	> 800 ng/dL	Discordant[b]	**Cell III** Effective concordance (All)	Numeric concordance

[b] Although some cases may be effectively concordant; the concordance calculation does not count them as effectively concordant.

Figure A-5-2: Illustration of Numeric Concordance (NC) and Effective Concordance (EC)



The table's cell boundaries are the lower and upper titration boundaries. In this concordance table, numeric concordance (NC) occurs when the dose titration decision is the same regardless of whether it is based on C_x or C_{avg}. This is depicted in the shaded cells which are on the diagonal of the 3×3 table. The Sponsor states that effective concordance should be considered in addition to numeric concordance. An effective concordance is the situation where the dose titration decision based on C_x is different than that based on C_{avg}, but the outcome of the C_x-based decision would still result in a dose that should yield a C_{avg} in the eugonadal T concentration range. Although not all subjects whose C_x and C_{avg} place them in off-diagonal cells (i.e., outside of numeric concordance) will be titrated into the eugonadal T concentration range (i.e., 252-907 ng/dL), the Sponsor states that many will be, and that these cases should be included in the determination of total concordance (i.e., numeric concordance + effective concordance). Thus, total concordance is where either the dose titration decisions are the same based on C_x and C_{avg} (i.e., numeric concordance) or where the dose titration decisions based on C_x, while different than based on C_{avg},

will still result in a C_{avg} that is within the eugonadal T concentration range (i.e., effective concordance).

Effective concordance can be estimated based on the following rationale:

1. T exposure can be approximated as dose proportional, so it is possible to predict the change in C_{avg} with change in dose.
2. The titration thresholds (i.e., 350-800 ng/dL) fall within the eugonadal T concentration range (i.e., 252 - 907 ng/dL), and the eugonadal T range is wide (i.e., 3.5-fold) compared to the largest dose increment (i.e., 33%, from 237 to 316 mg TU BID) or largest dose decrement (i.e., 25%, from 316 to 237 mg TU BID) allowed in each titration step. This means that, for some patients, even if there is a mismatch between the titration decision in the study and the titration decision based on a status sample, this would still allow movement within the eugonadal T concentration range.

Let's consider the following scenarios:

1. Subjects who have C_{avg} between 252 and 350 ng/dL and C_x between 350 and 800 ng/dL (Part of Cell I in Table A-5-2 and Figure A-5-2): The original C_{avg} based titration would have up-titrated the dose by an increment of 33% and the expected C_{avg} would still be a maximum of 466 [350*1.33] which would be well within the eugonadal T concentration range. With the new titration algorithm based on C_x, although there would be no up-titration, those subjects would still be in the eugonadal T concentration range for C_{avg}.

2. Subjects who have C_{avg} between 350 and 682 ng/dL and C_x < 350 ng/dL (Part of Cell II in Table A-5-2 and Figure A-5-2): The original C_{avg} based titration would have no dose change. With the new titration algorithm based on C_x, there will be an up-titration by up to a largest dose increment of 33%. In the extreme scenario, a subject with a C_{avg} of 682 ng/dL would be expected to have a C_{avg} of 907 ng/dL [682*1.33] with this up-titration and still the subject would not exceed the upper boundary of the eugonadal T concentration range.

3. Subjects who have C_{avg} between 350 and 800 ng/dL and C_x > 800 ng/dL (Cell III in Table A-5-2 and Figure A-5-2): The original C_{avg} based titration would have no dose change. With the new titration algorithm based on C_x, there will be a down-titration by up to a largest dose decrement of 25%. In the extreme scenario, a subject with a C_{avg} of 350 ng/dL would be expected to now have a C_{avg} of 262.5 ng/dL [350*0.75] with this down-titration and still the subject would be in the eugonadal T concentration range.

Such analysis of the study data for a single status sample at 4 h (C_{4h}) post-morning dose vs. C_{avg} demonstrated that for Visit 2 and Visit 4b, the total concordance was 88.0% and 93.1%, respectively (Table A-5-3). These total concordances reflect a numeric concordance of 63.9% and 58.6% and an effective concordance of 24.1% and 34.5% for Visit 2 and Visit 4b, respectively. The Sponsor believes that this indicates that titration based on C_{4h} can effectively adjust a subject's dose such that his C_{avg} is in the eugonadal T concentration range and supports the effective use of a single status sample (e.g., C_{4h}) in the real world clinical setting to assess the T response to JATENZO and make necessary dose adjustments.

Table A-5-3: Numeric Concordance and Effective Concordance Between Single Draw (C_{4h} = sample at 4 hour post-dose) and C_{avg} Based Titration at Visit 2 and Visit 4b (Study CLAR-15012)

Visit 2 (Effective + Numeric Concordance = 88.0%)					
		C_{avg}			
	Titration boundaries	**< 350 ng/dL**	**350 to 800 ng/dL**	**> 800 ng/dL**	**Total**
C_4	**< 350 ng/dL**	38.6%	1.2% (EC minimal)	0%	39.8%
	350 to 800 ng/dL	28.9% (EC = 18.1%)	22.9%	0%	51.8%
	> 800 ng/dL	0%	6.0% (EC = 6.0%)	2.4%	8.4%
	Total	67.5%	30.1%	2.4%	100%
Visit 4b (Effective + Numeric Concordance = 93.1%)					
		C_{avg}			
	Titration boundaries	**< 350 ng/dL**	**350 to 800 ng/dL**	**> 800 ng/dL**	**Total**
C_4	**< 350 ng/dL**	32.7%	0% (EC = 0%)	0%	32.7%
	350 to 800 ng/dL	27.8% (EC = 22.2%)	22.8%	0%	50.6%
	> 800 ng/dL	1.2% (EC = 0%)	12.3% (EC = 12.3%)	3.1%	16.6%
	Total	61.7%	35.1%	3.1%	100%

C_4 = concentration 4 hours after morning dose; C_{avg} = average observed concentration over 24 hours;
EC = effective concordance, when the titration decision based on C_4 results in a dose that will generate a C_{avg} in the eugonadal T range (i.e., 252-907 ng/dL)

The Sponsor also conducted such analyses with a single status sample at 2 h (C_{2h}) and 6 h (C_{6h}) post-morning dose. Table A-5-4 presents the concordance table for Visit 2 and Visit 4b for C_{2h} and C_{6h}.

Table A-5-4: Concordance Table for Single Draw (C2 = sample at 2 h post-dose; C6 = sample at 6 h post-dose) and C_{avg} Based Titration at Visit 2 and Visit 4b (Study CLAR-15012)

Visit 2

		Average Concentration			
	Range	< 350 ng/dL	350 -800 ng/dL	> 800 ng/dL	Total (N=166)
C2	< 350 ng/dL	35.5%	6.0% (Cell II)	0%	41.5%
	350 -800 ng/dL	30.7% (Cell I)	9.6%	0.6%	40.9%
	> 800 ng/dL	1.2%	14.5% (Cell III)	1.8%	17.5%
	Total	67.4%	30.1%	2.4%	100%

		Average Concentration			
	Range	< 350 ng/dL	350 -800 ng/dL	> 800 ng/dL	Total (N=165)
C6	< 350 ng/dL	62.4%	10.9% (Cell II)	0%	73.3%
	350 -800 ng/dL	4.8% (Cell I)	16.4%	1.2%	22.4%
	> 800 ng/dL	0%	3.0% (Cell III)	1.2%	4.2%
	Total	67.2%	30.3%	2.4%	100%

Visit 4b

		Average Concentration			
	Range	< 350 ng/dL	350 -800 ng/dL	> 800 ng/dL	Total (N=162)
C2	< 350 ng/dL	30.2%	4.3% (Cell II)	0%	34.5%
	350 -800 ng/dL	28.4% (Cell I)	12.3%	0.6%	41.3%
	> 800 ng/dL	3.1%	18.5% (Cell III)	2.5%	24.1%
	Total	61.7%	35.1%	3.1%	100%

		Average Concentration			
	Range	< 350 ng/dL	350 -800 ng/dL	> 800 ng/dL	Total (N=162)
C6	< 350 ng/dL	49.4%	10.5% (Cell II)	0%	59.7%
	350 -800 ng/dL	11.7% (Cell I)	21.6%	1.9%	35.4%
	> 800 ng/dL	0.6%	3.1% (Cell III)	1.2%	4.9%
	Total	61.7%	35.2%	3.1%	100%

Source: Sponsor's analysis

The comparison of numeric, effective, and total concordance for the concentrations obtained at three single draw sampling points (C_{2h}, C_{4h}, and C_{6h}) with C_{avg} based titration are presented in Table A-5-5 below. The numeric concordance (NC) and total concordance (TC) for both 4 h and 6 h sampling was reasonable (e.g., 64% and 88% for C_{4h} and 80% and 98% for C_{6h} for visit 2.

Table A-5-5: Comparison of concordance for three Single Draw sampling (C_{2h}: sample at 2 hour post-dose; C_{4h}: sample at 4 hour post-dose; C_{6h}: sample at 6 hour post-dose) and C_{avg} Based Titration at Visit 2 and Visit 4b (Study CLAR-15012)

	Numeric Concordance	**Effective Concordance in Different Cells**			**Total Concordance = Numeric + Effective**
		Cell I	**Cell II**	**Cell III**	
Visit 2					
C_{2h}	**46.9%**	12.7%	5.4%	14.5%	**79.5%**
C_{4h}	**63.9%**	18.1%	0.0%	6.0%	**88.0%**
C_{6h}	**80.0%**	4.2%	10.9%	3.0%	**98.1%**
Visit 4b					
C_{2h}	**45.0%**	15.4%	3.7%	18.5%	**82.6%**
C_{4h}	**58.6%**	22.2%	0.0%	12.3%	**93.1%**
C_{6h}	**72.2%**	9.9%	10.5%	3.1%	**95.7%**

Source: Adapted from Sponsor's analysis

Median T_{max} for this oral administration product is ~2 h. So, the Sponsor's proposed time window of 3-5 h is likely to have some samples that mimic C_{max} rather than C_{avg} for the same subject depending on the sampling time post-dose across different visits for the same dose. This may unduly influence titrations towards lower dose. On the other hand, a shallower PK profile over 4-6 h time window means that it could likely yield less extreme measurement values and it would not be as sensitive to the sampling time for the same individual across different visits.

Conclusion:

Based on the above evidence and rationale, from the labeling perspective, the Clinical Pharmacology review team concluded that a 4-6 h post-morning dose window for single blood draw sampling for titration decisions would be more appropriate than a 3-5 h window proposed by the Sponsor, with titration thresholds of 350 and 800 ng/dL for up- and down-titrations.

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/s/

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Final
(October 8, 2014)
Clinical Pharmacology Review
Office of Clinical Pharmacology (OCP)

NDA: 206089	**Date of Submission:**	January 3, 2014 (cover letter) January 3, 2014 (Receipt date) Electronic Document #: 1
Generic Name:		Testosterone Undecanoate (TU)
Proposed Brand Name:		(b) (4)
Formulation:		Soft Gelatin Liquid Filled Capsule
Strengths:		100 and 150 mg testosterone (T) = 158.3 mg and 237.46 mg as TU
Route of Administration:		Oral
Proposed Indications:		Males with primary hypogonadism and hypogonadotropic hypogonadism (congenital or acquired).
Proposed Dosage and Administration:		Titrated doses from 100 to 300 mg BID, initial dose 200 mg BID (2 capsules BID)
Type of Submission:		Original 505(b)(2) NDA
Sponsor:		Clarus Therapeutics Northbrook, IL
OCP Division:		Division of Clinical Pharmacology 3
Office of New Drugs (OND) Division:		Division of Bone, Reproductive and Urologic Products (DBRUP)
Primary Clinical Pharmacology Reviewer:		Sayed (Sam) Al Habet, RPh, PhD
Clinical Pharmacology Secondary Reviewer:		E. Dennis Bashaw, Pharm.D.
Primary Pharmacometric Reviewer:		Dhananjay D. Marathe, Ph.D
Pharmacometric Team Leader:		Jeff Florian, Ph.D.

TABLE OF CONTENTS

1.0 Executive Summary

1.1 Recommendation

From the Clinical Pharmacology perspective, this NDA is **NOT ACCEPTABLE** due to the following deficiencies:

- There was high variability in T levels and other metabolites associated with food intake (fasting versus fed) and % of fat in meals (day-to-day and within day variability). Based on the observed product variability, there is insufficient information at this time to provide labeling in the Dosage and Administration Section for administration of this product with reference to food. Any approach identified by the review team was limited in that substantial variability in product PK would remain and that compliance to the language (administer in a fasting state or to maintain a consistent diet) could not be ensured, which in turn could lead to undesirably high T levels.
- There was high exposure to the parent drug, testosterone undecanoate (TU), and its metabolite dihydro-TU (DHTU). For example the TU exposure was approximately 20 fold higher than T levels. Implications of these metabolite levels on safety cannot be assessed with the available data.
- The pivotal study marginally met the established primary efficacy criteria of 75% of patients falling within the target T Cavg of 300 ng/dL to 1000 ng/dL. However, based on the sensitivity analyses for the missing data, the primary efficacy parameters may become lower than 75%. In addition, the pivotal study had a fraction of subjects with on treatment testosterone (T) Cmax levels exceeding thresholds commonly utilized by the Agency. The observed fraction of Cmax outliers further underscores the variability associated with the product.
- The proposed starting dose should be revisited, particularly in subjects with lower body weight, and considerations should be given to initiating therapy at a lower dose. Baseline bodyweight showed some correlation to exposure, with higher exposures in subjects with low body weights. Such subjects could be initiated at a lower starting dose. A similar position was advocated by Advisory Committee panel members. Additional dosing strengths, including strengths to permit an increment or decrement by 25 mg may also permit more flexibility in dosing at the onset of treatment. However, the proposed product is currently available only in two strengths of 100 mg and 150 mg.
- The titration process should be revisited in a subsequent trial. Specifically, the criteria for up-titration should be increased from the currently selected 250 ng/dL, as these criteria may not identify patients with low C_{avg} for up-titration to achieve T levels within the desired target range of 300-1000 ng/dL.
- There were changes in various cardiovascular (CV) biomarkers, including increase in blood pressure with administration of oral TU relative to baseline in the clinical trials and relative to the control arms. These observations may be associated with higher androgen exposure with oral TU compared to other marketed T products.

1.2 Phase 4 Post-Marketing Commitment (PMC) or Requirement (PMR)

Not applicable at this time.

1.3 Summary of Important Clinical Pharmacology Findings:

Background and Overview of the Product:

This is a 505(b)(2) application for the first oral soft gelatin capsule containing Testosterone Undecanoate (TU). The product formulated as a proprietary Self-Emulsifying Drug Delivery System (SEDDS) containing TU as a testosterone (T) prodrug. The formulation contains a lipid matrix that is designed to promote the absorption of TU via the intestinal lymphatics and thus eliminate and/or reduce first-pass hepatic effect so that the resulting serum T concentrations fall within the normal range of 300 ng/dL to 1000 ng/dL..

The drug will be available in two strengths of 100 mg and 150 mg TU immediate release (IR) liquid filled soft gelatin capsules. This is equivalent of 158.3 mg and 237.46 mg as TU. The doses throughout this review will be based on T dose, not TU dose (e.g., 100 mg and 150 mg).

The proposed starting dose is 200 mg (2 x 100 mg) twice daily in the morning and in the evening to be administered with food (i.e., not on empty stomach). The dose can be adjusted (up- or down-titrated) in 50 mg increments, through a combination of the 100 and 150mg capsules, to a maximum of 300 mg twice daily or a minimum of 100 mg twice daily.

The proposed indication is for testosterone replacement therapy (TRT) in males for the conditions associated with a deficiency or absence of endogenous testosterone such as primary hypogonadism (congenital or acquired) and hypogonadotropic hypogonadism.

Submitted Studies:

The sponsor submitted 6 clinical pharmacology studies including 2 Phase III studies (Studies 09007 and 12011) with a sub-study in Study 09007 to evaluate the cardiovascular (CV) risk of T. In addition, there is an ongoing long-term extension safety study (Study # 12010) to the 12 month Study 09007. The potential CV risk, among other issues, with the class of TRT therapies was discussed at the FDA Advisory Committee (AC) meeting held on September 17, 2014 and for this NDA on September 18, 2014 (see later summary of the AC recommendation). A separate section in this review is designated to address, in part, the analysis of selected biomarkers for CV risk that were obtained in this NDA. As stated above, the sponsor designated a sub-study to specifically monitor selected recognized biomarkers in Study 09007, in comparison to the marketed T comparator, AndroGel® also known as “T-gel” .

Testosterone Pharmacokinetics (PK) Data:

T and TU concentrations were determined by a validated liquid chromatography tandem mass spectrometry (LC-MS/MS). The sponsor also conducted a series of experiments to demonstrate that TU is not hydrolyzed to T in the blood collection tubes (i.e., there was no *in vitro* hydrolysis of TU to T by esterase enzymes during blood collection and assay process). This was further confirmed by the sponsor’s response dated August 6, 2014 to the Agency’s inquiry dated July 25, 2014 (for details see the Analytical Section 2.6).

- **Effect of Food:**

Two studies demonstrated an increase in the absorption and exposure of T and TU. Specifically in one study the effects of different percent of fat in consumed meals were evaluated. Compared to fasting, the T Cavg was tripled after consumption of food containing 50% fat. In addition, there was a trend for higher T levels after PM (evening) doses compared to AM (morning) dosing that may be related to the somewhat

higher fat content in dinner meals and volume consumed compared to breakfast. There was high inter-subject variability in T levels which is primarily associated with differences in food quality/content and quantity/volume among patients.

Three labeling options are discussed in this review with respect to food: 1) on empty stomach, 2) irrespective of food, and 3) maintenance of usual diet and % of fat. All of these options have pros and cons. However, whichever option is to be implemented, patient's compliance is critical for the optimal therapy.

- **Variability:**

There was wide variability with T levels throughout all studies and in particular after food (see also titration algorithm section below). For example, in Phase III Study 09007, the Cmax in two patients were markedly high: one had a level of 8250 ng/dL and the other 7650 ng/dL. Such high T level is unacceptable with any T product. The spaghetti plot from this study as well as the effect of food studies were presented at the FDA Advisory Committee held on September 18, 2014 (these are also discussed in greater details in the main body of this review). While the availability of oral TU would provide the convenience of easy oral administration than the gel, nasal, and IM injections, it appears that it is a product with "double-edge sword" due to the inherent wide variability with food, potential for high exposure, and potential for CV risk.

- **Dose Proportionality and Steady State:**

From the PK studies, it appears that there was dose proportionality in T levels up to 400 mg TU doses. There was a relatively good relationship between Cavg and Cmax as well as with the titration time point (window) of 3-5 hour and 4-6 hours post dose. There was no prolong accumulation of T levels even at 4 weeks with 200 mg BID dosing as seen by comparison of baseline screening levels and post-dose C_{min} levels for each patient in Study 09009 (in fact, the C_{min} levels were actually numerically lower than baseline screening levels for the majority of the patients). The steady-state for T and its main metabolites, dihydrotestosterone (DHT) and estradiol (E_2), are reached within the first 7 days of dosing. Therefore, this justifies the initial titration time on Day 7 after the start of therapy (see below).

Testosterone Levels in Phase III Studies:

Based on Phase III studies (Study 09007 and 12011), approximately 87% of subjects achieved the 24 h average T concentration (Cavg) within the targeted/normal range of 300-1000 ng/dL in one study (Study 09007) and 75% in another study (Study 12011). In both studies, the predefined success criteria is at least 75% of patients must achieve the target range with lower limit of 95% confidence interval (CI) >65%. Study 12011 barely passed (i.e. point estimate 75% and lower bound 66%).

The secondary criteria is related to the maximum T concentration (Cmax) to be <1500 ng/dL and not >2500 ng/dL. Depending on the titration day, overall the percentage of subjects with Cmax above the criteria were higher in the first study (09007) compared to the second study (12011). In addition, compared to oral TU in Study 09007, none of the patients in the AndroGel® arm had a Cmax >1500 ng/dL on Day 30 (**Table 1**) and Day 365 (shown later). However, 4 subjects had a Cmax >1500 ng/dL on Day 90 (**Table 1**).

In comparison to, AndroGel® 1% (the comparator testosterone product in Study 09007), the T level following oral TU was more variable. Only 3 patients (2%) in the AndroGel® arm had a Cavg outside the upper T limit of 1000 ng/dL at Day 90 (day of primary efficacy evaluation) (**Table 2**) and no patients

(0%) at the end of the study on Day 365 (shown later in the review). The Applicant determined that the titration algorithm in Study 09007 was less aggressive in terms of down-titrations based on the unacceptably high Cmax seen in some of the oral TU-treated patients. Therefore, the Applicant revised the titration algorithm and conducted a new Study (12011). This new study used the proposed to-be-marketed dosing regimen and titration algorithm.

Table 1. Percent of Subjects With Cmax Within Selected Concentration Range in Each Clinic Visit in Studies 09007 and 12011. *Source: 09007 (Tables 6 and 1) and 12011 (Tables 6 and 18)*

Cmax (ng/dL)	Study 09007				12011	
	Day 30		Day 90		Day 30	Day 114
	Oral TU	T-Gel	Oral TU	T-Gel	Oral TU	Oral TU
>1500-<1800	12.0% (19/158)	0% 0/156)	14.1% (21/149)	2.7% (4/149)	9% (12/133)	8.6% (10/116)
>1800-<2500	8.2% (13/158)	0% (0/156)	12.8% (19/149)	4.0% (6/149)	7.5% (10/133)	6% (7/116)
>2500	7% (11/158)	0% (0/156)	13.4% (20/149)	0.7% (1/149)	2.3% (3/133)	3.4% (4/116)

Table 2. Percent of Subjects With Cavg Within Selected Concentration Range in Each Clinic Visit in Studies 09007 and 12011. *Source: 09007 (Tables 6 and 1) and 12011 (Tables 6 and 18)*

Cavg (ng/dL)	Study 09007				12011	
	Day 30		Day 90		Day 30	Day 114
	Oral TU	T-Gel	Oral TU	T-Gel	Oral TU	Oral TU
<300	9.7% (15/155)	41.0% (64/156)	6.8% (10/146)	18.8% (28/151)	9.8% (13/133)	23.3% (27/116)
>300-<1000	81.9% (127/155)	59.0% (92/156)	**83.6%** (122/146)	**79.2%** (118/149)	85.7% (114/133)	**75%** (87/116)
>1000	8.4% (13/155)	0.0% (0/156)	9.6% (12/149)	2.0% (3/149)	4.5% (6/133)	1.7% (2/116)

In both studies, those subjects who had T concentrations (either 3-5 hr or 4-6 hr sampling time) above certain predefined thresholds (1100 ng/dL for Study 09007 and 700 ng/dL for Study 12011) were titrated down to 100 mg or 150 mg BID and those who had low overall T levels were titrated up to either 250 mg or 300 mg BID. By Days 90 or 114 and at the end of the study (Day 365) 75%-85% of the patients were stabilized on the titrated dose (**Table 2**). In the short term study (Study 12011), 75% of the subjects achieved Cavg by the end of the study on Day 114 (**Table 2**). However, considering the variability in the data and differences in study designs, the maximum 300 mg BID dose appears to be adequate in certain patients for the proposed indication.

TU PK Data and Safety Perspective:

From the safety perspective, the levels of the parent drug (prodrug), TU, and its metabolite, 5α-dihydrotestosterone undecanoate (DHTU) were considerably higher than T levels by approximately 20-fold on a ng/dL basis. However, their levels decline rapidly during the 12 hours prior to the evening dose. Overall, the following observations and comments can be made:

- As expected, the ratio of DHT/T and DHTU/TU were also high. A high concentration of TU (but not to the same extent seen here) was also observed with another orally marketed TU outside of the US administered at lower doses than oral TU (e.g., Andriol® TU capsules).

- Based on the receptor binding study the binding affinity was extremely low being 1.23% and 0.7% for TU and DHTU relative to 100% and 83% for T and its metabolite DHT, respectively.
- The dog toxicology study revealed that TU was tolerated following 10 times the equivalent human dose for oral TU.

Therefore, at this time the long term effects of the high levels of TU and its metabolites are unknown at this time.

Pharmacodynamics (PD)/Hormonal Effects:

From the physiological and pharmacodynamics perspective, the administration of TU produces a somewhat greater reduction in luteinizing hormone (LH) and follicular stimulating hormone (FSH) compared to the equivalent dose of AndroGel®. Such an effect is expected from the known pharmacological actions of T. This could also be related to the T exposures since the average T exposures were higher with oral TU than AndroGel® in the Phase III study 09007 which contained both of these arms. In the second Phase III study 12011, the average T exposures were lower than those achieved with AndroGel® in Study 09007, based on cross-study comparisons, however, the LH and FSH were not measure in this trial..

Safety and Effect on Cardiovascular System:

As stated earlier, in both Phase III studies the sponsor monitored several biomarkers associated with the potential cardiovascular (CV) risk of testosterone replacement therapy (TRT). In addition, in Study 09007, the sponsor conducted a sub-study in 24-29 patients in each arm to further investigate the CV risk and monitor specific biomarkers. While, there were noticeable differences in some of the monitored biomarkers from baseline and between the two routes of administration (i.e., oral TU vs Androgel®), the clinical impact of such differences after chronic administration is unknown at this time.

Furthermore, there was a trend of an increase in blood pressure (BP) from baseline after oral TU. The magnitude was higher after oral TU than AndroGel® in Study 09007. A similar, but reduced, impact of blood pressure was also seen in Study 12011. The algorithim used in Study 12011 that resulted in reduced average plasma T levels (relative to that which was seen in Study 09007) is the one proposed for labeling. The reader is directed to the FDA Clinical Review which contains the Medical Officers interpretation of this data and a discussion on the blood pressure effects observed during drug development.

Titration Algorithm:

The proposed titration algorithm increases/decreases oral TU dose by increments of 50 mg BID based on PK measurements obtained within a window of 3-5 hours post morning dose after at least 7 days of treatment with initial starting dose of 200 mg BID TU appears to be reasonable. However, a subset of patients may require multiple titration steps to achieve target T levels, as was observed from the Phase III studies.

There are two potential limitations with the algorithm: 1) the proposed titration threshold and 2) available dosing strengths. The thresholds utilized in 12011 (down titration at 700 ng/dL; up titration at 250 ng/dL) may have contributed to the lower C_{avg} levels observed from 12011 compared to 09007. The proposed algorithm results in down titration of a subset of subjects with C_{avg} within normal T level range of 300-1000 ng/dL and would not up titrate subjects with low C_{avg} <300 ng/dL unless the PK measurement for titration was <250 ng/dL. Overall, the titration algorithm employed in study 12011 and proposed in the label resulted in C_{avg} <300 ng/dL for 23.3% of patients and an overall population C_{avg} of 388 ng/dL.

Appropriate titration thresholds, which take into account product variability and normal target T levels, should continue to be evaluated for this product.

In addition, the 100 mg dose titration increments utilized in 09007 may have contributed to an increase in the number of C_{max} outliers compared to that observed in 12011, which utilized 50 mg dose titration increments. Therefore, the sponsor may further reduce the number of C_{max} outliers by developing 25 mg and/or 75 mg strengths to permit 25 mg increment adjustments during the titration process.

Effect of Body Weight on Titration and Potential Alternative Starting Dose based on Weight:

Based on the analysis of the data from both studies, it appears that the patients with higher baseline T had a stable lower dose and vice versa after the end of titrations by following the respective titrations schemes. An alternative optimal dosing algorithm to minimize failures of high Cmax based on demographic covariate information was evaluated. The analysis suggested that across the two Phase III studies, the patients with baseline body weight < 82 kg as a subgroup had higher median C_{avg} and a higher probability of exceeding the C_{max} safety thresholds (>1500, >2500 ng/dL etc.) compared to the rest of the population for the same initial dose of 200 mg BID. The clear safety impact of such C_{max} excursions is unknown at this time because of the lack of sufficient evaluable safety data and the nature of the trials.

In case these C_{max} excursions, albeit for a limited time before getting possibly down-titrated based on individual titration approach, are considered a safety issue, then an alternative dosing algorithm could be proposed wherein this subgroup of patients (body weight< ~80 kg) could be started with an initial dose of 150 mg BID instead of 200 mg BID. Such approach may satisfy the desired T exposure requirements from both C_{max} and C_{avg} perspective.

Pediatric Waiver:

The target patient population is men over 18 years of age. Therefore, the sponsor has requested a full waiver from conducting studies in the pediatric population for ages 0 to <18 years of age. The sponsor has submitted a Pediatric Study Plan (PSP) to the IND 78,104 in advance of this NDA (pending review).

Conclusions:

Administration of oral TU was associated with high within- and between-subject variability, including an impact of food (fat content) on drug exposure. This variability impacts the ability to titrate subjects to a normal T range while also simultaneously increasing the number of subjects with outlying T levels. Alternative titration thresholds should continue to be evaluated and additional dosing strengths (i.e., 25 mg and 75 mg) could be made available. Together, these may assist in maintaining subjects within the target range.

The systemic and local effects of high levels of TU, DHTU, and other hormonal and physiological changes affected by this product are unknown at this time. In addition, the sponsor had provided additional long term safety information based on the post-marketing information of similar products marketed outside the US – these data are being reviewed by the clinical team (see Clinical-Stats review for more discussion on these issues).

Regarding the potential CV risks of TRT, overall there was a noticeable difference in some of the biomarkers between oral TU and AndroGel®, yet the long term clinical significance of these differences is unknown at this time. Therefore, FDA presented some the above mentioned issues in reference to TRT

in general at the AC meeting held on September 17, 2014 (Day 1) and in reference to this NDA on September 18, 2014 (Day 2).

Summary of the FDA Advisory Committee (September 17 and 18, 2014):

Below is the brief summary of the advisory committee decision for Day 1 and Day 2 (for details see AC transcripts, the Clinical Reviews, and **Appendix 4.5 for the clinical pharmacology slides**).

Day 1 (Indications and CV Risk):

Indications: The AC panel voted 20 to 1 to change the current indication. The general consensus of the panel is that the T products should be indicated only for the so called "classic hypogonadism". In addition, there was general agreement that there is no evidence of benefits in the so called "age-related hypogonadism". For the later indication, the panel recommended controlled clinical trials with clinical outcomes to be conducted.

CV Risk: With regard to cardiovascular (CV) risk, all published research articles had limitations with conflicting findings. In other words, some show a potential for increased risk and others show a potential for decreased risk with TRT. Based on the information discussed and presented, the panel concluded that there is a weak signal for CV risk associated with TRT. However, the available data cannot exclude CV risk. Therefore, the labels of all T products may need to reflect the potential risk. The panel voted 20 vs. 1 for the FDA to require CV safety study to further assess the potential of CV risk and in particular for specific indication (s).

Day 2 (Oral TU):

The vote was 12 vs. 8 that the efficacy had not been adequately established for oral TU. To support approval, the panel voted 18 vs. 3 indicating that there was an unfavorable benefit/risk profile for this product.

The primary reasons for the unfavorable voting for this oral TU are: missing efficacy data, failed sensitivity analyses, large number of subjects with high Cmax, wide variability in T levels, and most importantly unpredictability of T levels associated with the variable fat content in food. In addition, there was some concern about the high T levels and the associated increase in some of pharmacodynamics endpoints such as blood pressure, hematocrits, and HDL.

Based on all the above, from the clinical pharmacology perspective, the NDA is **deficient** in several aspects as listed under recommendation.

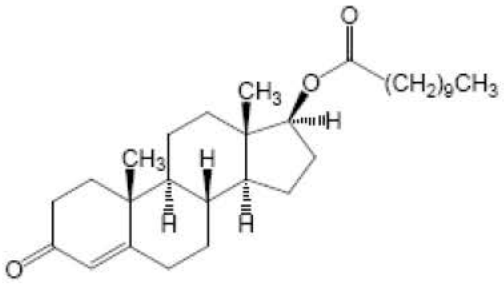
2. Question Based Review

2.1 General Attributes/Background

2.1.1 What are the highlights of the chemistry and physico-chemical properties of the drug substance and formulation of the drug product?

For detailed discussion of the formulation and drug product, please see the Biopharmaceutics Section 2.5. TU is a fatty-acid ester prodrug of T with the molecular weight of 456.7 daltons and has the following structural formula:

Figure 2.1.1-1. Structural Formula of TU (*source Sponsor's Proposed Label, Section 11 Description)*



The formulation was manufactured (b) (4) **(Table 2.1.1-1).** The formulation included several pharmacologically inactive ingredients. The final product is an immediate release (IR) liquid filled soft gelatin capsule. It will be available in two strengths of 100 mg and 150 mg of T equivalent to 158.30 mg and 237.46 mg of TU, respectively.

Table 2.1.1.1. TU Formulation Composition

Ingredients	Amount (mg)		
	100 mg T Capsule	**150 mg T Capsule**	**Remarks**
Testosterone Undecanoate	158.30 TU	237.46 TU	Active Ingredient
Oleic Acid	(b) (4)		
Borage Seed Oil			
Butylated Hydoxytoluene			
Peppermint Oil			
Castor Oil (Cremophor)			
Total Fill Weight			
Soft Gelatin Capsule Shell	**See ONDQA/CMC review for details**		

What is the Rationale and Mechanism of Absorption?

As stated above, the soft gelatin capsule dosage form is a lipid-based SEDDS delivery system containing the TU equivalent of 100 and 150 mg of testosterone. The use of a lipid-based delivery system was selected due to the low aqueous solubility of TU and to facilitate its absorption in the body, primarily, via the lymphatic system to avoid the "first pass" effect when absorbed via the portal vein.

The fill formulation is made up of (b) (4) According to the sponsor, the fill formulation remains a solution until the capsule is taken orally. Once ingested, the capsule disintegrates and the fill formulation comes in contact with the aqueous media of the gastrointestinal tract. Subsequently, the dissolved TU is delivered (in emulsified form) to the site of absorption (e.g., the intestinal lymphatics in the small intestine and not the portal vein).

2.1.2 What are the proposed mechanism(s) of action and therapeutic indication(s)?

The mechanism of T and DHT are well established. Briefly, endogenous androgens, including T and DHT, are responsible for the normal growth and development of the male sex organs and for maintenance of secondary sex characteristics. These effects include the growth and maturation of prostate, seminal vesicles, penis and scrotum; the development of male hair distribution, such as facial, pubic, chest and axillary hair; laryngeal enlargement, vocal cord thickening, alterations in body musculature and fat distribution.

Male hypogonadism results from insufficient secretion of T and is characterized by low serum T concentrations with accompanying signs and symptoms.

Male hypogonadism can present as primary hypogonadism caused by defects of the gonads, such as Klinefelter's Syndrome or Leydig cell aplasia. Secondary hypogonadism is the failure of the hypothalamus or pituitary to produce sufficient gonadotropins: Follicle Stimulating Hormone (FSH), and Luteinizing Hormone (LH).

2.1.2.2 Proposed Indications:

According to the sponsor's originally submitted draft label on January 3, 2014, TU is indicated for replacement therapy in males for conditions associated with a deficiency or absence of endogenous testosterone:

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

injury from tumors, trauma, or radiation. These men have low testosterone serum concentrations, but have gonadotropins in the normal or low range.

2.1.3 What are the proposed dosage(s) and route(s) of administration?

The recommended starting dose of TU is 200 mg of T (two 100 mg capsules), taken orally twice daily in the morning and the evening with food (i.e., not on an empty stomach).

Dose Adjustment (per the sponsor's proposed label dated January 3, 2014)

(b) (4)

Table 2.1.3-1. Titration Steps (Based on Proposed Label dated January 3, 2014)

(b) (4)

Contraindication:

(b) (4)

2.1.4. What are the primary studies submitted in this NDA?

The sponsor submitted 6 clinical pharmacology/PK studies including two Phase III studies with PK and PD components. The synopsis of each study is as follows:

Study CLAR-07004 (Pilot Study):

This was a pilot prototype and will not be discussed in detail any further as it was a pilot PK study conducted in 12 hypogonadal men using a crossover design. The objectives of the study were to assess the acute tolerability and to determine the single day serum PK profile for two oral formulations of T-esters (one T-enanthate (TE) and one T-undecanoate (TU) administered once (QD) and twice-daily (BID)). The other purpose of the study was the selection of a testosterone ester for future development. This study used a SEDDS formulation for both esters. Subjects received the treatment after breakfast only and/or breakfast and dinner as follows:

Treatment A: 400 mg T (as TE) QD (one dose only after breakfast)
Treatment B: 200 mg T (as TU) QD (one dose only after breakfast)
Treatment C: 200 mg T (as TU) BID (100 mg/dose) (two doses after breakfast and dinner)
Treatment D: 400 mg T (as TU) BID (200 mg/dose) (two doses after breakfast and dinner)
Treatment E: 800 mg T (as TE) BID (400 mg/dose) (two doses after breakfast and dinner)

Table 2.1.4.1 Summary of T PK parameters (source: Study 07004, Table 14.4.4.a, Page 14)

Parameters	Treatment A (TE QD, 400 mg) (n=12)	Treatment B (TU QD, 200 mg) (n=12)	Treatment C (TU BID, 100 mg) (n=12)	Treatment D (TU BID, 200 mg) (n=12)	Treatment E (TE BID, 400 mg) (n=12)
Cavg (ng/dL)	293±148	246±77	281±89	385±132	316±167
Cmax (ng/dL) (0-12 h)	-	-	470±247	626±267	572±388
Cmax (ng/dL) (0-24h)	731±571	557±252	-	-	-
Cmax (ng/dL) (12-24h)	-	-	466±160	718±333	523±337
AUC (ng.h/dL)	7023±3548	5907±1840	6751±2145	9252±3173	7595±4020

Reviewer's Comments:

Based on this study, following 200 mg twice daily of TU, 67% of the subjects achieved the Cavg above 300 ng/dL (lower normal eugonadal limit). The TU formulation performed better than TE in delivering T. Overall, it appears that the TU formulation is less variable than TE formulation.

Study CLAR-08005 (Repeat Dose):

This study was designed based on the PK data from the previous study 07004. This was a repeat-dose crossover PK study with a food effect in one arm at a maximum dose of 800 mg daily. This study used two T-esters (TU alone and a combination of TU and TE). The objective of the study was to assess the acute tolerability and PK of two oral formulations of T-esters (TU, TU + TE) in 29 hypogonadal adult male subjects at 4 study sites. Subjects received the four treatments after breakfast or dinner for a total of 29 doses.

Based on this study, it appears that there was dose proportionality in T concentration over the tested doses and also there is correlation between the Cmax and Cavg. A high fat meal markedly increased both the Cmax and AUC compared to fasting.

Study CLAR-09008 (Effect of Food):

This was a definitive food effect study to evaluate the effect of fat contents in meals ranging from 10% to 50% at the highest proposed dose of 300 mg. The administration of TU after a meal containing 50% fat increased the T level by about 3 fold compared to fasting.

Study CLAR-09009 (Steady-State):

This was a PK steady-state study at 200 mg BID dose for 28 days in 15 hypogonadal men. The trough level of T, DHT, and E_2 were monitored periodically prior to the AM doses and during full PK profiles on Day 28. The steady state was achieved within 7 days. While the study was small (n=15), 87% of the subjects achieved the goal Cavg of 300 to 1000 ng/dL.

Study CLAR-09007 (One Year Dose Titration):

This was the first Phase III study using an active comparator, AndroGel® (1% T-Gel). All subjects were titrated after 30 days of 200 mg BID doses then reevaluated after three months of treatment (Day 90) and continued on the maintenance dose regimen until Day 365. This study also contains a sub-study to specifically evaluate and monitor the CV risk.

Study CLAR-12011 (Dose-Titration Optimization):

This is the pivotal Phase III dose titration study and was designed based on data from the previous Phase III study that had a dose titration algorithm that was less aggressive in terms of down-titration threshold. In this study, all subjects were titrated, if needed, on Day 30 and Day 72. In this study the full PK profiles were obtained on Day 114.

Extension Study CLAR-12010:

This is a long-term safety study which is a 1-year extension for Study 09007. Interim results from this study were not submitted in the original NDA but have been submitted as part of the 120-day safety update.

Reviewer's Comments:

Both Phase III studies used relatively similar designs with some notable exceptions as shown in the table below:

Table 2.1.4.2. Comparison in Study Designs

Variable	**Study 09007 (First Study) N=160 in each arm**	**Study 12011 (Second Study) N=144**
Design	**Group A** (Oral TU): Starting dose is 200 mg BID (AM and PM) **Group B** (AndroGel®): Starting 50 mg T QD	Single Arm (oral TU only) Starting dose: 200 mg BID
Titration **Down Titration**	Increment or decrement by **100** mg BID Based on **T>1100** ng/dL	Increment or decrement by **50 mg** BID Based on **T>700**
Time Points	4-6 h post AM dose	3-5 h post AM dose

For example, Study 09007 had an Androgel® active comparator arm and was 12 months in duration. In contrast, Study 12011 was a single arm study of 4 months duration. The trials also had different titration design features. For example, the titration was based on 100 mg increment or decrement in the dose for Study 09007 compared to 50 mg changes in Study 12011. Therefore, Cmax was overall higher in the first study compared to the second study (**Table 1** in Executive summary). However, in the second study the Cavg was slightly lower than in the first study with some patients having lower Cavg than the targeted concentrations (**Table 2** in Executive summary). Therefore, an alternative optimal titration rule to minimize both of these failures (i.e., minimize high Cmax and minimize low Cavg) may be possible.

The primary conclusion from these two studies was that both studies achieved the primary efficacy endpoint (there were issues with the results from sensitivity analyses – see the clinical review for details) but that there were some patients with unacceptably high Cmax, particularly in Study 09007, which used a less aggressive titration scheme for down-titration (see also **Tables 1 and 2** shown later in the conclusion/summary section for both Phase III studies).

2.1.4.1 What are the *in vitro* Studies Conducted in this NDA?

In vitro dissolution experiments were conducted to establish the link between the Phase II hard gelatin capsules and Phase III soft gelatin capsules (see the Biopharmaceutics Section 2.5). The sponsor also performed receptor binding studies with various androgens (**see Section 2.2.1**).

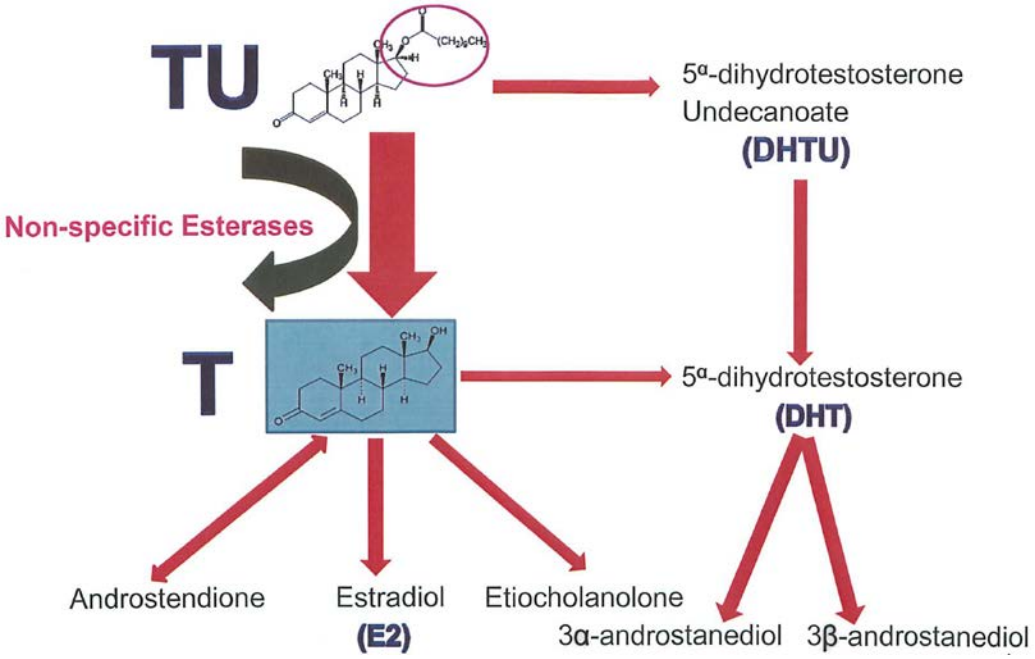
2.2 General Clinical Pharmacology

2.2.1 What are the Characteristics of Drug Metabolism?

As discussed in the earlier sections, TU is a fatty-acid ester prodrug of T that must undergo hydrolysis by estereases to release T. It is formulated as a lipid-based delivery system with high lipophilicity to be absorbed primarily via the lymphatic system to avoid the first pass effect (the bioavailability of T after oral administration is approximately 4-7% due to the extensive first pass effect; see (Tauber et al, Eur J Drug Metab Pharmacokinetic 11:145-149, 1986 and Andriol® Canadian Monograph, November 15, 2011, Control # 149280).

During the absorption process, TU is reduced to 5α-dihydrotestosterone undecanoate (DHTU), which is also absorbed via the lymphatic system. From the lymphatic system, TU and DHTU are released into the circulation via the thoracic duct. Both TU and DHTU are hydrolyzed to yield T and 5α-dihydrotestosterone-DHT (Bagchus et al, Pharmacotherapy, 23 (3):319-325, 2003). Furthermore, T is also metabolized to other pharmacologically active metabolites such as estradiol-E_2 (**Figure 2.2.1-1**).

Figure 2.2.1.-1. Metabolic Pathway of T and TU



What is the Binding Affinity of TU to the Receptor?

The sponsor conducted *in vitro* studies to evaluate the androgen receptor (AR) binding affinity of various androgens produced after the administration of TU (Study 013325-02). Although the binding affinity of TU and DHTU to AR is low compared to T (**Table 2.2.1-1**), no information is available on the potential local and/or systemic pharmacological activities of these androgens, specifically following chronic administration.

As shown in the above figure, the source of DHT which as an active metabolites is from TU, DHTU, and T.

Table 2.2.1-1. Binding to Androgenic Receptor (Source: *in vitro* Polar Screen Study # 013325-02)

Parameters	T	DHT	TU	DHTU
EC50 (nM)	7.04	8.51	573	1005
Relative Binding Affinity (%)	100	83	1.23	0.7

2.2.2 What efficacy and safety information (e.g., biomarkers, surrogate endpoints, and clinical endpoints) contributes to the assessment of clinical pharmacology study data? How were they measured?

The primary efficacy endpoint/biomarker in this NDA is T level and in particular the average testosterone concentration over 24 hours (Cavg). Cmax is one of the safety variables if it is over the acceptable threshold limits. Therefore, these two parameters drove the titration process and dose in Phase III studies as described in detail in the subsequent sections of this review.

Other safety parameters were monitored including some related to the pharmacodynamics effects of T such as hormonal levels and biomarkers associated with the CV risk of testosterone replacement therapy (TRT). These safety biomarkers will be discussed for Phase III studies in this review (for additional discussion and details see the clinical team review).

Study 09007 (First Phase III Study):

How the Study Was Designed?

This was a randomized, open-label, 2-arm, active controlled, 12-month, multicenter study of oral TU vs. Androgel® 1%, with approximately 150 hypogonadal men in each arm. The study included dose titration based on serum T concentration assessed at **4-6 h** post AM dose. Subjects were randomized into the following two groups:

Group A (Oral TU): 2 x 100 mg capsules (i.e., 200 mg per dose) twice daily (BID) x 30 days (i.e., total daily dose = 400 mg)

Group B (Transdermal T-gel): 5 gram of 1%-gel (AndroGel®) once daily (QD) to shoulders, upper arms and/or abdomen.

There were two titration periods, one on Day 42 (based on Day 30 data) and the other on Day 74 (based on Day 60 data) if necessary. The primary objective of this study was to determine the efficacy of oral TU in hypogonadal men for androgen replacement therapy following approximately 12 weeks (i.e., ~90 days) of continuous therapy by identifying:

- The percentages of treated subjects that had 24-hour serum T average concentrations (Cavg) between 300 and 1000 ng/dL. The success criteria is ≥75% of patients with lower limit of 95% CI ≥65%.
- The percentages of treated subjects that had maximum serum T concentration (Cmax) values that were
    (a) Less than or equal to 1500 ng/dL
    (b) Greater than 1500 and less than or equal to 1800 ng/dL
    (c) Greater than 1800 and less than or equal to 2500 ng/dL
    (d) Greater than 2500 ng/dL

Serial PK samples were collected on the following days:

Day 30: At 0.5 and 0 hours pre-dose, and 1.5, 3, **4-6**, 8 and 12 hours post-dose of the morning drug administration).

Day 90: At 0.5 and 0 hours pre-dose, and 1.5, 3, **4-6**, 8, 12 (prior to the second dose), 13.5, 15, 16 to 18, 20 and 24 hours post-dose of the morning (AM) drug administration.

Day 365: At 0.5 and 0 hours pre-dose, and 1.5, 3, **4-6**, 8 and 12 hours post-dose of the morning drug administration.

How Many Subjects Were Within T Normal Range?

Based on this study, **83.6%** of patients achieved the Cavg goal range of 300 ng/dL to 1000 ng/dL by Day 90 and 85.0% by Day 365 after oral TU administration (**Table 09007-1**). With AndroGel®, Cavg was 79.2% and 75.6% on Day 90 and Day 365, respectively. The lower limit of the 95% confidence interval (CI) was 76.5% with oral TU and 71.8% with AndroGel® (i.e., met the goal).

Table 09007-1. Summary of the Success Rate for Obtaining T Cavg Values in the Eugonadal Range in Hypogonadal Men (source: study 09007, Table 2, Page 31).

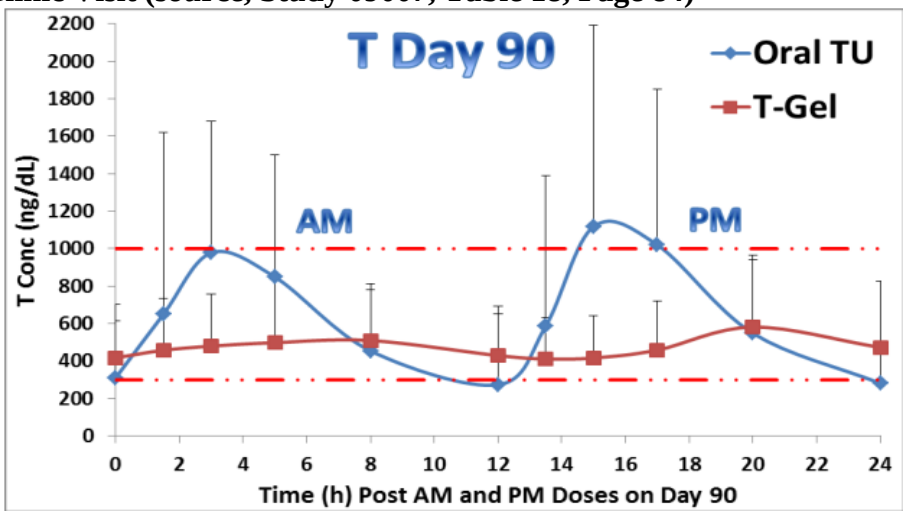
Observation Day & Time	Oral TU Treatment				Topical T-Gel Treatment			
	Cavg Evaluable	Cavg in 300-1000 ng/dL range		Lower 95% CI	Cavg Evaluable	Cavg in the 300-1000 ng/dL range		Lower 95% CI
	Total	N	%	%	Total	N	%	%
Day 90 Full	146	122	83.6%	76.5%	149	118	79.2%	71.8%
Day 30 AM	155	127	81.9%	NC	156	92	59.0%	NC
Day 90 AM	147	114	77.6%	NC	150	112	74.7%	NC
Day 90 PM	147	117	79.6%	NC	150	117	78.0%	NC
Day 365 AM	127	108	85.0%	NC	131	99	75.6%	NC

NC = Not calculated
Shaded cells indicate rates based on full 24-hour PK observations

Was There a Difference in the T Serum Profiles Among Visits?

Overall, the T serum concentration-time profiles were comparable in terms of magnitude of T levels and the variability among visits as shown, for example, for the Day 90 profiles (**Figure 09007-1).** The observed inter- and intra-subject variability in T levels was expected due to many factors and in particular food content. Overall, the mean value of T levels were within the normal range (see also above).

Figure 09007-1. Mean (±SD) Concentration-Time Profile for Serum Total T in Subjects on the Day 90 Clinic Visit (source, Study 09007, Table 18, Page 84)



In terms of Cmax, the mean values on Day 30, 90 and 365 ranged between 1100 ng/dL to 1676 ng/dL and occurred approximately 4 hours post-dose following both the morning and evening doses (**Table 09007-2).** For comparison, the mean Cmax ranged from 533 ng/dL to 817 ng/dL in the AndroGel® treatment group (**Table 09007-2**). The percentage of patients with Cmax ≥2500 ng/dL was unacceptably high; therefore, the sponsor revised the titration algorithm then conducted a new clinical trial (see also **Table 1** later in executive summary and conclusion sections).

The mean Cavg values were approximately 40%-50% of the Cmax concentrations in the oral TU treatment group, ranging from 524 ng/dL to 661 ng/dL, while the mean Cavg values in the AndroGel® treatment group ranged from 379 ng/dL to 489 ng/dL. It is noted that both Cmax and Cavg were consistently higher after oral TU than AndroGel®. Also, the variability in both PK parameters after oral TU appears to be higher than after the AndroGel® (**Figure 09007-1,** see also later discussion).

Table 09007-2. Mean (SD) of Primary PK Parameters for Serum Total T During Each PK Observation Period, by Treatment (Source, Table 23, Page 93 of 950, Study 09007).
Table 09007-2A: Full Day (i.e., Mean of AM and PM)

Parameters	Day 30 Full Day		Day 90 Full Day		Day 365 Full Day	
	Oral TU	AndroGel®	Oral TU	AndroGel®	Oral TU	AndroGel®
Cavg (ng/dL)	607±299	379±156	628±324	485±220	524±215	425±177
Cmax (ng/dL)	1261±785	533±255	1676±1408	817±480	1100±648	582±276
AUC (ng.h/dL)	7281±3592	4545±1869	15080±8226	11641±5282	6292±2581	5097±2130

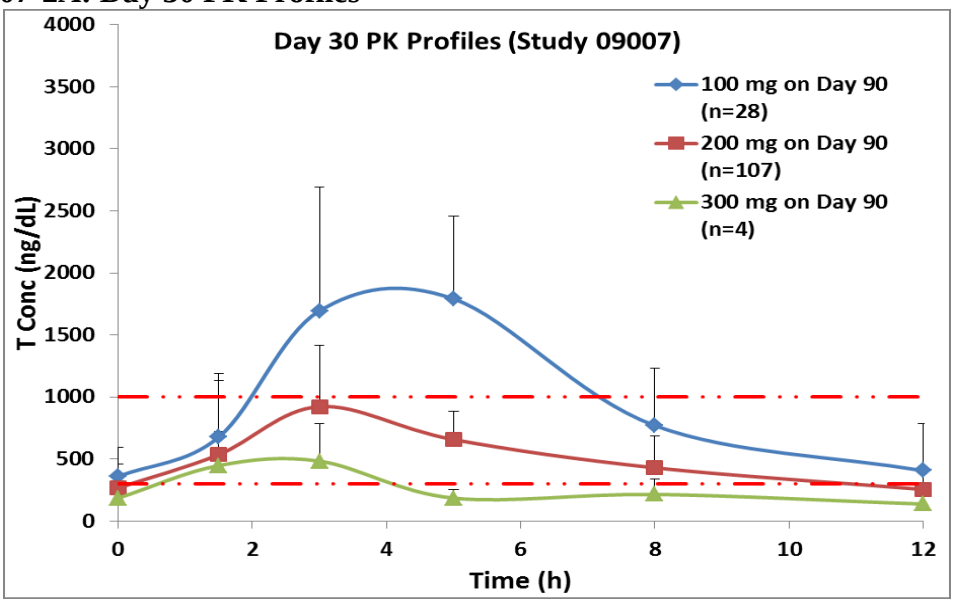
Table 09007-2 B: Day 90 (AM and PM):

Parameters	Day 90 AM		Day 90 PM		Day 90 Full Day	
	Oral TU	AndroGel®	Oral TU	AndroGel®	Oral TU	AndroGel®
Cavg (ng/dL)	592±399	478±235	661±399	488±251	628±324	485±220
Cmax (ng/dL)	1227±1055	685±414	1414±1222	703±405	1676±1408	817±480
AUC (ng.h/dL)	7106±4784	5740±2820	7935±4784	5863±3016	15080±8226	11641±5282

What is the Effect of Dose Titration on Serum T Concentration-Time Profiles?

The earlier **Figure 09007-1** shows the mean concentrations-time profiles for subjects regardless of the dose for oral TU or AndroGel®. However, **Figure 09007-2A-C** shows the mean concentration-time profiles for all subjects for oral TU per visit and titrated dose on Day 90. It should be noted that all subjects started with 200 mg BID on Day 1 until the titration days, Day 42 and Day 74 (if necessary) based on T concentrations on Day 30 and Day 60, respectively. Shown in these figures are the mean concentration-time profiles of subjects that were in the 100 mg, 200 mg and 300 mg BID dose groups on their Day 90 clinic visit (i.e., the mean concentration profiles for subjects that were titrated to 100 mg, 200 mg or 300 mg BID as their maintenance dose).

Figure 09007-2. Mean T Concentrations Grouped by the Day 90 Titration Defined Dose (Study 09007) (source, Study 09007, Table 18, Page 84)
Figure 09007-2A: Day 30 PK Profiles



Footnote to Figure 09007-2A: N=4 had Cavg <300 ng/dL and were titrated up to 300 mg, n=28 had Cavg >1000 ng/dL and were titrated down to 100 mg, and n=107 had Cavg between 300 and 1000 ng/dL and remained on the same 200 mg dose.

Figure 09007-2 B: Day 90 PK Profiles

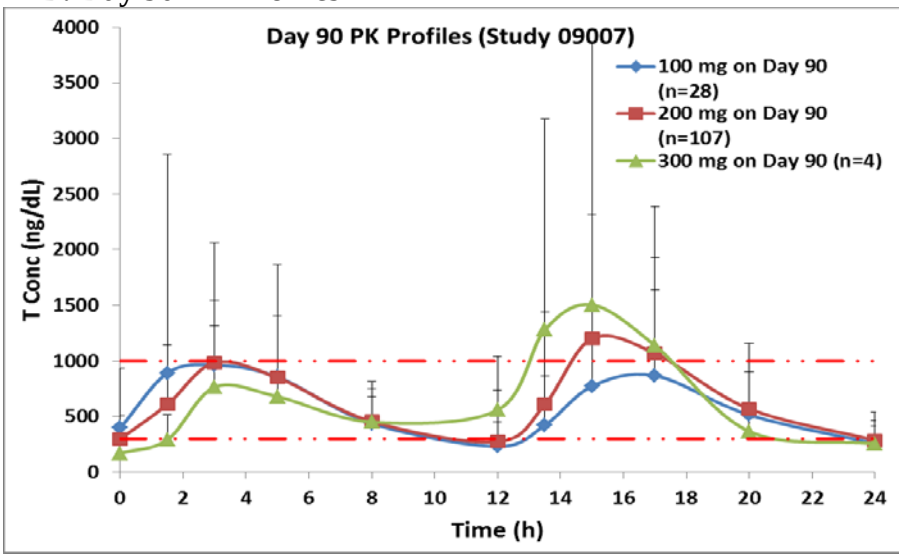
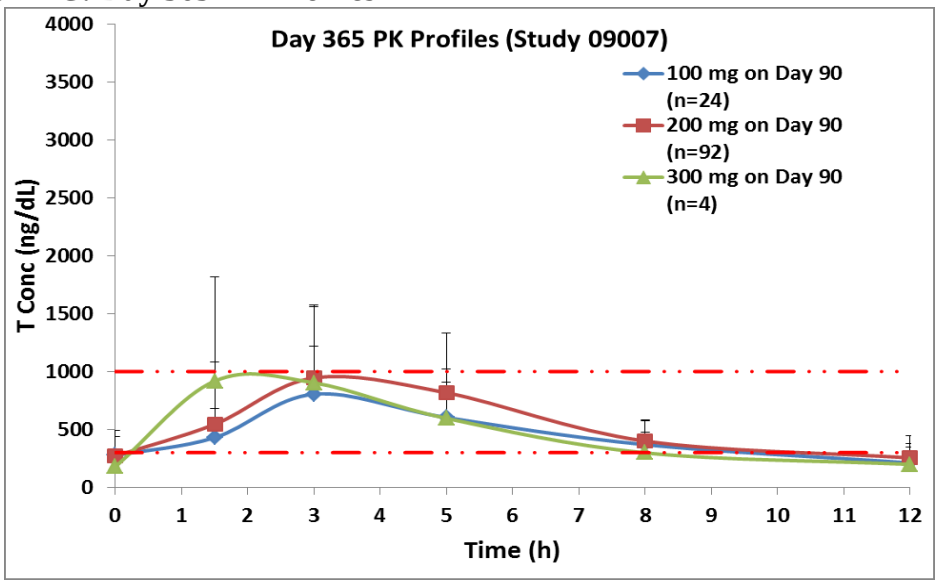


Figure 09007-2 C: Day 365 PK Profiles



On Day 30, when all three maintenance dose groups were receiving a 200 mg dose, the profiles for the three groups show substantial differences (**Figure 09007-2A)**. The Day 30 mean profile for the subjects that were titrated downwards to 100 mg BID by Day 90 (N=28, **Figure 09007-2B**) was above the upper bound of the eugonadal range for approximately half of the dosing interval when those subjects received the higher 200 mg dose.

The Day 30 mean profile for subjects that were titrated upwards to 300 mg by Day 90 (N=4) were below the lower limit of the eugonadal range for more than half of the dosing interval when those subjects received the lesser 200 mg dose. The number of subjects requiring 300 mg BID dosing was small (n=4). However, in clinical practice, some subjects may be needed to be titrated up to this dose level (300 mg BID.

The mean profile for subjects that were titrated to 200 mg BID by Day 90 (N=107) showed little difference between their Day 30 profile (when they also received the 200 mg BID) and their Day 90 profile following the AM dose (**Figures A and B**). Overall, the dose titration process shown above provided some adjustment in T exposure in most of the subjects.

The figure shows that on the Day 90 and Day 365 clinic visits the subjects in the 100 mg, 200 mg, and 300 mg oral TU dose groups had similar concentration-time profiles even though the T doses covered a 3-fold range (**Figures B and C**). The concentrations on Day 90 were lower following the AM dose than following the PM dose (**Figure B**). This could be a reflection of greater diversity in fat content and consumed volume in evening meals compared to breakfast. Such day-to-day variability in T level is of concern from the safety and efficacy perspective.

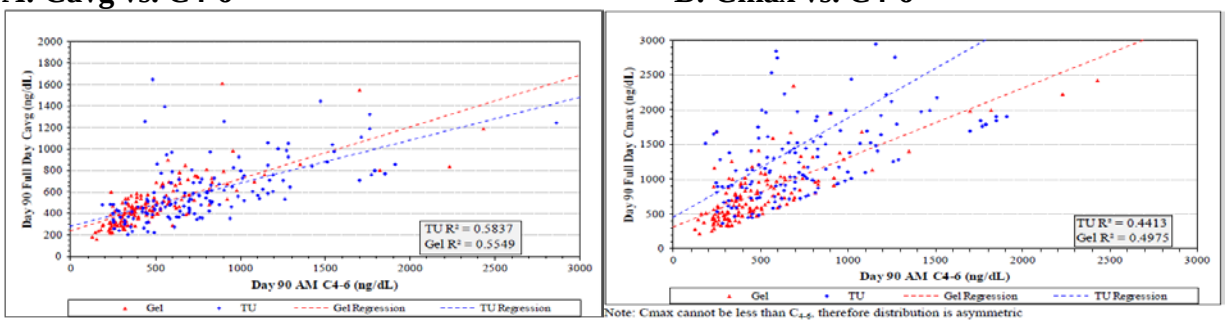
Was There a Relationship Between Cavg, Cmax, and T Concentration at C4-6 h?

The objective of the sponsor's titration scheme was to use a single time point in lieu of the 24-hour Cavg and/or the Cmax. The relationship between Cavg and the single point would be critical from the clinical and practical perspectives. As stated in the study design, the sponsor selected the 4-6 h time points post morning dose (C4-6 hours) based on the previous PK studies and also PK modeling.

Overall, there was some correlation between a single time point of 4-6 hours and Cavg as well as Cmax (**Figure 09007-3A&B, Tables 09007-3 and 4)**. The same is true for the relationship between Cavg and Cmax (i.e., a decrease or increase in Cmax values is associated with a decrease or increase in Cavg values).

Figure 09007-3A&B. Examples of the relationship between Cavg (Full Day), Cmax (Full Day), and C4-6 (AM) on the Day 90 Clinic Visit (Source Study 09007 Figure 15, Page 134 and Figure 25, Page 139)

A: Cavg vs. C4-6 **B: Cmax vs. C4-6**



As shown in **Tables 09007-3 and 09007-4** both Cavg and Cmax showed correlations with the C4-6 concentration following dosing. Comparison of these two PK parameters to each other indicates relatively reasonable correlation.

Table 09007-3. Summary of Regression Parameters for Cmax vs. C4-6, the Single Sample Surrogate (source Study 09007 Table 5, Page 38)

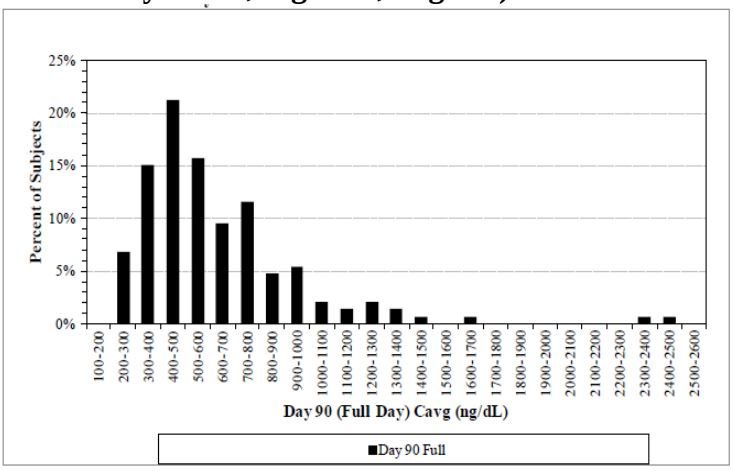
Clinic Visit	Regression	Slope	Intercept	R^2	$Cmax/C_{4-6}$ Mean	$Cmax/C_{4-6}$ SD
Day 90 Full	Cmax vs. C_{4-6} AM	1.4306	452	0.4413	2.3069	1.92620
Day 30 AM	Cmax vs. C_{4-6} AM	0.9182	451	0.4805	1.6684	1.10019
Day 90 AM	Cmax vs. C_{4-6} AM	1.3164	103	0.6627	1.5833	0.97640
Day 90 PM	Cmax vs. C_{4-6} PM	1.1705	215	0.6335	1.4592	0.73032
Day 365 AM	Cmax vs. C_{4-6} AM	0.8825	433	0.4327	1.6669	0.93508

Table 09007-4. Summary of Regression Parameters for Cavg vs. C4-6, the Status Sample for Cavg (source Study 09007, Table 4, Page 36)

Clinic Visit	Regression	Slope	Intercept	R^2	$Cavg/C_{4-6}$ Mean	$Cavg/C_{4-6}$ SD
Day 90 Full	Cavg vs. C_{4-6} AM	0.4004	286	0.5837	0.8730	0.46930
Day 30 AM	Cavg vs. C_{4-6} AM	0.4277	229	0.7169	0.8052	0.33272
Day 90 AM	Cavg vs. C_{4-6} AM	0.5342	136	0.7640	0.7713	0.29867
Day 90 PM	Cavg vs. C_{4-6} PM	0.4101	241	0.7307	0.7347	0.26944
Day 365 AM	Cavg vs. C_{4-6} AM	0.3095	290	0.4834	0.8126	0.31697

The distribution of 24-hour Cavg values for Day 90 is shown in **Figure 09007-4**. This figure breaks down the percentage of subjects achieving Cavg in increments of 100 ng/dL. Collectively and as discussed earlier, >75% of the subjects had Cavg values between 300 ng/dL and 1000 ng/dL. Furthermore, the Day 90 distribution for Cavg was similar in shape to the distributions observed for Day 365. The 12-hour Cavg values following the AM dose and the PM dose on Day 90 and Day 365 had similar distributions.

Figure 09007-4. Frequency Distribution of Total T Cavg (Full Day) Following Oral TU Doses on Day 90 (source Study 09007, Figure 2, Page 37)



As mentioned previously, the titration algorithm used in this study led to an unacceptable increase in Cmax in some patients prompting the sponsor to revise the algorithm and then conduct a new study (12011).

Was There a Difference in Variability Between AM and PM Dosing?

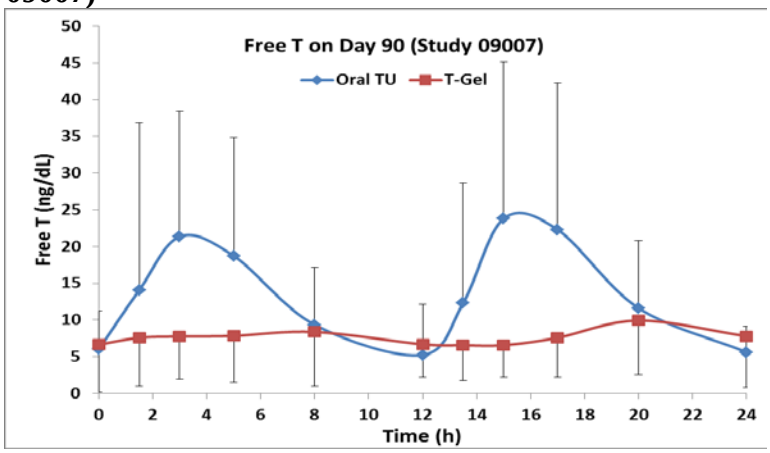
Overall, there appears to be greater variability in the systemic bioavailability following the evening dose as compared to the morning dose in some subjects. This resulted in the evening dose being associated with a higher Cavg value and higher Cmax in some subjects. This may be attributed to the higher fat content often associated with the dinner meals as compared to a breakfast meals. On average, the Cmax value for T after the PM dose of oral TU was approximately 36% greater than after the AM dose, while the Cavg was approximately 25% greater.

As stated earlier, this day-to day variability and the unpredictability in T levels and other androgens is of one of the major concern from the safety and efficacy perspective.

Is There a Relationship Between Free T (FT) and Total T (TT)?

Similar to DHT, following oral TU the mean concentration-time profiles for Free T (FT, protein unbound i.e., to sex hormone binding Globulin-SHBG) followed a similar pattern as the total T concentrations in both Phase III studies (e.g., Tmax). Following oral TU, mean FT concentrations increased for the first 3 to 4 hours post-dose and then declined over the remainder of the 12-hour dosing interval after both AM and PM dosing (**Figure FT-1**).

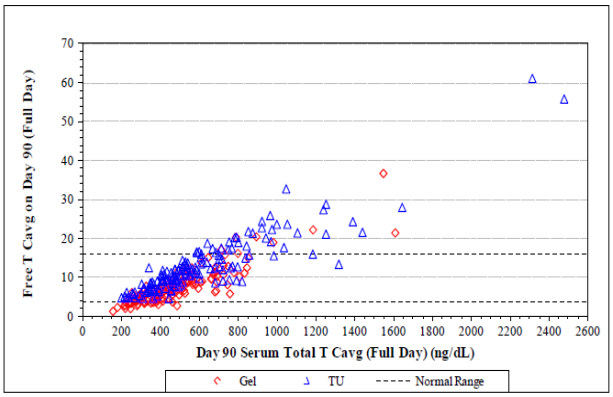
Figure FT-1. Mean (SD) Testosterone Free (FT) Profiles of Oral TU and Androgel® (T-gel) on Day 90 (Study 09007)



From the above Figure it should be noted that the free T levels after oral TU was substantially higher than that after Androgel®. In addition, the variability is as expressed in the SD bars is also wider than after Androgel® (see also pharmacodynamics Section 2.2.4, effect on SHBG discussion).

There was a relatively good relationship between the FT and TT in both Phase III studies (**Figure FT-2**). As expected, FT was substantially lower than TT. The variability in the data was similar to TT.

Figure FT-2. Relationship Between TT Cavg and FT Cavg (source Study 09007, Figure 6, Page 59).



Overall, it can be concluded that as expected FT/TT ratios were relatively similar, irrespective of the route of administration (Oral TU or AndroGel®, Study 09007).

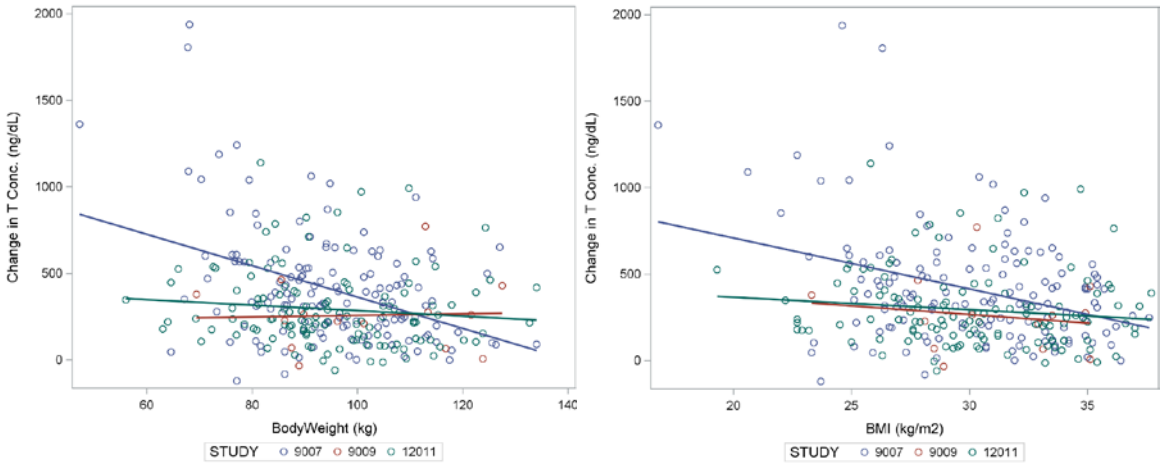
Is There Impact of Demographic Characteristics on T PK?

Weight, BMI, Age, Baseline T value and Race

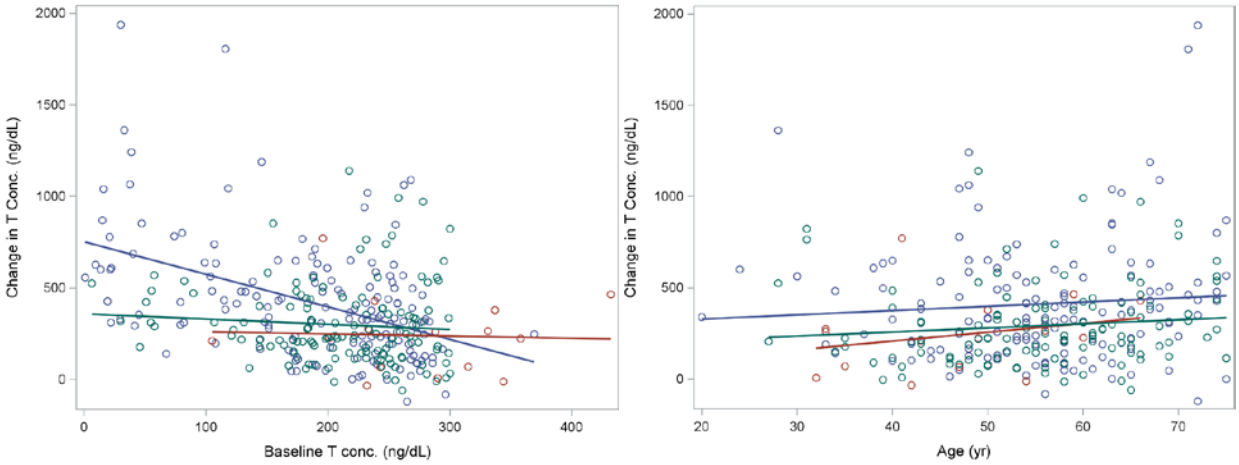
The Day 30 values of change from baseline in T exposure (ΔT_{avg} =Cavg at day 30 – Baseline screening T levels) were examined for dependence on the demographic parameters of subject age, weight, and body mass index (BMI). Based on pooled analysis of three studies including Study 09007, it appears that there was a trend towards higher T exposure with lower body weight/BMI (**Figure 09007-5**), which appears to be driven by Study 09007 rather than Study 09009 or 12011. There was no clinically relevant effect/trend of ΔT_{avg} with age or race.

Figure 09007-5: Relationship of change from baseline in C_{avg} T concentration (ΔT_{avg}) at approximately 4 weeks with baseline body weight (panel A), baseline BMI (panel B), baseline T conc. (panel C) and age (panel D) across the three studies with the same dose of 200 mg BID (Source Reviewer's Analysis, Study 09007, 12011 and 09009)

Panel A: Body Weight **Panel B: BMI**



Panel C: Baseline T concentration **Panel D: Age**



Study 12011 (Second Phase III Titration Study):

Overview of Study Design and Results:

Overall, the design of this study was similar to that of the first Study 09007 with few exceptions as follows (see also **Table 2.1.4.2 in the previous Section):**

- Titration time point was changed from **4-6** hours to **3-5** hours
- The duration of the study was shorter (i.e., 4 months instead of 12 months)
- Lower titration steps/dose (i.e., **50 mg** increment or decrement instead of **100 mg**)
- The addition of more titration days between Day 30 and Day 114, as needed
- Single arm study

In both studies, all subjects started with 200 mg BID dose until titration Day 42. Also, in both studies, TU was administered about 30 minutes after breakfast or dinner.

The percent of subjects achieving the Cavg goal was lower (75%) than in Study 09007 (83.6%). In addition, the lower boundary of the 95% CI was 66.1% in this study compared to 76.5% in Study 09007 (**Tables 09007-1, 12011-1, and 12011-2** (see also biostatistics and clinical team Reviews).

Table 12011-1. Summary of the Success Rate for Obtaining T Cavg Values in the Eugonadal Range in Hypogonadal Men (source Study 12011, Table 2, Page 29).

Observation Day & Time	Oral TU Treatment			
	Cavg Evaluable Total	Cavg in 300-1000 ng/dL range		Lower 95% CI
		N	%	%
Day 114 Full	116	87	75.0%	66.1%
Day 30 AM	133	114	85.7%	NC
Day 72 AM	130	100	76.9%	NC

NC: Not calculated

Table 12011-2. Mean (SD) of Primary PK Parameters for Serum Total T During Each PK Observation Period, by Treatment (Source, Table 22, Page 83 of 540, Study 12011).

Parameters	Day 30 (AM)	Day 72 (AM)	Day 114 (AM)	Day 114 (Full Day)
Cavg (ng/dL)	509±222	454±192	397±197	422±171
Cmax (ng/dL)	1106±708	928±515	827±504	1062±581
AUC (ng.h/dL)	6110±2665	5455±2307	4763±2350	10135±4111

Based on the mean T concentration-time profiles shown in **Figure 12011-1A** on Day 30 the following titration steps were made on Day 42:

- The T level in 28 subjects was within the range. Therefore, these subjects remained on 200 mg dose until Day 114 (**Figure 12011-1B**).
- The T level in another 28 subjects was above the range. Therefore, they were titrated down to a final dose of 100 mg BID.
- 58 subjects had sampled PK exceeding the upper titration threshold and so they were titrated down to a final dose of 150 mg BID.
- Only 4 subjects in this cohort had sampled PK levels below 250 ng/dL. Therefore, they were titrated up to the 250 mg BID dose.

Figure 12011-1B shows the results of the titration scheme for Study 12011, in which 75% of the subjects achieved the desired Cavg per the protocol.

Figure 12011-1. Mean T Concentrations by Dose, Grouped by their Day 114 Dose source Study 12011, Table 21, Pages 81 and 82)
Figure 12011-1A: Day 30 PK Profiles

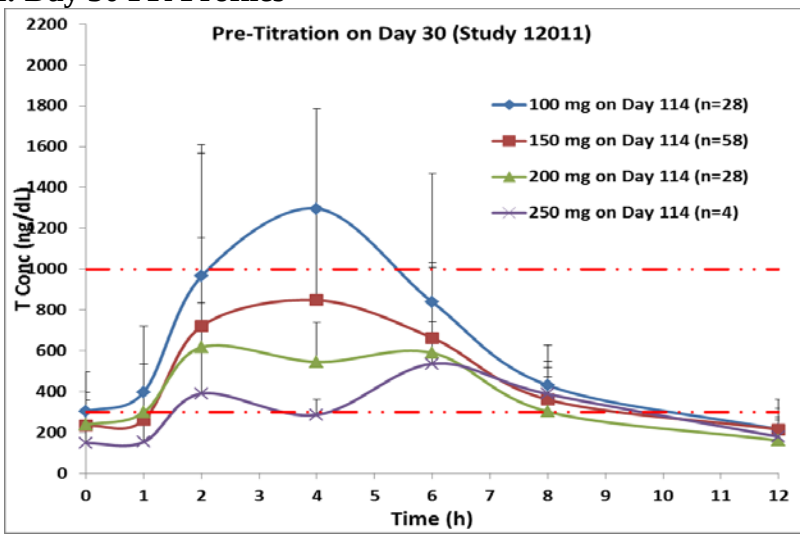
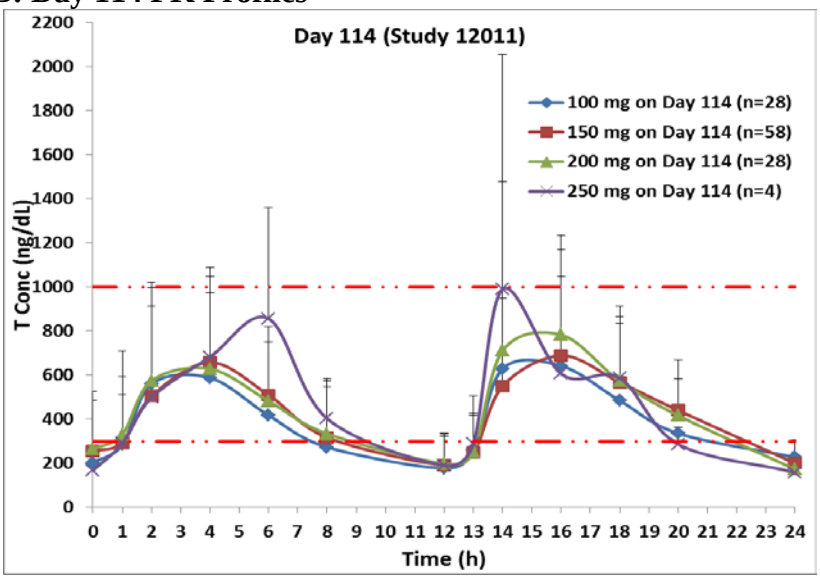


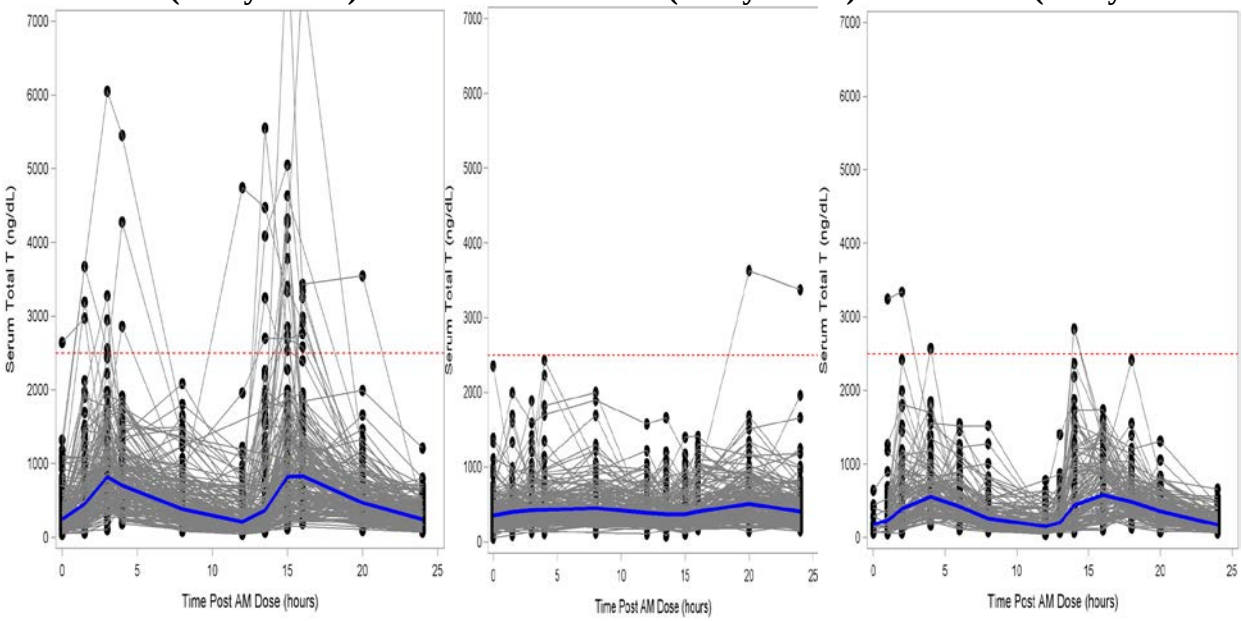
Figure 12011-1B: Day 114 PK Profiles



Additional Analysis on Titration and Variability (Study 12011 and 09007):

The set of Figures bellow show the spaghetti plots for T levels from Studies 09007 and 12011.

Spaghetti Plots A, B, and C: Spaghetti Plots for T Levels:
A: Oral TU (Study 09007) B: AndroGel (Study 09007) C: Oral TU (Study 12011



Key: Blue solid line respsents the mean and the red dostted line repsents the levels of 2500 ng/dL.

As shown in these figures, in Study 09007 oral TU demonstrated much higher variability compared to Androgel®. There were several subjects with level above 2500 ng/dL. In addition, two subjects had T levels off the scale of 7000 ng/dL. One subject had a level of 8250 ng/dL and

another had a level of 7650 ng/dL. While these two subjects represent extreme cases, considering the small sample size of the study, other patients could also be at such high level, if the original titration process in Study 09007 would have been implemented and specifically after high fat meals (see also the Biopharmaceutics Section 2.5 for additional discussion on the variability and food).

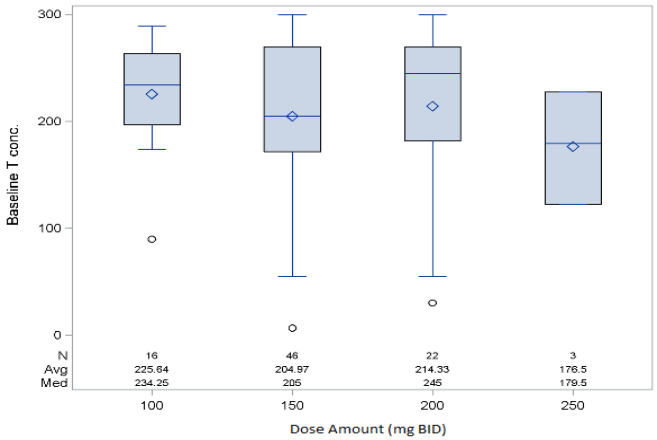
However, when the titration process was revised in Study 12011 by down titrating patients with T levels >700 ng/dL, the variability was less compared to Study 09007. Also, from these plots, the levels after PM dosing appears to be higher after AM dosing in both studies.

Based on these data, the variability in T serum levels after oral TU needs to be monitored, specifically in reference to the impact of food. This issue was extensively discussed at the AC meeting held on September 18, 2014. The primary concern of the AC panel is the difficulty in predicting T levels as most of patients will not comply with the administration instruction in reference to fat content of food. The variability appears to be inherent in this product, in addition to food effect. However, no consensus was reached by the panel on how the drug should be administered with respect to food. Some members called for additional studies to minimize variability and optimize titration. Again, from the safety and efficacy perspective, such high variability is one of the major concerns.

Effect of Baseline Measurement:

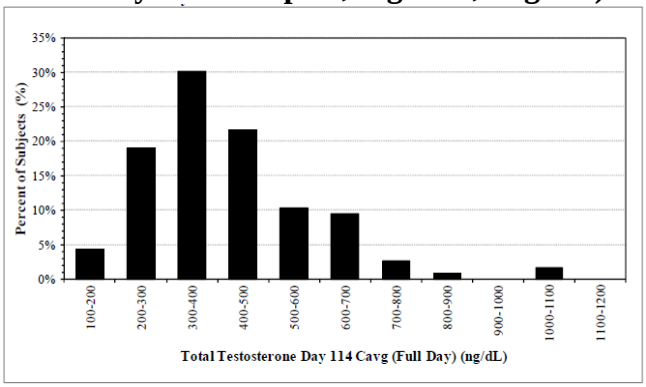
Additional analysis of the data was performed and revealed that patients with high pre-dose (baseline) T levels require a lower dose than those with lower baseline T to achieve a successful Cavg (**Figures 12011-2).** While this is not a surprising observation, some subjects could initially be started with lower doses than 200 mg BID. As shown above, 28 subjects were titrated down to 100 mg BID in this study. Based on this, a lower than 200 mg BID dose may be considered in some subjects, if lower strengths are available (e.g., 75 mg strength or even 25 mg strength to make 125 mg dose).

Figure 12011-2. Distribution of baseline T levels across subjects with different final doses (Source Reviewer's Analysis, Study 12011)



The distribution of 24-hour Cavg values for Day 114 is shown in **Figure 12011-3**. This figure breaks down the percentage of subjects with Cavg values in increments of 100 ng/dL. Collectively and as discussed earlier, 75% of the subjects had Cavg values between 300 ng/dL and 1000 ng/dL. Furthermore, the Day 114 distribution for Cavg was similar in shape to the distributions observed for the Day 30 and Day 72 PK visits. The 12-hour Cavg values following the AM dose and the PM dose on Day 114 also had similar distributions.

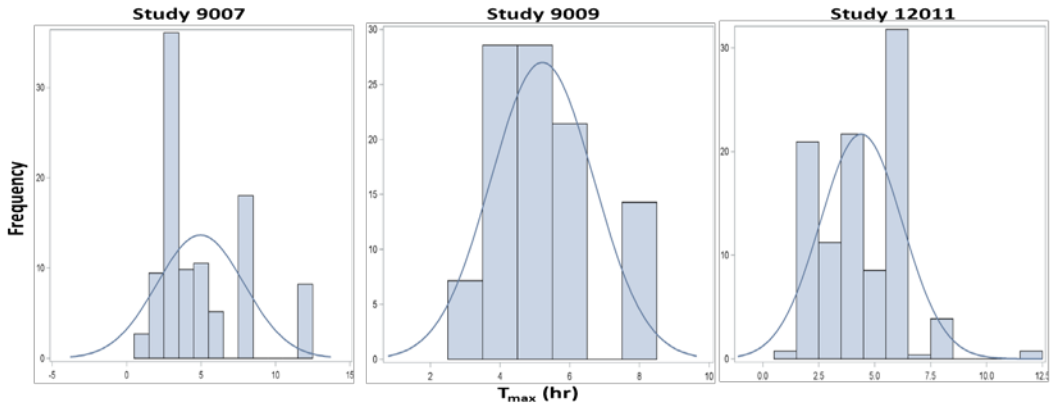
Figure 12011-3. Frequency Distribution of Total T Cavg (Full Day) Following Oral TU Doses on Day 114 (Source: Study 12011 Report, Figure 2, Page 34)



Further distribution analysis was performed by the pharmacometric team using the Tmax data from three studies (**Figure 12011-4**). This analysis confirmed that the sampling time of 3-5 h window provides the maximum probability of capturing the Cmax.

It should be noted, however, that the PK sampling time for Study 09007 was 1.5, 3, 4, 8, 12 hr post AM dose, for Study 09009 was 1.5, 3, 4, **5, 6**, 8, 12 hr post AM dose and for Study 12011 was 1, **2**, 4, **6**, 8, 12 hr post AM dose (the bolded and underscored samples points are different from the 09007 study(. Thus Study 09007 suffers from lack of sampling at **6 h** and might have more reporting bias towards Tmax of 3-4 hr due to missing possible Tmax at **6 h** in some patients.

Figure 12011-4: Frequency distribution of T_{max} (time for C_{max} of T exposure) after AM dosing across the three studies (Source Reviewer's Analysis, Study 12011, 09007 and 09009)

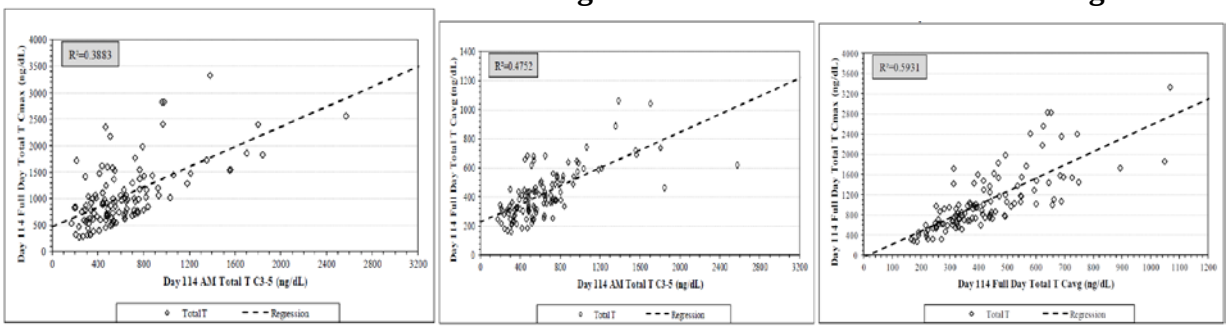


Is there a Relationship Between Cavg/Cmax and C3-5 in Study 12011?

As shown in Study 09007, there was also some relationship between the sampling time points of 3-5 hours and Cmax and Cavg in Study 12011 (**Figure 12011-5**). For all practical purposes, it indicates that using one time point between 3-5 hours post-dose is sufficient to provide adequate guidance for dose titration rather than using the Cmax or the 24 h Cavg.

Figure 12011-5. Relationship Between Cmax (Full Day) and C3-5 (AM) on the Day 114 Visit (Source, Study 12011, Figures 16, 26, 34, Pages 123, 130, 134, respectively).

A: Cmax vs. C3-5 **B: Cavg vs C3-5** **C: Cmax vs Cavg**

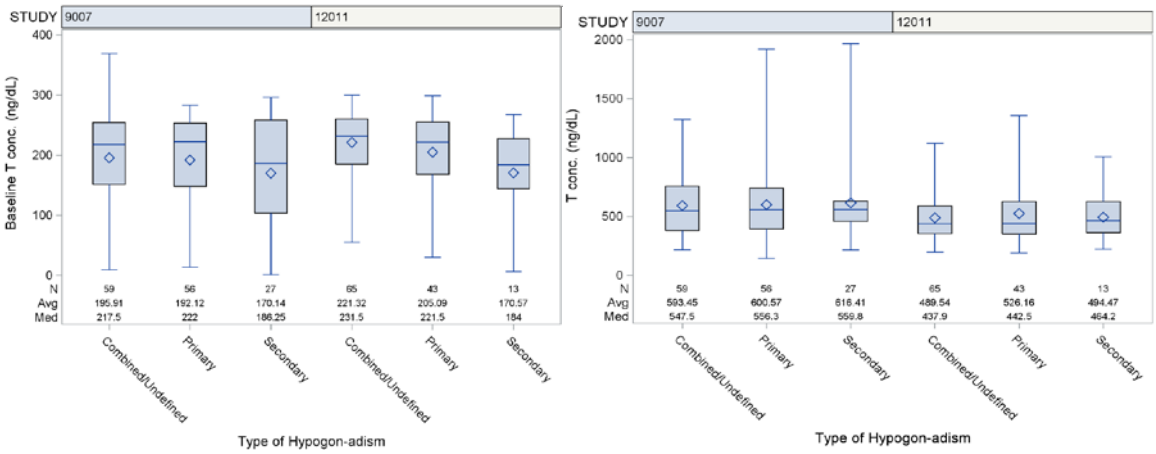


Was there a Difference in Cavg Between Phase III Studies?

Across both the phase III studies 09007 and 12011, the baseline T concentrations were lower in patients with secondary hypogonadism (median of 184-186 ng/dL) as compared to patients identified as either with primary (median of 222 ng/dL) or with combined/undefined hypogonadism (median of 217.5-231.5 ng/dL). But the treatment with 200 mg BID still resulted in similar C_{avg} T concentrations across all these etiologies in each of the Phase III studies (**Figure 12011-6**).

Figure 12011-6: Baseline T concentrations at screening and C_{avg} T concentrations attained at approximately 4 weeks with the same dose of 200 mg BID in patients with different etiologies of hypogonadism in each of the two phase 3 studies (Source Reviewer's Analysis, Study 12011 and 09007)

A: Baseline **B: After Treatment**



In addition, the spaghetti plots shown in the previous Section clearly differentiate the T levels between the two studies. The scale in these plots was at 7000 ng/dL. Overall the T levels from Study 12011 was below 3000 ng/dL compared to Study 09007.

Reviewer's Comments on Study 12011:

In many aspects, the overall observations from this study were similar to that of Study 09007 which include the following:

- There was high inter-subject variability in T-levels with %CV ranging from 40% to 60%. However, mean values for all days fall within the normal T level. The level of variability for this product is very concerning with or without food.
- The mean Cmax ranged from 827 to 1107 ng/dL and occurred approximately 4-4.5 hours post-dose following both the morning and evening doses, however, several patients had Cmax above 2500 ng/dL.
- It should be noted that in this study it was not necessary for any of the subjects to be titrated up to 300 mg BID dose. Thus, the maximum dose was 250 mg which is in contrast to that of Study 09007 in which some subjects were titrated up to the 300 mg dose. Irrespective of the dose, the profiles of serum T were comparable following all four doses of 100, 150, 200, and 250 mg on Day 114. However, these data should be interpreted carefully due to the small number of subjects who failed to achieve the goal T Cavg in each titration arm.
- Similar to Study 09007 (which used C4-6 hours), there was a good relationship between Cavg, Cmax, and C3-5 hours in all titration process (i.e., Cavg vs C3-5, Cmax vs C3-5, and Cavg vs Cmax).
- Also as shown in Study 09007, only the baseline body weight or BMI amongst all demographic characteristics had significant impact on T PK profiles. However, the titration design will accommodate for these differences in the final stable dose.

Overall Conclusions on Titration Process From Studies 09007 and 12011:

- The primary objective of both studies was to demonstrate the feasibility of achieving effective levels using various dosing titrations of TU following oral administration as a replacement therapy for T in hypogonadal men. The primary efficacy parameter was the 24 h Cavg to fall within the predefined target concentration range of 300-1000 ng/dL. Since this target is not expected to be achieved in all subjects, the success rate was set for at least 75% of subjects to fall within this range with the lower bound of the 95% CI to be $\geq$ 65%. These criteria were met in both studies, with point estimates of 83.6% and 75% with a lower bound of 76.5% and 66.1% for Study 09007 and 12011, respectively.

- Study 12011 marginally (75%) passed the criteria based on the overall data. However, based on the statistical review conducted by the Office of Biometrics, this study failed the primary efficacy criteria due to the missing data and inappropriate sensitivity analysis (see biostatics review dated October 2, 2014).

- In Study 09007 there were two arms, an oral TU arm and an AndroGel® arm. Overall, as expected, oral TU achieved higher T Cavg than AndroGel®, with more oral TU patients having unacceptably high T Cmax. The variability in AndroGel® was lower than that of oral TU.

- Overall, the titration process based on sampling between 3-5 hr post-dose was reasonable. However, the observed Cavg and Cmax values for T during the 24-hour period were high in some subjects in both studies, but being higher in Study 09007 than 12011 (**Tables Conclusion-1 and 2**). By Day 365, 2 patients out of 129 patients (3.9%) had a Cmax >2500 ng/dL as did 4 patients out of 118 patients (3.4%) on Day 114 in Study 12011. In contrast, in Study 09007, 20 (13.7%) oral TU patients had Cmax >2500 ng/dL at the primary efficacy timepoint compared to 0% (0/131) in the AndroGel® arm.

- The single sample time point collected at 3-5 h in Study 12011 post morning dose was adequate as a titration guide. The values at both time points were used for dose titration decisions and correlated with Cavg and Cmax.

- None of the subjects in Study 12011 were needed to be titrated up to the 300 mg dose. However, considering the small number of subjects and the expected variability in the data, the maximum dose should still be set to 300 mg BID, rather than 250 mg BID as observed in Study 12011.

- Both studies employed different titration designs. In Study 12011, the dose could be up or down-titrated by 50 mg BID as opposed to 100 mg BID in Study 09007. The titration design with small unit increments of 50 mg BID as well as inter-study variability led to fewer patients with Cmax>1500 or Cmax>2500 ng/dL in study 12011 compared to Study 09007 (**Tables Conclusion -1 and 2**).

  It should be noted that the inter-study variability was high: Study 09007 had more outliers of high Cmax as compared to study 12011 for the same dose of 200 mg BID. Also overall Cavg was higher for same dose of 200 mg BID at 4 weeks in study 09007 compared to study 12011. These study specific differences were not able to be reconciled by any potential imbalance of baseline demographic covariates.

- As shown earlier, the availability of dose titration by smaller increments/decrements (50 mg BID) is preferable to large units (100 mg BID) in order to satisfy the C_{max} thresholds, which is the safety concern. In addition, the availability of only two strengths of 100 mg and 150 mg capsules limits the flexibility of dose changes to only 50 mg increments or decrements (i.e., a combination of either dosage strengths). Therefore, the availability of lower strengths may be useful for providing more fine-tuned options for titration.

Table Conclusion-1: Summary of Number of and Percentage of Subjects Below, Within, and Above Cavg the Eugonadal Range for T in Each PK Observation Period in Studies 09007 and 12011

Parameters (ng/dL)	Study 09007				Study 12011		
Cavg	D 30 AM	D 90 AM	D 90 Full Day	D 365 AM	D 30 (AM)	D 114 AM	D 114 Full Day
<300 Oral TU	9.7% (15/155)	14.3% (21/149)	6.8% (10/146)	11.8% (15/127)	9.8% (13/133)	35.3% (41/116)	23.3% (27/116)
<300 T-gel	41.0% (64/156)	20.7% (31/151)	18.8% (28/151)	24.4% (32/134)	-	-	-
>1000	8.4% (13/155)	9.6% (12/149%)	9.6% (14/146)	3.1% (4/127)	4.5% (6/133)	1.7% (2/116)	1.7% (2/116)
>1000 T-gel	0.0% (0/156)	4.7% (7/150)	2.0% (3/149)	0.0% (0/131)	-	-	-
300-1000	81.9% (127/155)	77.6% (114/147)	83.6% (122/146)	85.0% (108/127)	85.7% (114/133)	62.9% (73/116)	75% (87/116)
300-1000 T-gel	59.0% (92/156)	74.7% (112/150)	79.2% (118/149)	75.6% (99/131)	-	-	-

Table Conclusion-2: Summary of Number of and Percentage of Subjects With Cmax Within Selcted Concentration Range in Each PK Clinic Visit in Studies 09007 and 12011

Parameters (ng/dL)	Study 09007				Study 12011		
Cmax	D 30 AM	D 90 AM	D 90 Full Day	D 365 AM	D 30 (AM)	D 114 AM	D 114 Full Day
0-1500	70.9% (112/158)	73.8% (110/149)	57.7% (86/149)	81.4% (105/129)	81.2% (108/133)	89.7% (104/116)	80.5% (95/118)
0-1500 T-gel	100% (156/156)	94.7% (142/150)	92.6% (138/149)	100% (131/131)	-	-	-
1500-1800	12.0% (19/158)	12.8% (19/149)	14.1% (21/149)	5.4% (7/129)	9% (12/133)	5.2% (6/116)	8.6% (10/116)
1500-1800 T-gel	0.0% (0/156)	2.0% (3/150)	2.7% (4/149)	0.0% (0/131)	-	-	-
1800-2500	8.2 % (13/158)	6.7% (10/149)	12.8% (19/149)	7.8% (10/129)	7.5% (10/133)	3.4% (4/116)	6% (7/116)
1800-2500 T-gel	0.0% (0/156)	3.3% (5/150)	4.0% (6/149)	0.0% (0/131)	-	-	-
>2500	7% (11/158)	5.4% (8/149)	13.4% (20/149)	3.9% (2/129)	2.3% (3/133)	1.7% (2/118)	3.4% (4/116)
>2500 T-gel	0.0% (0/156)	0.0% (0/150)	0.7% (1/149)	0.0% (0/131)	-	-	-

Source: Studies reports 09007 (Tables 6 and 17) and 12011 (Tables 6 and 18)

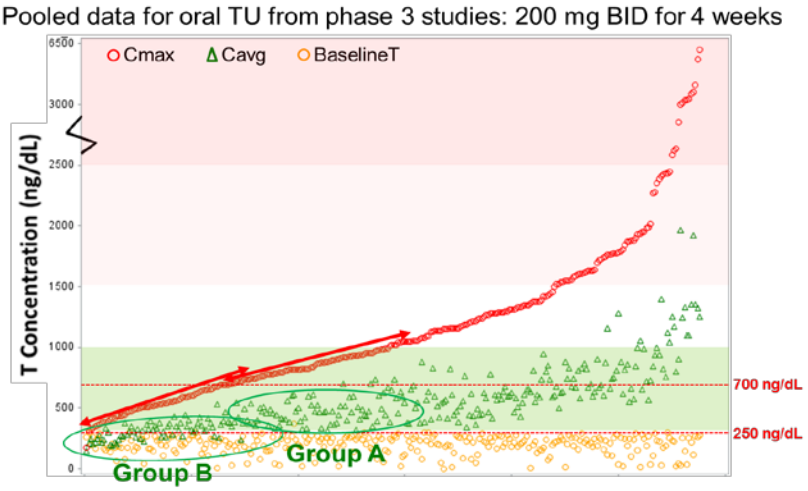
Summary of Pharmacometric Analysis:

The analysis of T levels achieved with a starting dose of 200 mg BID suggests there could be consideration for altering the proposed titration thresholds. Specifically, consideration can be given to raising the down-titration threshold to levels higher than 700 ng/dL and raising the up-titration threshold to levels higher than 250 ng/dL in order to increase the percentage of patients who would have T levels in the normal range of 300-1000 ng/dL.

Subjects listed as Group A in the figure below (**Figure Conclusion-1**) had C_{avg} values within the normal T level range, while a C_{max} between 700-1000 ng/dL. The proposed titration algorithm would result in a decreased dose in such subjects and may lead to Cavg that subsequently falls below the normal T range.

Also the threshold of 250 ng/dL selected for up-titration results in a subset of subjects (Group B in the figure) with C_{avg} near or below 300 ng/dL. Based on the proposed titration algorithm, these subjects would not have up-titration of their dose and may remain below the targeted range.

Figure Conclusions-1: Pooled baseline, Cavg, and Cmax observations at ~4 weeks (day 30) from both Phase 3 studies for 200 mg oral TU. Titration thresholds utilized in 12011 are listed as horizontal lines (250 and 700 ng/dL for up- and down-titration, respectively (Source Reviewer's Analysis, Study 12011 and 09007)



What are the PK Profiles of T and TU Metabolites?

In Phase II and Phase III studies the PK profiles of T and TU and their metabolites were evaluated. However, the focus is on the data from Phase III studies and when appropriate the data from other studies will be included in this section or referenced in other sections. The primary focus in this section is on T metabolites and the level of the parent drug (pro-drug), TU. In some instances, the data from the literature will be utilized to support the interpretation of the data from this NDA.

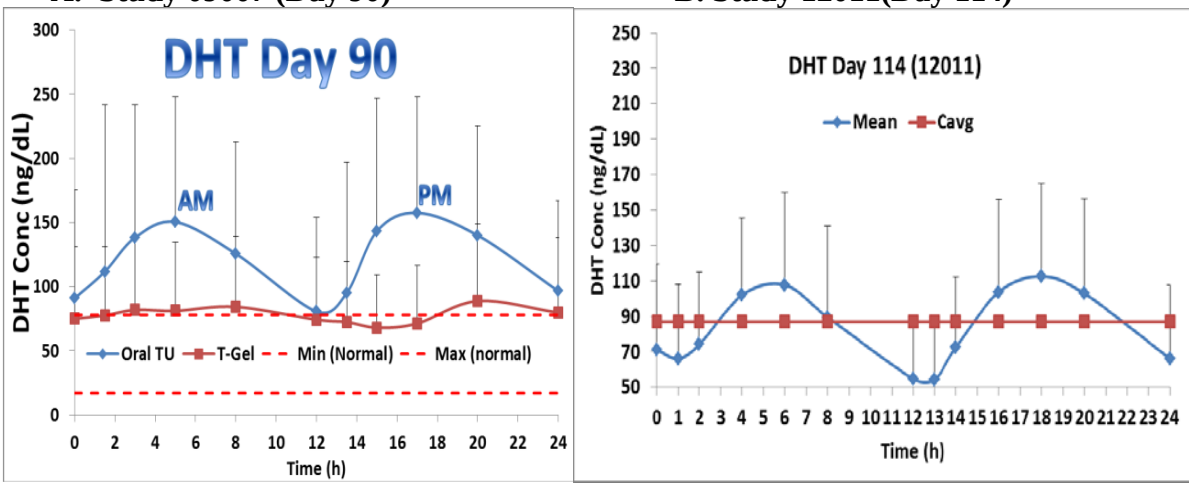
What is the Serum DHT Concentration-Time Profiles Following Oral TU?
What is the Difference in DHT Levels Between Oral TU and AndroGel®?

Per the Mayo Clinic database, the normal range for DHT in males >18 years of age is 112-955 pg/mL (http://www.mayomedicallaboratories.com/test-catalog/print/81479, accessed August 12, 2014). These values are equivalent to 11.2 ng/dL to 95.5 ng/dL. Another laboratory reports a normal range for adults of 30 ng/dL to 85 ng/dL (http://www.childrensmn.org/manuals/lab/chemistry/030858.pdf, accessed August 12, 2014).

As shown for T, the mean concentration-time profiles for serum DHT after oral TU was highly variable. But, overall it appears that the variability in DHT levels is comparable among all studies and in particular in Phase III studies (**Figures DHT-1).** Consistent with the observation for T levels, the DHT level in Study 09007 was also constantly higher than that in Study 12011. The DHT Cavg was 155 ng/dL on Day 90 in Study 09007 and was 87 ng/dL on Day 114 in Study 12011 (**Figure DHT-1**). The reported values after oral TU and specifically in Study 09007 was somewhat higher than the normal range values of DHT as reported in the literature (see above).

Figure DHT-1. Mean (±SD) Concentration-Time Profile for Serum DHT (source Study 09007 Table 31, Page 105 and Study 12011, Table 28, page 95)

A. Study 09007 (Day 90) **B. Study 12011(Day 114)**



Key: Dotted lines represent the normal range of 20 to 80 ng/dL from the literature.

As expected of DHT being a metabolite of T, its Tmax was delayed and the Cmax was broader and flatter than observed for T. In addition, DHT profiles were similar in shape/pattern to that of T profiles in which it was increased during the first 3-6 hours post-dose and then declined over the remainder of the 12-hour dosing interval. However, in Study 09007, a more consistent and less variable DHT profile was observed after AndroGel® as compared to after oral TU (**Figure DHT-1 and Table DHT-1).**

Table DHT-1. Mean DHT PK Parameters in Studies 09007 and 12011 (source PK Report, Section 16.5, Tables 10 and 11 for Study 12011 and 09007, respectively).

	Study 09007				Study 12011	
	Oral TU		AndroGel®		Oral TU (Full Day)	
Parameter	**Day 30 (Full Day)**	**Day 365 (AM)**	**Day 30 (Full Day)**	**Day 365 (AM)**	**Day 30 (AM)**	**Day 114 (Full Day)**
Cavg (ng/dL)	124	118	61	69	137	87
Cmax (ng/dL)	196	187	82	92	209	147
AUC (ng.h/dL)	1484	1412	738	830	1641	2085
DHT/T AUC Ratios	0.2117	0.2403	0.1598	0.1714	0.2916	0.2201

DHT concentrations are primarily determined by T systemic exposure. The mean DHT/T ratios appear to be lower with AndroGel® as compared to oral TU (**Table DHT-1**). The mean ratio ranged from approximately 0.21 to 0.29 in both studies. Similar patterns of DHT/T ratios were also observed in other studies (for further details on DHT/T and DHTU/TU ratios see **Section 2.2.3)**.

In summary, DHT levels after oral TU appears to be higher than AndroGel® and also is higher than the normal DHT levels in adult men. This increase in DHT serum levels and DHT/T ratio is additional concern associated with the safety this product.

What are the Levels of the Parent Drug (prodrug), TU, after Oral Administration?
Is all TU Converted to T Following Oral Administration?
What is the Clinical Significance of High Levels of TU?

The level of TU and its metabolites, dihydro-TU (DHTU), were measured in two studies: the effect of food study (Study 09008) and the first Phase III study (09007).

The above questions are relevant from both the safety and efficacy perspective of the product. As indicated throughout this review, the premise of the development program of this product is that TU would be absorbed via the lymphatic system. TU is partially hydrolyzed during the transport process by esterases as well as systemically following absorption to release T. Therefore, not only the T level is essential for the desired pharmacological effect, but the level of TU is also a critical component to ensure the availability to release of adequate levels of T. Its abundant availability in the lymphatic system and systemic circulation is questionable at this time from the safety perspective after chronic administration. In addition, it is unknown at this time if TU has any local effect at the site of absorption following chronic administration.

The TU serum concentrations were substantially higher than total T (**Table TU-1 and Figures TU-1 to 2).** As shown in these figures, the T levels followed the same pattern of TU in Study

09007 but at markedly different y-scales (**Figures TU-1).** The same trend was also observed following meals with different percentages of fat in Study 09008 (**Figures TU-2**).

Table TU-1. Summary of Primary PK Parameters for Serum TU Following the Day 90 AM Oral TU Dose (source Study 09007, Tables 45 and 46, Pages 125 and 126)

	All Subjects (n=26) on Day 90		
PK Parameters	**Mean**	**SD**	**CV (%)**
Cmax (ng/dL)	33348	19402	57.2
Cavg (ng/dL)	8752	5503	62.9
AUCt (ng.h/dL)	105030	66046	62.9
Tmax (h)	2.56	2.10	82.3
CL/F (L/h)	246.5	180	52

Figure TU-1. Mean (±SD) Concentration-Time Profile of TU Following 200 mg Oral TU in Subjects on the Day 90 Clinic Visit (Note differences in Y-scales) (Source: Appendices A5 and A 33, Pages 179 and 204 of 950, Study 09007)

A: Data on the Same Scale **B: Data on Two Different Scales**

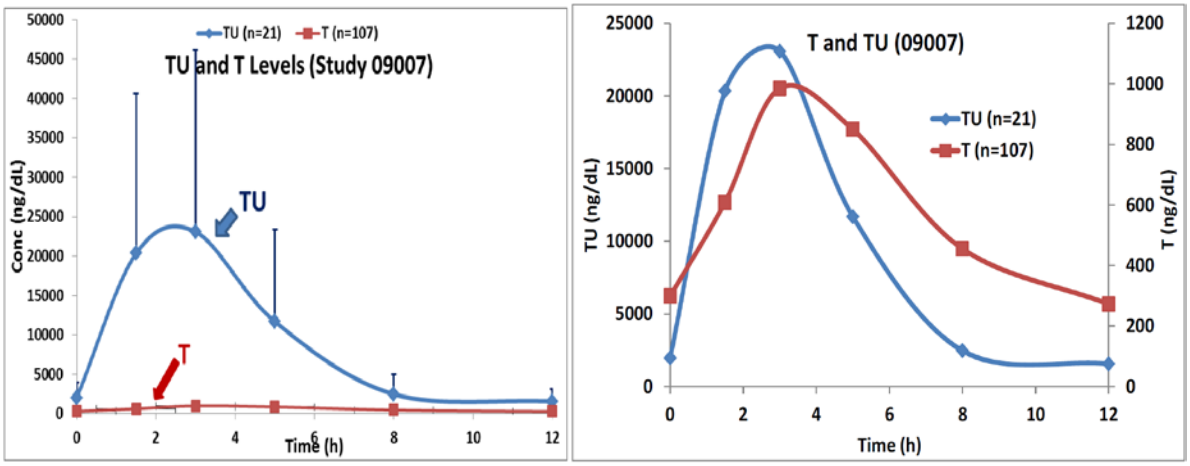
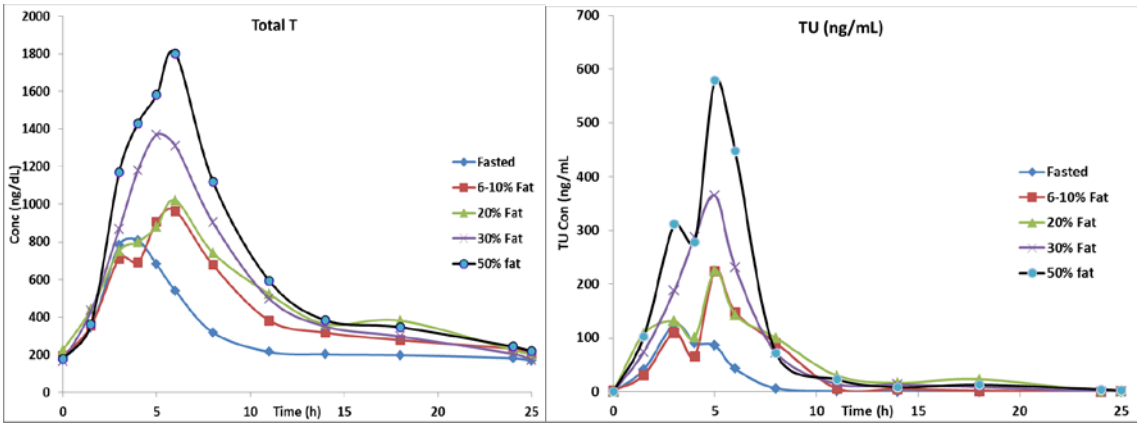


Figure TU-2. Mean of Serum T and TU Profiles Following 300 mg Oral TU Doses Following Overnight Fast or Meals with Different Percentage of Fat Content (source Study 09008 Tables 14.3-7 and 14.61-14.65)

A: T Profiles **B: TU Profiles**



As shown in **Table TU-1**, the mean Cmax and Cavg of TU were 33348 ng/dL and 8752 ng/dL, respectively**.** For comparison, the mean Cmax and Cavg of total T after all oral TU doses on Day 90 were 1676 ng/dL and 628.3 ng/dL, respectively (see earlier **Table 09007-2**). Based on this, the TU levels would be roughly 20-fold higher than T levels (see also **Figures TU-1 and 2**).

Reviewer's Comments on TU Levels:

The androgenic and/or other activities at such high systemic levels of TU after long term therapy is concerning. While, there was no evidence of TU accumulation in the plasma, but being a highly lipophilic ester compound its accumulation in fatty tissues is unknown at this time.

As discussed earlier in the metabolism **Section 2.2.1**, the binding affinity of TU to the receptor is extremely low compared to that of T (**Figure 2.2.1-1**). Furthermore, the sponsor conducted a toxicity study in dogs using the final oral TU formulation at doses up to 252 mg/kg/day (126 mg/kg BID) for 13 weeks (**Table TU-1**). Following these doses, the T and TU levels reached approximately 30,000 ng/dL and 7000 ng/mL (700,000 ng/dL) throughout the study, respectively (**Figure TU-3A&B and Table TU-2**). The profiles of T and TU are similar to that shown in humans in which T follows the same pattern of TU (**Figure TU-5 B**). Also, the level of TU obtained in dogs was approximately 17 times the peak of TU concentrations commonly observed in subjects during therapy. According to the sponsor, there was no evidence of toxicity in treated dogs (for details see PharmTox review).

Table TU-1. Dosage and Administration in Dogs (Source Study CLAR-PC-11001)

Maximum Human TU Dose (13.6 mg/kg/day)	Total Daily TU Dose (mg/kg)	Species Adjusted Dose (mg/kg)	Total Daily Dosing Volume (ml/kg/day)	Dosing Volume/BID Administration (ml/kg/dose)
3 x Human Dose	41	75.56	0.402	0.20
10 X Human Dose	136	251.85	1.34	0.67

Figure TU-3. Mean T and TU Serum Levels in Dogs on 252 mg/Kg Daily Dose (126 mg/kg BID) For 90 days (Source: Study CLAR-PC-11001, Table 3)

A: One Scale **B: Two Different Y-Scales**

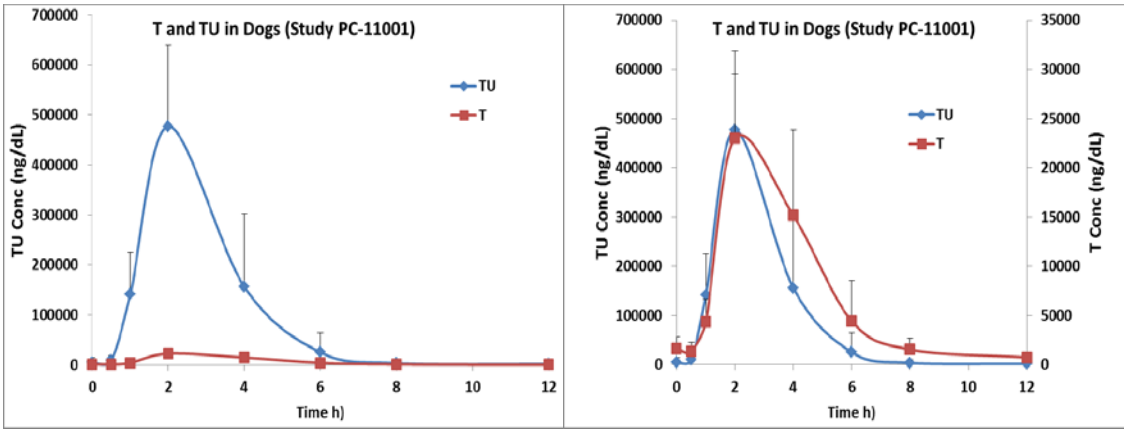


Figure TU-2. Mean PK Data After low (75.56 mg/kg) and High (251.85 mg/kg) Doses in Dogs (Study CLAR-PC-11001)

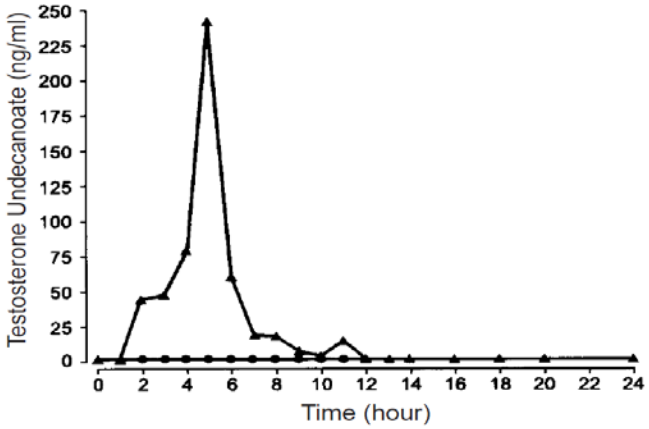
Entity	Low Dose (75.56 mg/kg)		High Dose (251.85 mg/kg)	
	Day1	Day 90	Day 1	Day 90
TU (ng/dL)	290,000	213,500	677,600	503,100
DHTU (ng/dL)	6200	3600	11,100	16,600
T (ng/dL)	11,763	13,696	34,786	26,257
DHT (ng/dL)	653	639	1435	1,084

What is the Magnitude of TU Levels in Marketed Products?

The same pattern of high TU levels was observed following marketed oral TU product Andriol® Testocaps® outside the US including Canada and Europe (reference Canadian Andriol® Monograph, 2011, control # 149280). In one published study, the TU concentration was substantially higher than that of T following an oral 80 mg single dose of Andriol® Testocaps® in 16 healthy subjects following an overnight fast and after meals (**Figure TU-4**, Bagchus et al, Pharmacotherapy, 23 (3): 319-325, 2003**)**. The mean Cmax of TU was 83 ng/dL after overnight fast and 29100 ng/dL after breakfast. The same trend was observed for T concentration in which the T Cmax was 66 ng/dL after fasting and 1070 ng/dL after breakfast (see Biopharmaceutics Section 2.5 for additional discussion on effect of food).

However, the dose and level of exposure are not the same as the current product. In addition, the formulation technologies are not the same either. Therefore, direct head-to-head comparison between two products cannot be justified.

Figure TU-4. Mean Plasma Concentration-Time Profiles of TU of Single Oral 80 mg Andriol® Testocaps® Administered After an Overnight Fast (close circles) and After Breakfast (closed triangles) in 16 Healthy Men (Source Bagchus et al, Pharmacotherapy, 23 (3): 319-325, 2003). Note the scale is in ng/mL (multiply by 100 to convert to ng/dL).

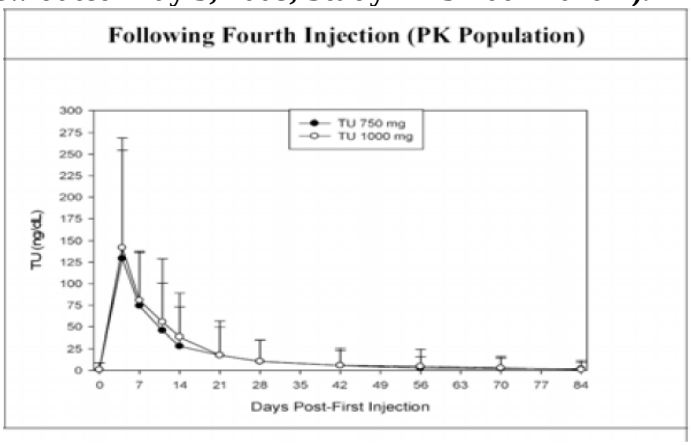


By Contrast, when TU was administered IM as in the case of the recently approved product, Aveed®, the Cmax of TU was substantially lower than after oral TU. The Cmax was approximately 140 ng/dL which occurred at approximately 4 days after 750 mg and 1000 mg IM injections of TU in hypogonadal men (**Figure TU-5**, NDA 22219 Approved March 5, 2014, see Clinical Pharmacology review dated May 5, 2008). Per the clinical pharmacology review for the

IM product, most of the blood samples were below the detection level of the assay for TU concentrations. This product was approved for IM injection every 10 weeks after the 4th week of the first injection.

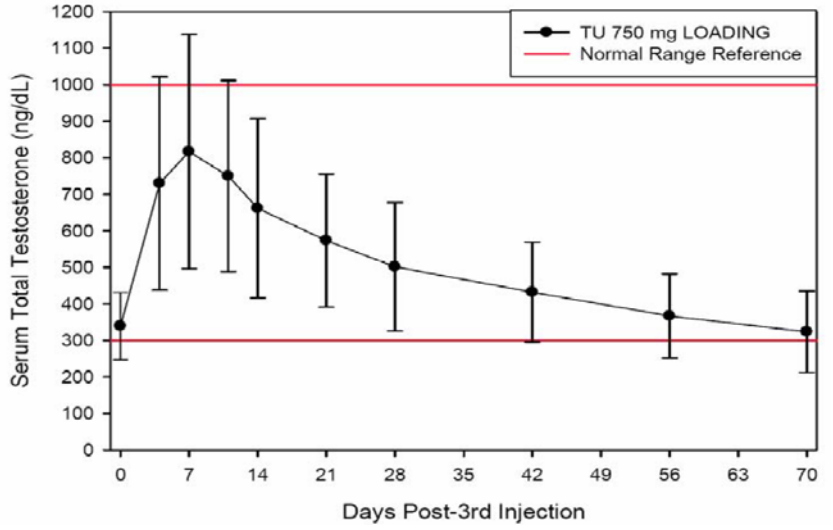
The marked difference in TU levels between the IM injection and oral administration indicates that TU is slowly released from the muscle compared to oral administration. The Cmax of TU after oral administration occurs at approximately 5 hours and the level reaches approximately undetectable levels by 12 hours.

Figure TU-5. Mean Plasma Concentration-Time Profiles of TU Following the Fourth Injection of 750 mg and 1000 mg of TU (Aveed) in Hypogonadal Men (Source Clinical Pharmacology Review dated May 5, 2008, Study IP157-001 Part A).



The most interesting observation from the above Figure is that after IM administration the TU level is extremely low after 24 days, yet it provides adequate T Cavg for 84 days before the next IM dose (**Figure TU-6**).

Figure TU-6. Mean (±SD) serum total T concentrations following the 3rd injection interval of Aveed 750 mg LOADING regimen, from Study IP157-001 Part C (Source: Clinical Pharmacology review dated May 5, 2008 for NDA 022219; the same Figure is also in the approved AVEED label dated March 5, 2014).



Conclusions in Reference to High TU Serum Levels:

Following oral administration of TU (Rextero™) the ratio of TU to T was >20 for Cmax. While TU does not appear to accumulation in the body based on the plasma concentration, the drug is known to be highly lipophilic that may accumulate in fatty tissues. At such high exposure of magnitude, the risk/benefit of the use of oral TU should be carefully evaluated based on the clinical endpoints in this NDA and other currently marketed oral TU outside the US and non-oral TU products.

Irrespective of the low affinity to the receptor, given the high levels relative to T, the potential long term safety of these high levels and any effect they may have at the receptor level is unknown (see the clinical review). In addition, post-marketing information of the currently marketed oral TU product outside the US (e.g., Andriol®) should be considered in the overall evaluation of the safety and efficacy data. However, the ability to rely on non-U.S. marketed TU products has many limitations including the fact that these products are given at lower doses than those proposed for Rextero™ and may result in lower systemic exposures to TU.

What is the Level of DHTU after Oral TU?

As discussed and shown in the earlier sections of this review, TU is converted to DHTU after absorption by 5-α-reductase enzyme (the same enzyme converting T to DHT). The DHTU that is formed can be de-esterified to DHT by nonspecific plasma and tissue esterases. Similar to TU, the levels of DHTU were also about 20-fold higher than T (**Figure DHTU-1 and Table DHTU-1**). The serum profiles of DHTU followed the same patterns of that of T and TU (note the figure is plotted with two y-scales for clarity).

Figure DHTU-1. Mean Concentration-Time Profile for T, TU, and DHTU in Subjects on the Day 90 Clinic Visit (source Study 09007, Tables 18, 21, and 47) (note the two y-scales)

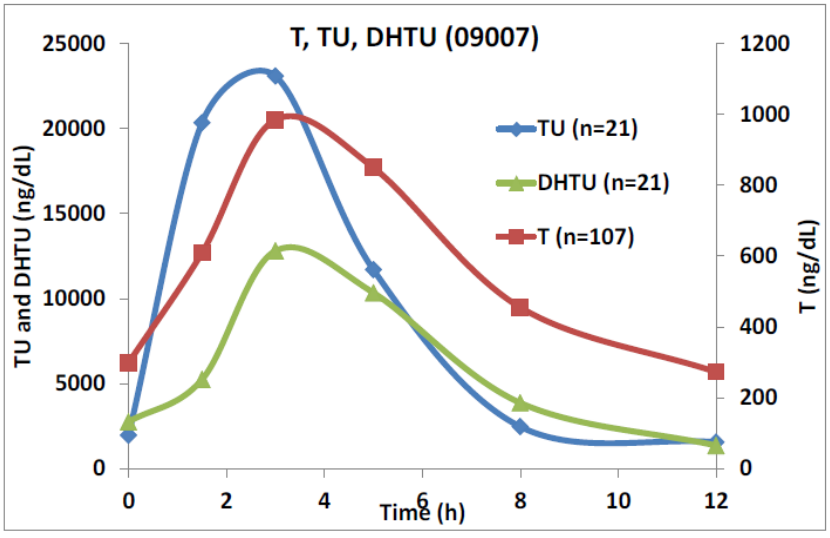


Table DHTU-1. Summary of Primary PK Parameters for Serum DHTU Following the Day 90 AM Oral TU Dose (Source Study 09007, Table 48)

	All Subjects (n=26) on Day 90		
PK Parameters	**Mean**	**SD**	**CV (%)**
Cmax (ng/dL)	14570	9601	65.9
Cavg (ng/dL)	5810	3500	60.3
AUCt (ng.h/dL)	69720	42010	60.3
Tmax (h)	3.52	2.23	63.4
DHTU/TU	0.7224	0.35457	49.1

As discussed previously and as shown in **Table DHTU-2**, the affinity of DHTU to the androgen receptor was even 2 fold lower than that of the TU compared to T (**refer to Section 2.2.1)**

Table DHTU-2. Binding to Androgenic Receptor (Source: *in vitro* Polar Screen Study # 013325-02)

Parameters	T	DHT	TU	DHTU
EC50 (nM)	7.04	8.51	573	1005
Relative Binding Affinity (%)	100	83	1.23	0.7

This is expected because DHTU is a bigger molecule than TU. As shown in the above table, the EC_{50} of TU and DHTU is approximately 80 and 140 fold lower than that for T, respectively. In addition, based on the same dog study described earlier, serum DHTU concentrations were approximately 166 ng/mL (i.e., 16,600 ng/dL). Similar patterns of ratios for all components DHT, T, and DHTU were also observed in other studies.

Conclusions for DHTU Data:

Similar to TU, the levels of DHTU are high. There is no evidence of accumulation of DHTU based on plasma levels, yet it may accumulate in fatty tissues. Finally, it should be reiterated that the source of DHT is from TU, T, and DHTU. While the binding affinity of TU and DHTU to the androgenic receptor is low, we need to consider the high systemic exposure of these hormones because the combination of TU, T, DHT, DHTU, and other derived metabolites, are responsible for the efficacy, pharmacodynamics activities, and the safety of oral TU product. The overall safety assessment of the product is referred to the clinical team.

Overall Reviewer's Comments on Phase III Studies for T, TU, and Metabolites:

- The success rate was achieved in both Phase III studies (i.e., ≥75%). The lower limit of the 95% CI was ≥65%. Yet the Pivotal Study 12011 was marginally passed, if not failed due to missing data and the sensitivity analysis per the biostatistics review dated October 2, 2014). The 24-hour T Cavg was within the goal range of 300-1000 ng/dL.
- There were Cmax outliers in both studies.
- The majority of the study population responded well to the initial 200 mg oral TU BID dose. Therefore, the titration was not necessarily in some patients and they continued with the initial 200 mg dose until the end of the study.

- There was some relationship between Cmax and Cavg for total T.
- The most critical observation from Phase III studies was that a single serum T sample collected 3-5 hours post AM dose appears to be adequate and practical for the routine titration process. The initiation of titration as early as Day-7 after the start of therapy is adequate. However, patients should continue to be monitored for optimal therapy.
- The PK profile of T was overall independent of demographic characteristics.
- The PM dose appears to show higher T than the AM dose and is most likely due to the high fat content, diversity, and volume in dinner compared to breakfast.
- DHT concentrations were slightly delayed relative to T concentrations. This is expected as a metabolite of T.
- TU and DHTU levels were almost 20 fold higher than T. The receptor affinity for both is extremely low compared to T. Yet considering the extremely high exposure of TU and DHTU and their inter-conversion to T and DHT, the long term safety cannot be disregarded.
- While there was a high variability in the data, there appears to be a relationship between Cmax and Cavg. In the same token, while the data shows that TU must be taken with food, one of the major concerns is the expected variability and unpredictability in T levels due to unrestricted food intake (see Biopharmaceutics Section 2.5). The high TU and DHTU levels after oral administration were expected, but there is no evidence of accumulation.
- The safety related objective of avoiding a significant number of Cmax concentrations in excess of 1500 ng/mL was clearly **not** met in Study 09007, but may be reasonably close to the targets for Study 12011.

Overall Conclusions:

Overall, the following conclusions can be made:

- The primary efficacy objectives were met in Study 09007 but marginally in Study 12011. There was an unacceptable increase in Cmax in a sizeable group of patients both studies and in particular in Study 09007.
- The single time point at 3-5 hours appears to be adequate for titration.
- The variability in all data was higher after oral TU compared to AndroGel®. This is one of the major concerns.
- Patients may benefit from an earlier titration on Day 7 as well as on Day 30 and thereafter.
- The high exposure to TU, DHTU, and DHT is very concerning from the long term safety perspective for this product.

2.2.3 What are the PK characteristics of the drug and its metabolites after multiple dosing?

In addition to the above studies and discussion of the PK characteristics of the parent drug TU and its components, T, DHT, estradiol (E_2), and DHTU, the sponsor conducted two multiple dose PK studies to specifically address the PK characteristics following multiple dosing of oral TU (Study 08005) and to determine the time to reach steady-state concentration (Study 09009). The focus of this Section of the review is on the relationship between T, TU, DHT, and DHTU.

The other known active metabolite of T, is estradiol (E_2) that will be discussed later. But, it should be noted that the data from all studies are consistent in reference to E_2 levels (see later discussion).

Study 08005 was a 7-day BID, crossover study in 29 hypogonadal men. One arm of the study was designed specifically to exam the effect of food. The total daily doses in this study were 400 mg and 600 mg as TU alone and 600 mg and 800 mg as a combination of TU and another ester Testosterone Enanthate (TE) as follows:

Period 1: Days 1-7 (TU alone):	300 mg BID = 600 mg daily x 7 days
Period 2: Days 22-28 (TU + TE):	400 mg BID = 800 mg daily x 7 days
Period 3: Days 43-50 (TU alone):	200 mg BID = 400 mg daily x 7 days
Period 4: Days 64-70 (TU + TE):	300 mg BID =600 mg daily x 7 days

Study 09009 was a PK steady-state study that used 200 mg BID for 28 days in 15 hypogonadal men. The trough levels of T, DHT, and E_2 were monitored periodically prior to the AM doses and during a full PK profile on Day 28. Each subject received a total of 31 doses of 400 mg T as TU (i.e., 200 mg T, BID), and a final morning dose of 200 mg T as TU. Serial blood samples were collected from each subject on Day 28/Day 32.

In both studies each dose was administered within 30 minutes after initiation of meals (breakfast and evening meals), except on Day 8 of Period 3 (Study Day 50) in Study 08005, the morning dose was administered following an overnight fast of at least 10 hours, and was followed by an additional 4 hours of fasting.

Overall, the data from both studies are somewhat comparable to that discussed above. For example, the T and DHT profiles from Study 08005 followed the same pattern (**Figure 2.2.3-1**). As expected, DHT and E_2 concentrations were considerably lower than the analogous T values for the trough concentration throughout the study and on Day 28 (**Figure 2.2.3-2 A-D**). As shown, the steady state concentration was achieved within 7 days for all three hormones (T, DHT, and E2).

Figure 2.23-1. Mean T and DHT Concentration-Time Profiles in all Periods on one Scale (source Study 08005 Tables 14.4 and 14.6)

A: T Profiles **B: DHT Profiles**

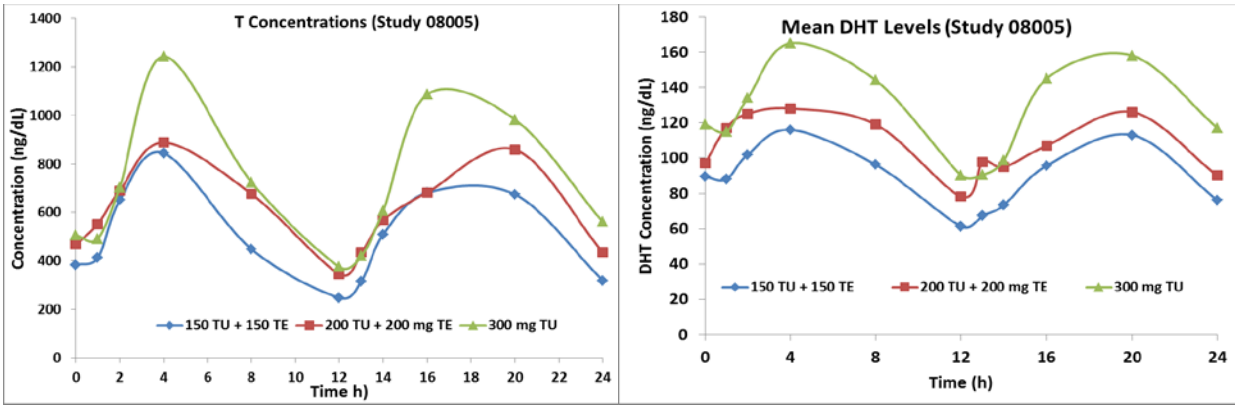


Figure 2.2.3-2 A to D. Mean Pre-dose Concentrations (Trough) and Baseline (screening) Concentrations for T, DHT, and E2 During 200 mg BID Dosing with Oral TU for 28 Days (source Study 09009, Tables 11.4.4.1.1.a and 11.4.4.1.3a))

A: Total T **B: DHT** **C: E_2**

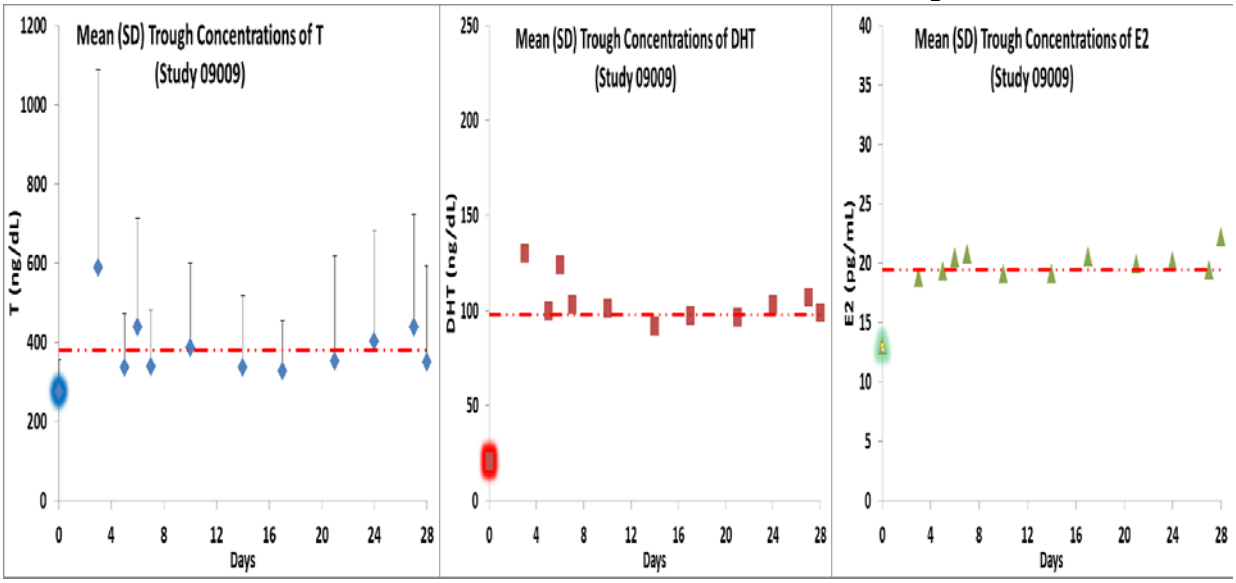
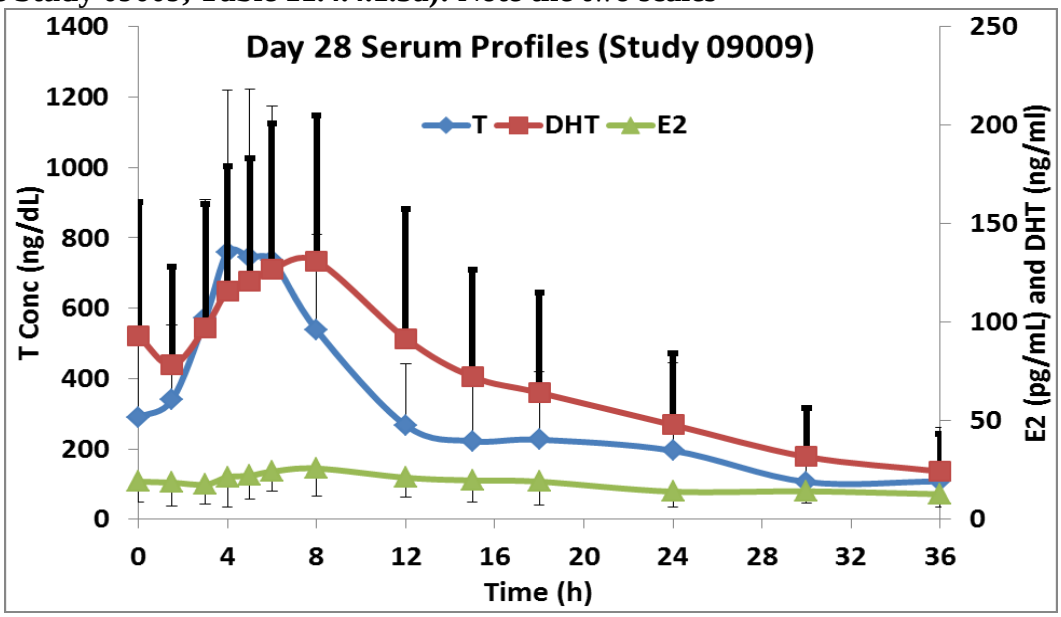


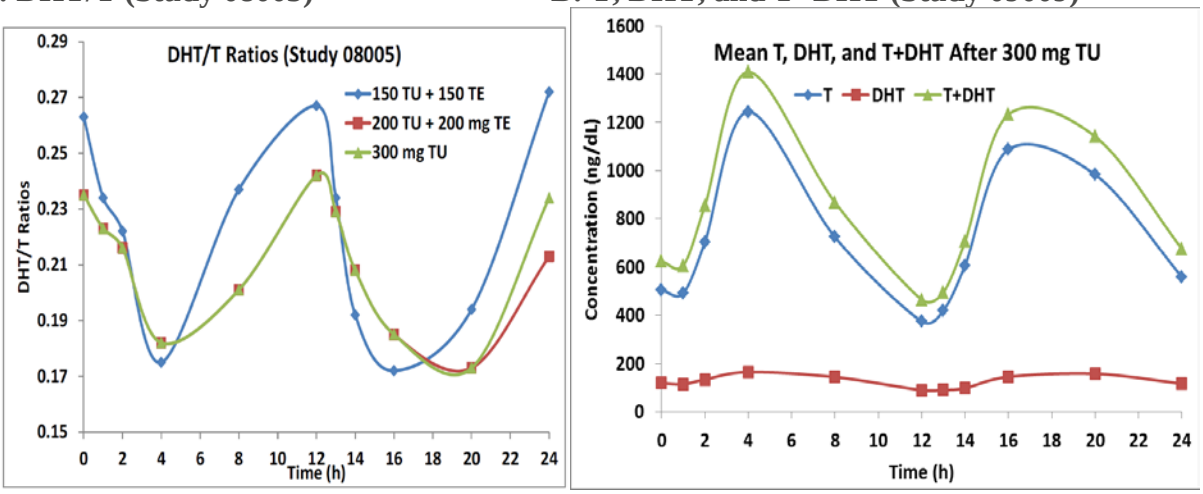
Figure 2.2.3-2 D. Mean (± SD) Concentration-Time profiles of T, DHT, and E2 on Day 28 (source Study 09009, Table 11.4.4.1.3a): Note the two scales



Following all treatments, there was a noticeable increase in DHT/T ratios (**Figure 2.2.3-3**). Due to the lag time involving conversion of T to DHT the observed nonlinear relationship with dose was expected. However, as T concentrations increase, DHT concentrations also increase, but at a lower rate. Therefore, DHT/T ratio was decreased with increasing T concentration.

As discussed earlier, total pharmacological activities of oral TU is expressed as the total exposure of TU, T, DHT, DHTU, and other metabolites. However, since both T and DHT have high affinity to the androgenic receptor, they are primarily responsible to the total androgenic activity. Therefore, the total androgen activity should roughly represent the sum of both T and DHT concentrations (see earlier discussion about receptor binding of both T and DHT). Therefore, the total levels of **T + DHT** is important for the final assessment of the safety and efficacy of the formulation. As expected, there was an increase in total T+DHT levels following all treatments (**Figure 2.2.3-3**).

Figure 2.2.3-3. Mean DHT/T Ratios and Sum of T + DHT
A: DHT/T (Study 08005) **B: T, DHT, and T+DHT (Study 09009)**



Source: Study 09005, Table 14.8 and 14/10) and Study 09009, Table 11.4.4.1.3a

Overall from all the studies in this NDA it was observed that the total androgen concentrations closely track those of T because T is the dominant contributor to the summed concentration.

As discussed previously, in all studies there was a good relationship between the T Cmax and T Cavg following all treatments; irrespective of formulation. These observations are essentially important for the potential titration process in which Cmax or Cavg can be used to optimize the therapeutic dose to achieve the desired T level.

There was consistent effect of food among all studies in terms of variability and increase in absorption. The marked increase in TU levels when administered with food was associated with the same patterns of all other androgens. The entire concept of the formulation technology and the development of oral testosterone was based on the premise of the solubility of T in oily/fatty condition and the absorption of the drug in the presence of high fat content via the lymphatic system (Kohn et al, World J Urol, 21:311-315, 2003, Yin et al, J Androl, 33 (2):190-201, 2012, Frey et al, Eur. J. Clin. Pharmacol 16:345-349, 1979, Horst et al, Klin. Wschr 54:875-879, 1976, Schnabel et al Clin End, 66:579-858, 2007, and Yin et al J Androl, 33 (6):1282-1290, 2012).

2.2.4 Safety and Pharmacodynamic Biomarkers:

This section of the review includes summary and highlights of the safety and biomarkers from the clinical pharmacology perspective. However, this summary, analysis, and interpretation of the data does not stand alone and should be considered as complementary to the safety and efficacy analysis performed by the Clinical Team and other review teams for this NDA. Therefore, the focus of this section is primarily on the pharmacodynamic aspect of testosterone therapy, in general, as well as the potential cardiovascular risk of long term therapy with testosterone from the clinical pharmacology perspective.

What are the Pharmacodynamic Effects and Safety of Oral Testosterone from the Clinical Pharmacology Perspective?

What is the Effect on Sex Hormone Binding Globulin (SHBG)?

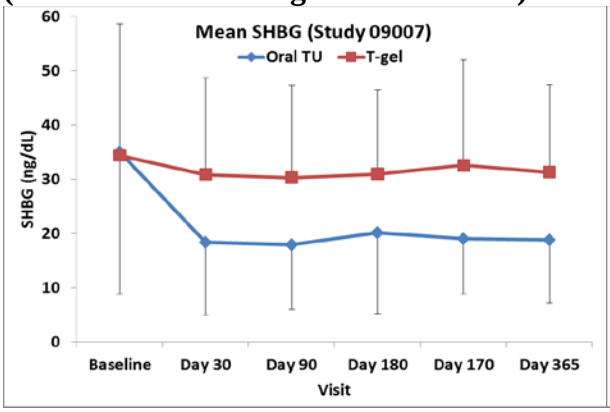
SHBG plays a key role in regulating bioavailable sex-steroid concentrations through competition to its high affinity binding sites. Therefore, any fluctuation of the SHBG concentration may play an important role on the pharmacological activities of T, DHT, and other sex-steroids.

In both Phase III studies, serum SHBG concentrations were determined prior to the start of therapy (baseline) and post treatment at different periods during therapy. While there was virtually no change in SHBG concentration after AndroGel® from baseline throughout the study, there was ~40-50% decline in SHBG concentration by Day 30 following oral TU in Study 09007 (**Figure SHBG-1**). This decline remains relatively constant throughout the study.

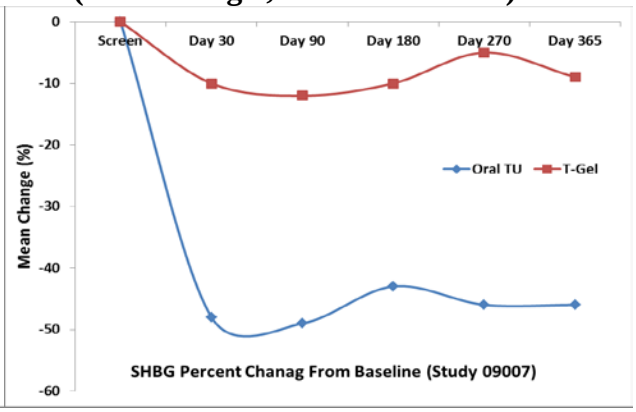
However, it should be noted that overall the mean SHBG concentrations were relatively within the normal range in both treatment groups (normal range in adults is approximately 20-60 nmol/L per Mayo Clinic database, http://www.mayomedicallaboratories.com/test-catalog/print.php?unit_code=91215, Accessed on May 23, 2014 and Elmlinger et al Clin Chem Lab Med, 40 (11):1151-1160, Dec 2002).

Figure SHBG-1A&B. SHBG Concentration-Time Profiles and Percent Change from Baseline (Study 09007)

A: SHBG Concentration (mean ± SD) (Source Table 37 Original submission)



B: Mean Percent Change (Source Aug 4, 2014 submission)



It should be noted that there was an apparent difference between oral TU and AndroGel® on SHBG levels. This difference is reflected in the differences in FT concentrations as also shown in the earlier section in **Figures FT-1 and 2**. As demonstrated in the above Figures, the lower SHBG concentrations are associated with higher FT concentrations.

The mechanism of reduction in SHBG level is probably a combination of saturation of the enzymes responsible for the synthesis of SHBG in the liver, in part, possibly due to some absorption via portal vein and/or increased its elimination (Ruokonen et al, J. Steroids, Vol. 23 # 1, 33-38, 1985, Conway et al International J of Andrology, 11: 247-264, 1988, and Pugeat et al, Molecular and Cellular Endocrinology 316, 53–59 2010).

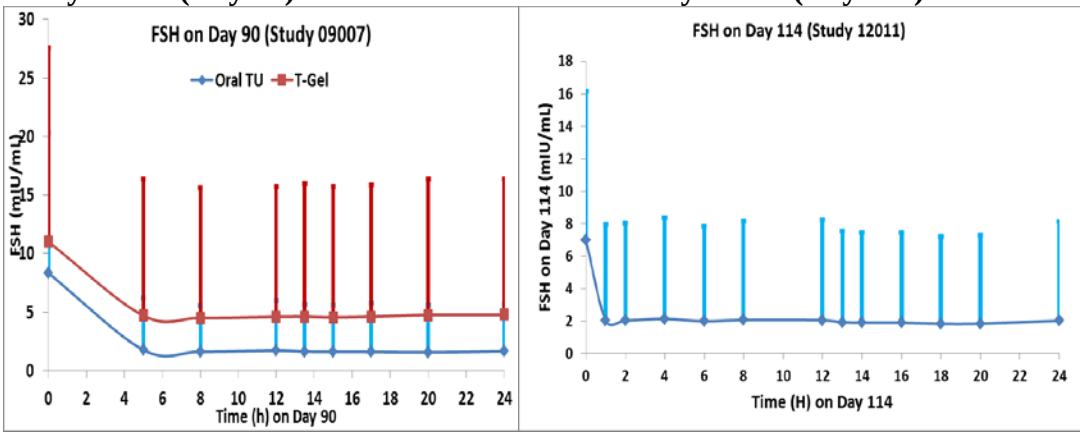
Overall, the clinical significance of the long term effect of changes in SHBG level is unknown at this time.

Was there an Effect on Follicle Stimulating Hormone (FSH)?

There was almost no fluctuation in the FSH concentration-time profiles on Day 90 (Study 09007) and Day 114 (Study 12011) as observed in both Phase III studies (**Figure FSH-1**). However, there was a noticeable high inter-subject variability in the levels. While, it is noted that the mean FSH concentrations were within the normal range before and during the treatment (Normal range in adults is 1.42-14.4 IU/L, per WebMD, http://www.webmd.com/women/follicle-stimulating-hormone?page=2, Accessed on April 18, 2014), FSH concentrations declined from the baseline/screening value in most patients during treatment (**Figures FSH-1 and 2**).

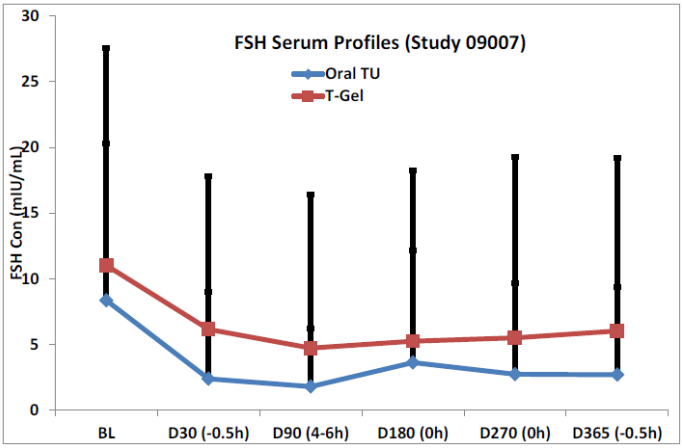
Figure FSH-1. Mean (±SD) Concentration-Time Profile for FSH at Screening-Baseline (zero time point) and on Days 90 and 114 in Studies 09007 and 12011.

A. Study 09007 (Day 90) **B. Study 12011 (Day 114)**



Reductions in FSH reflect the well-known negative feedback of T on gonadotropin secretion. The same mechanism of negative feedback was also seen for LH secretion (see LH Section below). Considering the differences in baseline between treatments, the FSH was consistently lower after the oral TU compared to AndroGel® on Day 90 and throughout the study (**Figures FSH-1 and 2**). This is not surprising as the T level was higher after oral TU than AndroGel® and hence there was greater suppression of FSH (i.e., negative feedback).

Figure FSH-2. Mean Serum FSH Over Time with Oral TU and AndroGel® **(T-Gel) (Source: Table 41, Page 119 of 950, PK Report, Section 16.5, Study 09007) (BL: Baseline/Screening)**



Was There an Effect on Luteinizing Hormone (LH)?

The profiles of LH followed similar profiles of FSH in all aspects, including patterns, variability, baseline, and treatment values, except for the actual units (**Figure LH-1**). As indicated for FSH, this pattern is expected from the pharmacological and negative feedback mechanisms of T on the normal secretion of FSH and LH. As also noted for FSH, oral TU suppressed LH secretion to a greater extent than AndroGel® (**Figure LH-2**).

Similar to the observations for FSH, there was almost no fluctuation in the LH concentration-time profile over the dosing interval.

Figure LH-1. Mean (±SD) Concentration-Time Profile for LH at Screening-Baseline (zero time point) and on Days 90 and 114 in Studies 09007 and 12011.

A. Study 09007 (Day 90) **B. 12011 (Day 114)**

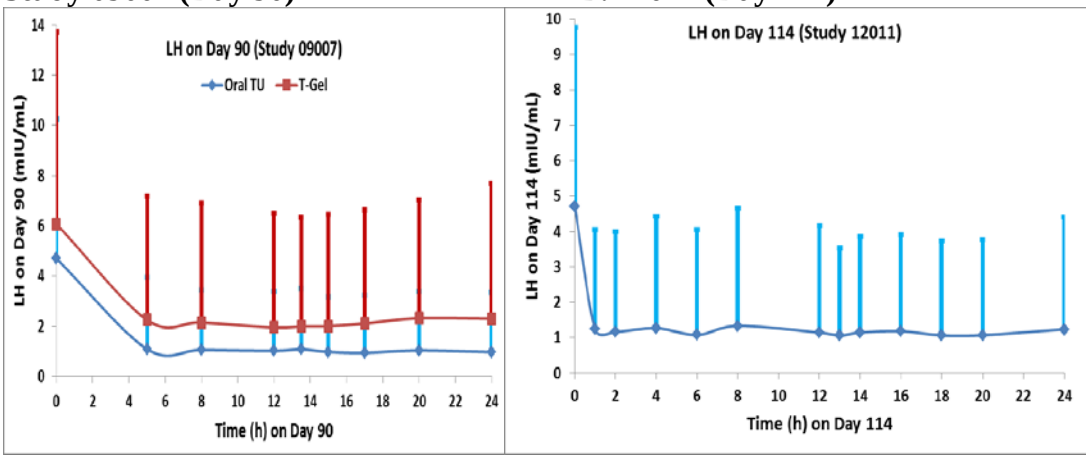
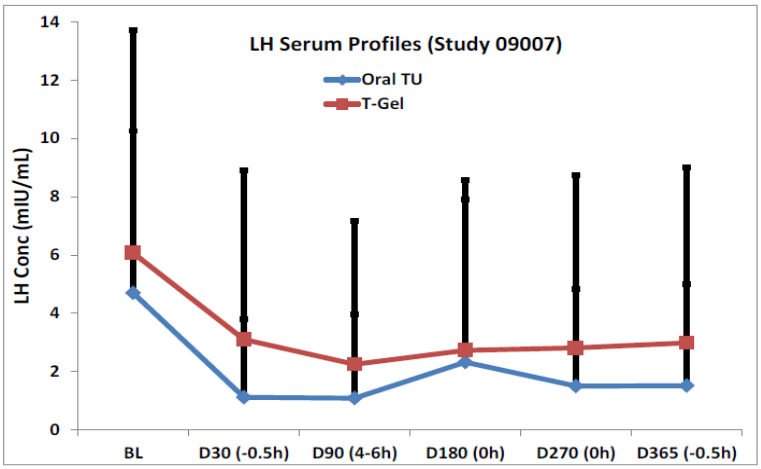


Figure LH-2. Mean Serum LH Over Time After Oral TU and Androgel® (**T-Gel) (Source: Table 43, Page 123 of 950, PK Report, Section 16.5, Study 09007) (BL: Baseline/Screening)**



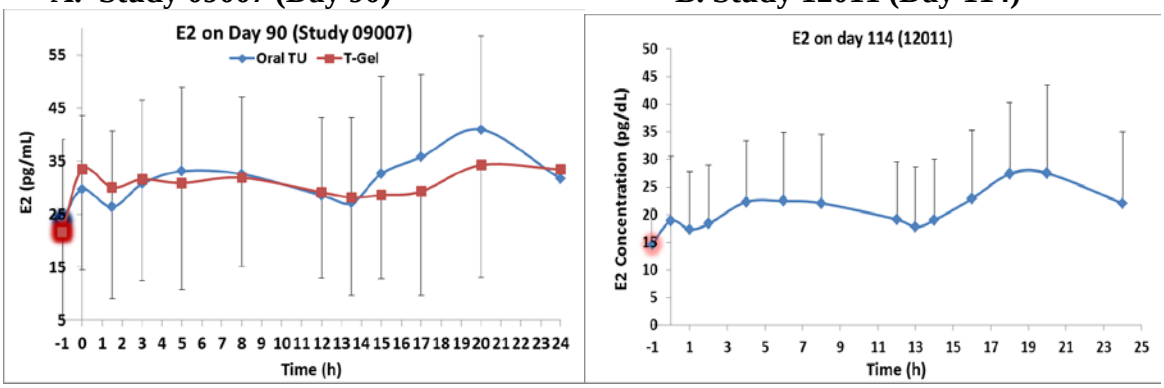
What is the Effect on Endogenous Estradiol (E2) Level?

As stated earlier, E_2 is one of the metabolites of T as a result of aromatization. Therefore, the serum concentrations of E_2 while patients were taking oral TU or Androgel® were slightly higher than the pretreatment E_2 values (**Figure E_2-1**). The mean Cavg at the primary efficacy timepoint ranged from approximately 33 pg/mL in Study 09007 to 22 pg/mL in Study 12011 (baseline E_2 level ~23 pg/mL and ~14 pg/mL in studies 09007 and 12011 respectively). Theses mean E_2 concentrations are within the range reported in the literature, which ranges from 10 to 40 pg/mL in adult men (http://www.mayomedicallaboratories.com/test-catalog/Clinical+and+Interpretive/84230, accessed August 13, 2014).

Unlike DHT or T, the serum concentration-time profiles for E_2 concentrations had less peak-to-trough fluctuation. However, like DHT the timing of the rise and fall of the concentrations was delayed by approximately 1 to 2 hours.

Figure E2-1. Mean (±SD) Concentration-Time Profile for E_2 (source Study 09007 Table 38 and Study 12011 36)

A. Study 09007 (Day 90) **B. Study 12011 (Day 114)**

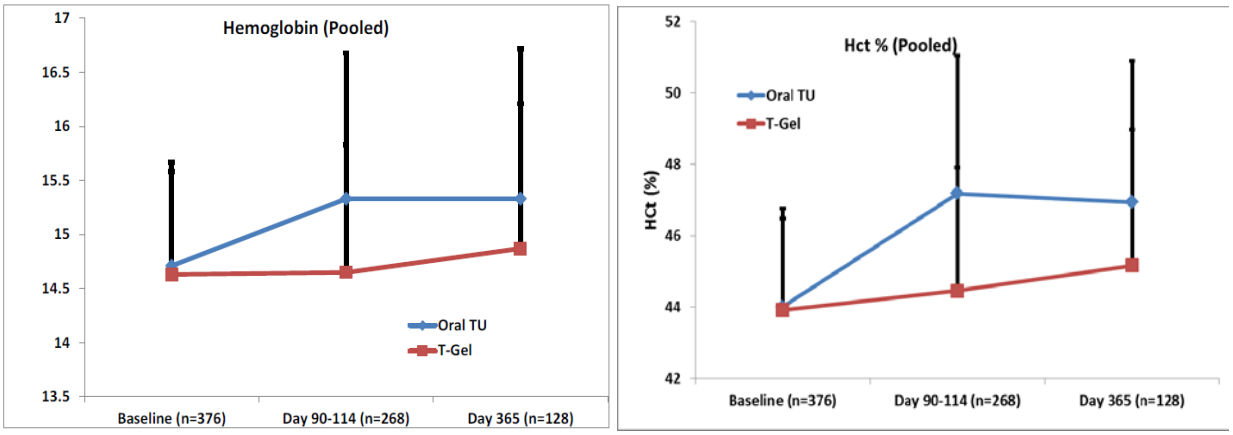


Based on these studies, there was essentially no systematic pattern of change in E_2 Cavg or the E_2/T ratios over the extended treatment time of 365 days in Study 09007. In terms of differences between oral TU and AndroGel®, overall the observed E_2 levels were slightly higher after oral TU than after AndroGel®, particularly after PM dosing. This observation has been consistent with total T, free T, and DHT data.

What is the Effect of Oral TU on Hematological Parameters?

In general, T therapy is associated with an increase in hemoglobin (Hb) and hematocrit (Hct) levels. This appears to be a well-known pharmacologic effect of T. Overall, Hb and Hct levels were higher after oral T compared to AndroGel® (**Figure HE-1**).

Figure HE-1. Pooled Effect of Hematological Parameters (Source: Tables 17 and 18, safety report)



2.2.5 Safety Endpoints and Cardiovascular Risk (CV):

What is the Rationale for CV Risk with Testosterone Replacement Therapy (TRT)?

Background:

On September 17, 2014, the FDA will be discussing the potential for cardiovascular risk associated with the class of testosterone replacement therapies. The scope of this review is limited to the current NDA only.

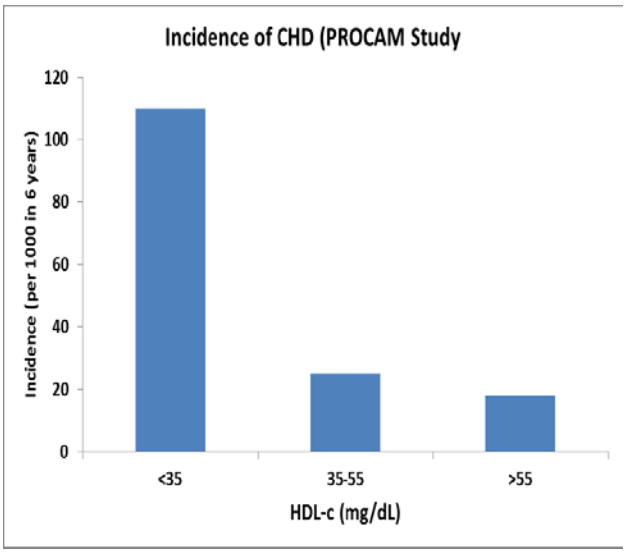
Lipid Panel and CV Risk:

There are several sources in the literature to indicate that TRT lowers serum High Density Lipoprotein-cholesterol (HDLc). Furthermore, it is recognized that elevated serum levels of HDLc are associated with reduced risk of coronary heart disease (CHD) or CV disease (CVD, **Figure HDL-1**). Thus, lowering HDLc levels with TRT may be a concern **(**Toth et al J Clinical Lipidology, 7:484-525, 2013 and the Framingham Study published by Abbott et al Arteriosclerosis, 8(3):207-211, 1988). Not shown in **Figure B** is that the total number at risk of

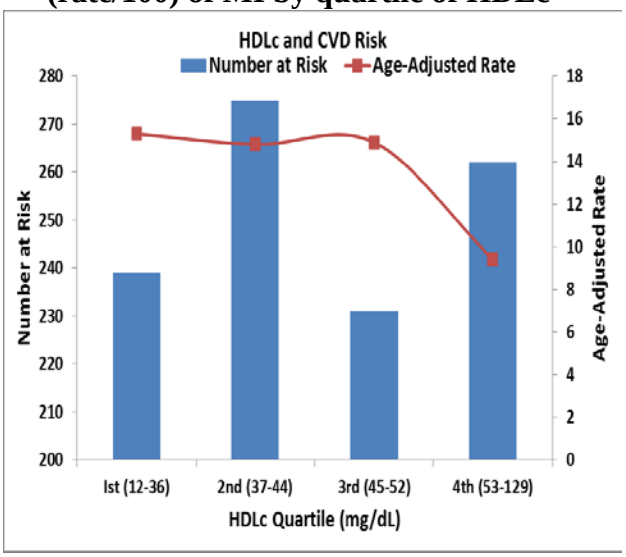
myocardial infraction (MI) was 1007, total number of events was 136, and the total aged-adjusted rate was 13.5.

Figure HDL-1. Incidence of Coronary Heart Disease (CHD) According to Concentration of HDL.
Figure A: Adopted from Toth et al J Clinical Lipidology, 7:484-525, 2013.
Figure B: Adopted from Framingham Study, Abbott et al Arteriosclerosis, 8(3):207-211, 1988

A:Incidence of CHD



B: men's age-adjusted 12- year incidence (rate/100) of MI by quartile of HDLc



What is the T Level in Hypogonadal Men?

Hypogonadal men may be at risk of cardiovascular disease (CVD) due to multiple factors including but not limited to: hypertension, obesity, inflammation, insulin resistance, and diabetes. While TRT may improve most of these risk factors such as increase in lean body mass, decrease in fat mass, improvement in insulin resistance, vasodilation, anti-inflammatory and anti-coagulatory properties, the primary concern is that TRT may increase CV risk by affecting other factors such as the reduction in high density lipoprotein (HDL) and other CV risk precursors.

CV Risk and Design of Phase III Studies:

Due to concerns of potential CV risk associated with TRT, the sponsor monitored a wide variety of CV risk factors and biomarkers following oral TU and AndroGel® in Study 09007. In addition to the lipid panel, other precipitating factors/biomarkers for CV risk were also measured such as High Sensitivity C-Reactive Protein (hsCRP), Lipoprotein Associated Phospholipase A2 (Lp-PLA2), Lipoprotein a [Lp (a)], and Apolipoprotein A1 (Apo-A1). The serum levels of these CV biomarkers are briefly discussed in the sections below.

Recent data have shown that HDL may not be a gold standard for prediction of CVD risk. For example, recent trials of products that increase HDL have not improved CV outcomes.

Therefore, in recent years other biomarkers have been considered such as "**cholesterol efflux capacity-CE**" and "anti-atherogenic sub-fractions" of HDL rather than HDLc in isolation (Khera et al NEJM, 364:127-35, 2011). As stated above, there are a host of enzymes and inflammatory biomarkers that can be measured to assess the inflammatory state (sPLA2 and Lp-PLA2). Other biomarkers have also been explored such as Phosphocholine Oxidized Phospholipids (PC -oxPL) and Apolipoprotein B (ApoB). Note, however, that use of these types of biomarkers is controversial and not widely accepted in the scientific community. Nonetheless, for completeness, the findings are presented below.

Based on the complexity associated with CVD risk, the sponsor conducted an **exploratory analysis as a sub-study** in Study 09007 to assess whether oral TU impacted "cholesterol efflux capacity-CE", atherogenic markers, HDL and LDL particle metrics compared to AndroGel®. This sub-study was conducted in a cohort of 57 subjects (28 on oral TU and 29 on AndroGel®). The data from this sub-study will be briefly described later in this review.

2.2.6 What are the Primary Safety Endpoints and Biomarkers?

In this review, the CV biomarker data from all Phase II and III studies are pooled for analysis. However, the emphasis is on Phase III study 09007 which is the longest study that includes an active comparator, AndroGel®. The analysis includes a total 537 subjects from the 6 studies (377 subjects treated with oral TU and 160 subjects treated with AndroGel®. Depending on the monitored parameters, the analysis represents the laboratory data from all 6 studies and in particular both Phase III studies on Days 28-30, 90 or 105, 114, and 365.

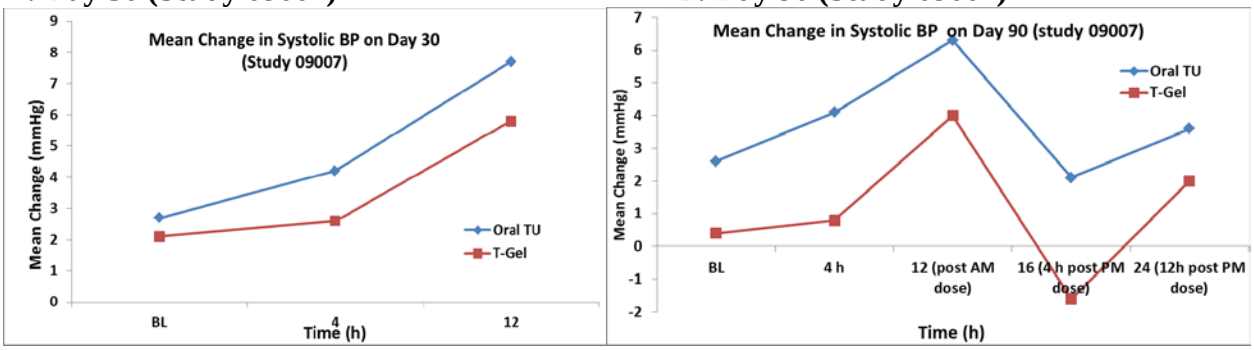
Cardiovascular Biomarkers/Endpoints:

Effect on Systolic and Diastolic Blood Pressure:

During the course of the study, there was a noticeable increase in systolic (SBP) and diastolic (SBP) blood pressure after oral TU compared to baseline. Blood pressures also increased with Androgel®, but to a lesser extent. **Figure BP-1 and 2** is derived from data provided by the sponsor.

Figure BP-1 A& B: Mean Change in SBP From Baseline in Study 09007 (source August 4, 2014 submission).

A: Day 30 (Study 09007) **B: Day 90 (Study 09007)**



C: Day 365 (Study 09007) **D: Overall Mean (Study 09007)**

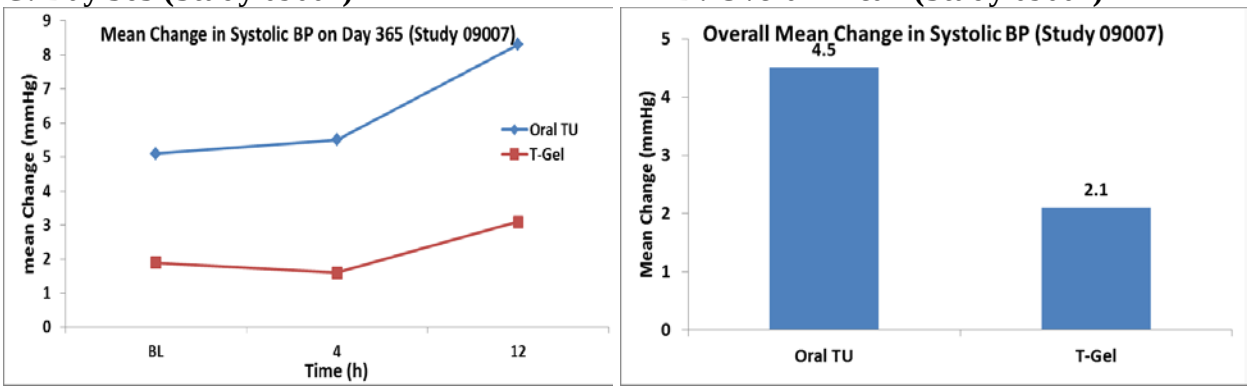
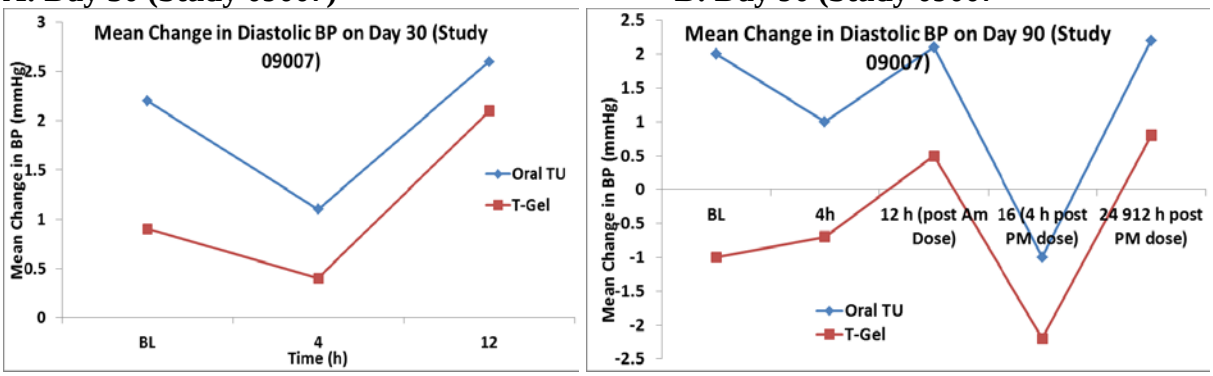
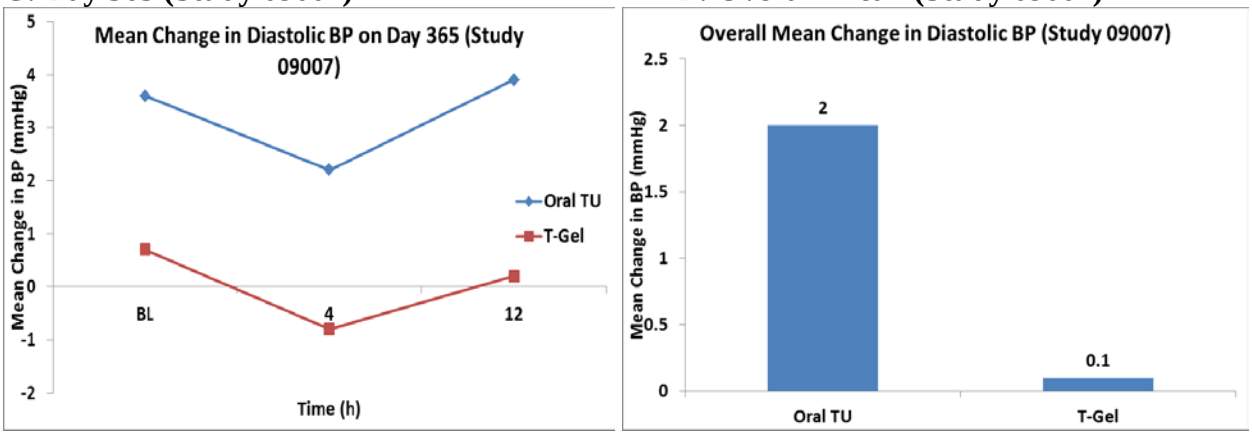


Figure BP-2 ABCD: Mean Change in DBP from Baseline in Study 09007 (source August 4, 2014 submission).

A: Day 30 (Study 09007) **B: Day 90 (Study 09007**



C: Day 365 (Study 09007) **D: Overall Mean (Study 09007)**



The same trend of increase in BP was also observed in Study 12011 (not shown). As with all comparisons to AndroGel®, it is important to remember that TU resulted in higher T exposures than AndroGel® due to a less aggressive down-titration algorithm for TU in Study 09007 that was subsequently abandoned. While it is recognized that the AndroGel® provides slow release rate of T and the head-to-head comparison between the two formulations may not be justified due to the difference in release rates, it is the overall clinical outcome that matter. The sponsor believes that the differences between the oral TU and AndroGel® on both SBP and DBP "*are*

not clinically meaningful". The reader is directed to the FDA Clinical Review which contains the Medical Officers interpretation of this data and a discussion on the blood pressure effects observed during drug development.

What is the Effect of Oral TU on the Lipid Panel?

Overall, the effect of oral TU appears to be slightly different compared to AndroGel®. Briefly, it is known that triglycerides may be elevated in hypogonadal men. Such trends are observed from the slightly higher baseline triglyceride data prior to treatment with either oral TU or AndroGel® (**Figure 2.2.6-1**). Considering the high variability in the data, there was essentially no difference between treatment arms in triglyceride or total cholesterol (**Figure 2.2.6-1**). However, the trend is more obvious in reference to the effect on the high density lipoprotein (HDL) and low density lipoprotein (LDL). As demonstrated in **Figure 2.2.6-2** there is an obvious shift for lower HDL levels following oral TU compared to AndroGel®. The reverse appears to be true for higher LDL after TU than after AndroGel®. Again, it is unclear to what extent these differences are related to the differences in T exposures between TU and AndroGel®.

Figure 2.3.1.2-2. Pooled Effect on Triglyceride and Cholesterol (Source: tables 19 and 20, safety report)

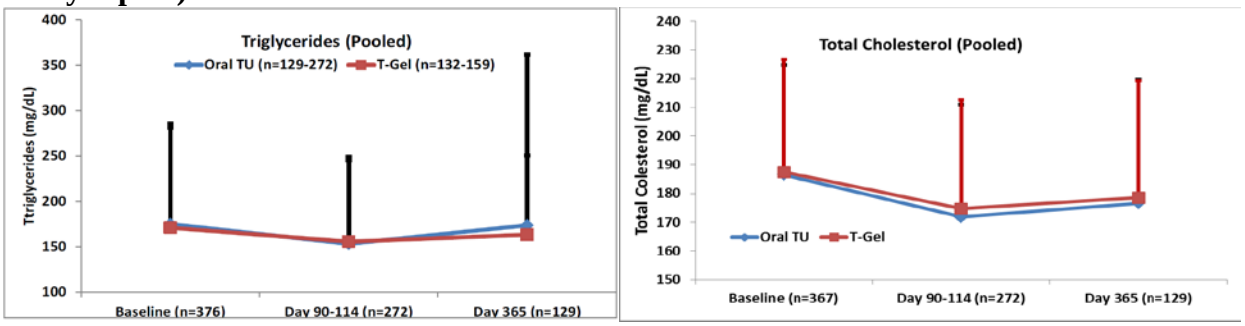
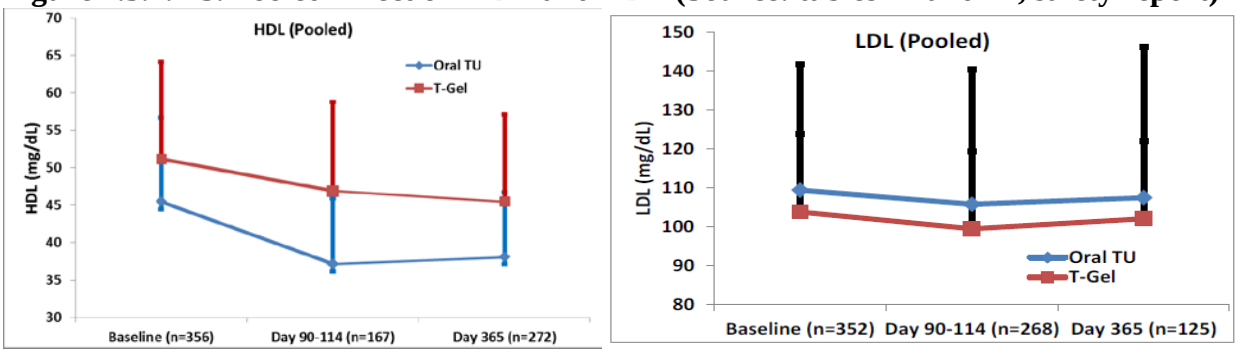


Figure 2.3.1.2-3. Pooled Effect on HDL and LDL (Source: tables 21 and 22, safety report)



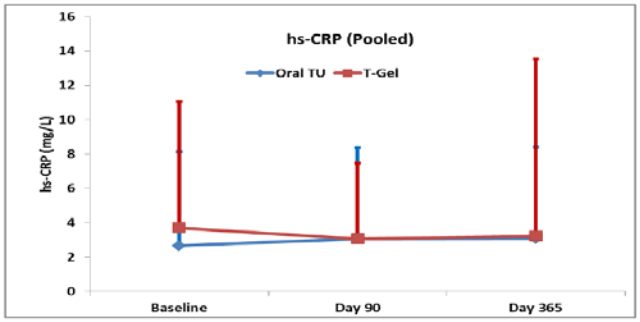
What is the Effect on High Sensitivity C-Reactive Protein (HsCRP)?

Based on the literature, high sensitivity c-reactive protein (hs-CRP) is an acute phase reactant protein and one biomarker that has been used to screen for potential CV risk. According to the literature, hs-CRP is a strong independent predictor of CV risk. Therefore, the risk is classified into three tiers based on the serum level of hs-CRP as follows:

- Low-Risk: < 1 mg/L
- Intermediate-risk: 1-3 mg/L
- High-risk: > 3 md/L

In Study 09007, there was essentially no difference in the hs-CRP levels following all treatments (**Figure CRP-1**).

Figure CRP-1. Effect on hs-CRP (Source: tables 22, Page 101, Study 09007)



In Study 09007, the mean (SD) baseline hs-CRP was 2.68 (5.47) mg/L and 3.71 (7.35) mg/L for oral TU and AndroGel®, respectively. At the Day 90-105 visit, the mean increase for the TU group was 0.397 mg/L and the mean decrease for the AndroGel® group was 0.662 mg/L. The same trend was observed on Day 365 with a mean increase of 0.20 mg/L for TU and a mean decrease of 0.449 mg/L for AndroGel®. The differences between the oral TU and AndroGel® groups were not statistically significant (p = 0.2781).

What is the Effect on Lipoprotein Associated Phospholipase A2 (Lp-PLA2)

Phospholipids are essential components of lipoproteins and cell membranes. These are composed of fatty acids bound to a glycerol backbone containing a polar head group and are substrates for phospholipases A2 (PLA2). The hydrolytic action of PLA2s on phospholipids generates fatty acids and lysophospholipids both of which are important lipid mediators and second messengers with a wide range of physiological and pathological effects, thus PLA2s are an important link between lipids and inflammation, both involved in atherosclerosis. Based on the literature, the circulating levels of PLA2s were shown as independent predictors of death and new or recurrent myocardial infarction (MI). There is some evidence to indicate that plasma PAF-acetylhydrolase (PAFAH) belonging to the PLA2 group VIIA that is also known as the lipoprotein-associated PLA2 (Lp-PLA2) is an independent cardiovascular risk factor.

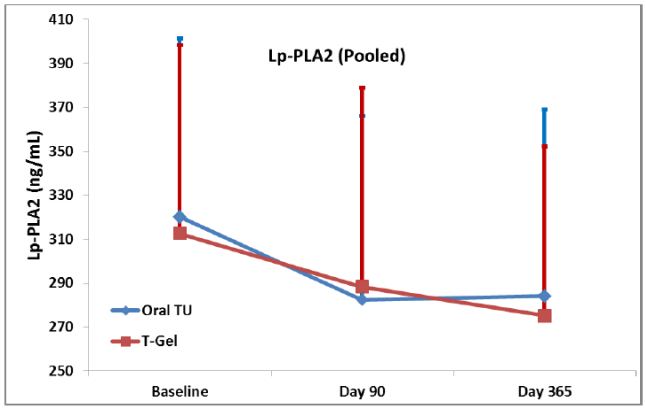
As PLA2s participate in various diseases, including atherosclerosis, where inflammation and lipid metabolism are key players, an understanding of their respective contributions and their mechanisms of action is important for the potential therapeutic approach. In addition to hs-CRP, Lp-PLA2 is recognized as biomarker for CV risk. It appears to be more specific in identifying CV risk than hs-CRP. It has been used in stratification of risk based on the following three tiers of serum levels:

- Low-risk: < 200 ng/mL
- Moderate-risk: >200 to 235 ng/mL

- High-risk: > 235 ng/mL

Following all treatments, there was a gradual decrease in the mean Lp-PLA2 levels from the baseline following all treatments. However, there was essentially no difference between oral TU and AndroGel® during all visits (**Figure LPA-1**).

Figure LPA-1. Effect on Lp-PLA2 (Source: Tables 23, Page 103, Study 09007)



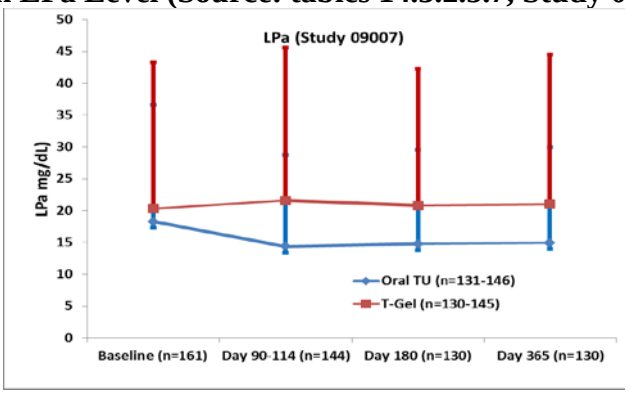
In Study 09007, the mean (SD) baseline Lp-PLA2 for both groups was similar: 320 (±81) ng/mL for the oral TU group and 312 (±85) ng/mL for the AndroGel® group. The absolute mean (±SD) change from baseline at the Day 90-105 visit was greater in the oral TU group, with a decrease of 39 (±86) ng/mL, compared to the AndroGel® group decrease of 27 (±78) ng/mL. At Day 365, the absolute mean (±SD) decrease for the oral TU group was 39 (±74) ng/mL compared to the AndroGel® group decrease of 37 (±78) ng/mL. Therefore, the differences between the oral TU and AndroGel® groups were not statistically significant (p = 0.4489).

What is the Effect on Lipoprotein a (LPa):

Lipoprotein a (LPa) is recognized as moderate and independent pro-atherogenic biomarker for CV risk. Based on the literature, it appears that the CV risk is high when the LPa level increases above 12 mg/dL.

In Study 09007, there was an apparent difference between oral TU and AndroGel® for the serum level of LPa (**Figures LPa-1**). In this study, overall, the mean values including, baselines, are above 12 mg/dL.

Figure LPa-1. Effect on LPa Level (Source: tables 14.3.2.5.7, Study 09007)



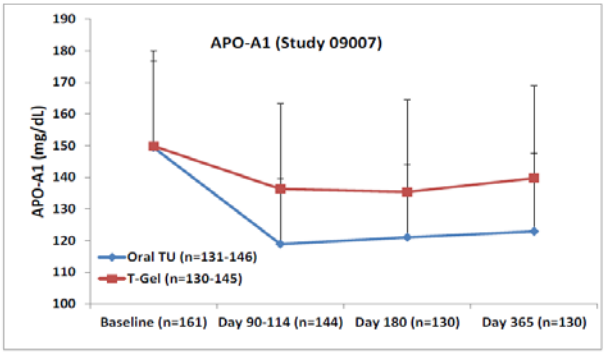
For the oral TU group, the mean (±SD) baseline of LPa was 18 mg/dL (±22) and for the AndroGel® group it was 20 mg/dL (±23). At Visit 4 (Day 90 or 105), the absolute mean decrease for the oral TU group was 3.96 mg/dL (±10) and for AndroGel® the increase was 1.82 mg/dL (±8.95). The same trend continued at Visit 7 (Day 365) where the absolute mean decrease for oral TU subjects was 4.00 mg/dL (±10.54) and the absolute mean increase for AndroGel® was 1.55 mg/dL (±9.19).

The differences between the oral TU and AndroGel® were statistically significant ($p < 0.0001$) with the oral TU group having a greater decrease in mean LPa levels.

What is the Effect on Apolipoprotein A1 (Apo-A1):

Apo-A1 is synthesized in the liver and intestine and is the major constituent of the HDL particle. Specifically, Apo-A1 is the main constituent of HDL and is a cofactor for lecithin cholesterol acyl-transferase (LCAT), a key enzyme in the reverse cholesterol transport (RCT) pathway, and it is the ligand for the ATP-binding cassette (ABC) protein. Based on the literature, the validity and utility of this biomarker over the use of HDL for CV risk is debatable. However, it is believed that Apo-AI is an important driver of HDL concentration. The mechanism and the complexity of the relationship between these biomarkers and associated precursors are beyond the scope of this review. In Study 09007, the mean baseline was approximately 150 mg/dL for both treatment groups (**Figure Apo-1**).

Figure Apo-1. Effect on Apo-A1 Level in All Patients (Source: Table 14.3.2.5.8, Study 09007)



Following the treatments, the decrease in the level was greater after oral TU than AndroGel® at all observation days. For example, the mean (±SD) reduction from the baseline at Visit 7 (Day 365) was 28.41 mg/dL (±26.90) following oral TU and 11.64 mg/dL (±28.98) after AndroGel® (**Figure Apo-1**).

What are the Results of the Sub-Study?

What are the Results of Cholesterol Efflux Capacity (CE) in the Sub-Study?

Briefly and as stated earlier there were 28 patients on oral TU and 29 in AndroGel® arms that completed the sub-study to further evaluate the CV risk in Study 09007. One of the key mechanisms by which HDL is anti-atherogenic is by mediating reverse cholesterol transport (RCT). This mechanism explains HDL's ability to mobilize cholesterol from macrophages in atherosclerotic plaques and transport it back to the liver for clearance (Khera et al, NEJM, 364-2, 127-35, 2011). It appears then that there is an inverse correlation between CE and biomarkers of CV risk.

Also as stated earlier, the primary objectives of this sub-study were to explore the effects of oral TU and AndroGel® on other biomarkers and specifically on 1) HDL cholesterol efflux capacity (CE) and HDL particle fractionation and metrics and 2) secretory sPLA2, PC-OxPL, and other immune complexes.

Overall, there was no major difference between the data obtained in the main study and the sub-studies except that a few biomarkers were specifically monitored in the sub-study only. From the sub-study the following conclusions can be made:

- There was separation between oral TU and AndroGel® cholesterol efflux capacity-CE (%) (**Figure Sub-study 1A**). Oral TU demonstrated a greater reduction in CE capacity from baseline compared to AndroGel®. However, the ratio of cholesterol efflux (CE)/total HDL particle number appears comparable between the two arms (**Figure Sub-study 1B**).
- There was a noticeable difference in the effect of Oral TU on HDLc compared to AndroGel® and a small effect on total HDL (**Figure Sub-study 2 A**). Differences between groups are also shown on the effect of small, medium, and large HDL particle number (**Figure Sub-study-3**).
- There were also differences between oral TU and AndroGel® on the effect on Apo A-1 and phosphocholine oxidize phospholipids (PC-oxPL) (**Figure Sub-study 4B**)
- There was virtually no difference between treatments on IgG ApoB-IC, IgM Apo-B IC immune complex to ApoB, and Phospholipase A2-sPLA2 (**Figure Sub-study 5).**

Figure Substudy-1 A&B. Mean ± SD Total Cholesterol Efflux (CE) Capacity Expressed as percent (%) (Figure A) and Ratio of CE/HDLtp (Figure B) in Oral TU Group vs. AndroGel® at Baseline and Days 90, 180 and 365 After Treatments (n=24-29, Source: Section 16.6, Tables 5.a and 6.a, Study 09007).

Figure A (CE %) **Figure B: Ratio of CE/HDLtp**

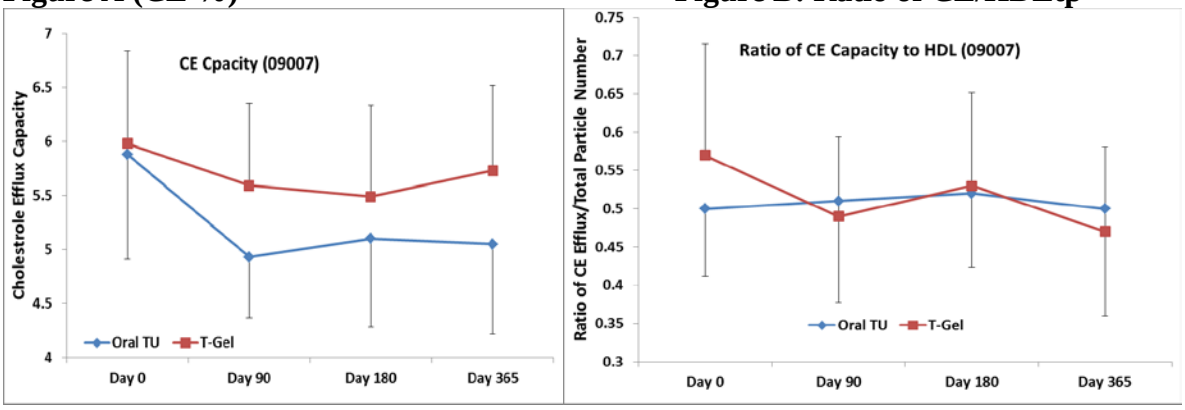


Figure Substudy-2 A&B. Mean ± SD HDLc (Figure A) and Total HDL (Figure B) in Oral TU Group vs. Androgel® (**T-gel) at Baseline and Days 90, 180 and 365 After Treatments (n=24-29, Source: Section 16.6, Tables 2.a and 4.1g, Study 09007).**

Figure A (HDLc) **Figure B (Total HDL)**

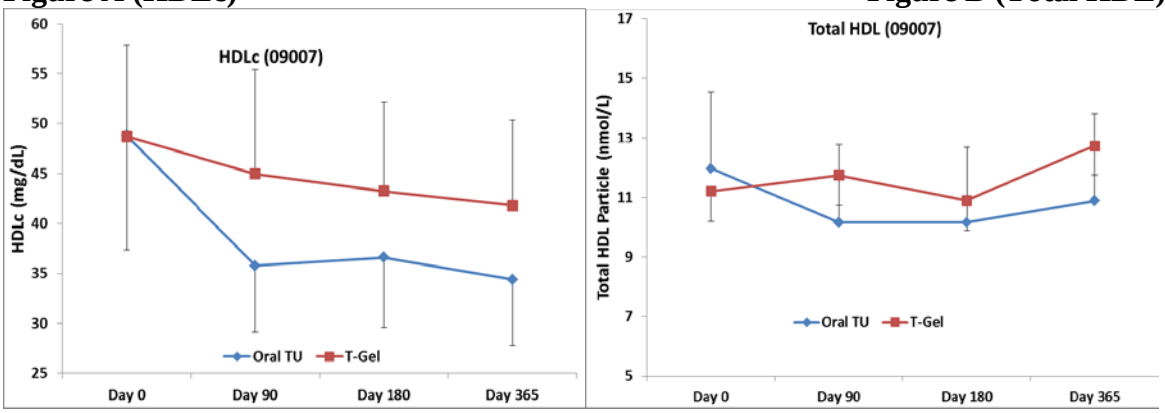


Figure Substudy-3 A, B, &C. Mean ± SD Small, Medium, and large HDL Particle Number Over Time with Oral TU Group vs. T-gel at Baseline and Days 90, 180 and 365 After Treatments (n=24-29, Source: Section 16.6, Tables 4.1a, 4.1.c, and 4.1.2, Study 09007).

A: Small HDL **B: Medium HDL** **C: Large HDL**

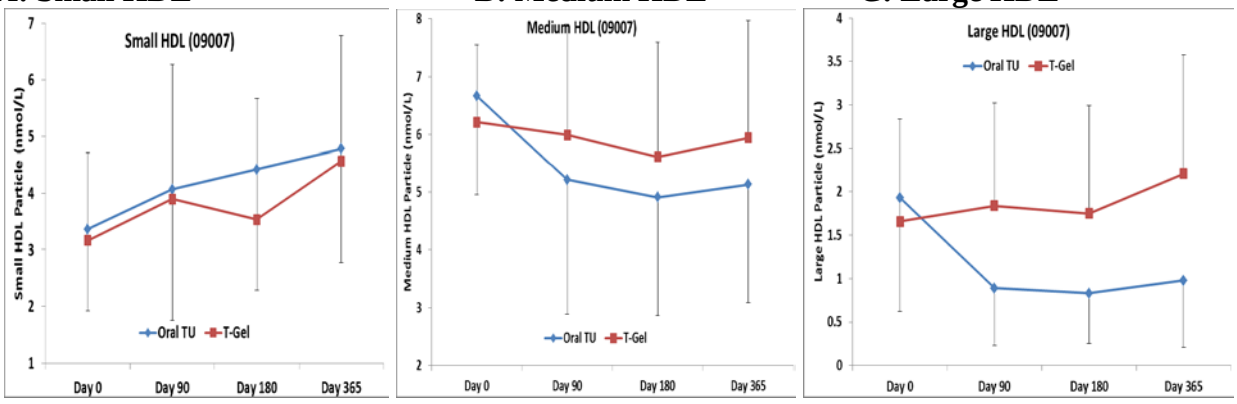


Figure Substudy-4. Mean ± SD Apo-1 and P-oxPL (AKA oxPL/apoB) Over Time with Oral TU Group vs. Androgel® (**T-gel) at Baseline and Days 90, 180 and 365 After Treatments (n=24-29, Source: Section 16.6, Tables 3.a and 14, Study 09007).**

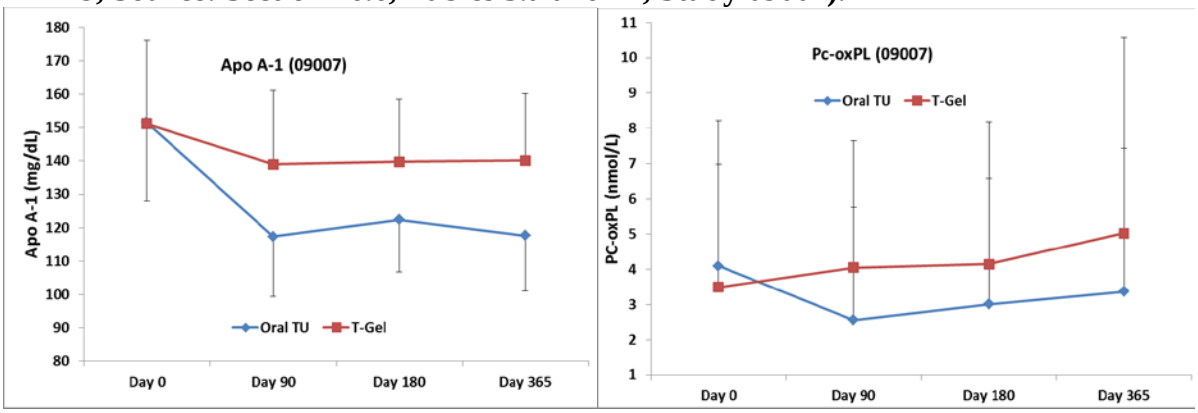
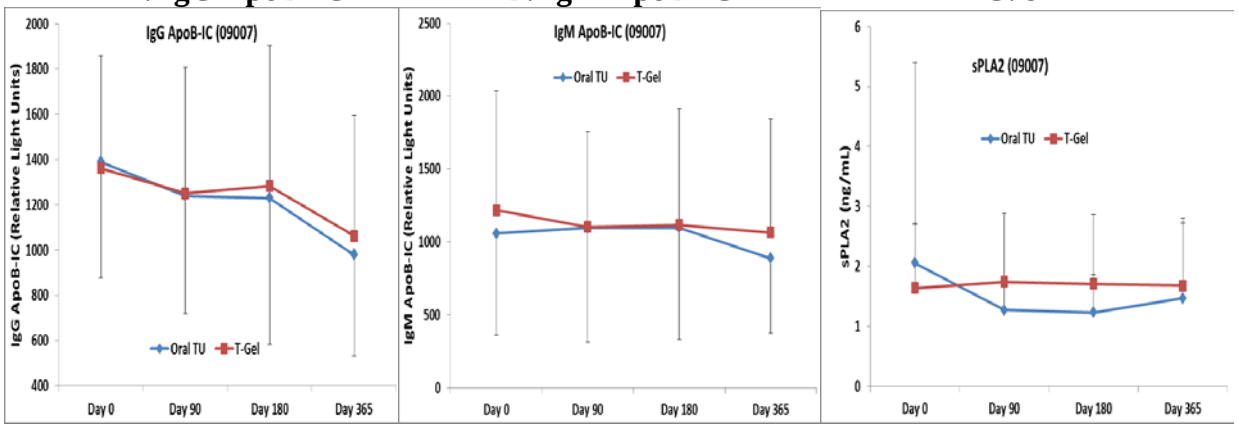


Figure Substudy-5 A &B. Mean ± SD IgG and IGM ApoB-IC and sPLA2 Over Time with Oral TU Group vs. Androgel® (**T-gel) at Baseline and Days 90, 180 and 365 After Treatments (n=24-29, Source: Section 16.6, Tables 15.a, 15.b, and 13, Study 09007).**

A: IgG ApoB-IC B: IgM ApoB-IC C: sPLA2



Overall Reviewer's Comments on CV Biomarkers from the Sub-Study:

Based on the above data from the sub-study, the following conclusions can be made:

- The level of ApoA1 was decreased from baseline over time. The magnitude of the reduction was greater after oral TU than AndroGel® (i.e., ~20% vs 7 %).
- There was a decrease in cholesterol flux capacity by Day 90 in both treatment groups with greater reduction after oral TU. By Day 365 the level returned to baseline after AndroGel®, but remained low after oral TU. The clinical significance of this difference is unknown at this time.
- There was separation between oral TU and AndroGel® on HDLc and large HDL particle throughout the study. The effect remains until Day 365.

- Compared to AndroGel®, oral TU decreased PC oxPL from baseline, with values remaining somewhat reduced at Day 365. In contrast, concentrations of PC oxPL slightly increased over the course of the study with AndroGel®.

Overall Conclusions on the Cardiovascular Risk of TRT:

From the clinical pharmacology perspective, at this time no definitive conclusions can be drawn in reference to the potential CV risk associated with chronic administration of oral TU. This finding, as outlined in the previous discussion, is based on both the relatively short duration of clinical experience (~1yr), the lack of a consistent trend in the monitored biomarkers, and the lack of a community consensus on which of the monitored biomarkers is the most definitive.

Summary of the Advisory Committee (AC) on CV Risk (September 17, 2014):

Based on the FDA AC meeting held on September 17, 2014 it was noted that all published research articles had limitations with conflicting findings in reference to the CV risk associated with TRT. In other words, some show a potential for increased risk while others demonstrated potential decreased in risk with TRT. In addition, other studies show low T was associated with CV risk. Based on the information discussed and presented, the panel concluded that there is a weak signal for CV risk associated with TRT. However, the available data cannot exclude CV risk. Based on the conflicting evidence and confusion, the labels for all T products may need to reflect the potential CV risk. The panel voted 20 vs. 1 for the FDA to require CV safety study to further assess the potential for CV risk and in particular for specific new indication (s).

On Day 2 of the AC meeting held on September 18, 2014 for this NDA, there was some discussion of the potential CV risk associated with high exposure of T and its metabolites by some members of the panel. However, the focus of the discussion was related to the high exposure, food effect and associated high variability, statistical issues, and some related pharmacodynamics parameters.

2.2.7 Does this Drug Prolong the QT or QTc Interval?

No formal Thorough QT study was conducted by the sponsor.

Considering the history of testosterone therapy and the mechanism of action on the endocrine system, a thorough QTc study with testosterone products is not required at this time.

2.3 Intrinsic factors

2.3.1 Does age, race, or organ dysfunction affect the PK of the drug? What dosage regimen adjustments are recommended for the subgroups?

Overall based on all studies, there was no noticeable effect of age or race on the PK of T. The drug will only be indicated for men. Therefore, no information is available in females. There was an effect of body weight/BMI on the PK of T with higher exposure levels for smaller body weight (or BMI) for the same dose. Since the proposed dosing consists of titrations based on the

T exposures, this weight effect would be automatically taken care of in the final stable dose for each individual.

Regarding the starting dose of 200 mg BID, patients with bodyweight < ~80 kg had a higher probability of exceeding the C_{max} thresholds defined as safety limits (>1500, >2500 ng/dL etc.) compared to the rest of the population for the same initial dose of 200 mg BID. The clear safety impact of such C_{max} excursions is unknown at this time. In case these C_{max} excursions, albeit for a limited time before getting possibly down-titrated based on the individualized titration approach, are considered a safety issue, then these patients (bodyweight < ~80 kg) could be started with an initial dose of 150 mg BID instead of 200 mg BID in order to satisfy the desired T exposure requirements from both the C_{max} and C_{avg} perspectives.

2.3.2 Effect of Renal Impairment

No formal PK study was conducted in patients with renal impairment.

2.3.3 Effect of Hepatic Impairment

No formal PK study was conducted in patients with liver impairment.

2.4 Extrinsic factors

2.4.1 What extrinsic factors such as drugs influence exposure and/or response and what is the impact of any differences in exposure on pharmacodynamics?

The primary extrinsic factor that markedly affects the absorption and the PK of T and TU is food and specifically the fat content in food. This has been discussed in earlier sections (**Figure TU-1 to TU-6**) and in more detail in the Biopharmaceutics **Section 2.5.1**.

2.4.1.1 What is the Effect of Other Drugs on TU?

No formal studies were conducted to investigate the effect of other drugs on the PK of T or TU. It should be noted that the current labels of T approved products such as Aerogel® and the recently approved IM TU, Aveed®, list only the pharmacodynamics effects with insulin, oral anticoagulants, and corticosteroids. This is a class language with all T products.

As noted in the metabolism section, TU is hydrolyzed to TU by non-specific esterases in blood, liver, intestinal walls, and other tissues. At this time, no drugs were identified that can inhibits or interfere with the synthesis of esterases and/or hydrolysis of TU to T by esterases. The sponsor believes that once TU is hydrolyzed to T and released in the systemic circulation, it is expected to behave like other T products. Therefore, the sponsor did not conduct drug-drug interaction with TU. The sponsor's current proposed label includes the same class language as other T products.

While the sponsor did not conduct metabolically based drug-drug interaction studies with oral TU since it is primarily hydrolyzed by non-specific esterases, there are potential of other drugs

that may affect the absorption of TU from the GI tract. Drugs that modify stomach pH such as antacids and ulcer drugs such as proton pump inhibitors may affect the absorption of oral TU.

2.4.1.2 What is the Effect of TU on Other Drugs?

No formal studies were conducted to investigate the effect of TU on the PK of other drugs. These will be addressed in the label.

2.5 General Biopharmaceutics

2.5.1 *In vitro* Dissolution:

Initially, TU was formulated as a hard shell liquid filled capsule. These capsules were used in the Phase 2 clinical program. Later, the sponsor decided to encapsulate the liquid fill in a soft gelatin capsule for the commercial product. The soft gelatin capsule formulation was used in both Phase III studies.

Per the Agency's recommendation dated April 22, 2009 (Type C meeting held on March 23, 2009, IND 78104), the sponsor performed *in vitro* dissolution studies to bridge hard gelatin capsules used in Phase II studies with soft gelatin capsules used in Phase III studies.

Based on ONDQA review dated September 18, 2014 the following conclusions were made in reference to the *in vitro* dissolution method development and data:

- *"The proposed dissolution method and method validation are acceptable.*
- *The proposed acceptance criteria Q= (b) (4)% at 30 minutes is acceptable.*
- *The Applicant has provided adequate stification for the differences observed between the hard shell capsule and soft gelatin capsule dissolution profiles using the proposed dissolution method. <u>Since PK data was generated using both the hard shell capsules and soft gelatin capsules, comparative dissolution profiles are unnecessary to bridge the hard shell capsule and soft gelatin capsule formulations.</u>"*

Based on the above recommendation made by ONDQA, no action is necessarily from the clinical pharmacology perspective (see ONDQA review dated September 18, 2014 for details).

2.5.2 What is the Effect of Food?

Two studies were conducted by the sponsor to address the effect of food. The first study was part of the repeat dose study in hypogonadal men (Study CLAR-08005) and the second study was a definitive study to evaluate the effect of different percentages of fat content in meals (Study CLAR-09008).

From Study 08005, there was a marked increase in T and DHT levels when TU was administered with food compared to overnight fast (**Figures 2.5.1.1 and Table 2.5.1.1**). In this test period of the study (i.e., period 3) 2 x 200 mg TU capsules were administered in one arm after an overnight fast that was continued for an additional 4 hours after drug administration. In the fed arm of the study, the same dose was administered 30 minutes after breakfast.

Figure 2.5.1.1. Mean T and DHT Concentrations in Treatment Period 3 Following 200 mg TU BID on day 7/8 Post AM Dose (Study 08005 and Table 2.5.1.1).

A: T Profiles **B: DHT Profiles**

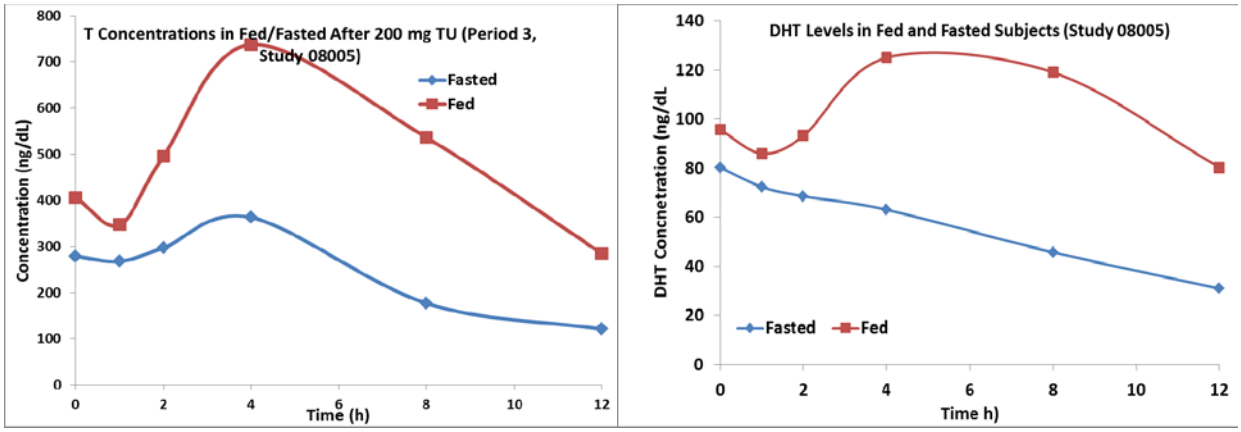


Table 2.5.1.1. Summary of Food-Effect Comparison in Treatment Period 3 (200 mg of T, as TU, BID (Study 08005)

	After High Fat Breakfast		While Fasting		Geometric Mean of Individual Ratios
	Arithmetic Mean	Geometric Mean	Arithmetic Mean	Geometric Mean	
C_{max} (ng/dL)	955	854	394	365	0.426
AUC_{0-12} (ng•hr.dL)	6217	5682	2894	2692	0.471
Administration under fed conditions (high fat breakfast) was used as the reference					

The same trend was also observed in the definitive effect of food study for T, TU and metabolites (Study 09008). This study was conducted at the maximum dose of 300 mg as 3 x 100 mg TU capsules following an overnight fast that continued for about 4 hours post drug administration. In the fed portion of the study the dose was administered 30 minutes following the consumption of breakfast containing 6-10%, 20%, 30%, and 50% of fat (Table **2.5.1.2).**

Table 2.5.1.2. Food Composition Parameters

Treatments	Total Energy (Kcal)	Total Weight (g)	Total Lipid (g)	Total Carbo-hydrate (g)	Total Protein (g)
Fasting	0	0	0	0	0
6-10% Fat	853	662	9	182	27
20% Fat	887	662	20	159	26
30% Fat	894	662	30	139	26
50% Fat	878	662	49	92	25

As shown in the above table, the % of fat content corresponds to approximately 10 grams to 50 grams of lipid. There were no changes in the total calories, total weight, and total protein in these arms. The mean total calories were approximately 870 Kcal, the total weigh was 662 grams, and total protein was 26 grams. However, there was gradual decrease in total amount of carbohydrate from 182 grams to 92 grams to maintain the total calories. It should be noted that the 6 to 10 % fat arm was based on the range reported by the sponsor, depending on the amount or volume of food being consumed by each subject.

Results:

Based on this study there was a gradual increase in androgen levels with an increase in percent of fat content (**Figures 2.5.1.2-4 and Table 2.5.1.3**).

Figure 2.5.1.2. Mean T, TU, and DHT Concentrations-Time Profiles in Fed and Fasted Conditions After 300 mg (3 x 100 mg) Capsules (source Study 09008 Tables 14.3-7, 14.46-14.50, 14.61-14.65).

A: T Profiles **B: TU Profiles** **C: DHT**

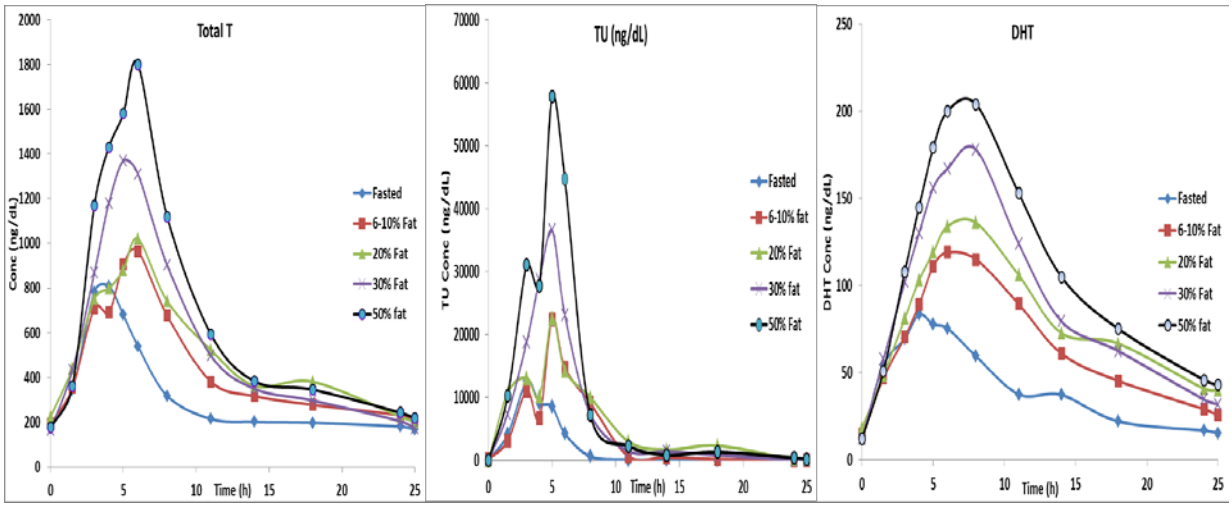


Figure 2.5.1.3. Individual and Mean (solid line) T Cavg and T Cmax in Fed and Fasted Conditions After 300 mg (3 x 100 mg) Capsules (Reviewer's Analysis based on Study 09008, Table 11.4.4.12.a).

A: T Cavg (All Subjects, n=16) **B: T Cmax (All Subjects, n=16)**

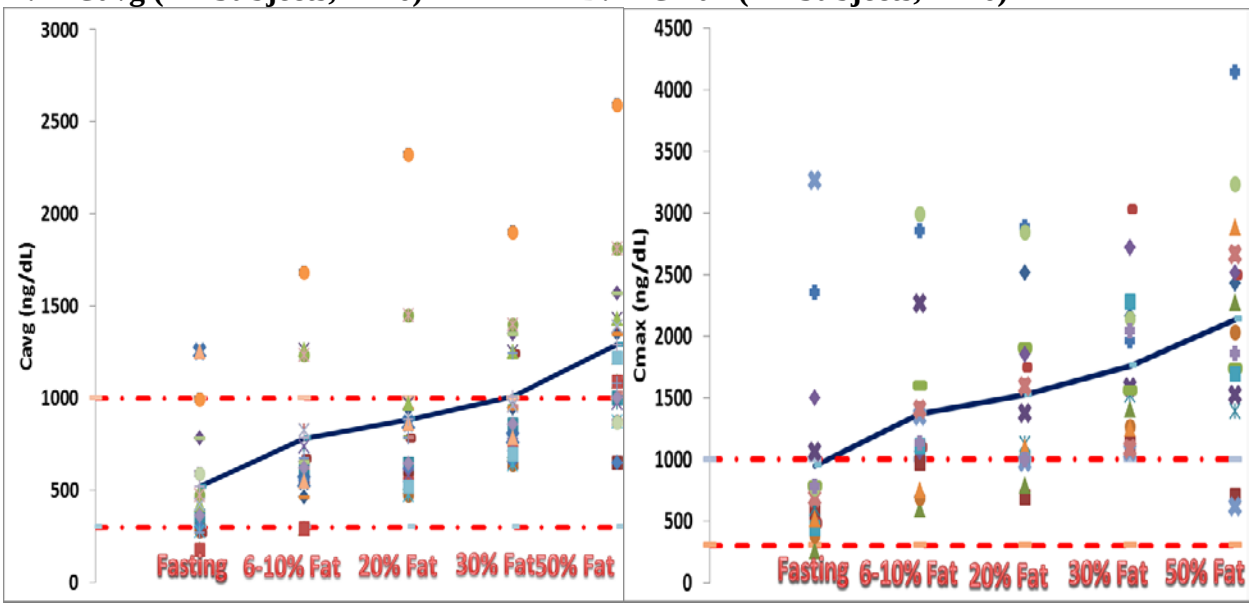


Figure 2.5.1.4. Individual and Mean (solid line) TU Cavg and TU Cmax in Fed and Fasted Conditions After 300 mg (3 x 100 mg) Capsules (Reviewer's Analysis based on Study 09008, Table 11.4.4.12.a).

A: TU Cmax (All Subjects, n=16) **B: TU AUC (All Subjects, n=16)**

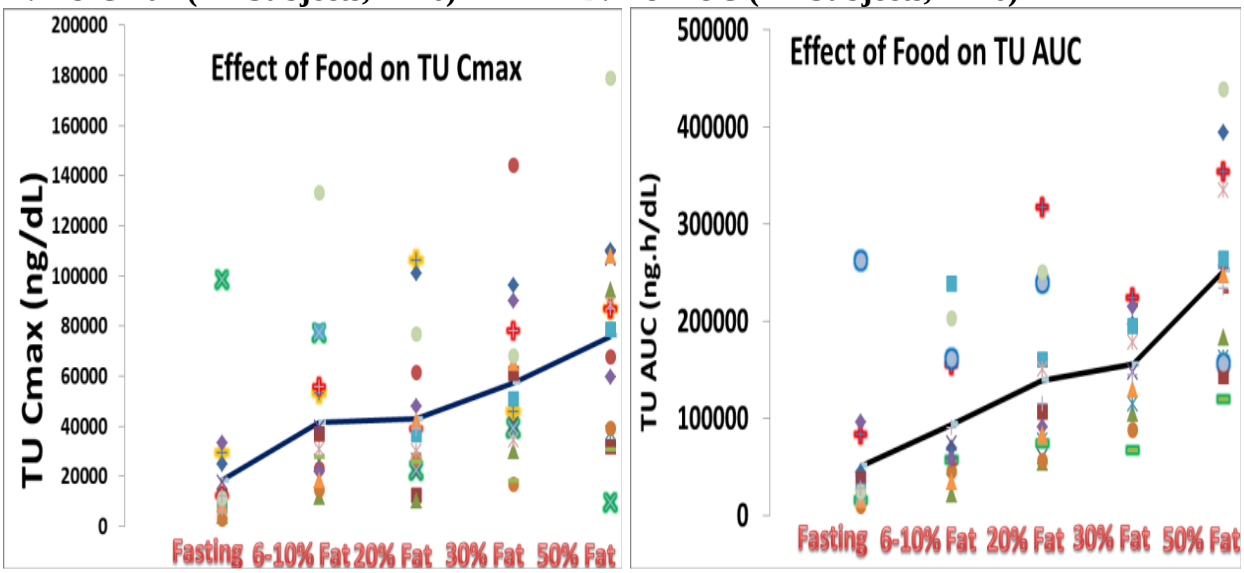


Table 2.5.1.3. Mean (± SD) PK Parameters of Androgens in Fed and Fasted Conditions After 300 mg (3 x 100 mg) Capsules (source Study 09008, Tables 11.4.4.1.2a, 11.4.4.1.5a and 11.4.4.1.8a).

Parameters	Fasting	6-10% Fat	20% Fat	30% Fat	50% Fat
Cmax (ng/dL)					
T	948 ± 798	1370 ± 732	1520 ± 711	1760 ± 598	2140 ± 901
TU	18400 ± 23000	41400 ± 32100	42900 ± 29200	57300 ± 33000	75900 ± 41700
DHT	102 ± 78	150 ± 100	174 ± 93	202 ± 102	230 ± 118
Cavg (ng/dL)	526 ± 324	781 ± 385	884 ± 505	1010 ± 356	1260 ± 477
AUC (ng.h/dL)					
T	7787 ±3671	10853 ± 4287	12461 ± 5027	13633 ± 3775	16457 ± 5581
TU	51000 ± 66000	93700 ± 67600	139300 ± 81600	155800 ± 52700	252200 ± 94300
DHT	987 ± 676	1658 ± 1128	2021 ± 1270	2302 ± 1405	2738 ± 1859

Reviewer's Comments on Effect of Food:

While there is a clear relationship between the fat content of the meal and the level of androgens following TU administration, the primary issue with such observation is the meal-to-meal and day-to-day variability in androgens levels driven by the variability in fat content of food.

The sponsor proposed that the drug should be taken with food (i.e., not on empty stomach). In general, the presence of food enhances the absorption of certain drugs as a result of an increase in blood supply at the site of absorption in the gastrointestinal (GI) tract. However, in the case of TU, the mechanism of enhancement of TU absorption is only partially associated with increased blood supply at the absorption site in the GI tract. The designed mechanism of this dosage form is to increase absorption via the lymphatic system through an increase in both the lipophilicity and emulsification of the TU in the presence of fat.

At the time of writing this review, no labeling changes are recommended in terms of how the drug should be administrated in reference to meal and fat contents in order to minimize the variability and improve the predictability of androgen levels. The following three options were presented at the FDA AC meeting on September 18, 2014 (**see appendix 4.5 for the slides**):

Option 1 (Fasting): Since there was relatively some absorption after fasting, then the drug can be given on empty stomach. If so, T level will be relatively predictable with less fluctuation. However, the dose may need to be increased, possibly doubled. That would create another safety issues if the patient do not comply with the instruction and may take the drug with food. Therefore, the T exposure will be markedly increased if inadvertently or even deliberately administered with high dose.

Furthermore, patients will quickly learn the potential effect of fat and may miss use and abuse the drug by deliberately taking it with high fat food to enhance the absorption. This is particularly dangerous if the prescribed dose increased in fasting conditions. Yet, it is recognized that it can also be miss used with any dose.

For this option, patient compliance would be the essence of the successful therapy. Patients may be instructed to specifically take the drug immediately after waking up in the morning and before breakfast. But the evening dose would be challenging, depending on patients personal and work life style.

Based on the PK data, this option can be implanted, but with high risk of over exposure and over dosing, inadvertently or deliberately, if the dose is increased. Also, based on the PK data, if oral TU is administered on empty stomach at the regular dose of 100 to 300 mg BID, the desired T levels of 300-1000 ng/dL will not be achieved in many patients.

Option 2 (irrespective of food): The drug can be given irrespective of food at the same recommended dose (i.e., with or without food). While this may be more practical, convenience, and may increase patient's compliance, the titration process will be more complicated and challenging. In addition, the T levels would be highly fluctuating as in **Option 1**.

Non-compliant patients or those patients who are expected to be non-compliant should start at the lowest dose and then titrate up, if needed. However, those non-compliant patients are expected not to return to the clinic for titration follow up.

Option 3 (maintain usual diet and % fat): In this option the patient must control the % of fat in meals. While this may better predicts and control of T levels and is in some way in alignment with the Phase III studies, patients will have difficulty in assessing fat content in meals.

However, considering everything, the third option appears to be the best option (if not the only option). But the label must clearly emphasize consistency and adherence to the usual diet. If the patient changes diet for example from his/her usual diet to vegetarian diet and vise-versa, patient must undergo new titration process.

Each of the above option has challenges. The key issues are compliance and non-compliance. For example, the issue with options 1 and 2 is that Phase III studies were conducted with food. Therefore, without adequate clinical trial titration data with options 1 and 2, it may be difficult to justify these two options. Option 3 will minimize variability in absorption due to food effect, but as mentioned above, it is difficult and impractical to maintain every day.

Summary of AC Meeting in reference to Food (September 18, 2014):

The above three options were presented at the FDA AC meeting on September 18, 2014. While some members of the panel were stunned with the variability presented at the meeting and others were skeptical about the entire approach. Yet, the committee members and the Agency did not reach consensus on how the drug should be administered with reference to food. Overall, the majority of the committee members voted against the approval of the product.

Conclusion:

At the time of writing this review, no internal consensuses have been reached on what additional studies are needed or how the drug will be administered with respect to food. Based on the internal discussion and the AC outcome, there is no "ideal" option without pros and cons. While the availability of oral TU would provide the convenience of easy oral administration than the gel, nasal, and IM injects, it appears that it is a product with "double-edge sword" due to the inherent wide variability with food, potential for high exposure, and potential for CV risk.

The final point is that whichever option is to be implemented or the hybrid of the three options, patient's compliance is critical for the optimal therapy. Therefore, without additional studies to optimize the administration regimen in reference to food, fat content, and the titration process, from the clinical pharmacology perspective these are considered major deficiencies among others for this product.

2.5.3 Was the to-be-Marketed Formulation Used in the Clinical Trials?

Yes the to-be-marketed formulation was used in both Phase III clinical trials (Studies 12011 and 09007).

As indicted earlier, the sponsor switched from a hard gelatin capsule used in Phase II studies to a soft gelatin capsule used in Phase III studies. The sponsor conducted an *in vitro* dissolution experiment using the soft and hard gelatin capsules (see earlier Section 2.5.1 and ONDQA review dated September 18, 2014). Based on the ONDQA review, the in vitro dissolution method was acceptable.

In addition, from the clinical pharmacology perspective, the sponsor submitted extensive PK data from Phase III studies utilizing the to-be-marketed dosage forms. Therefore, it is not necessarily to conduct bioequivalence studies between the two dosage forms.

2.5.4. Is there Potential for Dose Dumping with Alcohol?

The issue of "dose dumping" in the presence of alcohol is usually a concern with extended release and/or controlled release formulations. Since the proposed to-be-marketed formulation is an immediate release formulation, no dose dumping would be expected at this time.

However, alcohol could interrupt the emulsification of TU by direct solubilization. The product is soluble in alcohol and may disrupt the lymphatic absorption. The scenario is that if the drug is administered in the presence of alcohol it could become solubilized and then absorbed normally. In this circumstance, the first pass effect could be high. Although somewhat theoretical, the potential impact on bioavailability is sufficient to include appropriate language in the label to avoid the administration of oral TU in the presence of alcohol.

2.5.4 Are the method and dissolution specifications supported by the data provided by the sponsor?

Overall, the *in vitro* dissolution methodologies needs further work to establish the link between the hard gelatin capsules and the soft gelatin capsules. The final assessment of the method specifications is referred to ONDQA and CMC teams.

2.6 Analytical Section

As indicated in several sections of this review, the principle analyte was T concentrations. The primary focus of Phase III studies was on the PK and T levels. However, additional analytes of interest (DHT, TU, and DHTU) were monitored in this NDA. In both Phase III studies DHT was measured, while TU and DHTU were only measured in Study 09007.

Serum T, DHT, TU, and DHTU were assayed using a sensitive and specific validated liquid chromatography tandem mass spectrometry (LC-MS/MS) method at the (b) (4) The following is a summary of the validation parameters for each analyte:

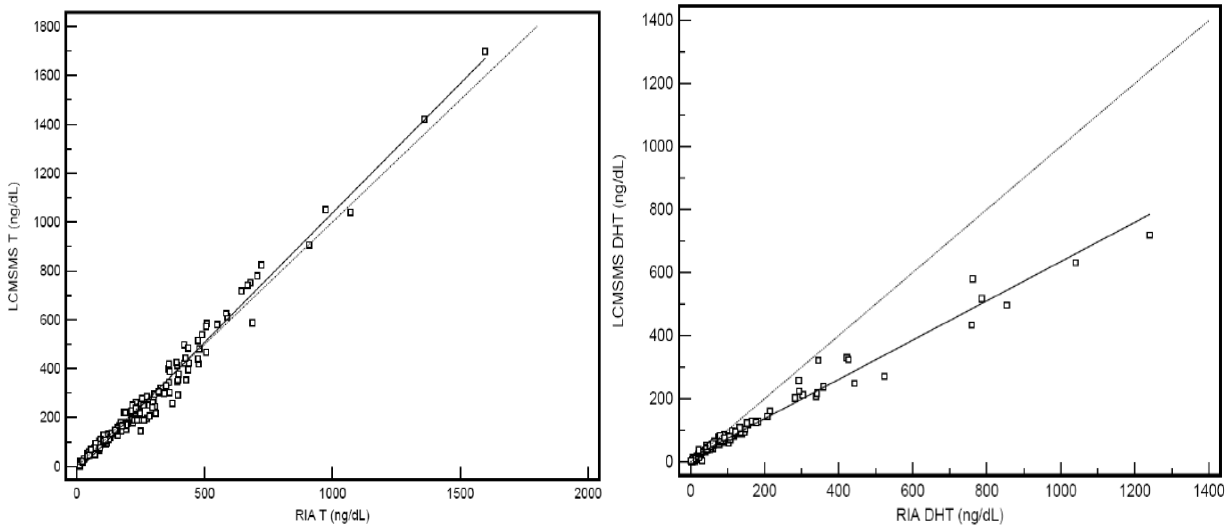
Analyte	Range[1] (ng/dL)	Dilution Range[2] (ng/dL)	Precision[3] (%CV)	Accuracy Range[4] (%)
T	2 to 2000	10000.00	5.8-7.2	99.1-99.9
DHT	2 to1000	5000.00	7.8 to 12.1	95.2 to 105.7
TU	1 to 3000	24000.00	7.6 to 10.4	97.5 to 98.8
DHTU	1 to 3000	24000.00	9.3 to 15.4	95.6 to 98.8

[1] *Assay range and Lower Limit of Quantification (LLOQ)*
[2] *Assay range after dilution with upper Limit of Quantification (ULOQ)*
[3] *%CV for Quality control (QC) samples*
[4] *Accuracy range of QC samples*

The sponsor submitted a validation report related to sensitivity and specificity of all components. In addition, the sponsor conducted experiments comparing other established methodologies with the used LC-MS assay. **Figure 2.6-1** shows example of the correlation between LC-MS and the established radioimmunoassay (RIA) for T and DHT.

Figure 2.6-1. Relationship Between LC-MS and RIA for the Determination of Serum T and DHT.

A: T **B: DHT**



The above figures show that both methods are identical for the determination of serum T and DHT. The same relationship was also shown in the published reports from the same laboratories used LC-MS method contracted by the sponsor for this product. These reports also include validation parameters for the LC-MS for all components (Wang et al., Steroid, 73:1345-1352, 2008 and Shiraishi et al., Clin Chem 54 (11): 1855-1863, 2008).

For TU, the intra-assay %CV was <7.91% for all runs, including low (~3000 ng/dL), medium (~10000 ng/dL) and high (~30000 ng/dL) TU serum concentrations. The inter-assay %CV was 7.55%, 10.42%, and 7.55% for the low (~1000 ng/mL), medium (~10000 ng/dL), and high (~100000 ng/dL) TU serum concentrations, respectively

For DHTU the mean intra-and inter-assay %CV was <13.93% and <15.4% for all pool runs of low (~3000 ng/dL), medium (10000 ng/dL) and high (~23000) serum DHTU concentrations, respectively.

Is There In Vitro Conversion of TU to T During Serum Analysis?

Synopsis:

The *in vitro* conversion of TU to T in blood and serum during the analytical procedure and blood collection in test tubes is moot point based on the Office of Scientific Investigation (OSI) inspection report dated August 8, 2014 by Dr. Young M Choi and the follow up clinical pharmacology special review by Dr. Chongwoo Yu dated September 19, 2014 under the NDA 206089 and IND (b) (4).

Background:

On June 30, 3014 (b) (4) sent a correspondence reporting that there is a conversion of TU in serum into T during blood collection process. Based

on this conversion, they reported a potential increase in T concentration by about 35% compared to the true concentration.

Sponsor's Data:

The sponsor and the analytical lab were aware of such *in vitro* conversion and conducted a series of *in vitro* experiments to rule out such conversion. The results of these experiments were published in the above cited papers in the analytical section by Wang et al 2008 and Shiraishi et al 2008. In addition, OSI inspected the data and validated the sponsor's observation and blood collection process.

Reviewer's Comments:

In addition to OSI inspection, the following conclusions can be made based on Dr. Yu's review:

- As indicated above, the potential conversion of TU to T has been previously reported in the literature
- No *in vitro* hydrolysis of TU to T was observed *in vitro* at a super concentration of 1000 ng/mL (100,000 ng/dL) of TU.
- The use of esterase inhibitors such as sodium fluoride (NaF) may help minimizing the hydrolysis from TU to T. However, this may not always be practical as some clinics may not have NaF tubes available.

OSI Inspection:

As stated above, the OSI inspection reports for Studies 09007 and 12011 and non-clinical/analytical sites were completed. No issues were identified (OSI inspection report dated August 8, 2014). The following conclusion was made in OSI report: "*clinical and bioanalytical data from* (b) (4) *are acceptable for further review*".

Sponsor's Response to the IR Analytical Letter Dated July 25, 2014:

The sponsor was requested to provide the following information listed in the IR letter dated July 25, 2014:

- Literature reports the potential of hydrolysis testosterone undecanoate (TU) that can result in an over-estimation of testosterone (T) concentration. We note that there is no documentation on the investigation of this issue submitted in your bioanalytical method validation report. In addition, we note that no bioanalytical study reports (i.e., method performance reports) were submitted for any clinical trials.
    - Submit any information/data generated during the evaluation of this matter and provide your rationale/approach of how you have accounted for the potential over-estimation of T concentration due to the hydrolysis of TU during your bioanalysis.

- In addition, submit bioanalytical study reports (i.e., performance reports) for all clinical trials including the Studies CLAR-09007 and CLAR-12011 supporting your new drug application.

- Reference is made to the Agency's *Bioanalytical Method Validation Guidance* (http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm064964.htm). Submit missing information from your bioanalytical method validation report including (but not limited to) the following:
  - Detailed information on your bioanalytical method (e.g., sample preparation details, HPLC gradient conditions, and mass spectrometer conditions)
  - Complete serial chromatograms from 20% of subjects, with standards and QCs from those analytical runs
  - Information on bench-top and processed sample (i.e., auto-sampler) stability assessments
  - Detailed information on how the effect of collection tubes was evaluated (e.g., how endogenous T concentrations were determined, the description of the collection tube type by color)
  - Detailed information on how incurred sample reanalysis (ISR) was conducted (e.g., how ISR samples were selected, the total number of study samples, and the percentage [%] of ISR samples)

Sponsor's Response to the IR Letter Dated July 25, 2014:

On August 6, 2014 the sponsor responded to the above requests and submitted all the requested information totaling 6542 pages of document. The following is a summary of the sponsor's response:

In vitro hydrolysis: Prior to starting clinical studies, the sponsor confirmed that TU would not be hydrolyzed *in vitro* (see also above discussion). The sponsor cited the above literature article by Wang et al and provided supported data. The sponsor demonstrated no impact on measured T concentrations by TU (see detailed discussion of the data below).

Bioanalytical study reports: As requested, the sponsor submitted the bioanalytic study reports for all analytes measured in Studies 09007 and 12011.

Bioanalytical method: The sponsor submitted detailed information on each of the bioanalytical method and the standard operating procedure (SOP) for each analyte including but not limited to sample preparation, HPLC gradient, mass spectrometer conditions as well preparation of calibration standards and quality controls (QCs).

Complete serial chromatograms: The sponsor submitted serial chromatographs from 20 % of the subjects with standards and quality controls for all analytes.

Samples processing and stability: The detailed information on bench-top and processed sample stability were submitted along with the validation Report of each analyte.

Effect of collection tubes: The detailed information on the effect of collection tubes was provided including the validation report of each Analyte.

Incurred sample reanalysis (ISR): The sponsor stated that ISR was conducted in approximately 5 % of samples according to the published FDA Guidance.

Summary of *In Vitro* Hydrolysis Data:

Rationale: The observed high concentration of TU in blood may interfere with serum T measurements because the possible hydrolysis to T by esterases present in the blood during blood collection and processing. Therefore, the sponsor provided the following data to demonstrate that no TU conversion to T occurred *in vitro* during the blood collection, processing and assay.

Synopsis of the Experiments:

The sponsor also used another testosterone ester, testosterone enanthate (TE) as a comparator in the *in vitro* experiments. The details of these experiments can be found in the above cited papers. Briefly, TU and TE were added to the plain blood collection tube (red top) or the NaF tube (light grey tube containing 30 mg NaF). The tubes were spiked with series of concentration up to 1000 ng/mL (100,000 ng/dL) of TU and TE.

Results:

The results are summarized in

The following is the summary of the data submitted by the sponsor on August 6, 2014 (see **Tables 2.6.-1 and 2, Figures 2.6.2-4, and Dr. Yu's limited review to *in vitro* hydrolysis review)**:

- Addition of TE to blood in red top tubes (no additive) resulted in a dose dependent increase in serum T levels. The concentration of serum T measured were increased by approximately 73 ng/dL and 740 ng/dL at TE concentration of 100 ng/mL (10,000 ng/d) and 1000 ng/mL (100,000 ng/dL), respectively (**Table 2.6-1**). However, when NaF coated tubes were used the hydrolysis of TE was reduced due to inhibition of esterases. By contrast, when TU was added, T levels were not significantly increased (**Figure 2.6-2 and 3**). This indicates that TU is not hydrolyzed in the red top tubes with no additives. Furthermore, the addition of either T esters did not affect the concentration of serum DHT measured.

- Addition of both TU and TE to blood in red top tubes showed the same result as addition of TE alone showing that the increase in serum T concentration was due to the hydrolysis of TE but not TU (**Table 2.6-1 and Figure 2.6-2**).

- The presence of fluoride decreased the serum T by about 20% and serum DHT measurements by 16% compared to blood collected in red top without TE+TU due to

interference in the steroid assays. The increase in serum T due to the hydrolysis of TE to T was prevented by fluoride.

What is the Effect of NaF on Serum T and DHT?

The sponsor conducted an experiment to test the effect of T esters on the measurement of T and DHT. This experiment was conducted using tubes containing tubes 30 mg NaF (light grey) or 10 mg NaF (dark grey). As shown in **Table 2.6-2 and Figure 2.6-4**, mean serum T (269.3 ng/dL) measured from four blood samples collected in grey top tubes were approximately 79% of the values measured from blood that was collected in plain tubes (346 ng/dL). Serum DHT levels in blood collected in tubes with NaF were approximately 80% of the DHT levels when blood was collected in tubes with no additives (fluoride tube 11.05 ng/dL; plain tubes 14.2 ng/dL).

Using data from the 4 subjects in **Tables 2.6-1 and 2**, for blood collected in red top versus light grey (fluoride 30 mg) tube, serum T was approximately 82% of the value in the light grey tube and serum DHT was approximately 80 % of the value in the light grey tubes compared with the red top (no additive). These data showed that collection of blood in fluoride containing tubes will actually lower serum T and DHT (not increase).

It should be noted that the sponsor did not use fluoride containing tubes for the collection of samples for hormone measurements, except for the measurement TU in Study 09007.

Table 2.6-1 Individual and Mean *In vitro* Hydrolysis Data of TE and TU Esters (Source: August 6, 2014 submission, Appendix 1)

Testing effect of adding TE or TU and TE+TU in blood on T/DHT Measurement by LCMSMS — Date 12/03/2007

Tube	Collection Tube	Spiked with	ng/ml	Subject BB T (ng/dL)	Subject BB DHT (ng/dL)	Subject AA T (ng/dL)	Subject AA DHT (ng/dL)	Average AA and BB T (ng/dL)	Average AA and BB DHT (ng/dL)	Average T (ng/dL)	Average T (nmol/l)	Average DHT (ng/dL)	Average DHT nmol/L
1	Red top	TE	0	315	27.3	205	13.7	260.0	20.5	259.0	8.98	20.1	0.69
2	Red top	TE	0	315	25.8	201	13.7	258.0	19.8				
3	Red top	TE	10	319	22.9	218	13.9	268.5	18.4	259.8	9.01	18.3	0.63
4	Red top	TE	10	290	22.7	212	13.7	251.0	18.2				
5	Red top	TE	30	328	24.4	230	14.4	279.0	19.4	269.0	9.33	19.2	0.66
6	Red top	TE	30	298	23.7	220	14.2	259.0	19.0				
7	Red top	TE	100	344	22.4	311	13.8	327.5	18.1	331.8	11.50	18.2	0.63
8	Red top	TE	100	359	23	313	13.6	336.0	18.3				
9	Red top	TE	300	361	20.4	324	14.4	342.5	17.4	341.5	11.84	17.7	0.61
10	Red top	TE	300	370	22.2	311	13.9	340.5	18.1				
11	Red top	TE	1000	984	24.3	1180	15.6	1082.0	20.0	999.3	34.65	19.3	0.67
12	Red top	TE	1000	908	24.1	925	13.3	916.5	18.7				
13	Red top	TU	0	300	23.2	219	14.4	259.5	18.8	257.0	8.91	18.7	0.64
14	Red top	TU	0	301	24.7	208	12.6	254.5	18.7				
15	Red top	TU	10	309	24.3	214	15.0	261.5	19.7	267.3	9.27	20.5	0.70
16	Red top	TU	10	319	27.3	227	15.3	273.0	21.3				
17	Red top	TU	30	273	21.6	218	15.8	245.5	18.7	255.3	8.85	20.3	0.70
18	Red top	TU	30	305	25.7	225	18.0	265.0	21.9				
19	Red top	TU	100	300	24.4	234	18.5	267.0	21.5	255.5	8.86	20.6	0.71
20	Red top	TU	100	272	20.5	216	19.1	244.0	19.8				
21	Red top	TU	300	322	27.2	224	14.2	273.0	20.7	249.8	8.66	19.1	0.66
22	Red top	TU	300	236	21	217	13.8	226.5	17.4				
23	Red top	TU	1000	283	24.1	249	14.2	266.0	19.2	277.0	9.60	20.2	0.70
24	Red top	TU	1000	329	26.6	247	16.0	288.0	21.3				
25	Red top	TU+TE	0	308	26.9	218	16.8	263.0	21.9	263.0	9.12	21.3	0.73
26	Red top	TU+TE	0	282	25.6	244	15.8	263.0	20.7				
27	Red top	TU+TE	10	305	24.8	232	14.9	268.5	19.9	268.3	9.30	20.5	0.70
28	Red top	TU+TE	10	303	25.8	233	16.3	268.0	21.1				
29	Red top	TU+TE	30	298	25.4	223	14.5	260.5	20.0	261.3	9.06	20.1	0.69
30	Red top	TU+TE	30	298	25.3	226	15.0	262.0	20.2				
31	Red top	TU+TE	100	376	25.7	275	15.6	325.5	20.7	342.8	11.88	20.4	0.70
32	Red top	TU+TE	100	391	25.6	329	14.6	360.0	20.1				
33	Red top	TU+TE	300	373	25.9	259	15.7	316.0	20.8	330.0	11.44	20.5	0.70
34	Red top	TU+TE	300	377	26.1	311	14.1	344.0	20.1				
35	Red top	TU+TE	1000	1170	30.7	1380	18.6	1275.0	24.7	1177.5	40.83	23.4	0.81
36	Red top	TU+TE	1000	1080	27.6	1970*	16.8	1080.0	22.2				
37	Lt Gray	TU+TE	0	262	19.7	195	12.4	228.5	16.1	215.3	7.46	15.6	0.54
38	Lt Gray	TU+TE	0	239	18.6	165	11.7	202.0	15.2				
39	Lt Gray	TU+TE	1000	397	19.8	302	12.6	349.5	16.2	340.0	11.79	16.1	0.55
40	Lt Gray	TU+TE	1000	370	19.1	291	12.7	330.5	15.9				

Table 2.6-2 Effect of Fluoride Containing Tubes on Serum T and DHT Measurements (Source: August 6, 2014 submission, Appendix 1)

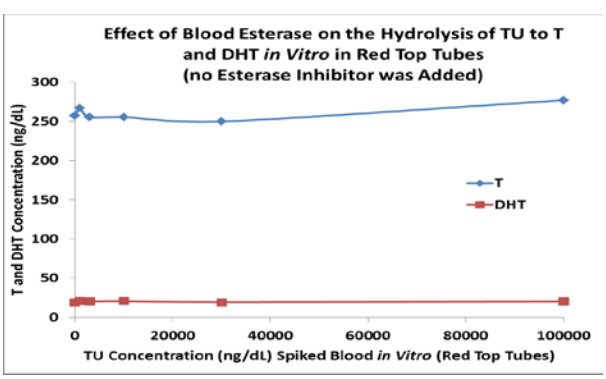
Measurement of T and DHT with red/grey/light grey top tubes

		T ng/dL			Mean			% of red		
Date	Subject	Red	Grey	Light Grey	Red	Grey	Light Grey	Red	Grey	Light Grey
11/15/2007	1	433	327		420.5	325			77.3	
	1	408	323							
11/9/2007	2	368	296		395	282.5			71.5	
	2	422	269							
11/28/2007	3	320	282	283	337.5	276	292		81.8	86.5
	3	355	270	301						
	4	231	192	189	231	193.5	178		83.8	77.1
	4		195	167						
12/3/2007	AA	205		195	203		180			88.7
	AA	201		165						
	BB	315		262	315		250.5			79.5
	BB	315		239						
								Mean %	78.6	82.2

		DHT ng/dL			Mean			% of red		
Date	Subject	Red	Grey	Light Grey	Red	Grey	Light Grey	Red	Grey	Light Grey
11/15/2007	1	23.5	17.1		22.5	17.45			77.6	
	1	21.5	17.8							
11/9/2007	2	18.8	15.4		19.4	15.3			78.9	
	2	20	15.2							
11/28/2007	3	17.1	16.5	15.2	18.7	15.7	15.5		84.0	82.9
	3	20.3	14.9	15.8						
	4	14.2	11.3	11.3	14.2	11.05	10.85		77.8	76.4
	4	14.2	10.8	10.4						
12/3/2007	AA	13.7		12,4	13.7		12.1			88.3
	AA	13.7		11.7						
	BB	27.3		19.7	26.6		19.2			72.2
	BB	25.8		18.6						
								Mean %	79.5	79.9

Figure 2.6-2. Effect of Blood Esterase on the *in Vitro* Hydrolysis of TU and TE to T and DHT in Red Top Tubes (Source: August 6, 2014 submission, Appendix 1).

A: TU **B: TE**



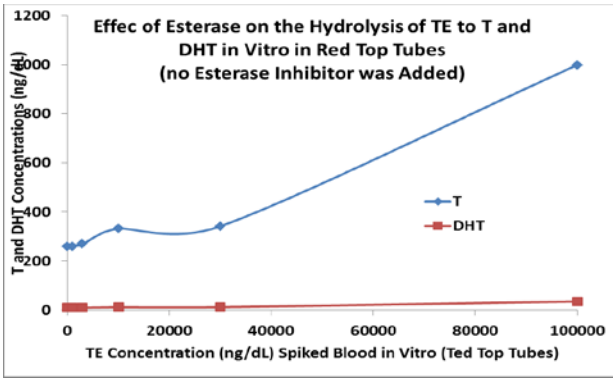


Figure 2.6-3. Effect of Blood Esterase on the *in Vitro* Hydrolysis of TU and TE to T in Red Top Tubes (Source: August 6, 2014 submission, Appendix 1).

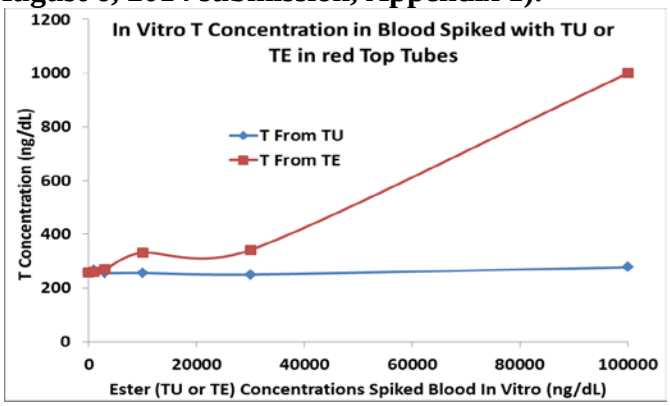
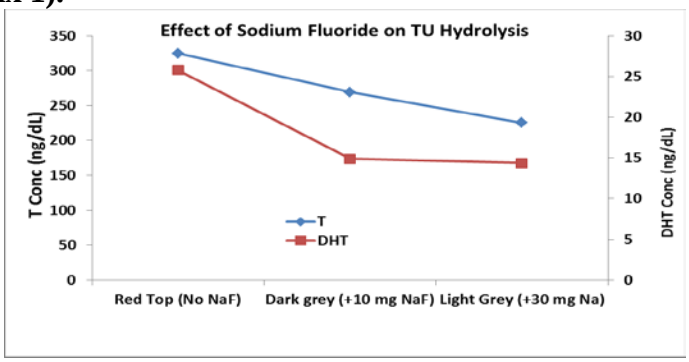


Figure 2.6-4. Effect Sodium Floride (NaF) on TU Hydrolysis (Source: August 6, 2014 submission, Appendix 1).



Conclusions:

The overall conclusion is that there is no specific issue or concern in reference to the blood collection procedures and assay of TU and its metabolites. From the clinical pharmacology perspective, the sponsor's responses are acceptable.

3.0 Labeling Comments:

Due to the deficiencies listed under the recommendation, no labeling comments are necessary at this time. All labeling meetings and discussion have been canceled.

4.0 Appendices

4.1 Sponsor's Proposed Label

Not applicable (see above)

4.2. Individual Study Review (Selected Studies)

Study CLAR-08005:

Study Title: "*Phase IIa, Repeat Dose, Pharmacokinetic Study of Oral Testosterone Ester Formulations in Hypogonadal Men*"

Objectives:

The objectives of this study were to determine the following:

- The steady-state serum PK profile for an oral formulation of TU at two dose levels administered twice-daily (BID) to hypogonadal men
- The effect of food on the steady-state PK of the TU formulation
- The effect of the combined dosing of testosterone enanthate (TE) and TU in a single formulation

Study Design:

This was repeat dose (BID X 7 days), cross-over, PK study (with food effect examined in one arm) in 29 hypogonadal men. On Days 1 to 7 of each period (and Day 8 of Period 3), subjects were administered doses according to the regimens identified shown in **Table 08005-1**. On study Days 7, 28, 49, 50, and 70, the time of administration were recorded. There was a minimum of 7-day washout interval between each period. Upon completion of the study, each subject had received all 4 dose levels.

Table 08005-1. Treatment and Dosing Regimens

	Period 1 (Days 1-7)	**Period 2 (Days 22-28)**	**Period 3 (Days 43-50)**	**Period 4 (Days 64-70)**
Treatments	TU 300 mg BID x 7 days	TU+TE 400 mg BID x 7 days	TU 200 mg BID **x 8 days**	TU+TE 300 mg BID x 7 days
Drug and Dose (all as capsules)	3 x 100 mg TU BID	2 x 100 mg TU + 1 x 100 mg TE BID	2 x 100 mg TU BID (**Day 8 fasting**)	2 x 150 mg TU + 1 x 150 mg TE BID
Total Daily Dose	600 mg	800 mg	400 mg	600 mg

Each dose was administered orally with 240 mL of room temperature water **within 30 minutes <u>after initiation of meals</u>** (breakfast and evening meals). As shown above, each treatment period was for 7 days, except on **period 3** in which subjects **fasted overnight on Day 7** and dosed the drug on **Day 8** (Study Day 50) in the morning. Subjects continued fasting on Day 8 for additional 4 hours post drug administration.

What are the Test Products?

The study drug was administered as number "00" hard gelatin capsules containing TU or a combination of TU and testosterone enanthate (TE) formulated in a self-emulsifying drug delivery system (SEDDS).

PK Blood Samples:

Blood samples for the determination of T, DHT, and E2 concentrations were collected at appropriate intervals after all treatments over 12 or 24 hours.

Study Subjects:

Of the 45 subjects screened for the study, 29 hypogonadal male subjects were enrolled and received at least one dose of study drug.

Results:

There was increase in T levels from baseline (Cmax, AUC, Cavg) following all treatments. For better visualization of the data it is presented in the bar chart (**Figures T08005-1A-C)** and in **Table T08005-2**.

Figure T08005-1A-C. Mean (±SD) T Cmax in all Periods (Study 08005)

A: Cmax **B: AUC** **C: Cavg**

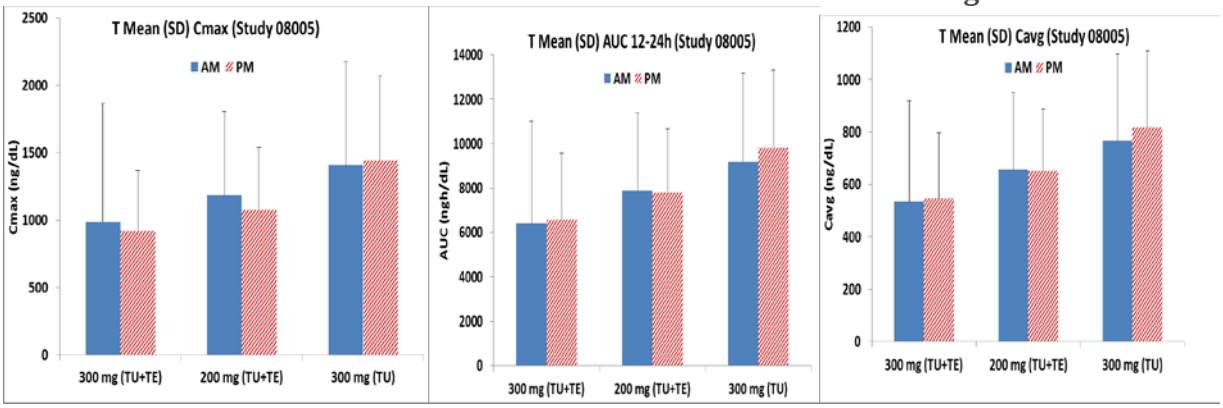
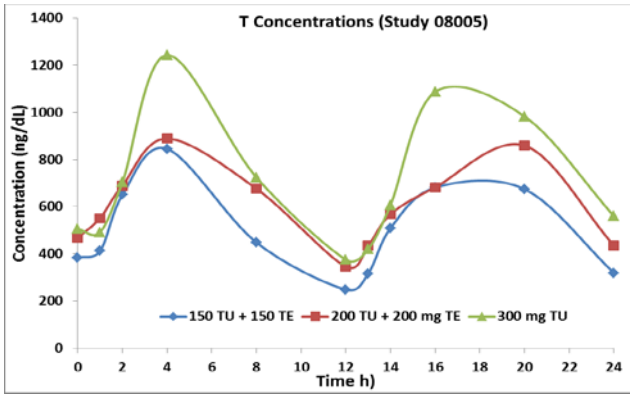


Table 08005-2. Comparison of Steady-State AM and PM PK of T with BID Dosing (Study 08005)

	Period 1 300 mg TU BID		Period 2 400 mg TU+TE BID		Period 4 300 mg TU+TE BID	
	AM Dose	**PM Dose**	**AM Dose**	**PM Dose**	**AM Dose**	**PM Dose**
Cmax (ng/dL)	1410±771	1441±627	1184±620	1078±460	990±874	922±450
$AUC_{0\text{-}12h}$ (ng.h/dL)	9179±3990	9830±3489	7881±3524	7812±2837	6401±4614	6580±3000
Cavg (ng/dL)	765±333	819±291	657±294	651±236	533±385	548±250

The plasma concentration-time profiles for T after administration of the three treatments are shown on one scale following all periods in **Figure T08005-2.**

Figure T08005-2. Mean T Concentration-Time Profiles in all Periods on one Scale (Study 08005)



It should be noted that in <u>all test periods</u>, the drug was administered 30 minutes after breakfast and dinner. However, in period 3 the 200 mg TU dose was administered in one arm after overnight fast and continued for additional 4 hours after drug administration. **Figure T08005-3 and Table T08005-3** demonstrates a marked increase in T level after TU being administered with food compared to fasting. The same data was shown in the confirmatory food effect study with different percentage of fat content in meals (**for details see also Study 09008**).

Figure T08005-3. Mean T Concentrations in Treatment Period 3 Following 200 mg TU BID on day 7/8 Post AM Dose (Study 08005).

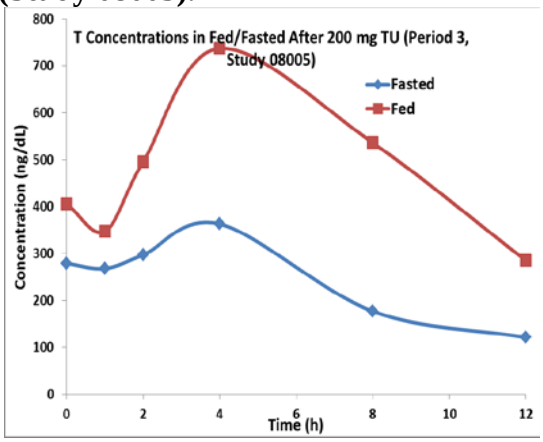
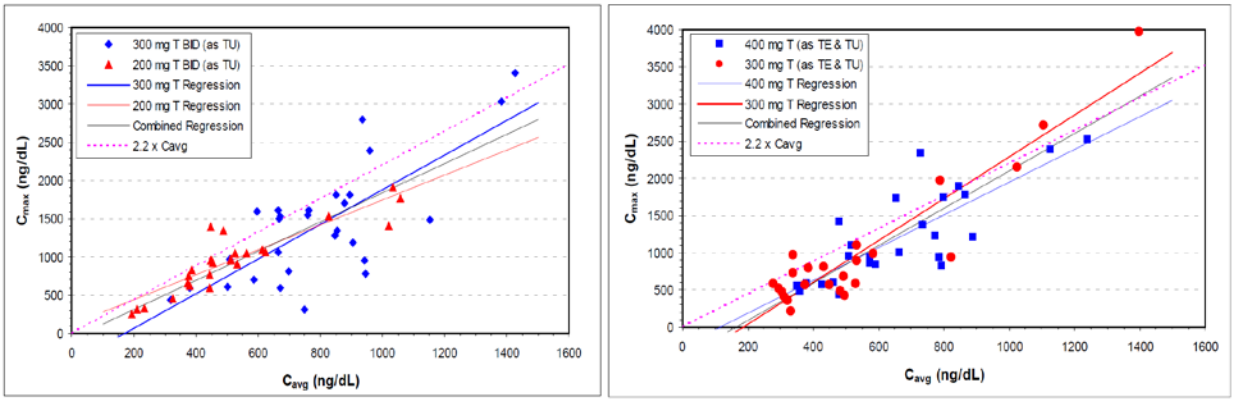


Table T08005-3. Summary of Food-Effect on T Levels in Treatment Period 3 (200 mg of T, as TU, BID (Study 08005)

	After High Fat Breakfast		While Fasting		Geometric Mean of Individual Ratios
	Arithmetic Mean	Geometric Mean	Arithmetic Mean	Geometric Mean	
C_{max} (ng/dL)	955	854	394	365	0.426
AUC_{0-12} (ng•hr.dL)	6217	5682	2894	2692	0.471
Administration under fed conditions (high fat breakfast) was used as the reference					

As shown in other studies (e.g., 09007 and 12011), there was good relationship between the Cmax and Cavg following all treatments, irrespective of formulation (**Figure T08005-4AB**). These observations are essentially important for the potential titration process in which Cmax or Cavg can be used to optimize the therapeutic dose to achieve the desired T level (for details see also Phase III studies 09007 and 12011).

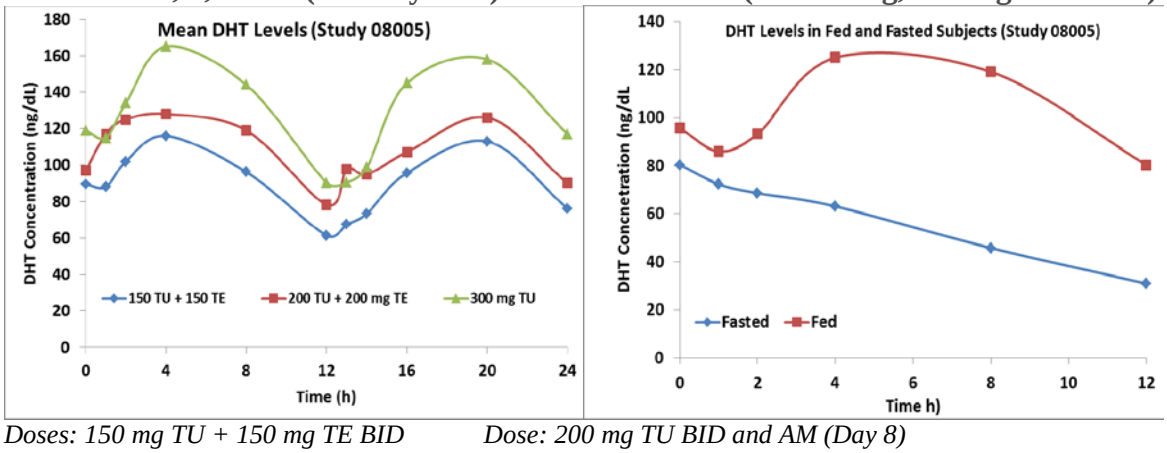
Figure T08005-4. Correlation between T Cmax and T Cavg at Steady-State with BID Administration:
A: TU Formulation **B: TU + TE Formulation**



The DHT profiles followed the same patterns of the T profiles (**Figure DHT08005-1**), including the effect of food in fasting and fed subjects (**Figure DHT08005-2**).

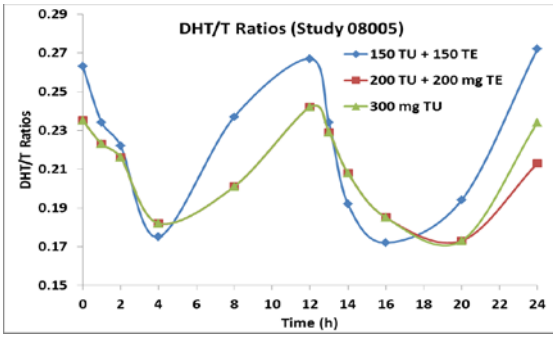
As expected, DHT concentrations were considerably lower than the analogous T values. Following all treatments, there was noticeable increase in DHT/T ratios (**Figure DHT08005-3**). Due to the lag time involving conversion of T to DHT the observed nonlinear relationship with dose was expected. However, as T concentrations increase, DHT concentrations also increase, but at slower rate. Therefore, DHT/T ratio was decreased with increasing T concentration.

Figure DHT08005-1. Mean DHT Concentration-Time Profiles in <u>all Periods</u> (Study 08005)
A: Periods 1, 2, and 4 (fed only BID) **B: Period 3 (fed/fasting, 200 mg AM Dose)**



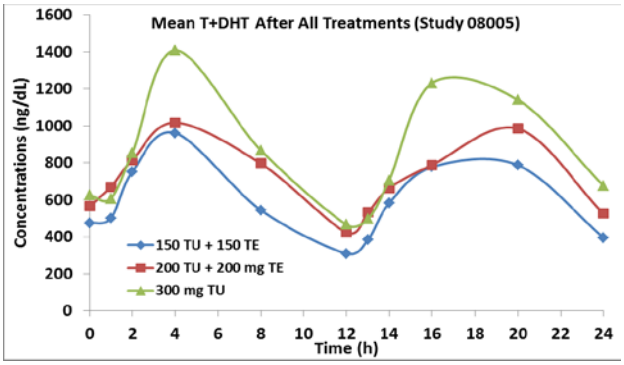
Doses: 150 mg TU + 150 mg TE BID *Dose: 200 mg TU BID and AM (Day 8)*
200 mg TU + 200 mg TE BID
300 mg TI BID

Figure DHT08005-3. Mean DHT/T Ratios in all Periods on one Scale (Study 08005)



Since both T and DHT have androgen activity, total androgen activity should represent the sum of both T and DHT concentrations. Therefore, the total levels of T + DHT is important for the final assessment of the safety and efficacy of the formulation. As expected, there was increase in total T+DHT levels following all treatments (**Figure DHT08005-4**).

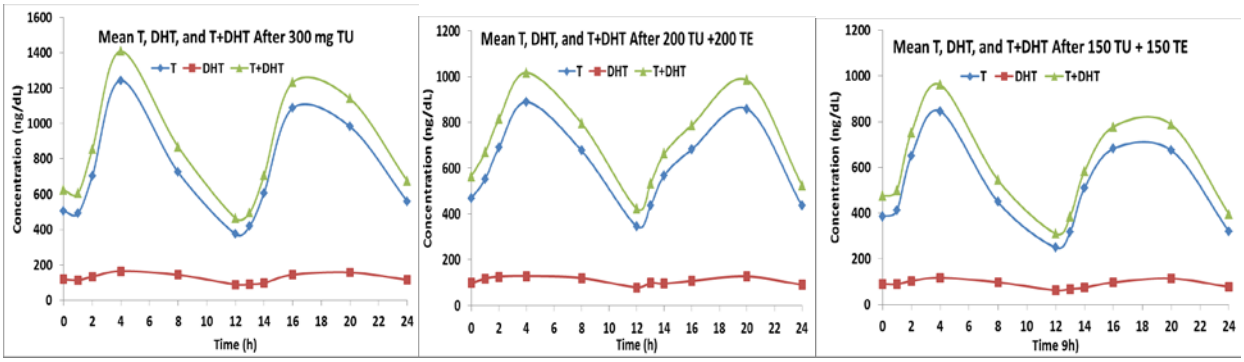
Figure DHT08005-4. Mean T+DHT Concentrations Following All Treatments (Study 08005)



The second set of Figures show the levels of T, DHT, and T+DHT separately at each dose (**Figures DHT08005-5ABC**). From these figure, total androgen concentrations were closely track those of T concentrations because T is the dominant contributor to the summed concentration.

Figure DHT08005-5. Mean Total Androgens Concentrations (Study 08005)

A: Period 1 **B: Period 2** **C: Period 4**



Period 1: 300 mg TU BID, Period 2: 200 mg TU + 200 mg TE BID, and Period 4: 150 mg TU + 150 mg TE BID

The other known active metabolite of T, is estradiol (E2). Overall, mean E2 concentrations at the end of each treatment period were approximately 2 to 3 times the initial pre-treatment level (**Table E208005-1**). In Treatment Periods 1, 2 and 4 the E2 concentrations at the end of the PM dosing interval of Day 7 were approximately 20% to 25% greater than prior to Day 7 AM dose.

Table E208005-1. Mean (±SEM) Estradiol (E2) Concentrations (ng/dL) by Treatment Period (Study 08005)

	Baseline		**Period 1 300mg TU**		**Period 2 200 mg TU + 200 mg TE**		**Period 3 (Fed) 200 mg TU**		**Period 3 (Fasted) 200 ng TU**		**Period 4 200 mg TU + 200 mg TE**	
Study Day	0	0	7	7	28	28	49	49	50	50	71	71
Treatment Day	0	0	7	7	7	7	7	7	8	8	7	7
Time (h)	0	0.5	0	24	0	24	0	12	0	12	0	24
Mean (ng/dL)	10.7	10.6	27.1	32.9	19.0	24.6	22.8	21.3	25.1	15.4	18.6	23.5
SD (ng/dL)	8.1	6.7	10.6	14.4	13.3	11.9	8.3	9.4	10.0	10.0	9.9	10.8

Conclusions (Study 08005):

- Overall, considering the variability in the data, there was relatively low diurnal variation in T levels. The concentration-time profiles following the AM dose and the PM dose were somewhat comparable.
- The T levels after TU and TU+TE increased with increase in dose.
- Administration of TU with a high-fat meal increased T and DHT levels by about 50% compared to fasting.
- There was good relationship between Cmax and Cavg.
- Overall, TU appears to be more effective than TE at increasing serum T concentrations when administered as oral SEDDS formulation.
- There was parallel relationship between T and DHT levels. However, the conversion of T to DHT was relatively nonlinear.
- Overall, estradiol (E2) concentrations were increased from baseline following all treatments.

Study CLAR-09009 (Steady-State Study):

Title: "*Pharmacokinetic Study to Determine Time to Steady-State of an Oral Testosterone Undecanoate (TU) Formulation in Hypogonadal Men*"

Objectives:

The objective of the study was to determine the time to reach steady-state when hypogonadal men are treated for 28 days BID at a dose of 200 mg TU (2 x 100 mg capsules).

Study Design:

This was steady-state PK study at 200 mg BID dose for 28 days. The trough level of T, DHT, and E2 were monitored periodically prior to the AM dosing and at a full PK profiles on Day 28. The study was conducted in 15 hypogonadal men.

Each dose-compliant subject received a total of 31 daily doses of 400 mg T as TU (i.e., 200 mg T, BID), and a final morning dose of 200 mg T as TU. Doses were administered as capsules, with subjects instructed to take doses 30 minutes after initiation of breakfast and dinner. As stated above, in addition to the trough concentrations, serial blood samples over 36 hours were collected from each subject on Day 28/Day 32.

Results:

Concentrations of T, DHT and E2 reached steady-state by Day 7 of treatment. Concentrations of T and DHT were greater on Day 3 than on Day 5, indicating that a period of time was required for the exogenously administered T to suppress endogenous T production (**Figures 09009-1A,B,C and 09009-2**).

The mean Cmax, Cavg, and Cmin concentrations at steady-state (morning dose of Day 28) for T were 995 ng/dL, 516 ng/dL and 199 ng/dL, respectively.

Figure 09009-1. Mean Pre-dose Concentrations for T, DHT, and E2 During 200 mg BID Dosing with TU for 28 Days (Study 09009)

A: T Trough **B: DHT Trough** **C: E2 Trough**

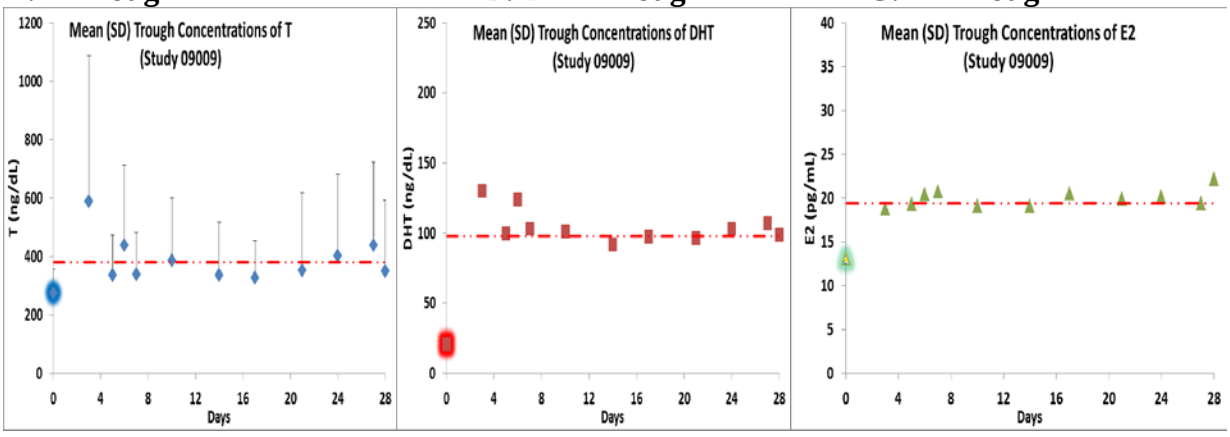
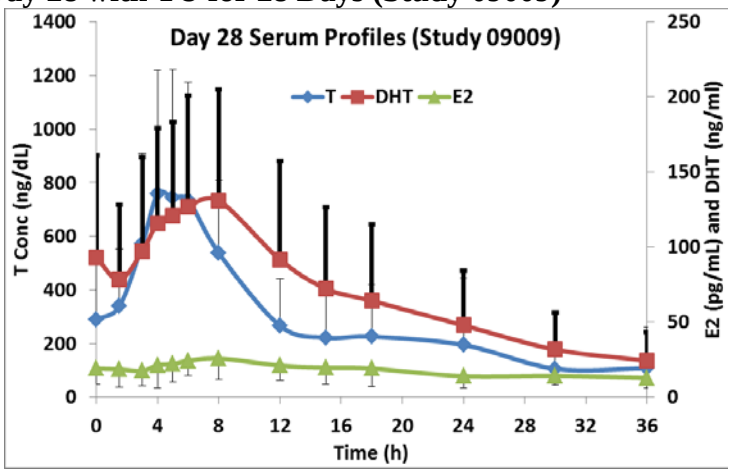


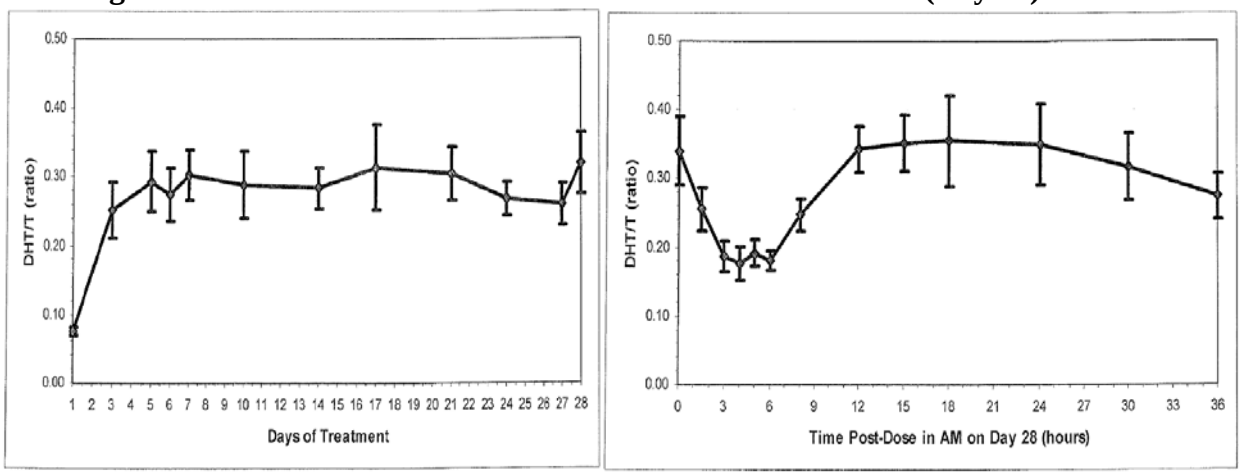
Figure 09009-2. Mean (SD Serum **Concentrations for T, DHT, and E2 After Final 200 mg BID AM Dose on Day 28 with TU for 28 Days (Study 09009)**



Serum DHT and E2 profiles followed the same pattered of T profiles so as the ratios of DHT/T (**Figure 09009-3A&B**). Following all treatments, there was noticeable increase in DHT/T ratios (**Figure 09009-4**). Due to the lag time involving conversion of T to DHT the observed nonlinear relationship with dose was expected. However, as T concentrations increase DHT concentrations also increase, but at slower rate. Therefore, DHT/T ratio was decreased with increasing T concentration.

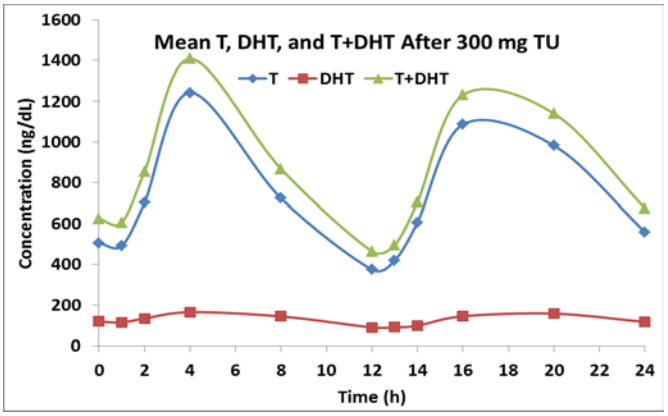
Also shown in **Figure 09009-3B**, the DHT/T ratio had not returned to its pre-treatment values by the time the final sample was collected. This indicates that the endogenous T production was still suppressed. This is expected feedback mechanism of from exogenous T.

Figure 09009-3. Mean (±SEM) DHT/T Ratios pre-Dose (trough, Figure A) and at Steady-State (Day 28, Figure B) with and After 200 mg BID Dosing with TU (Study 09009)
A: Trough **B: Final AM Dose (Day 28)**



Since both T and DHT have androgen activity, total androgen activity should represent the sum of both T and DHT concentrations. Therefore, the total levels of **T + DHT** is important for the final assessment of the safety and efficacy of the formulation. As expected, there was increase in total T+DHT levels following all treatments (**Figure 09009-4**).

Figure 09009-4. Mean DHT/T Ratios and Sum of T + DHT



Overall from this study and other studies in this NDA it was observed that the total androgen concentrations closely track those of T because T is the dominant contributor to the summed concentration.

As observed in all other studies, there was high inter-subject variability in all data including T, DHT, and E2 (**Figure 09009-5 and Table 09009-3**). The high variability in T and other androgens is a reflection of many endogenous and exogenous factors including but not limited to food contents, quantity, and ability to convert TU to T and other androgens.

Figure 09009-4. Distribution of Steady-State (Day 28) Cmax, Cmin, and Cavg Values for T, DHT, and E2, and DHT/T Ratios in Subjects Receiving 200 mg BID TU (Study 09009)

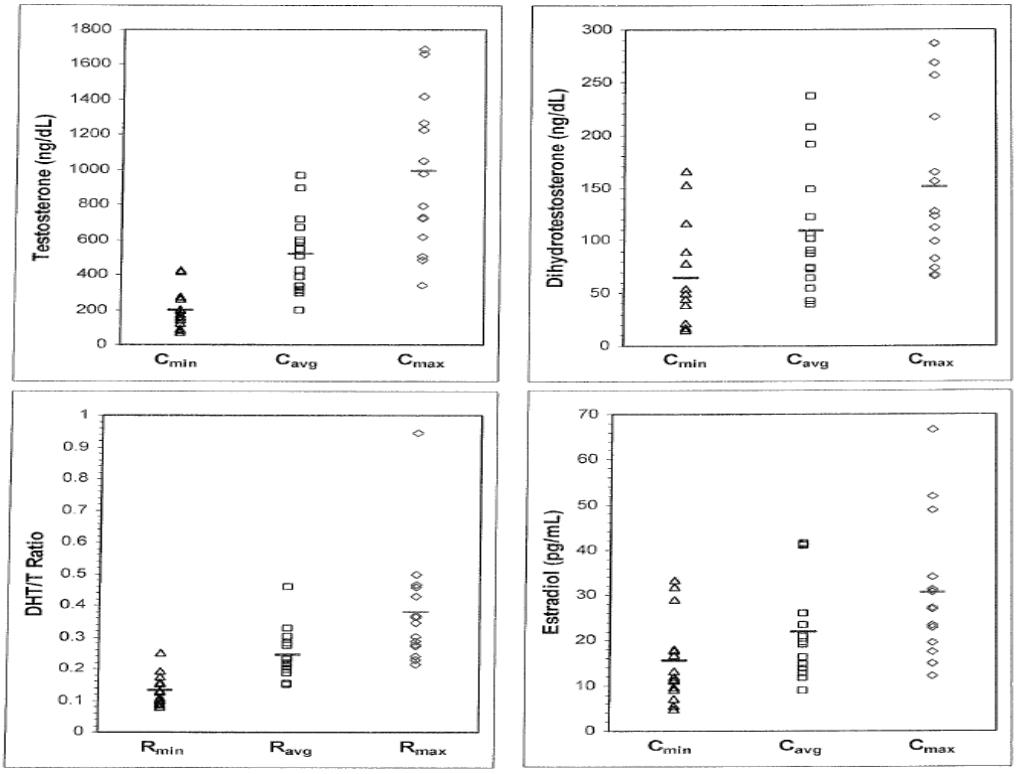


Table 09009-3. Mean ± SD (CV%) Steady-State PK Parameters for T, DHT, and E_2 on Day 28 of Treatment with 200 mg BID of T, as TU (Study 09009)

Parameters	T	DHT	E_2
Cmax (ng/dL)	995 ±436 (43.9%)	151 ±75 (49.5%)	30.6 ±14.9 (48.7%)
Cavg (ng/dL)	516 ±226 (43.7%)	109±61 (55.8%)	22.0±10.9 (49.8%)
$AUC_{(0-12)}$ (ng.h/dL)	6197 ±2708 (43.7%)	1312±732 (55.8%)	264±131 (49.8%)

Reviewer's Comments:

The results show that T concentrations and other bio-converted androgens remain essentially constant from at least Day 7 onward for the remainder of the study period. This suggests that the steady state is achieved within 7 days of treatment. This important observation as patient titration could be initiated as early as on Day 7 after the therapy.

As observed in other studies, DHT concentrations closely track T concentrations, and the fluctuations in DHT concentrations are reflections of similar trends in the T concentration. Similarly, E2 pre-dose concentrations indicate that mean pre-dose E_2 concentrations increased progressively until Day 7, after which they remained essentially constant for the remainder of the 28 days of dosing.

Conclusions:

The primary conclusions from this study were:

- T, DHT and E_2 concentrations reached steady-state within the first 7 days of dosing. Therefore, patients may start dose titration by Day 7 after the initiation of therapy.
- As expected, endogenous T production was suppressed by the administration of exogenous T.
- T concentrations did not return to pretreatment levels as quickly because of the suppression of endogenous T production/release is not so rapidly reversed.
- DHT and DHT/T values increased several fold (4- to 7-fold) during the treatment

Study CLAR-09008:

Study Title: "*Phase II Study of the Effect of Food With Various Levels of Fat on the Pharmacokinetics of an Oral Testosterone Undecanoate Formulation in Hypogonadal Men*"

Objectives:

To determine the effect of food containing various amounts of dietary fat on the PK of oral TU at a dose of 300 mg TU administered in the form of 3 capsules each containing 100 mg T (corresponding to 158.3 mg TU).

Study Design:

This was five-period, four-sequence, cross-over, PK study with a washout period of at least 4-10 days as follows:

Treatment A (Fasting):	Single dose of 3 x 100 mg TU capsules (300 mg) after overnight fast.
Treatments B (Very Low fat):	Single dose of 3 x 100 mg TU capsules (300 mg) after breakfast containing 6-10% fat
Treatment C (Low Fat):	Single dose of 3 x 100 mg TU capsules (300 mg) after breakfast containing 20% fat
Treatment D (Normal Fat):	Single dose of 3 x 100 mg TU capsules (300 mg) after breakfast containing 30% fat
Treatment E (High Fat):	Single dose of 3 x 100 mg TU capsules (300 mg) after breakfast containing 50% fat

In each occasion, drug was administered 30 minutes after the breakfast. In each period, subjects were confined to clinical facilities from approximately 2 to 3 hours prior to initial dosing scheduled at 09:00 until after collection of the 25-hours post-dose PK blood sample (overnight stay). The study was conducted in sixteen (16) hypogonadal male subjects with aged ranged from 25 to 64 years. The majority of subjects were whites (88%) and the remainders were blacks (6%) or other (6%).

What is the Rationale for Dose Selection?

In a Phase I1a study (CLAR-08005) the dose was 200 mg BID for 7 days. That dose resulted in average serum T levels within normal range (between 300 and 1000 ng/dL) in 78% of subjects. The dose of 300 mg in the current food effect study was selected to represent the maximum recommended single dose.

Drug Administration, Treatments, and Procedures:

Subjects were required to fast overnight for a minimum of 10 hours prior in all occasions until about 4 hours post dosing. The dose-associated breakfast meals were comprised of

approximately 870 calories in all treatment with varying percentage of fat as shown in **Table 09008-1** (also see **Attachment 1** for details on the content of each meals**)**.

Table 09008-1. Food Composition Parameters

Treatments	Total Energy (Kcal)	Total Weight (g)	Total Lipid (g)	Total Carbohydrate (g)	Total Protein (g)
Fasting	0	0	0	0	0
6-10% Fat	853	662	9	182	27
20% Fat	887	662	20	159	26
30% Fat	894	662	30	139	26
50% Fat	878	662	49	92	25

As shown in the above table, the % of fat content corresponds to approximately 10 grams to 50 grams of lipid. There were no changes in the total calories, total weight, and total protein in these arms. The total weigh was 662 grams and total protein was 26 grams. However, there was gradual decrease in total amount of carbohydrate from 182 grams to 92 grams to maintain the total calories. It should be noted that the 6 to 10 % fat arm was based on the range reported by the sponsor, depending on the amount or volume of food being consumed by each subject.

In this study, subjects were asked to consume the entire breakfast meal within 30 minutes. No food other than the meals and snacks provided were consumed. With the exception of the volume administered at the time of dosing, fluids were not permitted until 1 hour after dosing, but water was permitted *ad libitum* at all other times during the confinement. However, during the fasting treatment period, no water was allowed for 4 hours after drug administration.

Subjects were not allowed to consume grapefruit products for 7 days prior to Day 1 and throughout the study, until after Day 30. Subjects abstained from alcohol-based products during periods of confinement. In addition, subjects were asked to refrain from smoking during confinement in the clinical facility and were instructed not to take or use any recreational drugs (e.g., marijuana) throughout the duration of the study.

PK Blood Samples:

The pre-dose three blood samples (3) were collected at 2 h, 1 h, and within 5 minutes prior to administration of the dose. Blood samples were then collected serially at 1.5, 3, 4, 5, 6, 8, 11, 14, 18, 24, and 25 hours post-dose.

PK Parameters:

The primary PK parameters were the Cavg, Cmax, Tmax, and AUC for T, DHT, and TU.
Results:

From this study there was marked increased in T, DHT, and TU levels when oral TU was administered with food compared to overnight fast (**Figures 09008-1-3 and Table 09008-2**).

Figure 09008-1. Mean T, TU, and DHT Concentrations-Time Profiles in Fed and Fasted Conditions After 300 mg (3 x 100 mg) Capsules (source Study 09008 Tables 14.3-7, 14.46-14.50, 14.61-14.65).

A: T Profiles **B: TU Profiles** **C: DHT**

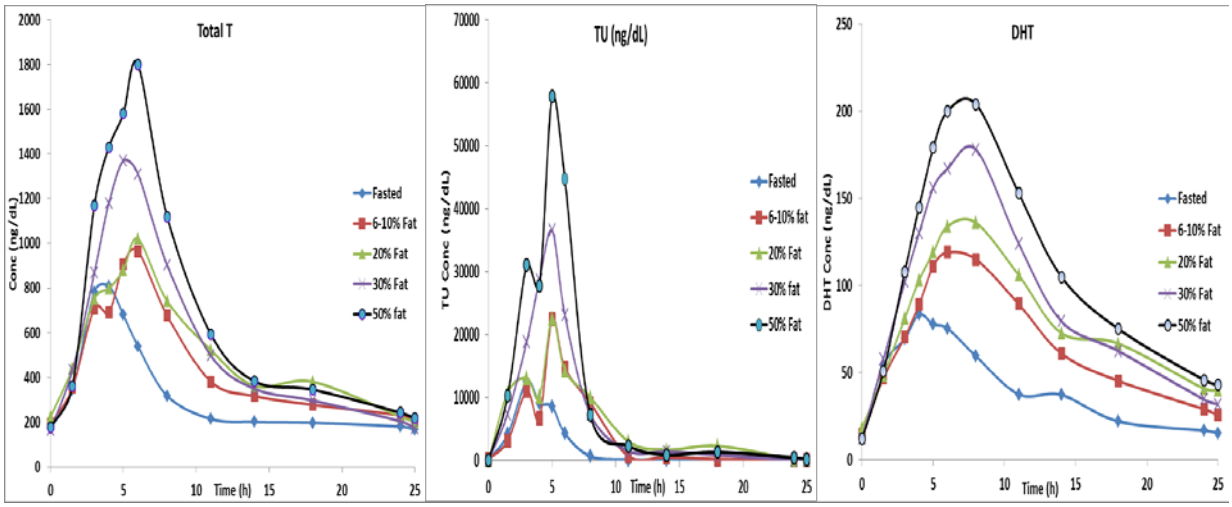


Figure 09008-2. Individual and Mean (solid line) T Cavg and T Cmax in Fed and Fasted Conditions After 300 mg (3 x 100 mg) Capsules (Reviewer's Analysis based on Study 09008, Table 11.4.4.12.a).

A: T Cavg (All Subjects, n=16) **B: T Cmax (All Subjects, n=16)**

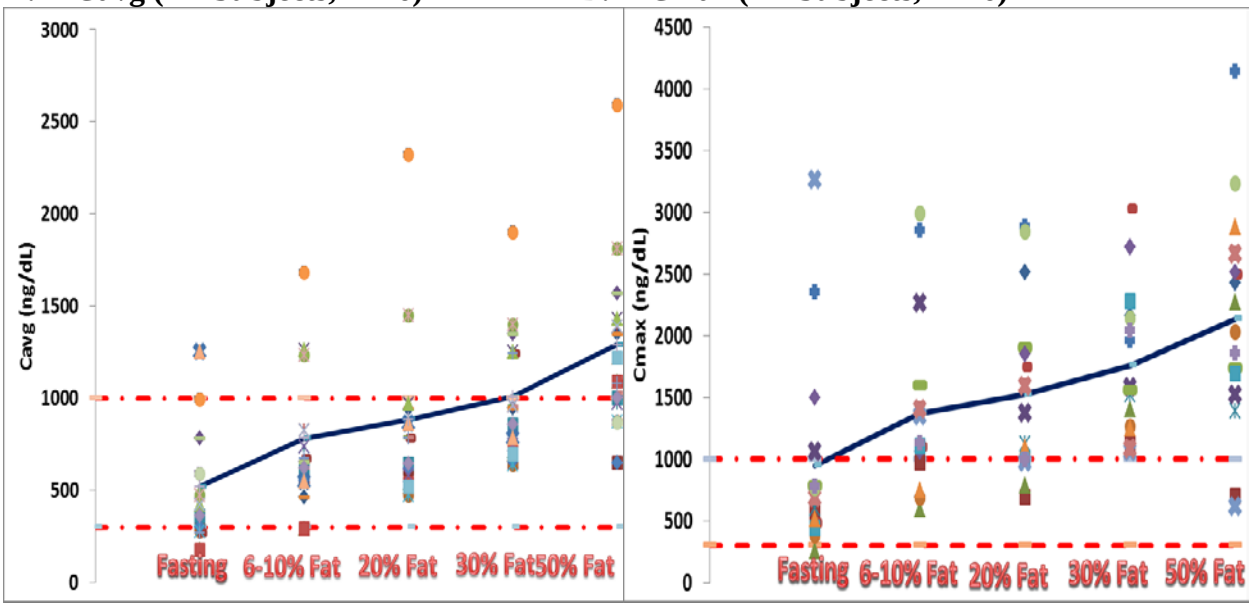


Figure 09008-3. Individual and Mean (solid line) TU Cavg and TU Cmax in Fed and Fasted Conditions After 300 mg (3 x 100 mg) Capsules (Reviewer's Analysis based on Study 09008, Table 11.4.4.12.a).

A: TU Cmax (All Subjects, n=16) **B: TU AUC (All Subjects, n=16)**

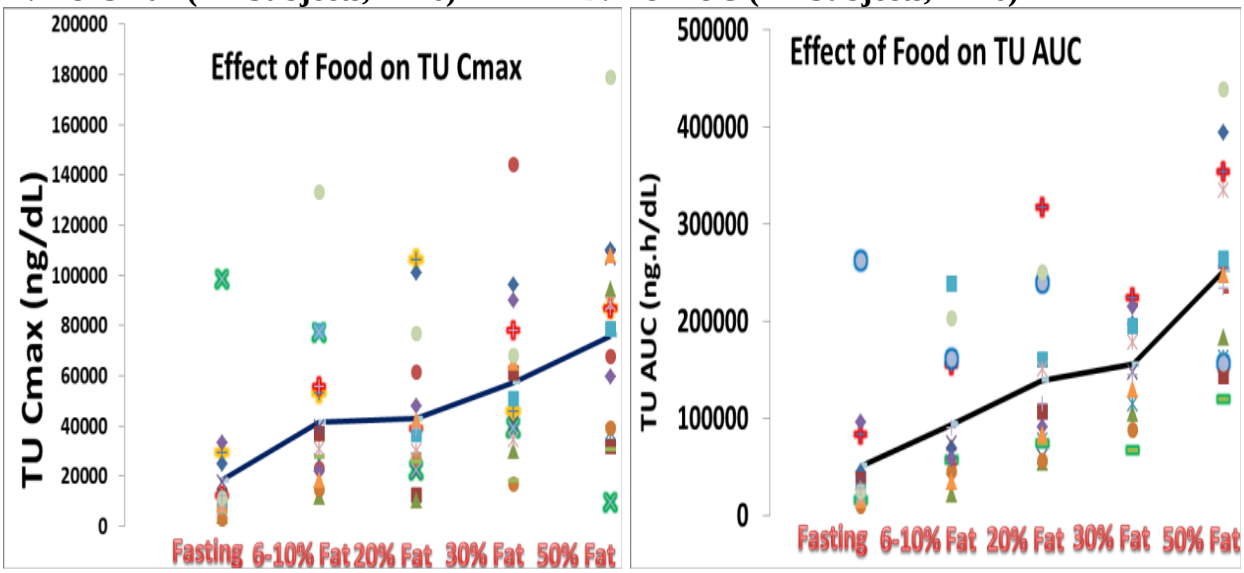


Table 09008-2. Mean (± SD) PK Parameters of Androgens in Fed and Fasted Conditions After 300 mg (3 x 100 mg) Capsules (source Study 09008, Tables 11.4.4.1.2a, 11.4.4.1.5a and 11.4.4.1.8a).

Parameters	**Fasting**	**6-10% Fat**	**20% Fat**	**30% Fat**	**50% Fat**
Cmax (ng/dL)					
T	948 ± 798	1370 ± 732	1520 ± 711	1760 ± 598	2140 ± 901
TU	18400 ± 23000	41400 ± 32100	42900 ± 29200	57300 ± 33000	75900 ± 41700
DHT	102 ± 78	150 ± 100	174 ± 93	202 ± 102	230 ± 118
Cavg (ng/dL)	526 ± 324	781 ± 385	884 ± 505	1010 ± 356	1260 ± 477
AUC (ng.h/dL)					
T	7787 ±3671	10853 ± 4287	12461 ± 5027	13633 ± 3775	16457 ± 5581
TU	51000 ± 66000	93700 ± 67600	139300 ± 81600	155800 ± 52700	252200 ± 94300
DHT	987 ± 676	1658 ± 1128	2021 ± 1270	2302 ± 1405	2738 ± 1859

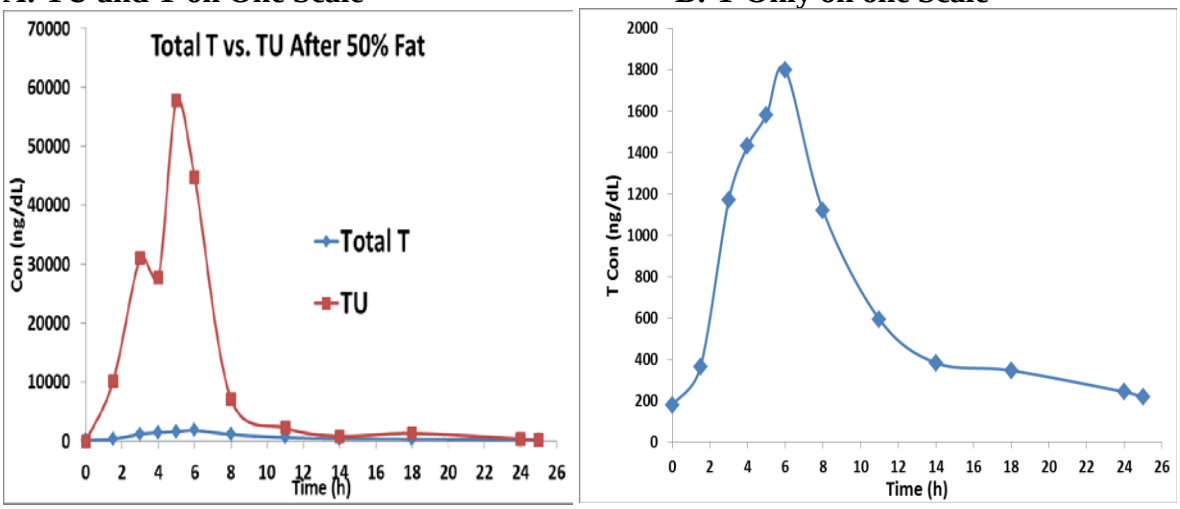
As shown above, there was clear gradual increase in all androgen levels with increase in percent of fat content of the food. Comparing to fasting, both T Cavag and T Cmax were increased (**Figure 09008-2**). After fasting, there was some variability in the data with mean Cmax approximately 950 ng/dL and the Cavg was 526 ng/dL (**Table 09008-2**).

While, there was high variability in the data across all arms, there was substantial improvement in the absorption with increase in % of fat. Given that there was some observed T level after fasting; one may consider administering the drug after fasting to minimizing the variability associated with food. If so, the dose may need to be increased. Yet this may raise both safety and efficacy issues as will be discussed in more detail below.

The same trend of food effect on T levels was observed for TU Cmax and AUC (**Figure 09008-3 and Table 09008-2**). It is clearly shown that TU level is approximately 20 fold higher than T level after 50% fata (**Figure 09008-4A & B**). As shown in the Figure below, when the T profile was plotted on the expanded scale for clarity, the T profile follows the TU profile. In addition, the half-life of T was slightly longer than that of TU. It is clear from the data that food affects predominantly the extent of TU absorption and has little, if any, impact on the rate or extent of conversion of TU to T.

Figure 09008-4. Mean T and TU Concentrations-Time Profiles After Meals Containing 50% (source Study 09008 Tables 14.3-7, 14.46-14.50, 14.61-14.65).

A: TU and T on One Scale **B: T Only on one Scale**



Reviewer's Comments on Effect of Food:

Overall, based on this study, taking the drug under fasting conditions yielded marked reduction in TU absorption. However, taking it with meals with very low fat content (6-10% fat) may also result in small TU absorption that would warrant dose adjustment to meet the targeted therapeutic range of 300-1000 ng/dL.

The study was conducted at the maximum recommended dose of 300 mg. As sated above, the mean concentrations achieved were relatively high, even under fasting conditions. However, considering the observed variability in the data, the administration of TU under fasting condition would not always produced adequate Cavg without increasing the dose to above 300 mg. The issue with increasing the dose does not guarantee patients compliance and may lead to high Cmax, if patients taking the drug with food.

There is a clear relationship between the fat content of the meal and the level of androgens following TU administration. The primary issue with such observation is the meal-to-meal and day-to-day variability in androgens levels was driven by the variability in fat content of food.

The sponsor proposed that the drug should be taken with food (i.e., not on empty stomach). In general, the presence of food enhances the absorption of certain drugs as a result of an increase

in blood supply at the site of absorption in the gastrointestinal (GI) tract. However, in the case of TU, the mechanism of enhancement of TU absorption is partially associated with increased blood supply at the absorption site in the GI tract. But the actual mechanism in the case of oral TU is the increase in the absorption via the lymphatic system which is primarily associated with increase in the lipophilicity and emulsification of the TU in the presence of fat.

At the time of writing this review, no labeling changes are recommended in terms of how the drug should be administrated in reference to meal and fat contents in order to minimize the variability and improve the predictability of androgen levels. There are at least three options in reference to oral TU administration:

Option 1 (Fasting): Since there was relatively some absorption after fasting, then the drug can be given on empty stomach. If so, T level will be relatively predictable with less fluctuation. However, the dose may need to be increased, possibly doubled. That would create another safety issues if the patient do not comply with the instruction and may take the drug with food. Therefore, the T exposure will be markedly increased, if inadvertently or even deliberately administered with high dose.

Furthermore, patients will quickly learn the potential effect of fat and may miss use and abuse the drug by deliberately taking it with high fat food to enhance the absorption.

For this option, patient compliance would be the essence of the successful therapy. Patients may be instructed to specifically take the drug immediately after waking up in the morning and before breakfast. But the evening dose would be challenging, depending on patients personal and work life style.

Based on the PK data, this option can be implanted, but with high risk of over exposure and over dosing (inadvertently or deliberately), if the dose is increased. Also, based on the PK data, if oral TU is administered on empty stomach at the regular dose of 100 to 300 mg BID, the desired T levels of 300-1000 ng/dL will not be achieved in many patients.

Option 2 (irrespective of food): The drug can be given irrespective of food at the same recommended dose (i.e., with or without food). While this may be more practical, convenience, and may increase patient's compliance, the titration process will be more complicated and challenging. In addition, the T levels would be highly fluctuating as in **Option 1**.

Option 3 (maintain usual diet and % fat): In this option the patient must control the % of fat in meals. While this may better predicts and control of T levels and is in some way in alignment with the Phase III studies, patients will have difficulty in assessing fat content in meals.

However, considering everything, the third option appears to be the best option (if not the only option). But the label must clearly emphasize consistency and adherence to the usual diet. If the patient changes diet for example from his/her usual diet to vegetarian diet and vise-versa, patient must undergo new titration process.

Each of the above option has challenges. For example, the issue with options 1 and 2 is that Phase III studies were conducted with food. Therefore, without adequate clinical trial titration data with options 1 and 2, it may be difficult to justify these two options. Option 3 will minimize variability in absorption due to food effect, but as mentioned above, is difficult and impractical to maintain every day.

Summary of AC Meeting in reference to Food (September 18, 2014):

The above three options were presented at the FDA AC meeting on September 18, 2014. While some members of the panel were stunned with the variability presented at the meeting and others were skeptical about the entire approach, yet, the committee members and the Agency did not reach consensus on how the drug should be administered with reference to food. Overall, the majority of the committee members voted against the approval of the drug without additional safety and efficacy data.

Conclusion:

While there was clear relationship between the fat content and the level of androgens, the primary issue with such observation is the meal-to- meal and day-to-day variability in androgens levels as driven by the variability in fat content of food. Based on the data from this study, the sponsor proposed that the drug should be taken with food (i.e., not on empty stomach).

The observed variability will always be expected, unless the patients control the % fat in the daily diet. Therefore, clear language and instruction should be included in the label to clearly state that the % of fat in the diet should be relatively consistent.

At the time of writing this review, no internal consensuses have been reached on what additional studies are needed or how the drug will be administered with respect to food. Based on the internal discussion and the AC outcome, there is no “ideal” option without pros and cons. While the availability of oral TU would provide the convenience of easy oral administration than the gel, nasal, and IM injects, it appears that it is a product with “double sword” due to the inherent wide variability with food, potential for high exposure, and potential for CV risk.

Additional study(s) are needed to optimize the titration, timing, and effect of food to minimize the associated variability.

Attachment 1 (Food Content in Study 09008):

Based on the tables shown below, all meals in four arms comprised of three parts:

- Bread
- Fruit
- Smoothie

However, ingredients will vary according to the prescribed amount of fat. The following tables show the detail of each meal used in this study:

10% Fat

Amount (g))

72 White bread, regular, commercial (=potatobread)
150 Milk, canned, evaporated, nonfat
75 Banana, fresh or ripe
15 Jam, strawberry, Smuckers, 12044
250 Ice creams, BREYERS, 98% Fat Free Vanilla
100 Strawberries, frozen, sweetened

Total = 662 g

20% Fat

Amount (g))

72 white bread, regular, commercial (=potato bread)
17 Jam, strawberry, Smuckers,
30 Banana, fresh or ripe
116 Strawberries, frozen, unsweetened
153 Milk, canned, evaporated, nonfat
133 Ice cream and frozen desserts, regular (11 % fat), vanilla or other flavors (include chocolate chip)
76 Ice creams, BREYERS, 93% Fat Free Vanilla
10 Sugar, white granulated

Total = 662 g

30% Fat

Amount (g))

72 White bread, regular, commercial (=potato bread)
15.5 Butter, regular, salted
70 Banana, fresh or ripe
152 Milk, canned, evaporated, nonfat
110 Ice cream and frozen desserts, regular (11 % fat), vanilla or other flavors (include chocolate chip)
142.5 Strawberries, frozen, unsweetened
100 Ice creams, BREYERS, 98% Fat Free Vanilla

50% Fat

Amount (g))

36 White bread, regular, commercial (=potatobread)
7 Butter, regular, salted
50 Cream, whipping, heavy 37%
200 Ice creams, BREYERS, Vanilla No Sugar Added,
150 Evaporated milk, undiluted, whole
75 Strawberries, raw
4 Egg, white, dried
140 Frozen novelties, ice type, pop, with lowcalorie sweetener

Total = 662 g

Study CLAR-09007:

Study Title: "PHASE III, ACTIVE-CONTROLLED, SAFETY AND EFFICACY TRIAL OF ORAL TESTOSTERONE UNDECANOATE (TU) IN HYPOGONADAL MEN"

PK Report Title: "*A Pharmacokinetics Evaluation of Testosterone, Free Testosterone, Dihydrotestosterone, Estradiol, Follicle Stimulating Hormone, Luteinizing Hormone, Sex Hormone Binding Globulin, Testosterone Undecanoate and Dihydrotestosterone Undecanoate following Administration of Oral Testosterone Undecanoate or Transdermal Testosterone Gel to Hypogonadal Men in A Phase 3 Clinical Study*"

Objectives:

Primary Objectives: The primary objective of this study was to determine the efficacy of Oral TU in hypogonadal men. The primary efficacy parameter is the percentages of treated subjects with T Cavg between 300 and 1000 ng/dL. The primary safety parameters is the percentage of subjects with Cmax not greater than 1500 ng/dL and no subjects should be over 2500 ng/dL.

Secondary Objectives: The secondary objectives of this study was to assess the effectiveness of dose titration at steady-state, based upon a single serum T sample obtained at 4-6 hours post AM dose. In addition, the safety of T was assessed by monitoring several pharmacodynamics parameters including but not limited to hormonal and cardiovascular biomarkers. The sponsor also conducted a sub-study to specially investigate the CV risk of this product in approximately 30 subjects in each treatment arm (for detail see clinical team review).

Study Design:

This was a randomized, open-label, 2-arm, active controlled, 12-month, multicenter study of oral TU in approximately 150 hypogonadal men in each arm. The study includes dose titration based on serum T concentration assessed at 4-6 h post AM dose. Based on the T baseline serum concentration subjects were divided into the following two groups:

Group A (Oral TU): 2 x 100 mg capsules (i.e., 200 mg per dose) twice daily (BID) x 30 days (i.e., total daily dose = 400 mg)
Group B (Transdermal T-gel): 50 mg T (5 gram) of 1%-gel (AndroGel®) once daily (QD) to shoulders, upper arms and/or abdomen.

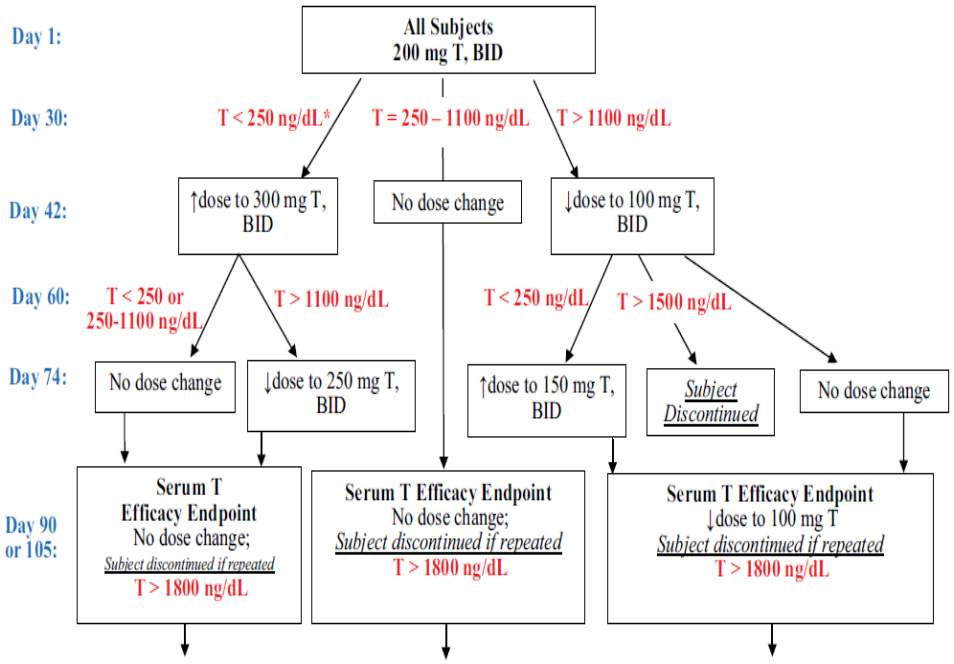
Titration:

Based on the T levels, patients were titrated up or down by 100 mg BID increment or decrement after oral TU to the maximum dose of 300 mg BID and the minimum of 100 mg BID. For the Androgel® group, it was by 25 mg increment or decrement the maximum of 100 mg QD and minimum of 25 mg QD.

On Day 30 (± 3 days), serum T sampling was collected and measured after morning dose. Based on the T concentration in this sample, the need for dose titration was determined based on the

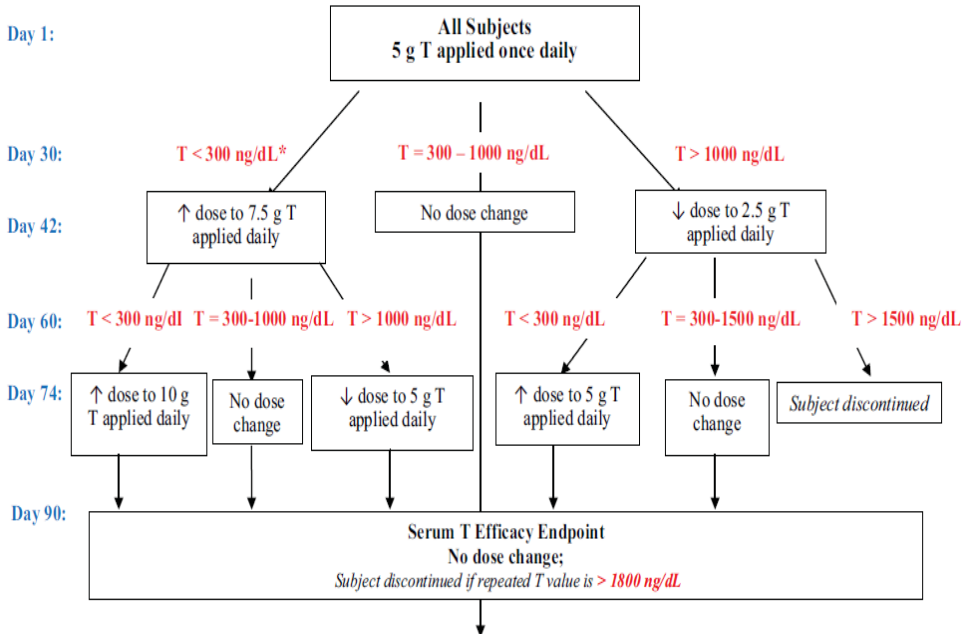
criteria established in the decision trees (flow charts) shown in **Figures 09007-1** for oral TU, in **Figure 09007-2** for Androgel®**,** and final titration in **Figure 09007-3** for Days 180, 270, and 365**.**

Figure 09007-1. Day 1 to Day 105 Study Dose Titration Scheme for Subjects Randomized to Oral TU (Group A)



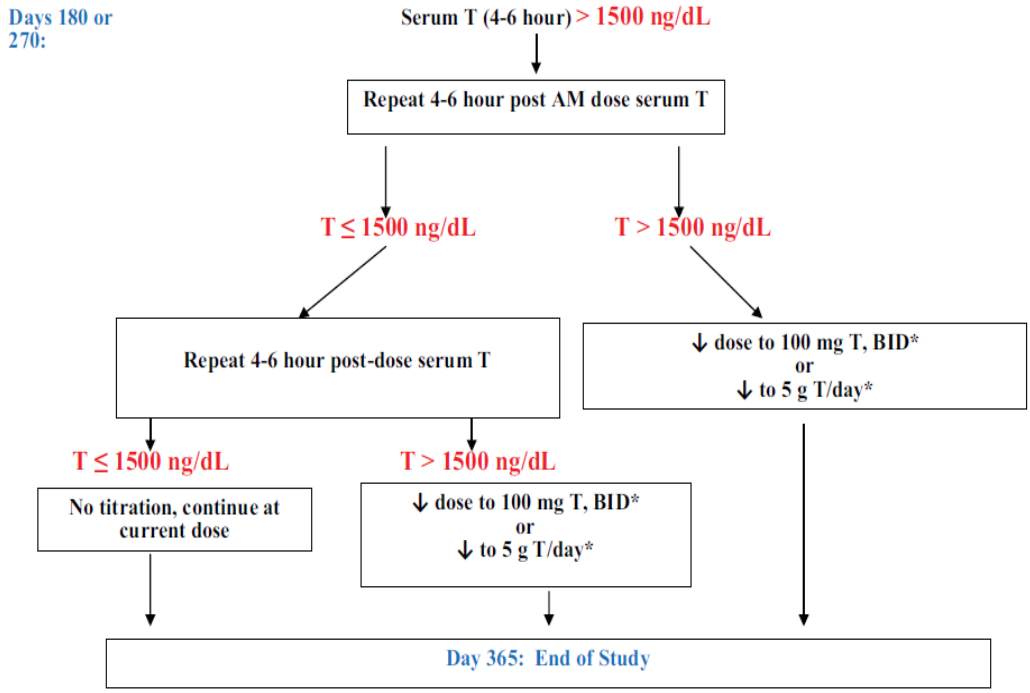
For Days 180, 270, and 365 (see Figure 09007-3)

Figure 09007-2. Day 1 to Day 105 Study Dose Titration Scheme for Subjects Randomized to Transdermal Androgel® **(T-Gel) (Group B)**



For Days 180, 270, and 365 (see Figure 09007-3)

Figure 09007-3. Study Dose Titration Scheme for Days 180 and 270 for Both Treatment Groups (A and B)



*Subjects already at 100 mg T, BID or 5 g T/day will have no additional titration and will be discontinued.

It should be noted that the titration was designed to be performed for the first time on Day 30. However, only if required, dose titration may also be performed on Day 42 (± 3 days) for Treatment Period 2 (Days 42 to 90). This pitfall of the design was corrected in the follow up study 12011 (see Study 12011).

Those subjects whose dose was titrated on Day 42 were re-evaluated on Day 60 (± 3 days), with dose adjustments made as necessary on Day 74 (±3 days) as displayed. Serum T sampling was performed on Day 90 (± 3 days), or for oral TU subjects who had dose titration on Day 74, on Day 105 (± 3 days). If serum T level was >1800 ng/dL, the sample was repeated. However, if the second assayed T concentration was > 1800 ng/dL then the subject will be discontinued.

Following the 4-6 h post AM dose sample collection on Days 180 and 270, subjects with serum T >1500 ng/dL underwent a repeat analysis and dose adjustments were made. Subjects whose dose was already at 100 mg T, BID and who had a confirmed 4-6 hour serum T level of >1500 ng/dL on two determinations following either Day 180 or 270 was discontinued.

Serial PK samples for the determination of T, TU and other metabolites were collected over 12 or 24 hours on Days 30, 90 or 105, and 365 following morning doses.

Drug Administration and Treatments:

For oral TU, subjects were instructed to take the drug 30 minutes after food. According to the sponsor "*When subjects were confined to the clinical facility, they were provided a regular diet prior to the scheduled dose*". However, the sponsor did not provide details on the so called "*regular diet*". There were no food restrictions for subjects randomized to receive transdermal Androgel®.

Statistical Analysis:

Briefly, if at least 75% of the subjects' Cavg were between 300 and 1000 ng/dL (normal range) and the lower limit of a 95% CI on the percentage of subjects in the normal range was not below 65%, then clinical efficacy was to be deemed to have been demonstrated (for details see the biostatistics review).

Study Subjects and Disposition:

The mean (SD) age and BMI (SD) of the safety population was 54.9 (11.10) years and 29.95 (3.927) kg/m2, respectively. Overall, 269 subjects (83.8%) were white and 287 subjects (89.4%) were not Hispanic or Latino (for details on demographic characteristics of patients see the biostatistics and clinical team reviews).

A total of 325 subjects were enrolled in this study. Of these subjects, 315 were included in the PK population and 146 were included in the efficacy population. A total of 300 subjects completed the treatment period from Day 0 to Day 90.

Results:

Table 09700-1 summarizes the efficacy results for each of the PK visits. Of the 146 subjects evaluable for efficacy in the oral TU treatment group on Day 90, 122 (83.6%) had Cavg values within the targeted T eugonadal concentration range of 300 ng/dL to 1000 ng/dL. The lower limit of the 95% confidence interval (CI) about this proportion was 76.5%. Both of these values exceed the minimum efficacy requirements of 75% within the target range and a 65% lower bound on the 95% CI.

On Day 365, 85.0% of the subjects (108 out of 127) achieved a T level within the normal range following oral TU while 75.6% of the subjects (99 out of 131) following Androgel®. There was trend that the percentage of subjects was higher following oral TU compared to Androgel®. In addition, there was no much difference in terms of percentage in AM or PM monitoring and in particular after oral TU.

Table 09007-1. Summary of the Success Rate for Obtaining T Cavg Values in the Eugonadal Range in Hypogonadal Men (Study 09007).

Observation Day & Time	Oral TU Treatment				Topical T-Gel Treatment			
	Cavg Evaluable	Cavg in 300-1000 ng/dL range		Lower 95% CI	Cavg Evaluable	Cavg in the 300-1000 ng/dL range		Lower 95% CI
	Total	N	%	%	Total	N	%	%
Day 90 Full	146	122	83.6%	76.5%	149	118	79.2%	71.8%
Day 30 AM	155	127	81.9%	NC	156	92	59.0%	NC
Day 90 AM	147	114	77.6%	NC	150	112	74.7%	NC
Day 90 PM	147	117	79.6%	NC	150	117	78.0%	NC
Day 365 AM	127	108	85.0%	NC	131	99	75.6%	NC

NC = Not calculated
Shaded cells indicate rates based on full 24-hour PK observations

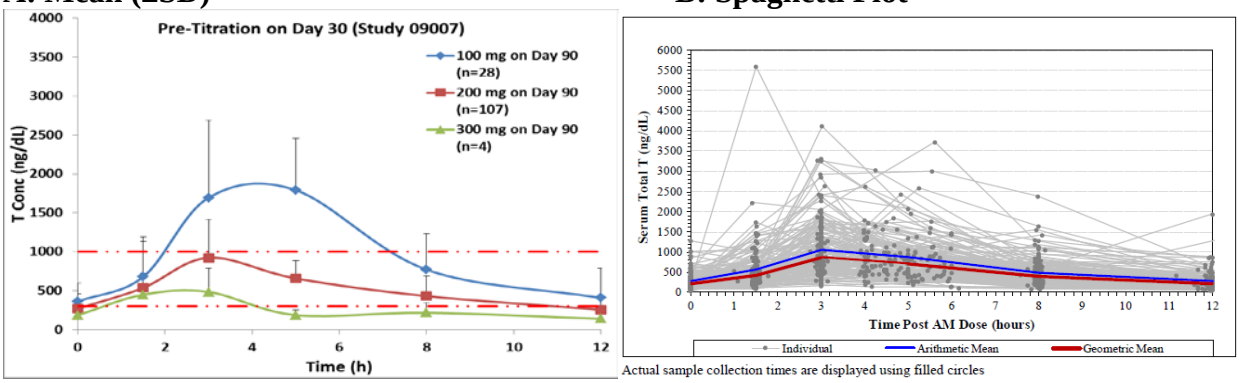
Was There a Difference in the T Serum Profiles Among Visits?

Overall, based on mean data, the T serum concentration-time profiles were comparable in terms of magnitude of T levels and the variability (**Figures 09007-4ABC to 09007-6ABC**). From the Spaghetti plots shown below, there was high variability in T level compared to Androgel®. In several subjects the T levels was above 2500 ng/dL. For instance, in two subjects the Cmax was 8250 and 7650 ng/dL on Day 90. Such high concentration is not acceptable from the safety perspective.

The observed inter and intra-subject variability in T levels was expected due to many factors and in particular food contents. However, as a mean values for all days, it falls within the normal T level (see also above).

Figure 09007-4. Mean (±SD) and Individual (Spaghetti Plot) Concentration-Time Profile for Serum Total Grouped by the Day 90 Titration Defined Dose (Study 09007)

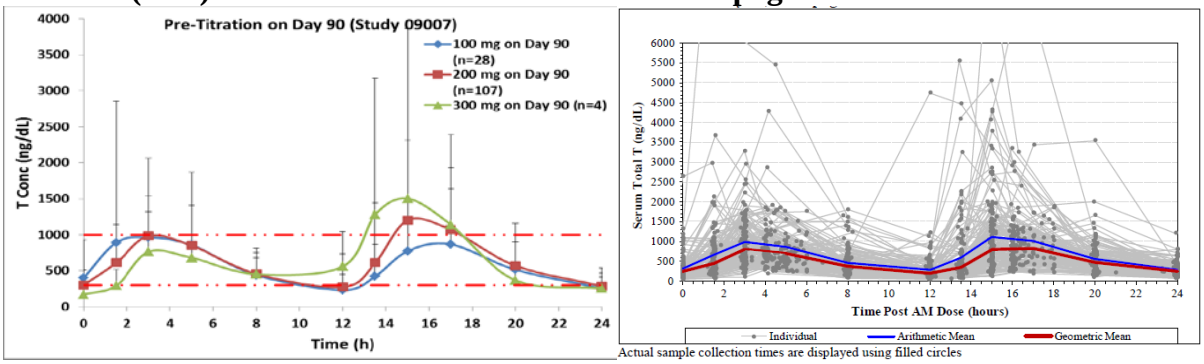
A: Mean (±SD) **B: Spaghetti Plot**



Footnote to Figure 09007-5A: N=4 had Cavg <300 ng/dL and were titrated up to 300 mg, n=28 had Cavg >1000 ng/dL and were titrated down to 100 mg, and n=107 had Cavg between 300 and 1000 ng/dL remain on the same 200 mg dose.

Figure 09007-5. Mean (±SD) and Individual (Spaghetti Plot) Pre-titration Concentration-Time Profile for Serum Total T in Subjects on the Day 90 Clinic Visit (Study 09007)

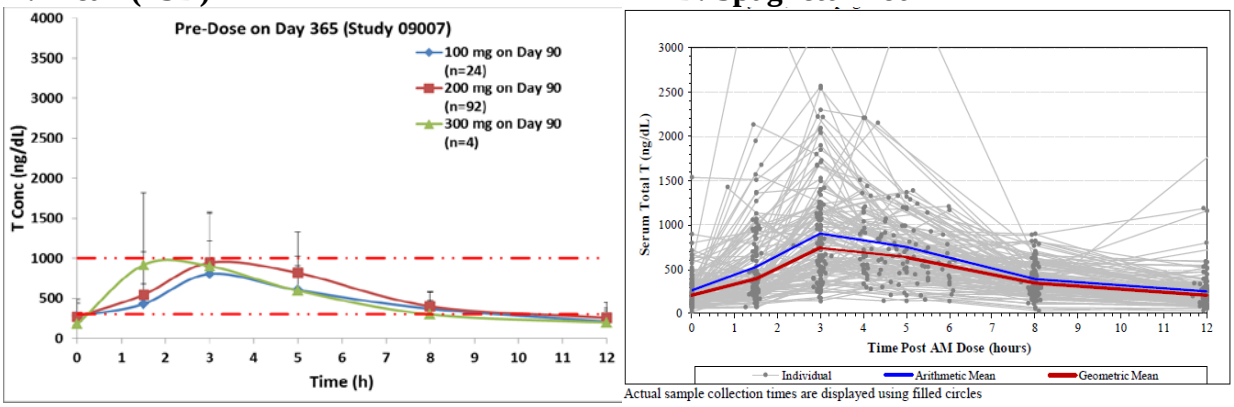
A: Mean (±SD) **B: Spaghetti Plot**



Actual sample collection times are displayed using filled circles

Figure 09007-6. Mean (±SD) and Individual (Spaghetti Plot) Pre-Dose Concentration-Time Profile for Serum Total T in Subjects on the Day 365 Clinic Visit (Study 09007)

A: Mean (±SD) **B: Spaghetti Plot**



Actual sample collection times are displayed using filled circles

In terms of Cmax, it ranged from the mean values of 1100 ng/dL to 1676 ng/dL and occurred approximately 4 hours post-dose following both the morning and evening Doses (**Table 09007-4).** For comparison, **t**he mean Cmax ranged from 533 ng/dL to 818 ng/dL in the Androgel® treatment group (**Table 09007-1**).

The mean Cavg values were approximately 40%-50% of the Cmax concentrations in the oral TU treatment group, ranging from 524 ng/dL to 661 ng/dL, while the mean Cavg values in the Androgel® treatment group ranged from 379 ng/dL to 489 ng/dL. Overall, the variability after oral TU appears to be higher than after the Androgel® (**Figures 09007-4 to 6 and Table 09007-2 A and B**).

Table 09007-2. Mean (SD) of Primary PK Parameters for Serum Total T During Each PK Observation Period, by Treatment (Source, Table 23, Page 93 of 950, Study 09007).
Table 09007-2A: Full Day (i.e., Mean of AM and PM)

Parameters	Day 30 Full Day		Day 90 Full Day		Day 365 Full Day	
	Oral TU	AndroGel®	Oral TU	AndroGel®	Oral TU	AndroGel®
Cavg (ng/dL)	607±299	379±156	628±324	485±220	524±215	425±177
Cmax (ng/dL)	1261±785	533±255	1676±1408	817±480	1100±648	582±276
AUC (ng.h/dL)	7281±3592	4545±1869	15080±8226	11641±5282	6292±2581	5097±2130

Table 09007-2 B: Day 90 (AM and PM):

Parameters	Day 90 AM		Day 90 PM		Day 90 Full Day	
	Oral TU	AndroGel®	Oral TU	AndroGel®	Oral TU	AndroGel®
Cavg (ng/dL)	592±399	478±235	661±399	488±251	628±324	485±220
Cmax (ng/dL)	1227±1055	685±414	1414±1222	703±405	1676±1408	817±480
AUC (ng.h/dL)	7106±4784	5740±2820	7935±4784	5863±3016	15080±8226	11641±5282

What is the Effect of Dose Titration on Serum T Concentration-Time Profiles?

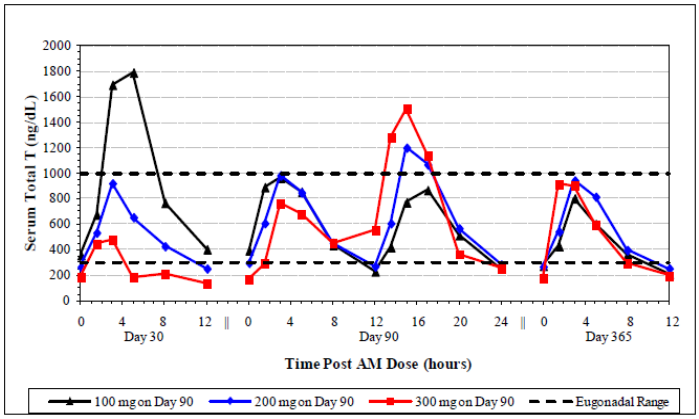
The above **Figures 09007-4 to 09007-6** show the mean concentrations-time profiles for subjects regardless of the dose for oral TU or the Androgel®. However, **Figure 09007-7** shows the mean concentration-time profiles for all subjects for oral TU per visit and titrated dose on Day 90. Shown in this figure the mean concentration-time profiles of subjects that were in the 100 mg, 200 mg and 300 mg BID dose groups on their Day 90 clinic visit (i.e., the mean concentration profiles for subjects that were titrated to 100 mg, 200 mg or 300 mg BID as their maintenance dose).

The concentrations on Day 90 were more slightly higher following the PM dose than the AM dose. On average, the Cmax value for T after the PM dose of oral TU was approximately 36% greater than after the AM dose, while the Cavg was approximately 25% greater. The sponsor's believe that this could be a reflection of greater diversity in fat content and amount being consumed in the evening meals compared to breakfast.
However, on Day 30, when all three maintenance dose groups were receiving a **200 mg** dose, the profiles for the three groups show substantial differences. The Day 30 mean profile for the subjects that were titrated downwards to 100 mg BID by Day 90 (N=28 dosed) was above the upper bound of the eugonadal range for approximately half of the dosing interval when those subjects received the higher 200 mg dose.

The Day 30 mean profile for subjects that were titrated upwards to 300 mg by Day 90 (N=4) was below the lower limit of the eugonadal range for more than half of the dosing interval when those subjects received the lesser 200 mg dose. The mean profile for subjects that were titrated to

200 mg BID on Day 90 (N=107) showed little difference between their Day 30 profile (when they also received the 200 mg BID) and their Day 90 profile following the AM dose.

Figure 09007-7. Mean T Concentrations Grouped by the Day 90 Titration Defined Dose (Study 09007)

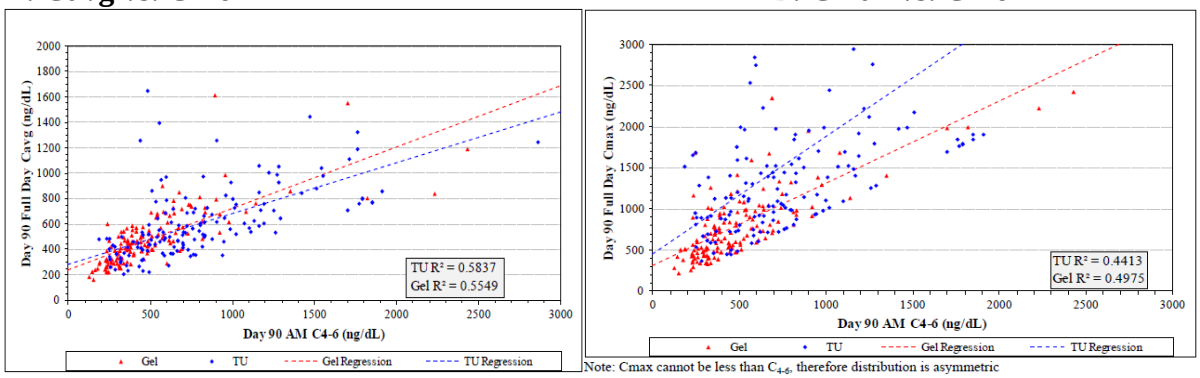


Is There a Relationship Between T Cavg, Cmax and Concentration at C4-6 h?

Overall, there was relatively reasonable correlation (yet not a perfect one) between Cavg, Cmax and C4-6 hours (**Figure 09007-8 AB**).

Figure 09007-8. Cavg (Full Day), Cmax and C4-6 on the Day 90 (Study 09007)

A: Cavg vs. C4-6h **B: Cmax vs. C4-6h**



Note: Cmax cannot be less than C_{4-6}, therefore distribution is asymmetric

Based on this data, overall a single time point can be used in lieu of serial blood samples for the titration purposes.

Reviewer's Comments on T PK Data:

The primary objective of this study was to identify the efficacy of TU following oral formulation as a replacement therapy for T in hypogonadal men. The primary efficacy parameter was the 24-h Cavg for T to fall within the predefined target concentration range of 300-1000 ng/dL. Since such range is not expected to be achieved in all subjects, the success rate was set for at least 75% of subjects to fall within such range with the lower bound of the 95% CI to be > 65%. These criteria were met in this study with 83.6% rate and lower bound of 76.5%, on Day 90.

In this study there were two arms. The oral TU arm and T-gel (AndroGel® 1%) arm. Overall, the T profiles after Androgel® were lower than that after oral TU. In addition, the variability after oral TU was much higher than after Androgel®. The observed Cmax values for T during that 24-hour period were high in relatively large numbers of subjects (e.g., 15% of subjects had Cmax >1500 ng/dL and 5% >1800 ng/dL on Day 90). None of the subjects in Androgel® had a concentration above 2500 ng/dl while several were after oral TU.

The single sample time point collected at 4-6 h post morning dose was adequate and practical than the 24 h AUC or Cavg measurement. The C4-6 h value used for dose titration decisions correlated relatively well with Cavg and Cmax.

It appears that some extrinsic factors play important role in the formulation performance, oral absorption, and the systemic availability of T following oral TU. Of particular interest is the effect off food and % fat (for details see effect of food Study 09008). As observed in this study, the level after PM dosing was higher than AM dosing. This could be associated with combination of higher % fat in dinner and volume being consumed than breakfast.

Overall, based on the data from this study there was no evidence of T accumulation over time. However, the safety and efficacy of high T exposure over a long term therapy is referred to the clinical/medical team (see Medical Officer's review).

Conclusions (T PK Data):

The following conclusions can be drawn from this study:

- Overall, the study met the dose adjustment algorithm (titration) criteria (i.e., >75% of the treated population had serum total T Cavg values within the normal range of 300-1000 ng/dL with the lower bound of the 95% CI > 65%). However, the study shows excessive number of treated subjects with Cmax values above of selected threshold targets as follows:
    - 58% rather than>85% had Cmax values <1500 ng/dL
    - 13% rather than <5% had Cmax values between 1800 and 2500 ng/dL
    - 13% rather than 0% had Cmax values >2500 ng/dL
- Overall, the T levels after oral TU is highly variable compared to more stable levels after Androgel®. As a whole, in contrast to oral TU, there was essentially no Cmax above the 1500 ng/dL after the Androgel®.
- The single time point 4-6 hours post-dose was adequate and feasible to optimize titration process.

In conclusion, oral TU and associated dose adjustment algorithm met the primary criteria for efficacy (i.e., Cavg), but failed the secondary safety criteria (i.e., Cmax). Comparing to Androgel®, the levels of T are more variable after oral TU. This is one of the major concerns with oral TU in addition to the associated variability with food and food content and specially % of fat.

Dihydrotestosterone (DHT) PK Results:

As shown for T, the mean concentration-time profiles for serum DHT after oral TU was highly variable but as a whole appears to be relatively constant among all treatments (**Figure DHT-1 A,B, and C**). In addition, DHT profiles were similar in shape/pattern to the T profiles in which it was increased during the first 3-6 hours post-dose and then declined over the remainder of the 12-hour dosing interval. As expected of DHT being a metabolite of T, its Tmax was delayed and the Cmax was broader and flatter than observed for T (mean DHT Tmax values were approximately 0.3 to 1.4 hour later than that of T).

However, a more constant and less variable DHT profiles were observed after Androgel® as compared to after oral TU (**Figures DHT-1ABC).** The mean DHT Cavg ranged from 118 ng/dL to 127 ng/dL for the oral TU treatment group, and from 62 ng/dL to 80 ng/dL in the Androgel® treatment group (**Table DHT-1**).

Figure DHT-1. Mean (±SD) Concentration-Time Profile for Serum DHT on Days 30, 90, and 365 Clinic Visit (Study 09007). The dotted line in Day 90 show the lower and upper limit of normal range from the literature (20-80 ng/dL)

A: Day 30 **B: Day 90** **C: Day 365**

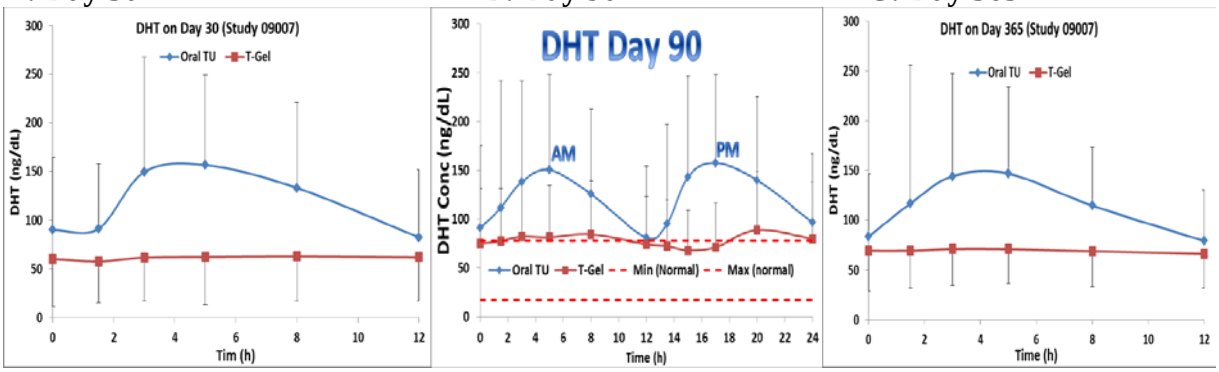


Table DHT-1. Mean DHT PK Parameters (source PK Report, Section 16.5, Table 11)

	Oral TU		Androgel®	
Parameters	**Day 30 (Full Day)**	**Day 365 (AM)**	**Day 30 (Full Day)**	**Day 365 (AM)**
Cavg (ng/dL)	124	118	61	69
Cmax (ng/dL)	196	187	82	92
AUC (ng.h/dL)	1484	1412	738	830
DHT/T (AUC Ratios)	0.2117	0.2403	0.1598	0.1714

There was no trend for the DHT concentrations to be increased in the subjects titrated to higher maintenance doses. The results indicate that the titration process not only controlled T concentrations by using dose adjustments to compensate for differing PK characteristics, but also controlled DHT concentrations. This indicates that DHT concentrations are primarily determined by T systemic exposure.

The mean DHT/T ratios following oral TU was higher than after and Androgel® (**Table DHT-1**). The difference was statistically significant (p>0.001, t-test). It should be noted that the DHT/T ratios at steady-state were approximately twice their pretreatment values in both treatment groups.

Reviewer's Comments on DHT Data:

The concentration-time profiles for DHT were similar in shape to those of T. The DHT serum profile had a broader peak, and was somewhat delayed relative to T, an attribute consistent with DHT being a metabolite of T. The DHT/T ratio after oral TU was higher than after Androgel®. Such high level of DHT is concerning.

Is There a Relationship Between Free T (FT) and Total T (TT)?

Following oral TU the mean concentration-time profiles for Free T (FT, protein unbound) followed a similar pattern as the total T (**Figures FT-1 ABC**). The Free T Cavg was about twice higher after oral TU than Androgel® at all visits (**Figures FT-1 and 2**). In addition, there was relatively good correlation between TT and FT (**Figure FT-2B**).

Figure FT-1. Mean (±SD) Concentration-Time Profile for Free T in Subjects on the Days 30, 90, and 365 Clinic Visit (Study 09007)

A: Day 30 **B: Day 90** **C: Day 365**

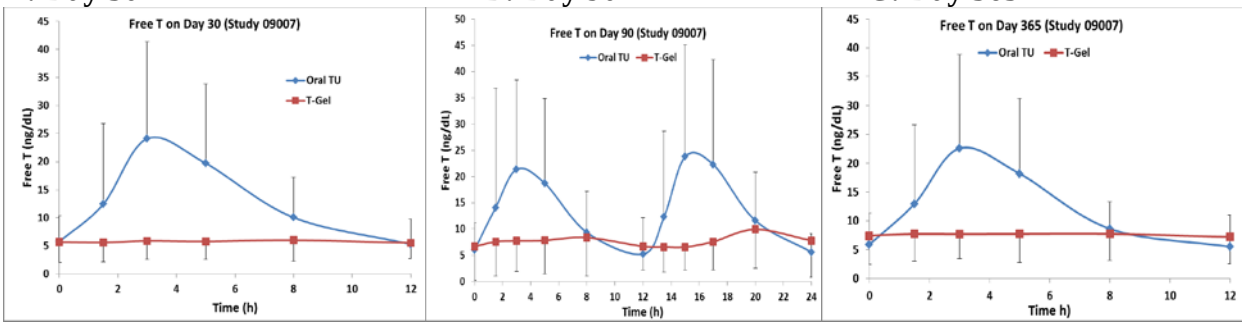
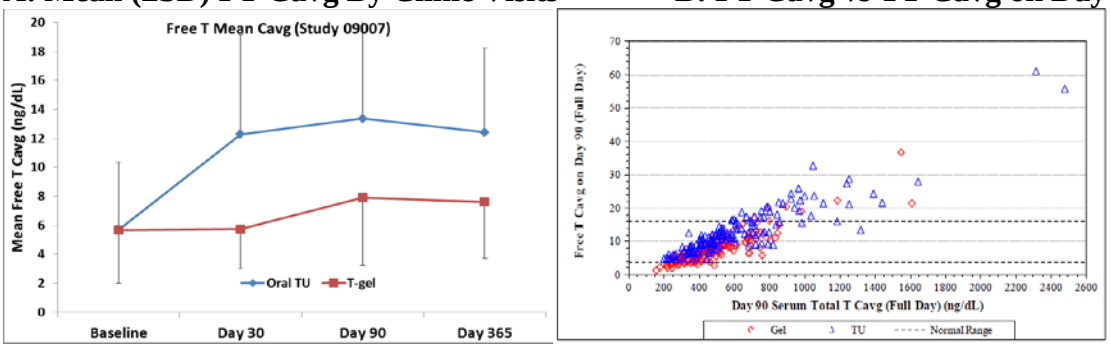


Figure FT-2. Free T Cavg and TT Cavg

A: Mean (±SD) FT Cavg By Clinic Visits **B: FT Cavg vs TT Cavg on Day 90**



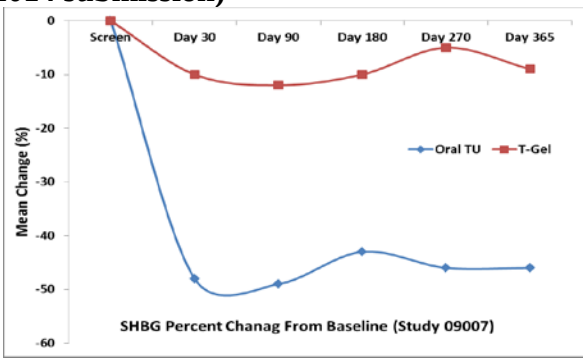
Conclusions on Free T:

From this data it can be concluded that FT levels after oral TU were higher than after Androgel®. There was an inverse relationship between free T and SHBG levels (see below).

What is the Effect on Sex Hormone Binding Globulin (SHBG)?

Serum SHBG concentration were determined prior to the start of therapy (baseline) and pre-dose on Days 30, 90, 180, 270, and 365 following oral TU and Androgel® treatments. While there was virtually no change in SHBG concentration after Androgel® from the baseline throughout the study, there was approximately 5 times decline in its concentration by Day 30 following oral TU (**Figures SHBG 1AB**). Such decline remains relatively constant throughout the study.

Figure SHBG-1 Mean Percent Change from Baseline in SHBG Concentration-Time Profiles (Source Aug 4, 2014 submission)



There was apparent difference on the effect on SHBG between oral TU and Androgel®. Such difference is related to the difference in FT concentrations. As shown in the previous section, the level of free T increased after oral TU but the SHBG level decreased (**Figure FT-2**). This is expected inverse relationship as SHBG has high affinity to T with limited capacity. Overall, the clinical significance of the long term effect of changes in SHBG level is unknown at this time.

Conclusions for SHBG:

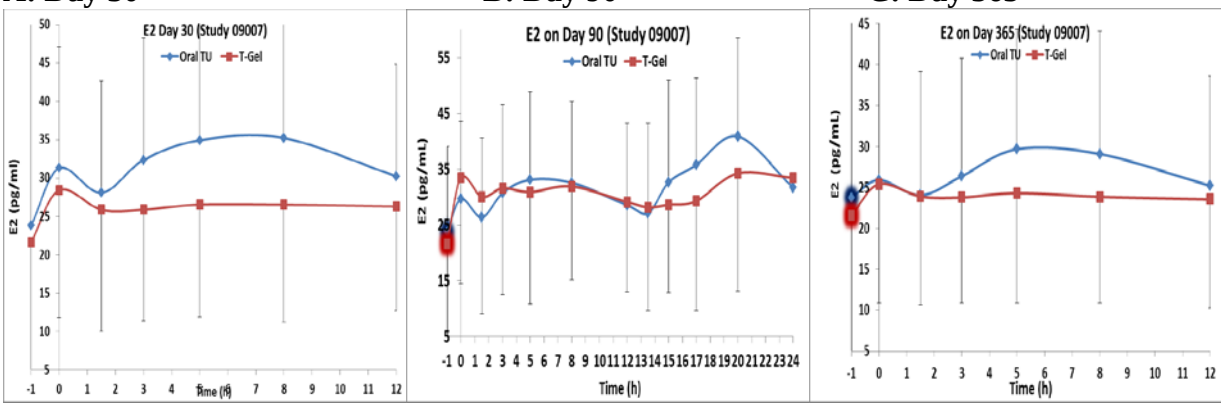
Overall, from this study it can be concluded that serum SHBG concentrations declined by approximately 50% by Day 30 after oral TU and remained stable throughout the study. However, after Androgel®, SHBG level remains relatively constant throughout the study but slightly reduced by approximately 9% from the baseline. There was inverse relationship between free T and SHBG.

What is the Effect on Estradiol (E_2)?

The mean concentration-time profiles for E_2 in all the subjects that received oral TU and Androgel® on Days 90, 30, and 365 are shown in **Figure E2-1ABC.** Overall, the serum concentrations of E_2 were higher than pretreatment following oral TU or Androgel®. In particular, the E_2 level was noticeably higher after PM dosing on day 90 compared to AM dosing.

Figure E2-1. Mean (±SD) Concentration-Time Profile for E_2 in Subjects on the Day 30, 90, and 365 Clinic Visit (Study 09007)

A: Day 30 **B: Day 90** **C: Day 365**



Conclusion on E_2:

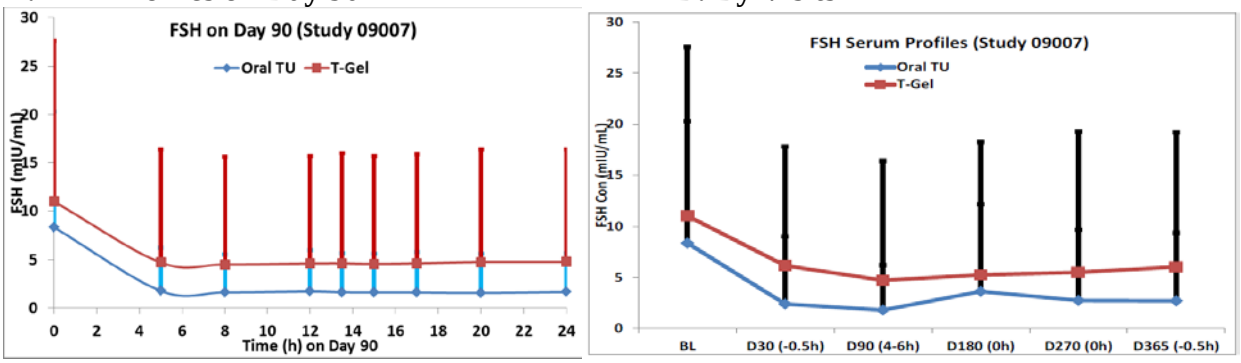
Overall the observed E_2 levels after oral TU are higher than after Androgel®. This observation has been consistent with total T, free T, and DHT data. The E2 levels remain constantly higher than the baseline throughout the study.

Was there Effect on Follicle Stimulating Hormone (FSH)?

There was almost no fluctuation in the FSH concentration-time profiles on Day 90 (**Figure FSH-1**). However, there was a noticeable inter-subject variability in the levels as expected. Also, it is noted that the mean FSH concentrations were within the normal range before and during the treatment (**Table FSH-1**). Yet, FSH concentrations appeared to decline in most of the subjects during treatments. Reductions in FSH reflect the well-known negative feedback of T on gonadotropin secretion. The same mechanism of negative feedback was also seen for LH secretion (see LH Section below).

Figure FSH-1. Mean (±SD) 24 Hour Concentration-Time Profile for FSH in Subjects on the Day 90 and Other Visits (Source: Table 41, PK Report, Section 16.5, Study 09007)

A: 24 h Profiles on Day 90 **B: By Visits**



FSH concentrations declined by the Day 30 visit in both treatment groups to a level that was maintained for the remainder of the entire 1 year duration of the study. The FSH was consistently

lower after oral TU compared to Androgel®, suggesting more inhibition due to the high T exposure. This is expected from the pharmacological action of T (i.e., negative feedback on FSH release).

Conclusion on FSH:

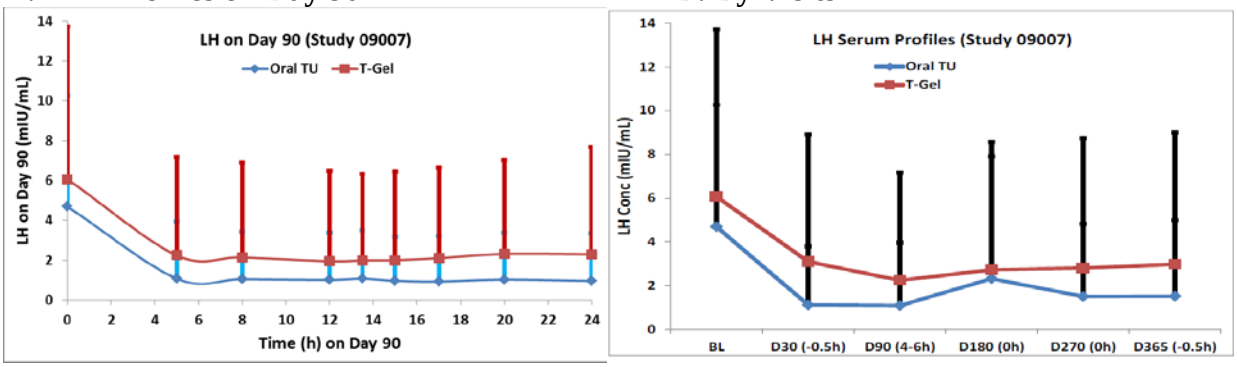
The extent of FSH decline was consistently greater following oral TU compare to Androgel®. Such decline in FSH levels following all treatments was consistent with the negative feedback of androgens on FSH secretion.

Was There Effect on Luteinizing Hormone (LH)?

The profiles of LH followed similar profiles of the FSH in all aspects such as but not limited to patterns, variability, baseline, and treatment values, except the actual units (**Figures LH-1 AB**). As indicated for the FSH, such pattern is expected from the pharmacological and negative feedback mechanisms of T on the normal secretion of FSH and LH. However, for comparison, oral TU suppressed LH secretion at greater extent than Androgel®.

Figure LH-1. Mean (±SD) 24 h Concentration-Time Profile for LH in Subjects on the Day 90 and Other Visits (Source: Table 43, Page 123 of 950, PK Report, Section 16.5, Study 09007)

A: 24 h Profiles on Day 90 **B: By Visits**



Similar to the observations for FSH, there was almost no fluctuation in the LH concentration-time profile over the dosing interval. Yet, Androgel® had lower fluctuation than oral TU. However, as observed in FSH, there was a high variability in LH concentrations throughout the study. Overall, the mean LH concentrations were within the normal range prior to the start of therapy, but had decreased to below the lower limit of the normal range during therapy.

Conclusion on LH:

The LH decline is consistent with the negative feedback of androgens on LH secretion. However, Androgel® appears to suppress LH secretion at lower extent than oral TU and the fluctuation and variability in LH levels appear to be lower than after oral TU.

What are the Levels of TU and DHTU, After Oral Administration?
Does all TU is Converted to T Following Oral Administration?
What are the Clinical Significant of High Levels of TU and DHTU?

These are critical questions in this review to evaluate the safety of the parent drug, TU, after oral administration. The TU and DHTU serum concentrations were substantially higher than total T (**Table TU-1 and 2 and Figures TU-1ABC).** The mean Cmax and Cavg of TU were 33948.00 ng/dL and 8752.00 ng/dL, respectively (**Table TU-1**). Based on this study, the mean Cmax and Cavg of total T after all oral TU doses on Day 90 were 1676 ng/dL and 628.3 ng/dL, respectively (see **Table 09007-2** in the earlier Section). Based on weight per volume basis, the TU exposure would roughly be 20-folds higher than T levels (**Figures TU-1 and TU-2**). The same trend was observed for DHTU (**Table TU-2 and Figure TU-1C**).

Table TU-1. Summary of Primary PK Parameters for Serum TU Following the Day 90 AM Oral TU Dose (Study 09007)

	All Subjects (n=26) on Day 90		
PK Parameters	**Mean**	**SD**	**CV (%)**
Cmax (ng/dL)	33348	19402	57.2
Cavg (ng/dL)	8752	5503	62.9
AUCt (ng.h/dL)	105030	66046	62.9
Tmax (h)	2.56	2.10	82.3
CL/F (L/h)	246.5	180	52

Table TU 2. Summary of Primary PK Parameters for Serum DHTU Following the Day 90 AM Oral TU Dose (Study 09007)

	All Subjects (n=26) on Day 90		
PK Parameters	**Mean**	**SD**	**CV (%)**
Cmax (ng/dL)	14570	9601	65.9
Cavg (ng/dL)	5810	3500	60.3
AUCt (ng.h/dL)	69720	42010	60.3
Tmax (h)	3.52	2.23	63.4
DHTU/TU	0.7224	0.35457	49.1

Figure TU-1ABC. Mean Concentration-Time Profile of T, TU, and DHTU Following 200 mg Oral TU in Subjects on the Day 90 Clinic Visit (Note differences in Y-scales) (Study 09007)

A: TU and T (One Scale) **B: TU and T Two Scales)** **C: T, TU, and DHTU (two 2cales)**

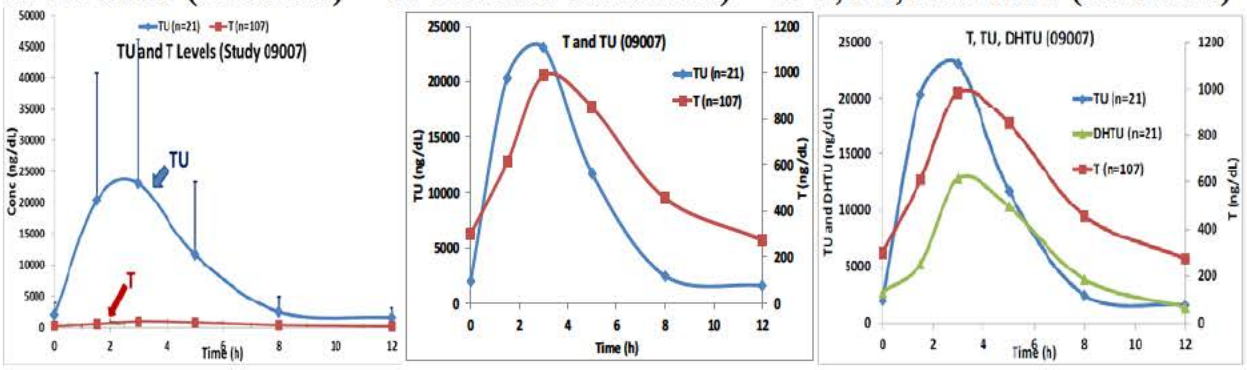
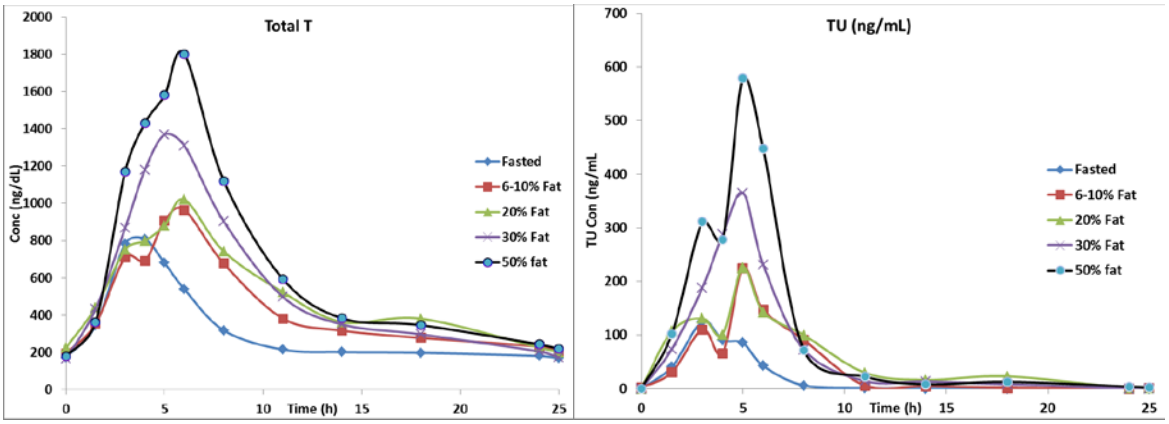


Figure TU-2. Mean of Serum T and TU Profiles Following 300 mg Oral TU Doses Following Overnight Fast or Meals with Different Percentage of Fat Content (source Study 09008 Tables 14.3-7 and 14.61-14.65)

A: T Profiles **B: TU Profiles**



Reviewer's Comments:

The observed high level of TU and DHTU was more than expected. At such high exposure, androgenic and non-androgenic pharmacological activities after long term therapy is concerning. It should be noted that from the clinical pharmacology and PK perspective, there was no evidence of TU or DHTU accumulation in the body after 365 days of treatment. However, based on the high lipophilicity of TU, it is expected to be widely distributed into the fatty tissues. Thus, it will be undetectable in blood.

It should be noted that based on pre-clinical data, the binding affinity of TU and DHTU to the receptor was extremely low compared to that of T (**Table TU-2,** see PharmTox review).

Table TU-2. EC50 and Relative Binding Affinities of Test Compounds

	T	DHT	P	TU	DHTU	TE	DHEA
EC_{50} (nM)	7.04	8.51	81.45	573	1005	142.7	916.4
Relative binding affinity (%)	100	83	8.64	1.23	0.70	4.93	0.77

DHEA=dehydroepiandrosterone; DHT=dihydrotestosterone; DHTU=dihydrotestosterone undecanoate; EC_{50}=the concentration that inhibits 50% of maximum binding; P=progesterone; T=testosterone; TE=testosterone enanthate; TU=testosterone undecanoate.

Irrespective of the low affinity to the receptor, this does not mean that at such high concentration other pharmacological effect associated with non-androgenic receptors can be ruled out. Therefore, the potential long term safety and risk of this product is unknown at this time.

Conclusions on High TU and DHTU Exposure:

The TU exposure is approximately 20 folds higher than T. The high exposure of TU and DHTU was more than expected. While there was no evidence of accumulation of TU and DHTU after 365 days of treatment, the potential long term safety of the product cannot be ruled out. Therefore, the risk/benefit of the use of oral TU should be carefully evaluated.

Overall Reviewer's Comments on Study 09007:

- The success rate in this study for oral TU was 83.6% (122/146). The lower bound of the 95% CI was 76.5%. However, the safety related secondary endpoint in reference to Cmax was **not** met. Approximately 40% of the oral TU treated subjects had Cmax values in excess of a 1500 ng/dL threshold, instead of the 15% or fewer that was targeted. In addition, 13% of subjects had a Cmax >2500 ng/mL instead of 0%. In addition, the Cmax was consistently higher after oral TU than Androgel®. The variability in all data was higher after oral TU compared to Androgel®.
- A single time point at 4-6 hours post dose appears to be adequate for titration.
- The PM dose appears to show higher T levels than AM dose as this most likely dependent on the high fat content in dinner compared to breakfast.
- SHBG concentrations decreased by approximately 5-times from the baseline after oral TU treatment than Androgel®. There was an inverse relationship between free T and SHBG levels.
- The level of E_2 was consistently higher than baseline after oral TU as compared to Androgel®.
- Also as expected from the negative feedback mechanism of T, the levels of FSH and T were decreased. The effect was more noticeable after oral TU than after Androgel®.
- TU and DHTU levels were almost 20 fold higher than T. The long term safety of such high exposure is unknown at this time.
- The DHT/T ratio was much higher after oral TU compared to Androgel®. The clinical significance of the high DHT level remains unknown at this time.

The final point is that, while the data shows that oral TU must be taken with food, one of the major concerns is the expected high variability and unpredictability in T levels due to unrestricted food intake, content, and specifically % of fat.

Study CLAR-12011:

Study Title: "PHASE III, OPEN-LABEL STUDY OF THE SAFETY AND EFFICACY OF ORAL TESTOSTERONE UNDECANOATE (TU) IN HYPOGONADAL MEN"

PK Report Title: "*A Pharmacokinetics Evaluation of Testosterone, Free Testosterone, Dihydrotestosterone, Estradiol, Follicle Stimulating Hormone, Luteinizing Hormone, and Sex Hormone Binding Globulin following Administration of Oral Testosterone Undecanoate to Hypogonadal Men in a Phase 3 Clinical Study*"

Objectives:

Primary Objectives: The primary objective of this study was to determine the efficacy of Oral TU in hypogonadal men following approximately 114 days. The primary efficacy parameter is the percentages of treated subjects with T Cavg between 300 and 1000 ng/dL. The primary safety parameters is the percentage of subjects with Cmax not greater than 1500 ng/dL and no subjects should be over 2500 ng/dL.

Secondary Objectives: The secondary objectives of this study was to assess the effectiveness of dose titration at steady-state, based upon a single serum T sample obtained at 4-6 hours post AM dose. In addition, the safety of T was assessed by monitoring several pharmacodynamics parameters as that in Study 09007.

Study Design:

Overall, the design of this study was similar to that of the first Study 09007 with few exceptions as follows:

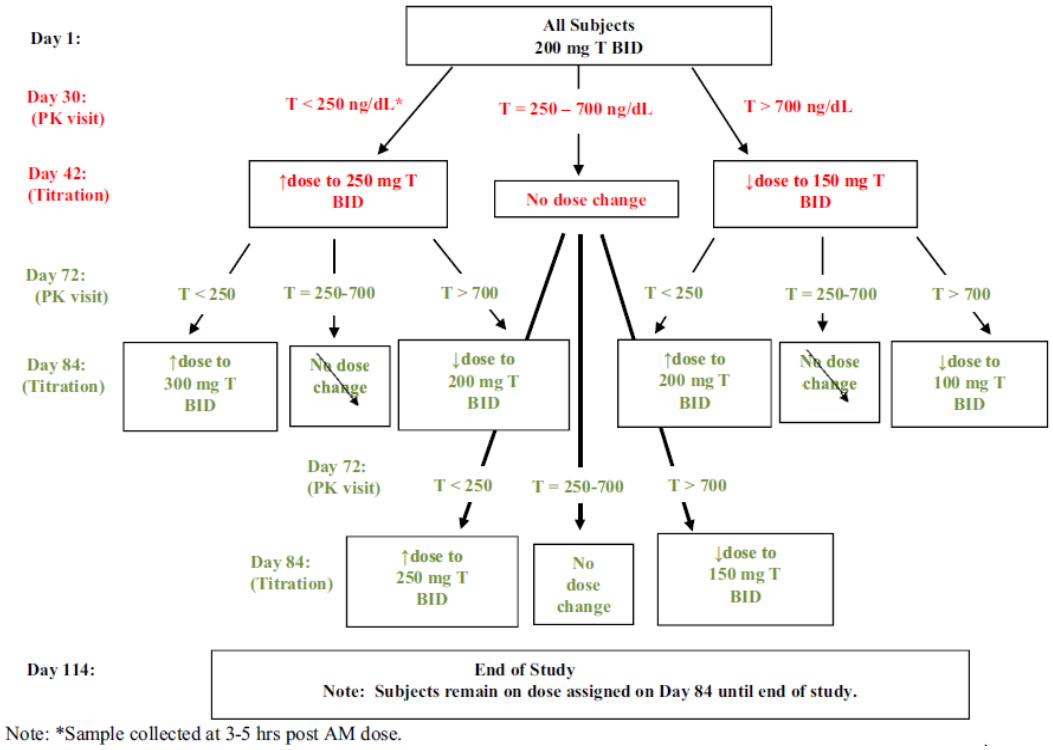
- Titration time point was changed from **4-6** hours to **3-5** hours
- The duration of the study was shorter (i.e., 4 months instead of 12 months)
- Lower titration steps/dose (i.e., **50 mg** increment or decrement instead of **100 mg**)
- The down titration was at a concentration of <700 ng/dL and in Study 09007 was at <1100 ng/dL.
- More titration days added between Day 30 and Day 114, as needed
- Single arm study

In summary, this was a 4-month repeat-dose, dose-titration in approximately 120 hypogonadal men between ages of 18 to 75 years with T concentration of <300 ng/dL. Subjects were treated with TU up to 114 days with 2 dose titration periods. The initial dose in all subjects was 200 mg BID administered 15 minutes after completion of a meal (i.e., not on an empty stomach). Serial PK samples were collected on days 30 and 114.

Titration:

The titration was performed as in Study 09007 as shown in **Figure 12011** with the exception sated above.

Figure 12011-1. Study Dose Titration Scheme



Note: *Sample collected at 3-5 hrs post AM dose.

What is the Rationale for Dose Selection?

As stated earlier, the doses of TU in this study were selected primarily based on results from Study 09007. Additional supporting data were also used based on Phase II study.

As shown in Study 09007, approximately 13% of subjects on Oral TU had a Cmax > 2500 ng/dL and 13% had a Cmax of 1800-2500 ng/dL. In that study some men who were not eligible for a second PK assessment at Day 60, as their Day 30 T levels were within the threshold algorithm, could have benefited from a second opportunity for titration on Day 60. Therefore, the titration scheme was revised including the single blood time point was changed from **4-6 hour** in Study 09007 to **3-5 hours** post morning dose in this study.

Subject received the following doses with food (**within 15 minutes after completion of a meal***). However, the sponsor stated that "*When subjects were confined to the clinical facility, they were provided a regular diet prior to the scheduled dose*". However, the sponsor did not provide details on the so called "*regular diet*"

Study Subjects and Disposition:

A total of 148 subjects were enrolled in this study: four subjects did not receive study treatment, leaving 144 subjects who received study treatment and were included in the safety population. Of these subjects, 133 were included in the PK population and 116 were included in the efficacy population. A total of 117 subjects completed all visits.

The mean (SD) age and BMI (SD) of the safety population was 54.8 (10.60) years and 29.88 (3.923) kg/m2, respectively. Overall, 114 subjects (79.2%) were white and 125 subjects (86.8%) were not Hispanic or Latino.

Results:

What is the Release Characteristics of Testosterone (T) from TU?
How Many Subjects Were Within T Normal Range?

Table 12011-1 summarizes the efficacy results for each of the PK visits. On Day 114, 75% of the subjects (87 out of 116) achieved a T level within the normal range. A comparable percentage was also shown in 3-5 h post morning doses on Days 30 and 72.

Table 12011-1. Summary of the Success Rate for Obtaining T Cavg Values in the Eugonadal Range in Hypogonadal Men (Study 12011).

Observation Day & Time	Oral TU Treatment			
	Cavg Evaluable Total	Cavg in 300-1000 ng/dL range		Lower 95% CI
		N	%	%
Day 114 Full	116	87	75.0%	66.1%
Day 30 AM	133	114	85.7%	NC
Day 72 AM	130	100	76.9%	NC

Was There a Difference in the T Serum Profiles Among Visits?

Overall, the T serum concentration-time profiles were comparable in terms of magnitude of T levels and the variability (**Figures 12011-2 to 12011-4**). The observed inter and intra-subject variability in T levels was expected due to many factors and in particular food contents. However, as a mean values for all days, it falls within the normal T level (see also above).

Figure 12012-1AB. Mean (±SD) T Concentrations-Time Profiles
A: Day 30 **B: Day 114**

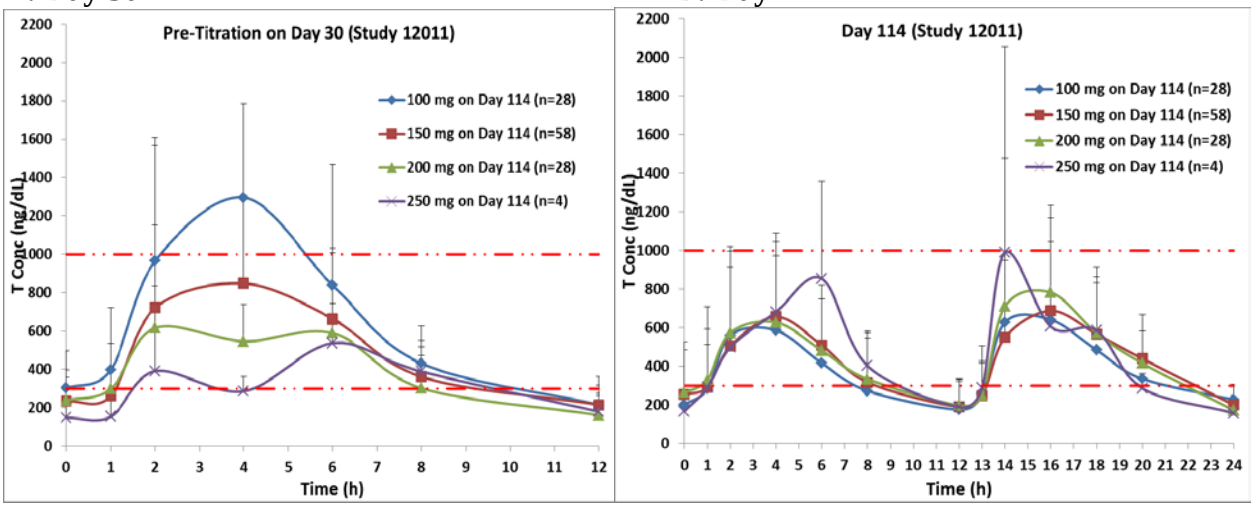


Figure 12011-3 AB. Individual T Concentration-Time Profiles for Oral TU Subjects on Day 30 (Spaghetti Plots)

A: Full Y-Axis on Day 30 **B: Expanded Y-Axis on Day 30.**

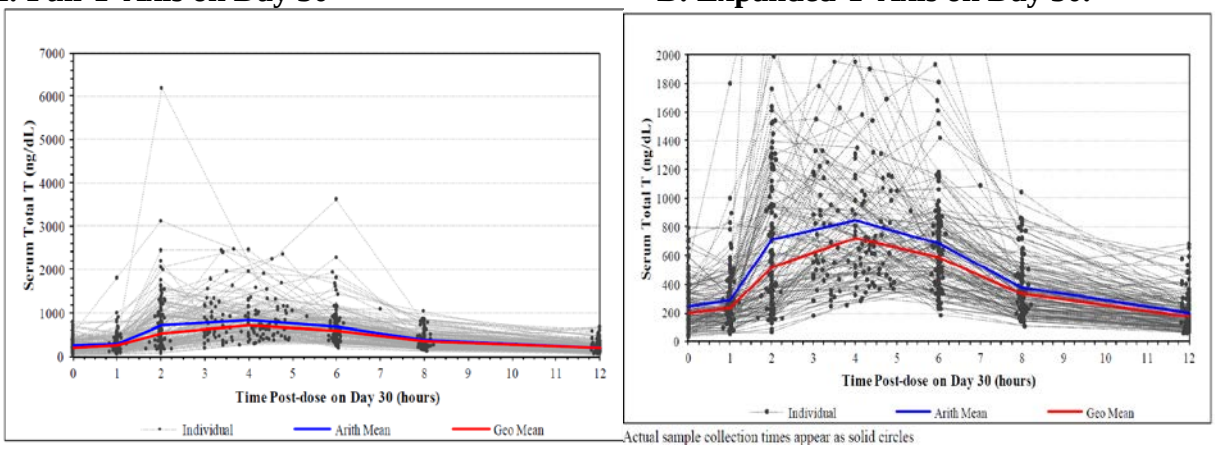


Figure 12011-4 AB. Individual T Concentration-Time Profiles for Oral TU Subjects on Day 114 (Spaghetti Plots)

A: Full Y-Axis on Day 114 **B: Expanded Y-Axis on Day 114.**

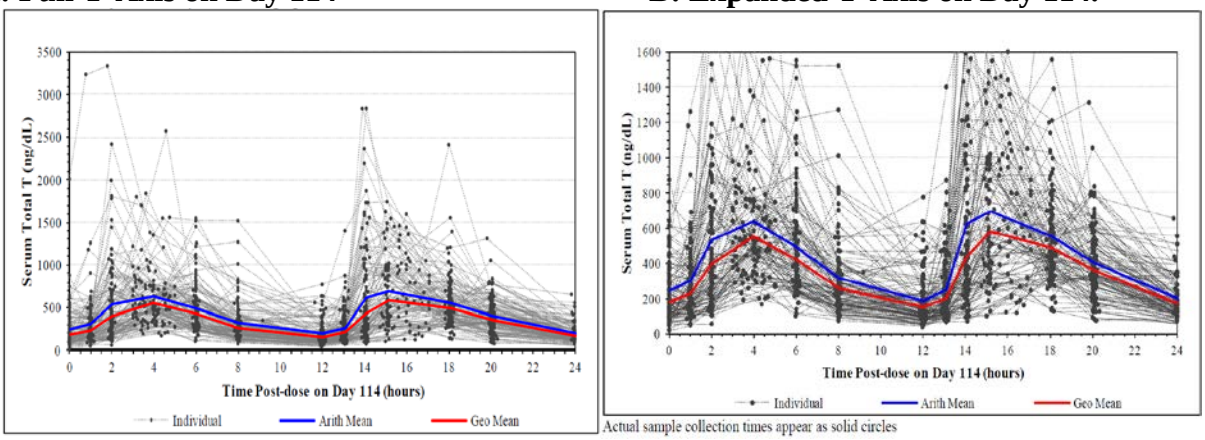


Figure 12011-2 AB shows the mean concentration-time profiles for all subjects per visit and titrated dose on Days 30 and 114. These profiles show the mean concentrations of subjects that were in the 100 mg, 150 mg, 200 mg and 250 mg dose groups on Day 114 (i.e., the mean Day 30 and Day 114 concentration profiles for subjects that were ultimately titrated to maintenance doses of 100 mg, 150 mg, 200 mg or 250 mg). It should be noted that no subjects were titrated to the 300 mg dose, so no profiles are shown.

Irrespective of the dose, on Day 114 the profiles of serum T are comparable following all four doses of 100, 150, 200, and 250 mg. By contrast, on Day 30 the profiles were substantially different than on Day 114 for 100, 150, and 250 mg doses, but not after 200 mg dose. Although, the number of subjects with a mean Cavg outside the goal concentrations was small mean, it is because the sample size in the study is small. However, in a large trial and in real life, this number will be high.

In terms of Cmax, there was high variability in which one patient had a Cmax above 6000 ng/dL (**Figures 12011-3 and 4**). However, the mean Cmax ranged from the 827 ng/dL to 1107 ng/dL and occurred approximately 4-4.5 hours post-dose following both the morning and evening Doses (**Table 12011-2).** The mean Cavg values were approximately 40%-50% of the Cmax concentrations, ranging from 398 ng/dL to 509 ng/dL. Again, there was a high variability in the PK parameters with CVs ranging from 40% to 60%.

Table 12011-2. Mean (SD) of Primary PK Parameters for Serum Total T During Each PK Observation Period, by Treatment (Source, Table 22, Page 83 of 540, Study 12011).

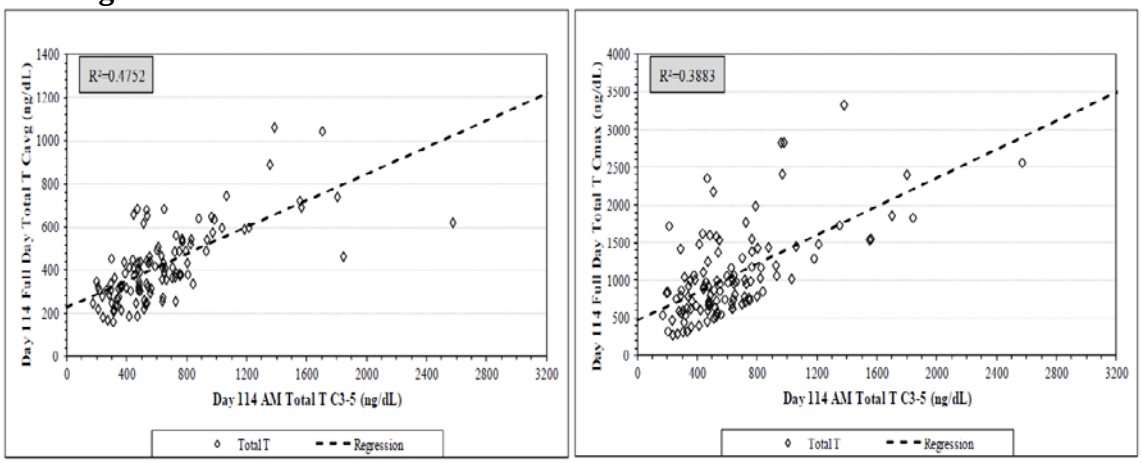
Parameters	Day 30 (AM)	Day 72 (AM)	Day 114 (AM)	Day 114 (Full Day)
Cavg (ng/dL)	509±222	454±192	397±197	422±171
Cmax (ng/dL)	1106±708	928±515	827±504	1062±581
AUC (ng.h/dL)	6110±2665	5455±2307	4763±2350	10135±4111

Is There a Relationship Between T Cavg and Cmax and Concentration at 3-5 h?

As shown in Study 09007, there was a relationship between Cavg and Camx and single point of 3-5h. Overall, the relationship was relatively reasonable (**Figure 12011-5**).

Table 12011-5. Summary of Regression Parameters for Cavg vs. C3-5h and Cmax vs. C3-5h

A: Cavg vs. C3-5h **B: Cmax vs. C3-5h**



Reviewer's Comments on T PK Data:

In this study, all subjects received 200 mg dose of TU on Day 0 through Day 42. Between Day 42 and Day 72 subjects requiring a dose change based on their Day 30 single blood sample result received either 150 mg or 250 mg of T, while those not requiring a dose adjustment continued on with 200 mg dose (**Figure 12011-2AB**).

As shown in **Figure 12011-2AB** serum T concentrations increased during the first 3-6 hours post-dose and then declined over the next 6 hours to approximately the pre-dose concentration.

On Day 114, at the time of the next dose at 12 hours post the first dose, the mean T level was below 300 ng/dL and following titration, the mean Cmax was within the normal range.

Taking into consideration all PK parameters including but not limited to Cmax and Tmax, the 3-5 hour sampling window appears to be adequate. Therefore, the choice of C3-5 sampling window appears to be clinically convenient alternative.

As stated in Study 09007, the most significant extrinsic factor that affect the absorption and PK of T and TU is food content and in particular the percentage of fat in the diet. Yet this may impact the titration process and potential safety and efficacy of the product.

Conclusions (T PK Data):

The following conclusions can be drawn from the evaluation of the T PK data:

- The oral TU formulation and the associated dose adjustment algorithm marginally met the criteria for acceptable efficacy as a testosterone replacement therapy in hypogonadal men. Based on this data, 75.0% of patients T Cavg within the predefined range of 300-1000 ng/dL were achieved. The lower bound of the 95% CI was 66.1%. These data are borderline success.
- Dose adjustment algorithm resulted in the study population distribution of Cmax values being as follows:
    - ❖ Approximately 80.5% (the predefined target was ≥85%) with Cmax ≤1500 ng/dL
    - ❖ Approximately 6%, (the predefined target was ≤5%) with Cmax between 1800 and 2500 ng/dL
    - ❖ Approximately 3.4% (the predefined target was 0%) with Cmax ≥2500 ng/dL.

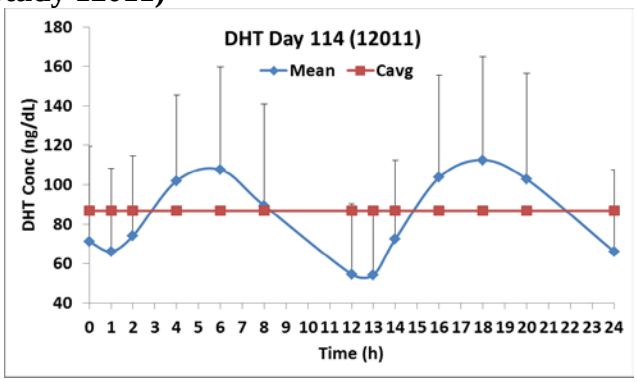
- The study confirmed that assessing the subject's T status based on a single blood sample at 3-5h post AM dose appears to be feasible from the clinical practice perspective.
- Based on the data, oral TU may need always be taken with food to enhance absorption. However, the primary issues is the variability associated with food content and % of fat that ultimately cause day-to-day high variability in T levels within and between subjects. As also observed in Study 09007, the T levels and variability appear to be higher after PM dosing than AM dosing.

In summary, oral TU and associated dose adjustment algorithm marginally met the criteria (75.0%) for acceptable efficacy as a T replacement therapy in hypogonadal men in this study.

Dihydrotestosterone (DHT) PK Results:

As shown for T, the mean concentration-time profiles for serum DHT was highly variable but as a whole appears to be relatively consistent among all treatments. **Figures DHT-1** shows DHT plasma-centration time profiles on Day 114. In addition, DHT profiles were similar in shape/pattern to the T profiles in which it was increased during the first 3-6 hours post-dose and then declined over the remainder of the 12-hour dosing interval. As expected of DHT being a metabolite of T, its Tmax was delayed and the Cmax was broader and flatter than observed for T (mean DHT Tmax values were approximately 0.3 to 1.4 hour later than that of T).

Figure DHT-1. Mean (±SD) Concentration-Time Profile for Serum DHT in Subjects on the Day 114 Clinic Visit (Study 12011)



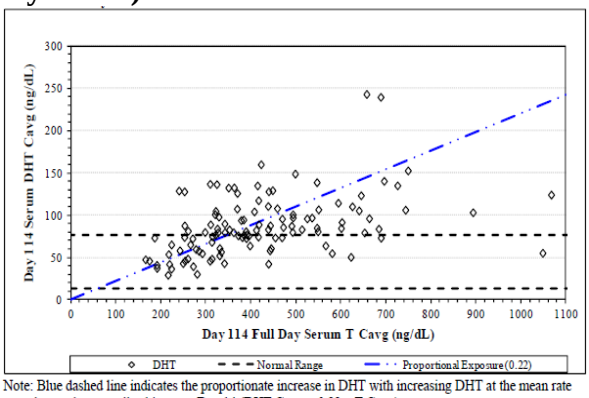
Although, the mean DHT concentrations in subjects at the titration adjusted dose were within the normal range for DHT in in some subjects, there was some variability in the data. Overall, DHT levels were higher than the normal range (**Table DHT-1**).

Table DHT-1. Summary of Primary PK Parameters for Serum DHT during Each PK Observation Period (Study 12011)

Parameter	Day 30 (AM)	Day 114 (Full Day)
Cavg (ng/dL)	137 (CV 48%)	87 (CV 41.5%)
Cmax (ng/dL)	209 (CV 50.8%)	147 (CV 40.5%)
AUC (ng.h/dL)	1641 (CV 47.8%)	2085 (CV 41.5%)
DHT/T AUC Ratios	0.2916 (CV 50.2%)	0.2201 (CV 39%)

At steady-state on the titration adjusted TU dose, the DHT Cavg values were approximately 4-times to 5-times higher than the pretreatment baseline concentration. Overall, there appears to be some relationship between T exposure and DHT exposure. In other words, DHT Cavg tends to be higher in subjects with higher T Cavg values (**Figure DHT-2**).

Figure DHT-2. Relationship between Serum DHT Cavg and Serum T Cavg on the Day 114 Clinic Visit (Study 12011)



Note: Blue dashed line indicates the proportionate increase in DHT with increasing DHT at the mean rate observed across all subjects on Day 14 (DHT Cavg = 0.22 x T Cavg).

The mean pretreatment DHT/T ratio of 0.076, increased 2-3-fold to a mean of approximately 0.22 on Day 114 on the titration adjusted dose. The mean DHT/T ratio on Day 114 tended to be lower in subjects with high T Cavg values compared to subjects that had T Cavg values at or below the lower limit of the eugonadal range (**Figure DHT-6**).

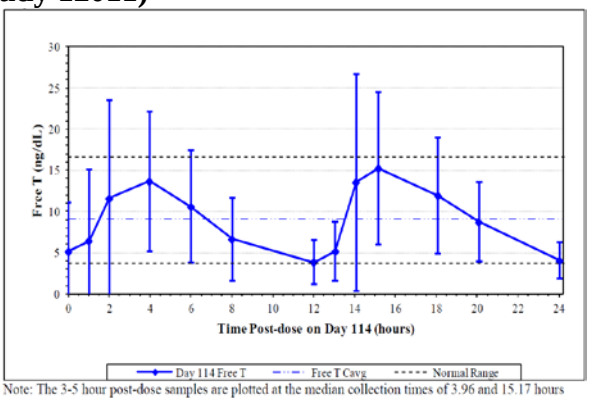
Overall, both the DHT concentrations and the DHT/T ratio at steady-state were substantially different from their baseline values determined prior to the start of T replacement therapy. The mean pretreatment concentration of DHT was 18 ng/dL as compared to the DHT Cavg of 87 ng/dL after treatment with TU.

In conclusion, DHT serum concentrations-time profiles are higher than baseline.

Is There a Relationship Between Free T (FT) and Total T (TT)?

As shown in Study 09007, the mean concentration-time profiles for Free T (FT, protein unbound) total T (TT) followed a similar pattern as the total T concentrations (**Figures FT-1).** However, as expected, FT was substantially lower than the TT. The variability in the data was similar to TT.

Figure FT-1. Mean (±SD) Concentration-Time Profile for Serum Free T in Subjects on the Day 114 Clinic Visit. (Study 12011)

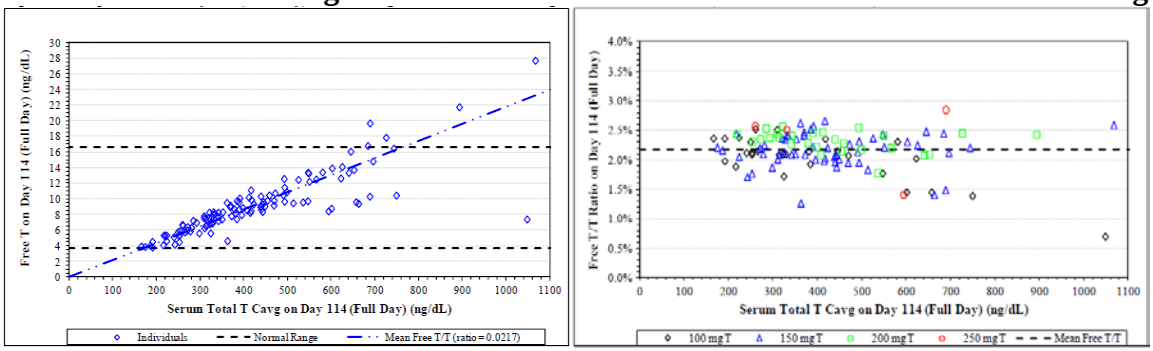


Note: The 3-5 hour post-dose samples are plotted at the median collection times of 3.96 and 15.17 hours

Also as expected, the concentration of FT appeared to increase with TU dose as TT concentration. Thus, there was relatively good relationship between the FT and TT (**Figure FT-2**). The ratios of FT/TT were relatively constant relative to TT Cavg on Day 114.

Figure FT-4. Free T and Total T Cavg on Day 114 (Full Day)

A: Free T vs. Total Cavg **B: Free T/TT Ratios vs Total Cavg**



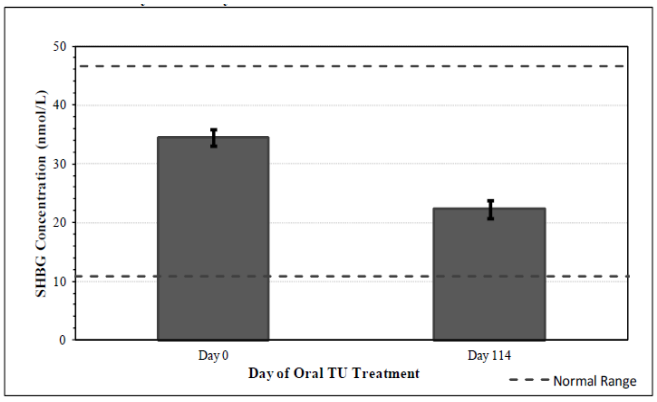
Conclusion in Reference to Free T:

From this data it can be concluded that FT/TT ratios were relatively constant in this study.

What is the Effect on Sex Hormone Binding Globulin (SHBG)?

Serum SHBG concentration were determined twice, once prior to the start of therapy and then, predose on Day 114, at steady-state on the titration adjusted oral TU dose. Also as shown in Study 09007, there was approximately 32% reduction in SHBG levels from the baseline by Day 114 (**Figure SHBG-1**).

Figure SHBG-1. Mean (±SEM) Concentration of Serum SHBG in Oral TU Subjects on the Day 0 and Day 114 Clinic Visits (Study 12011)



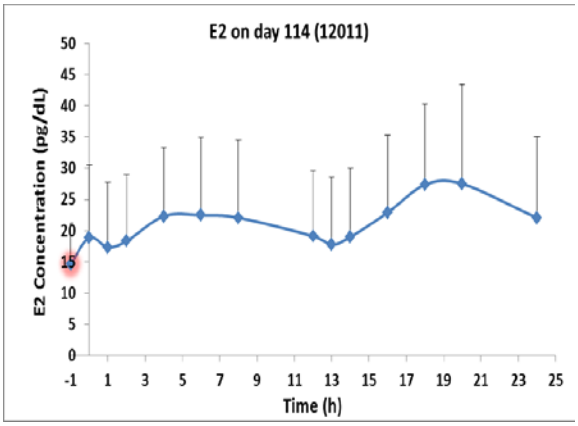
In conclusion, similar to that observed in Study 09007, there was an inverse relationship between SHBG production and free TT. Therefore, differences in serum SHBG concentrations were reflected in differences in FT concentrations and FT/TT ratios.

What is the Effect on Estradiol (E_2)?

The mean concentration-time profiles for E_2 in all the subjects that received oral TU on Day 114 are shown in **Figure E2-1.** Overall, the serum concentrations of E_2 on Day 114 were higher than pretreatment and in particular after PM dosing (22.2 pg/mL vs.14.8 pg/mL). Unlike

DHT or TT, the serum concentration-time profiles for E_2 concentrations had less of peak-to-trough fluctuation. However, like DHT, the timing of the rise and fall of the concentrations was delayed by approximately 1 to 2 hours. The pattern is consistent with the data from Study 09007.

Figure E_2-1. Mean (±SD) Concentration-Time Profile for Serum E_2 in Oral TU Subjects on the Day 114 Clinic Visit.

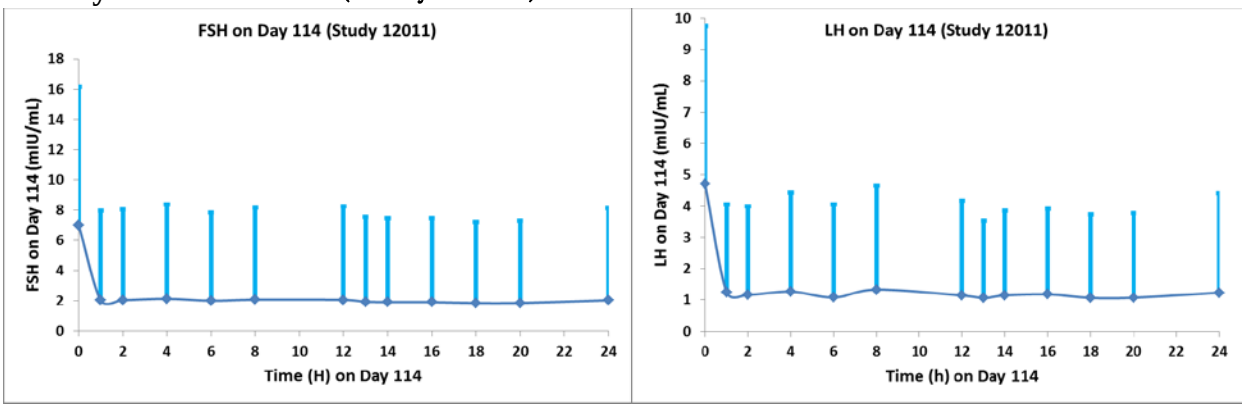


In conclusion, based on this data it can be concluded that the pattern of E_2 serum concentration-time profiles was similar to that of DHT in terms of delayed in time of appearance and shape. This would be expected as both DHT and E_2 are considered metabolites of T. Also as shown in Study 09007, the levels of E_2 after oral TU treatments were constantly higher than the baseline, in particular after PM dosing. The high level of E_2 after PM was consistently observed in other studies as was possibly due to the food fat content and quantity in dinner meals compared to breakfast meals.

Was there Effect on Follicle Stimulating Hormone (FSH) and Luteinizing Hormone (LH)?

Based on the mean data, there was almost no fluctuation in the FSH and LH concentration-time profiles on Day 114 (**Figure FSHLH-1AB**). However, there was a noticeable inter-subject variability in the levels. Overall, FSH and LH concentrations declined in most of the subjects during treatments. This is a reflection of the negative feedback of T on gonadotropin secretion.

Figure FSHLH-1. Mean (±SD) Concentration-Time Profile for Serum FSH in Subjects on the Day 114 Clinic Visit (Study 12011)



In conclusion, it is expected that the FSH and LH concentrations declines from baseline value in response to treatment.

Overall Reviewer's Comments on Study 12011:

This was a multi-center trial in 144 hypogonadal adult men to evaluate the efficacy and safety of oral TU over 4 month's treatment. The following is the overall summary:

- The efficacy objective of the study was marginally met by achieving a serum total T Cavg in the eugonadal range in 75.0% of the oral TU treated subjects. The lower limit of the 95% confidence interval was 66.1%.
- From the safety perspective as related to Cmax, the following conclusions can be made:
    - Approximately 80% of subjects had Cmax values ≤1500 ng/dL. Therefore, it did not meet the target goal of at least 85%.
    - The T Cavg values between 1500 and 1800 ng/dL was observed in approximately 6% of the subject.
    - There were 4 subjects with Cavg above 2500 ng/dL.
- Overall, on Day 114, the mean serum T Cavg was 422 ± 171 ng/dL.
- There was trend of relationship between T Cmax and T Cavg.
- As expected, DHT concentration, as T metabolite, was slightly delayed relative to T concentration. Overall, DHT Cavg was constantly higher during treatments than expected normal range. The mean DHT/T ratio values were twice the upper limit of normal.
- Other PK and PD parameters such as free T, SHBG, E_2, FSH, LH were monitor.
    - There was reduction in SHBG level and was inversely proportional free T.
    - The E_2 level was constantly higher than baseline and in particulate after PM dosing comparing to after AM dosing.
    - As expected form the negative-feedback mechanism of T, both FSH and LH levels were decreased throughout the therapy.
- One of the major concerns is the variability in day-to-day fat content of meals and associated variability leading to unproductivity in T levels.

Conclusions (Study 12011):

The most critical observation in this study was that a single serum T sample collected 3-5 hours post AM dose appears to be adequate and practical for the routine titration process. While there was a high variability in the data, there appear to be trend of relationship between Cmax and Cavg. In the same token, while the data shows that TU must be taken with food, one of the major concern is the expected variability and unpredictability in T levels due to unrestricted food intake.

4.3.1 Pharmacometric Review

OFFICE OF CLINICAL PHARMACOLOGY: PHARMACOMETRIC REVIEW

Application Number	NDA 206089
Compound	Testosterone Undecanoate (TU; Rextoro®); 100 mg and 150 mg Soft Gelatin Liquid Filled Capsules
Indication	For replacement therapy in males for conditions associated with a deficiency or absence of endogenous testosterone: • Primary hypogonadism (congenital or acquired) • Hypogonadotropic hypogonadism (congenital or acquired)
Submission Date	January 3, 2014
Sponsor	Clarus Therapeutics
Pharmacometrics Reviewer	Dhananjay D. Marathe, PhD
Pharmacometrics Team Leader	Jeffry Florian, PhD
Related IND	

SUMMARY OF FINDINGS

Key Review Questions

The purpose of this review is to address the following key questions:

1.1.1 What is the variability in testosterone (T) exposure with the Rextoro product and is there an effect of patient characteristics (type of hypogonadism, age, weight, BMI, race, baseline T levels) on PK (T exposure)?

This specific question was evaluated to address whether the proposed dosing is appropriate to achieve T exposures within the relevant threshold limits across the entire population and any subgroups or whether an alternate dosing regimen could be more suitable to achieve the desired results for the population/subgroup.

The results from pooled data across the three studies (Phase 3 studies 9007 and 12011 and study Phase 1 study 9009) suggest that for the treatment with a dose of 200 mg BID for 4 weeks results in a mean change from baseline in C_{avg} T concentrations (ΔT_{avg}) of 358 ng/dL. The CV% for the inter-individual variability in this response variable (ΔT_{avg}) as well as the absolute C_{avg} value is high (79.7% and 47.9% respectively). Also, there was considerable difference in responses achieved in each of these studies, with the study 9007 showing the largest median (or mean)

change from baseline in C_{avg} T exposure (median change of 351 ng/dL) as compared to the other two studies (median change of 227 ng/dL and 239 ng/dL in studies 9009 and 12011 respectively) (Figure 1).

Type of hypogonadism

As shown in Figure 2 below, across both the phase 3 studies 9007 and 12011, the baseline T concentrations were lower in patients with secondary hypogonadism (median of 184-186 ng/dL) as compared to patients identified as either with primary (median of 221.5-222 ng/dL) or with combined/undefined hypogonadism (median of 217.5-231.5 ng/dL). But the treatment with 200 mg BID till 4 weeks resulted in similar C_{avg} T concentrations across all these etiologies in each of the phase 3 studies (Figure 3).

Weight, BMI, Age, Baseline T value and Race

The univariate linear regression analysis of ΔT_{avg} with baseline bodyweight showed a significant trend of smaller ΔT_{avg} with higher body weight in study 9007 while the other two studies evaluated (12011 and 9009) had a much smaller slope for such relationship Similar results are also seen in analysis of ΔT_{avg} with baseline body mass index (Figure 4 A and B). The univariate linear regression analysis of ΔT_{avg} with baseline (screening) T concentration showed a trend towards higher changes in T conc. with smaller baseline T values (Figure 4 C). But again, this trend was much more prominent in study 9007 alone as compared to the other two studies. Lastly, there was no clinically relevant trend of ΔT_{avg} with age. Since the representation of difference race was small in all three studies considered evaluates here, the analysis for race was carried out by pooling the data across the three studies (9007, 9009 and 12011) which had 4 weeks exposure to 200 mg BID dosing. In this pooled dataset, besides “White” (n=235), the only other race with sufficient numbers for evaluation was “Black or African American (n=31). There was no clinically significant effect of race on PK variable of change from baseline in C_{avg} T exposure (data not shown).

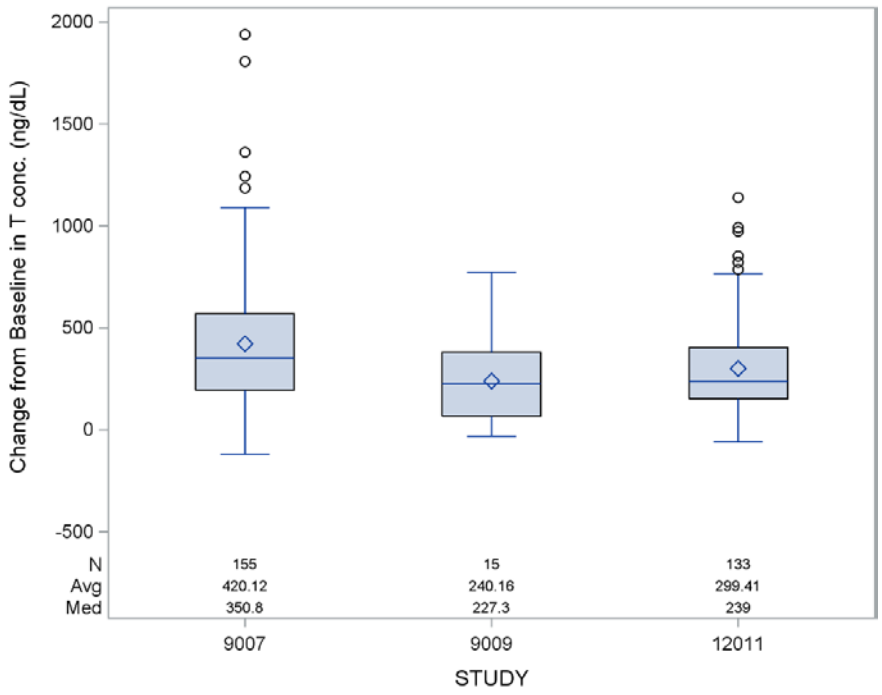


Figure 1: Change from baseline in C_{avg} T concentration at approximately 4 weeks (Cavg at 4 weeks – baseline T conc. at screening) across the three studies with the same dose of 200 mg BID. *Source: Reviewer's analysis*

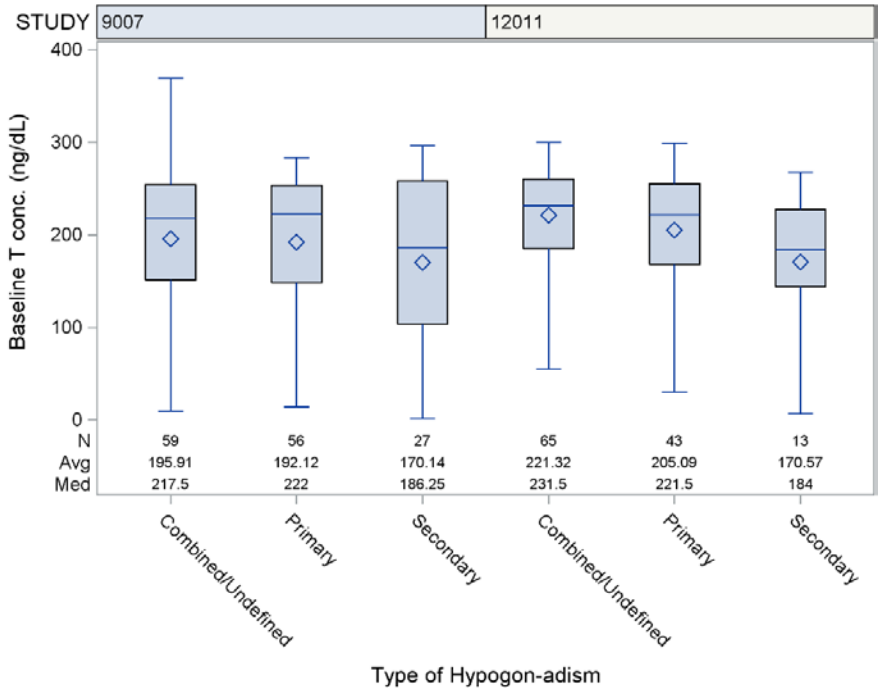


Figure 2: Baseline T concentrations at screening in patients with different etiology of hypogonadism in phase 3 studies. *Source: Reviewer's analysis*

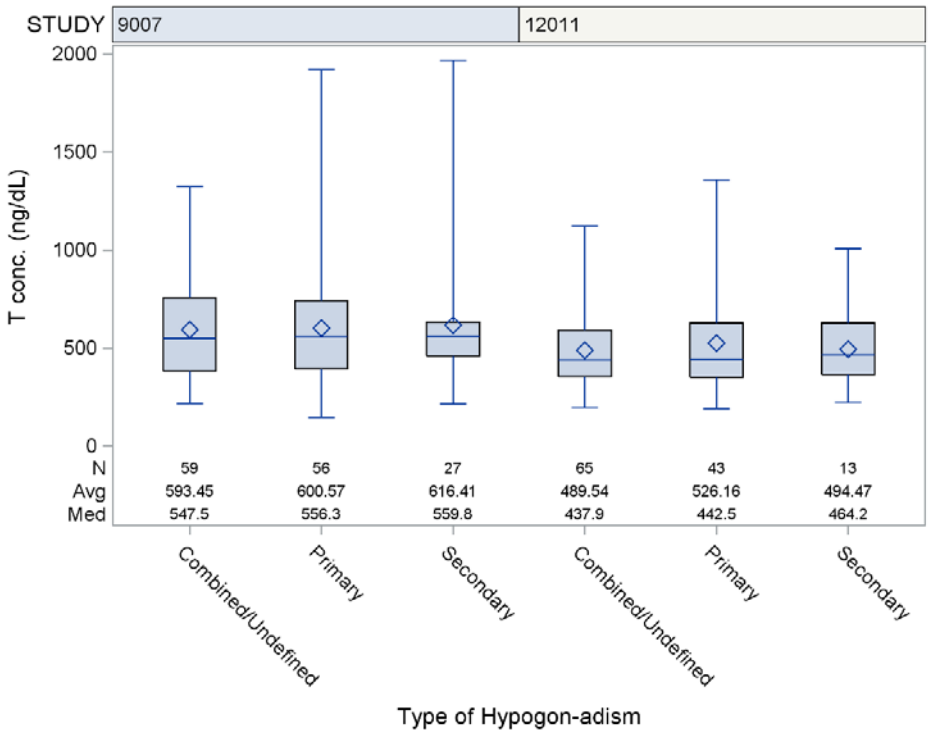
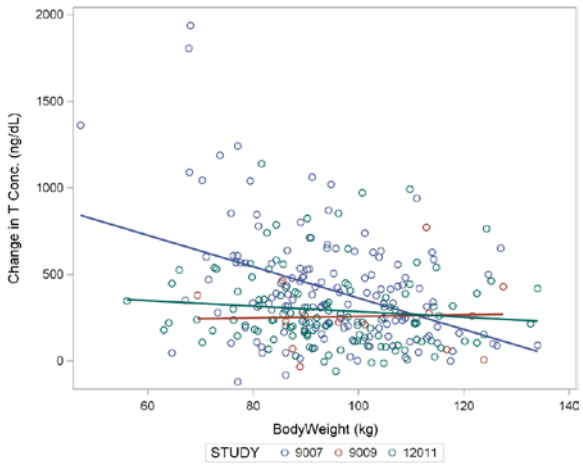
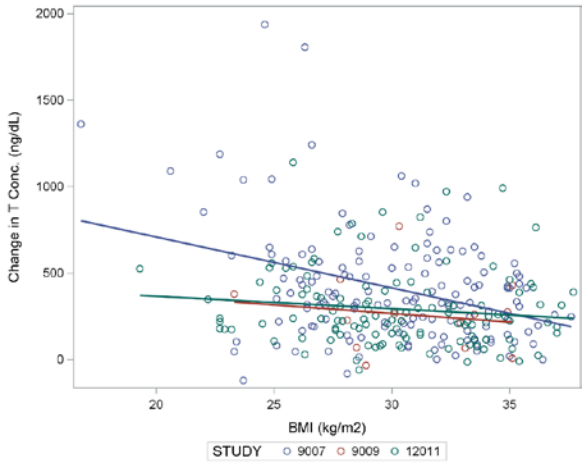


Figure 3: C_{avg} T concentrations attained at approximately 4 weeks with the same dose of 200 mg BID across different etiology of hypogonadism in each of the two phase 3 studies.
Source: Reviewer's analysis

A. 	B. 
C.	D.

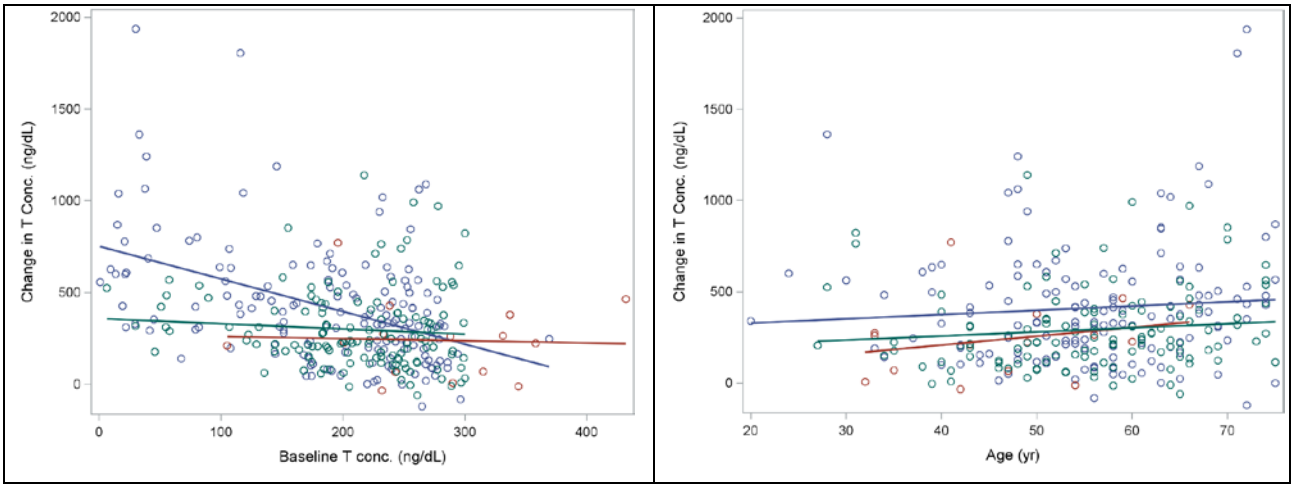


Figure 4: Relationship of change from baseline in C_{avg} T concentration (ΔT_{avg}) at approximately 4 weeks with baseline body weight (panel A), baseline BMI (panel B), baseline T conc. (panel C) and age (panel D) across the three studies with the same dose of 200 mg BID. *Source: Reviewer's analysis*

Towards prediction of response variable C_{avg} at 4 weeks with 200 mg BID dose, the baseline body weight was the most important explanatory predictor variable, and inclusion of this covariates leads to non-significance for any other covariates. Based on this result, further evaluation of T exposures with different body weight quantiles was carried out. This analysis at 4 weeks suggests that, across both the phase 3 studies 9007 and 12011, for the same dose of 200 mg BID, there was a continuous trend of higher C_{avg} and C_{max} for T exposures with lower baseline body weight, with highest values seen for the quantile with smallest body weight (<~82 kg) (Figure 5 A-B). Again the effect was more prominent in study 9007 compared to study 12011.

In general, the high inter-individual variability of response of change in T exposures from baseline as well as the resultant absolute T exposures in the population with the same dose of Rextoro (Figure 1) makes it difficult to predict individual responses and this issue can be best resolved by using the sponsor's proposed titration approach to find optimal individual dose based on sampling at 3-5 hours from dose intake for every individual. The reviewer's analysis also suggests that across the two studies, the patients with baseline body weight < 82 kg as a subgroup had consistently more median C_{max} and C_{avg} T exposures for the same dose of 200 mg BID across the population (Figure 5 A-B) and this subgroup also had the highest percentage of patients with Cmax above 1500 ng/dL compared to the higher bodyweight quantiles (Figure 5 C). This subgroup thus has a higher probability of exceeding the C_{max} thresholds defined as safety limits (>1500, >2500 ng/dL etc.) compared to the rest of the population for the same initial dose of 200 mg BID. The clear safety impact of such C_{max} excursions is unknown at this time because of the lack of sufficient evaluable safety data and the nature of the trials. In case these C_{max} excursions, albeit for a limited time before getting possibly down-titrated based on individual titration approach, are considered a safety issue, then an alternative dosing algorithm could be proposed wherein this subgroup of patients (bodyweight< ~80 kg) could be started with an initial dose of 150 mg BID instead of 200 mg BID in order to satisfy the desired T exposure requirements from both C_{max} and C_{avg} perspective.

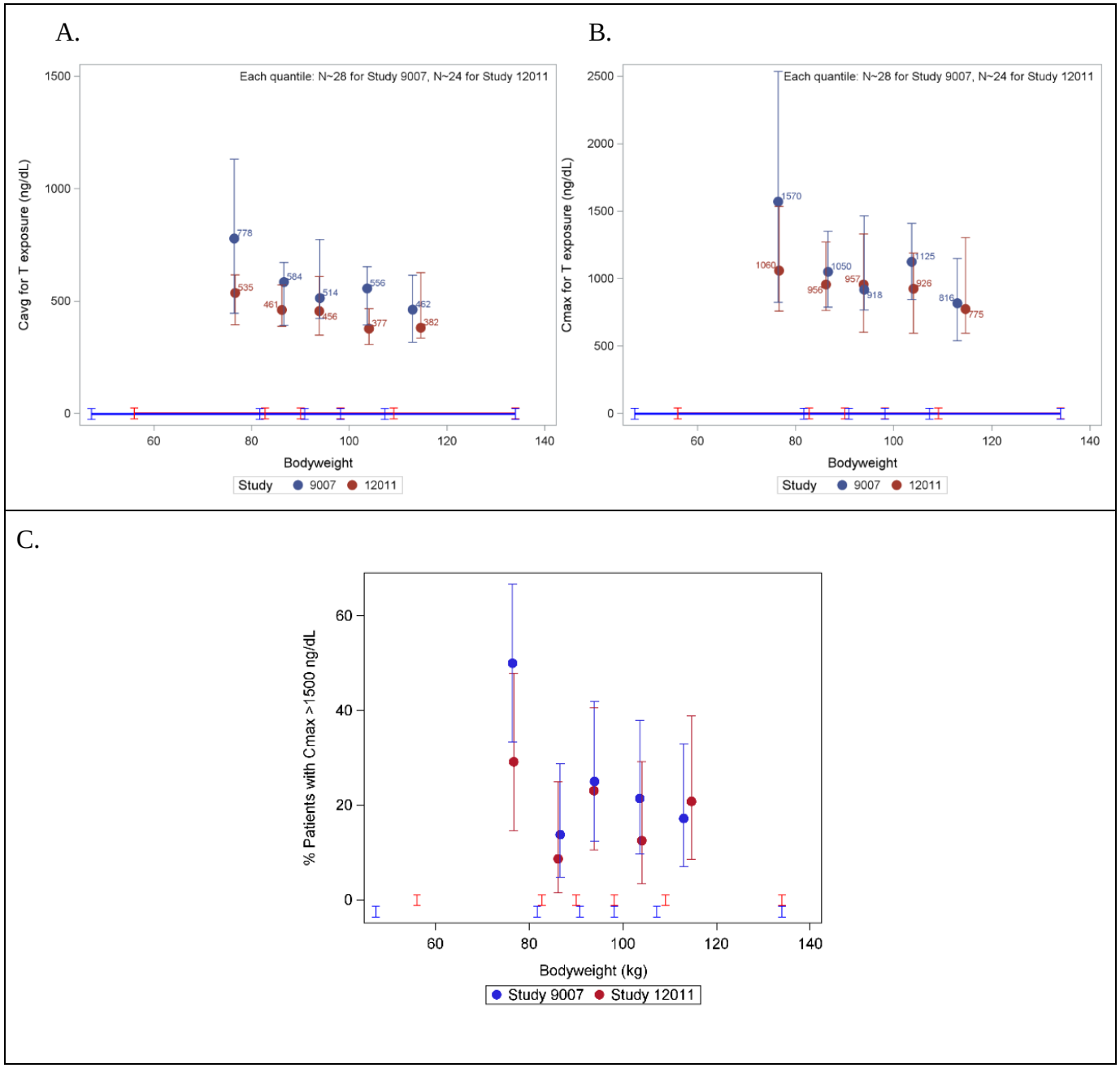


Figure 5: Distribution of T exposure related PK parameters C_{avg} (panel A), C_{max} (panel B) and percentage of patients with C_{max} above 1500 ng/dL (panel C) across different quantiles of baseline bodyweight at approximately 4 weeks when treated with the same dose of 200 mg BID across the two phase 3 studies for 4 weeks. *Source: Reviewer's analysis*

1.1.2 Is the proposed dose of 100-300 mg BID with initial starting dose of 200 mg BID reasonable and is the titration process appropriate?

The proposed dose of 100-300 mg BID with initial starting dose of 200 mg BID is reasonable. In case there are concerns of over-exposure due to patients being non-compliant to further dose titration visits after the initial prescription (as raised in the Advisory Committee meeting), a starting dose of 150 mg BID could be proposed for patients with bodyweight <80 kg since lower bodyweight is a significant correlate of higher plasma T concentrations in patients taking the same dose amount. Also there could be consideration for altering the proposed titration thresholds. Specifically, consideration can be given to raising the down-titration threshold to levels higher than 700 ng/dL and raising the up-titration threshold to levels higher than 250 ng/dL in order to increase the percentage of patients who would have T levels in the normal range of 300-1000 ng/dL.

Study 9009 in n=15 patients with a dose of 200 mg BID showed that at 4 weeks, only 2 patients failed to exceed the lower threshold of desired Cavg (>300 ng/dL) from efficacy perspective and just 2 patients out of 15 (13.3%) exceeded the upper threshold of undesired C_{max} levels (>1500 ng/dL) from safety perspective for T exposure (Figure 6). Moreover, 1 out of these 2 patients exceeding the upper C_{max} threshold had baseline T levels exceeding 400 (baseline T= 432 ng/dL) and thus may not have qualified for the testosterone therapy.

The two phase 3 studies, with an initial dose of 200 mg BID for 4 weeks, showed that at 4 weeks, only ~9.8% patients from each of the studies (n/N=15/155 for study 9007 and n/N=13/133 for study 12011) failed to exceed the lower threshold of desired Cavg (>300 ng/dL) from efficacy perspective. Also the percentage of patients with Cmax>1500 was 27.7% (n/N=43/155) for study 9007 and 18.8% (n/N=25/133) for study 12011.

Thus, the initial starting dose of 200 mg BID achieved T exposures within desired limits of C_{avg} and C_{max} for the majority of patients and seems to be the appropriate starting dose. In case there is a thought towards further reducing the percentage of patients that could exceed C_{max} thresholds with the starting dose, then an alternative of using 150 mg BID dose as the starting dose could be recommended in patients with bodyweight <80 kg as suggested in the first key question. There was no gradual accumulation of T levels even at 4 weeks as seen by comparison of baseline screening levels and post-dose C_{min} levels for each patient (in fact, the C_{min} levels were actually numerically lower than baseline screening levels for the majority of the patients).

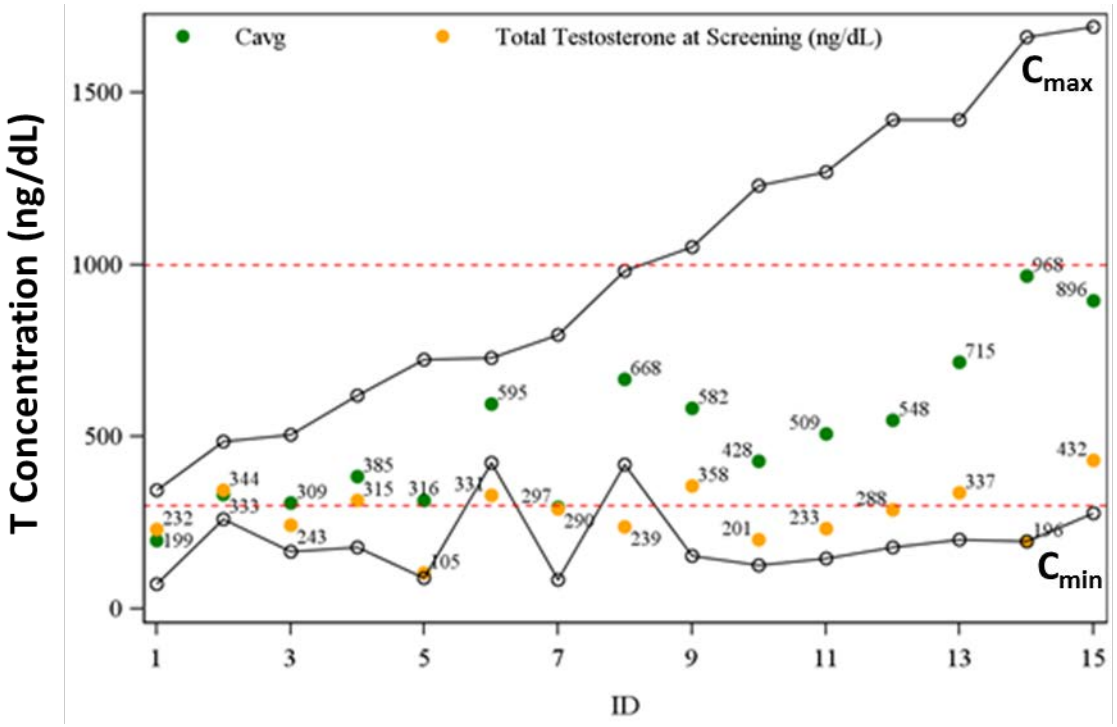
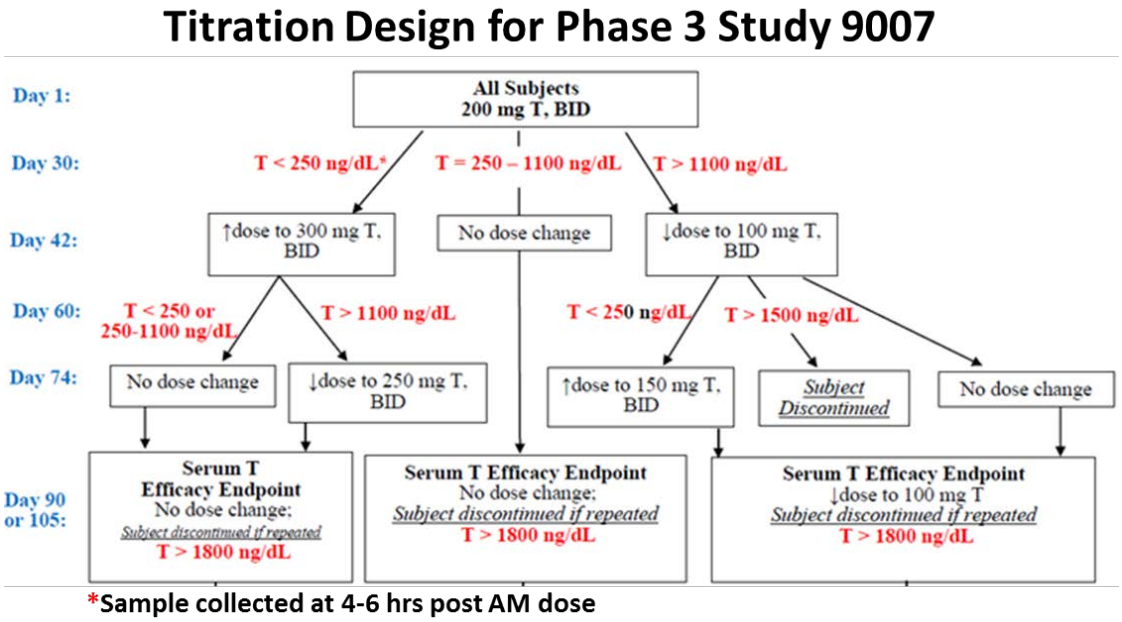


Figure 6: Plot of PK parameters related to T exposure for each individual in Study 9009 at 4 weeks with 200 mg BID dosing. The red dotted line depicts the upper (1000 ng/dL) and lower (300 ng/dL) threshold of desired target C_{avg} in these patients with hypogonadism. *Source: Reviewer's analysis*

The sponsor's dose titration algorithms utilized in the two phase 3 studies (9007 and 12011) after the initial starting dose of 200 mg BID is shown in Figure 7.

A.



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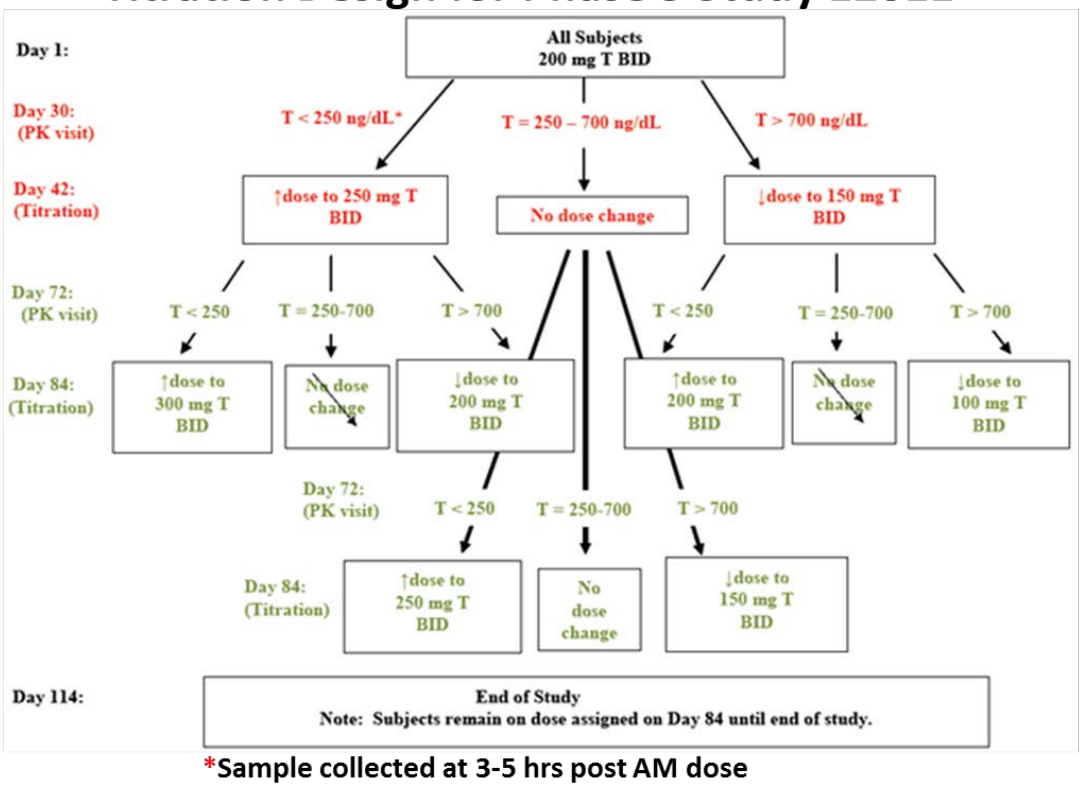


Figure 7: Titration designs for Phase 3 studies: Study 9007 (panel A) and Study 12011 (panel B). *Source: Figure 1 in sponsor's Clinical Study Report for Study 9007 and Study 12011*

In order to evaluate whether the PK sampling time of 3-5 hr is appropriate for using the titration decisions, the reviewer evaluated whether timing of peak T exposures (Tmax) is captured within this time window for most patients in each of the phase 3 studies. The Figure 8 shows the distribution of Tmax with morning (AM) dosing at 4 weeks (and at 60 or 72 days in select cases) for patients in study 9007, study 9009 and study 12011. The cumulative data from these studies show that the sampling in 3-5 hr time window would have the maximum probability of capturing C_{max} or concentrations closer to C_{max}. Since there is no accumulation of drug in each dosing cycle (as seen by C_{min} being very close to the baseline T levels), the sampled concentrations closer to C_{max} will have higher sensitivity in discriminating individual responses as compared to sampling away from T_{max}. Besides this, the sponsor's analysis also shows that there is good correlation between C3-5 (concentration at time between 3-5 hr from dosing) and C_{max} as well as C_{avg} (Figure 9).

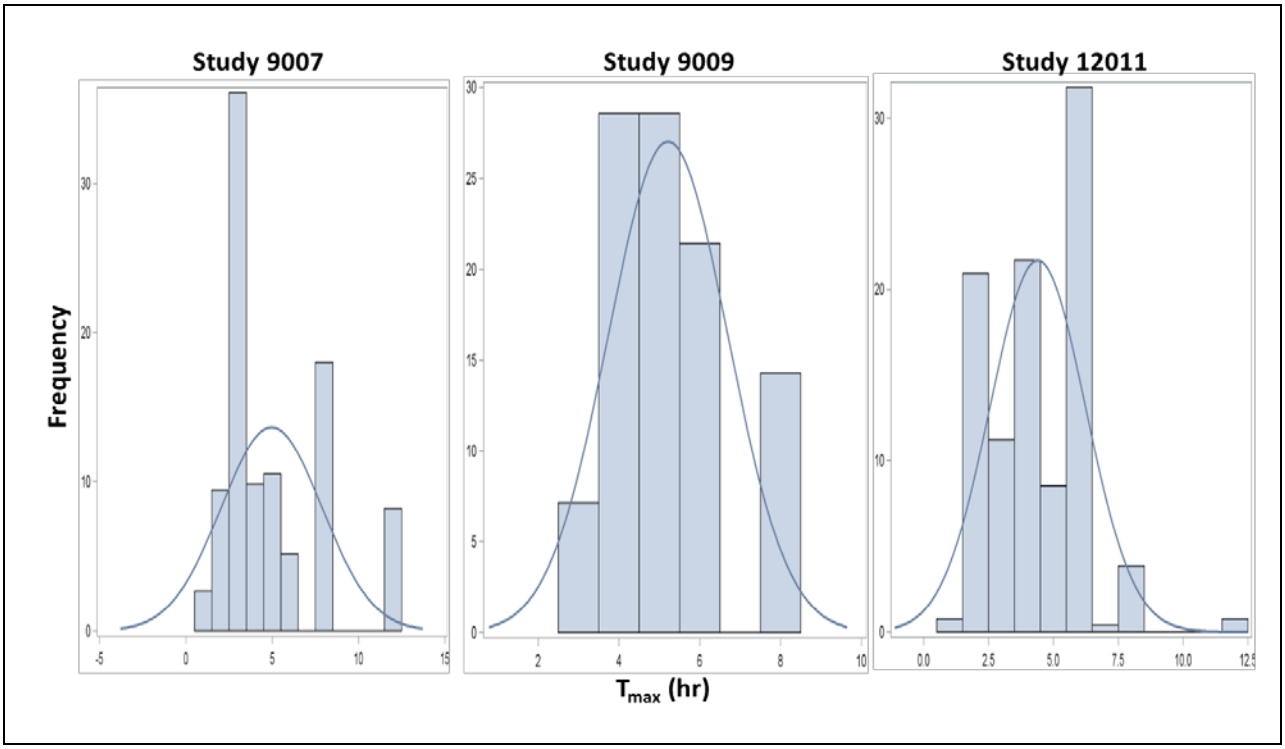


Figure 8: Frequency distribution of T_{max} (time for C_{max} of T exposure) after AM dosing across the three studies. The PK sampling time for study 9007 was 1.5, 3, 4, 8, 12 hr post AM dose, for study 9009 was 1.5, 3, 4, 5, 6, 8, 12 hr post AM dose and for study 12011 was 1, 2, 4, 6, 8, 12 hr post AM dose. Thus the study 9007 suffers from lack of sampling at 6 hr and might have more reporting bias towards Tmax of 3-4 hr due to missing possible Tmax at 6 hr in some patients. *Source: Reviewer's analysis*

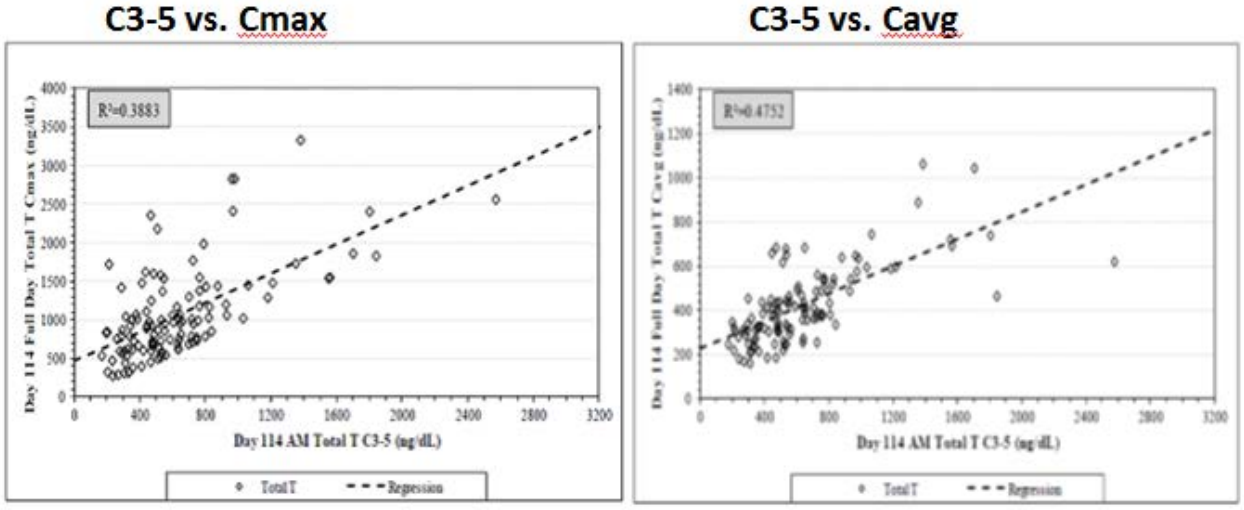


Figure 9: Correlation of C3-5 with Cmax and Cavg in phase 3 study 12011. *Source: Sponsor's analysis*

The two phase 3 studies 9007 and 12011 employed different titration designs as shown in Table 1. In Study 12011, the dose could be up or down-titrated by 50 mg BID as against 100 mg BID in study 9007. The titration design with smaller units (50 mg BID) for titration in study 12011 led to lesser number of patients with Cmax>1500 or Cmax>2500 ng/dL (the thresholds based on safety risk) compared to the study 9007 (Table 1). Overall, given that the variability of change in T concentration for the same dose is high across the individuals, as shown earlier, the availability of dose titration by smaller increments/decrements (50 mg BID) in dose is preferable to large units (100 mg BID) in order to satisfy the C_{max} thresholds, which is the safety concern.

Table 1: Results based on C_{avg} and C_{max} criteria in study 9007 and study 12011 on the day of primary efficacy evaluation (Day 90 for study 9007 and Day 114 for study 12011)

	Study 9007	**Study 12011**
C_{avg} <300 ng/dL	6.8%	23.3%
C_{avg} >1000 ng/dL	9.6%	1.7%
300≤ C_{avg} ≤1000	83.6%	75.0%
C_{max} >1500 ng/dL	41.1%	18.1%
C_{max} >2500 ng/dL	**13.7%**	**3.4%**

Source: Sponsor's Clinical Study Reports for Study 9007 and Study 12011

The analysis of T levels achieved with a starting dose of 200 mg BID across two phase 3 studies 9007 and 12011 suggests there could be consideration for altering the proposed titration thresholds. Specifically, consideration can be given to raising the down-titration threshold to levels higher than 700 ng/dL and raising the up-titration threshold to levels higher than 250 ng/dL in order to increase the percentage of patients who would have T levels in the normal range of 300-1000 ng/dL.

Subjects listed as Group A in the figure below (Figure 10) had C_{avg} values within the normal T level range, while a C_{max} between 700-1000 ng/dL. The proposed titration algorithm would result in a decreased dose in such subjects and may lead to C_{avg} that subsequently falls below the normal T range.

Also the threshold of 250 ng/dL selected for up-titration results in a subset of subjects (Group B in the figure) with C_{avg} near or below 300 ng/dL. Based on the proposed titration algorithm, these subjects would not have up-titration of their dose and may remain below the targeted range.

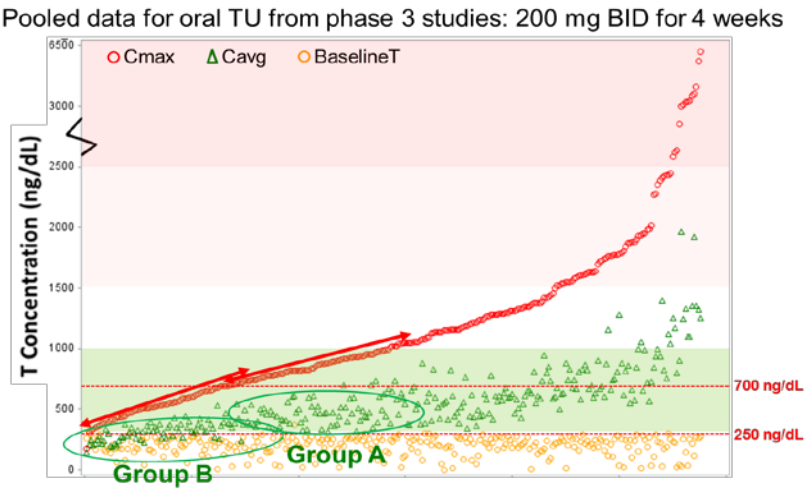


Figure 10: Pooled baseline, Cavg, and Cmax observations at ~4 weeks (day 30) from both Phase 3 studies for 200 mg oral TU. Titration thresholds utilized in 12011 are listed as horizontal lines (250 and 700 ng/dL for up- and down-titration, respectively. The target C_{avg} concentration of 300-1000 ng/dL is shown as green shaded region. *Source: Reviewer's Analysis, Study 12011 and 09007*

4.4 Filing Memo

Final
(February 18, 2014)

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	206089	Brand Name	Rextoro®
OCP Division (I, II, III, IV, V)	III	Generic Name	Testosterone Undecanoate (TU)
Medical Division	DBRUP	Drug Class	Androgen/Testosterone
OCP Reviewer	Sayed (Sam,) Al Habet, R.Ph., Ph.D.	Indication (s)	Replacement Therapy (see text below for details)
OCP Secondary Reviewer/Signer	Hae Young Ahn, Ph.D.	Dosage Form	Soft Gelatin Capsule, 100 mg and 150 mg
Pharmacometrics Reviewer Pharmacometrics Secondary Reviewer	Dhananjay D. Marathe, Ph.D. Jeff Florian, Ph.D.	Proposed Dosing Regimen	Starting dose: 200 mg (two 100 mg capsules), taken orally twice daily in the morning and the evening with meals (i.e., not on an empty stomach).
Date of Submission	January 3, 2014 (cover letter)	Route of Administration	Oral
Estimated Due Date of OCP Review	July 2014	Sponsor	Clarus Therapeutics, Northbrook, IL
Medical Division Due Date	September 2014	Priority Classification	Standard
PDUFA Due Date	December 3, 2011		

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	X			
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics and Pharmacodynamics (e.g., Phase I/III)	X	6		
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:	X	6		
multiple dose:	X	6		
Dose proportionality -				
fasting / non-fasting single dose:	X	1		
fasting / non-fasting multiple dose:				
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:	x			
Phase 3:	x			
PK/PD -				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:	x	2		
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				
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
***In vitro* Penetration Studies**				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		6		

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?		X		No change in formulation
2	Has the applicant provided metabolism and drug-drug interaction information?		X		Testosterone metabolism and DDI are well established.
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?	X			
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	X			
5	Has a rationale for dose selection been submitted?	X			
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	X			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	X			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	X			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
	Data				
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	X			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			X	
	Studies and Analyses				
11	Is the appropriate pharmacokinetic information submitted?	X			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	X			
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	X			
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the	X			

	need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?				
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			X	
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?		X		Sponsor submitted waiver
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	X			
	General				
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	X			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			X	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE? _____Yes_

Executive Filing Summary:

This is a 505(b)(2) application for the first oral soft gelatin capsule containing Testosterone Undecanoate (TU). The product is considered a new oral Self-Emulsifying Drug Delivery System (SEDDS) containing TU as a testosterone prodrug. According to the sponsor, the formulation contains a lipid matrix that is designed to promote the absorption of TU via the intestinal lymphatics and thus eliminate and/or reduce first-pass hepatic effect.

The sponsor is proposing two strengths of 100 mg and 150 mg TU immediate release (IR) capsules. The starting dose is 200 mg (2 x 100 mg) twice daily in the morning and in the evening to be administered on empty stomach. The dose can be adjusted in 50 mg increment to the maximum of 300 mg twice daily.

The proposed indication is for testosterone replacement therapy (TRT) in males for the conditions associated with a deficiency or absence of endogenous testosterone such as primary and hypogonadotropic hypogonadism (congenital or acquired).

It should be noted the following:

- The final to be marketed formulation is identical to that of Phase III
- The sponsor changed from hard gelatin capsule used in Phase II studies to soft gelatin capsule used in Phase III studies. *In vitro* dissolution data was used to establish the link between the two capsules.
- The analytical assay used to determine the serum concentrations of T and TU is validated LC/MS-MS. The assay is specific for T and TU as the two molecules are structurally very different.
- The design of the dosage form is to provide adequate conversion of TU to T to fall within the normal range of 300-1000 ng/dL. From the safety perspective, the dosage form was designed to prevent a complete and/or rapid conversion of TU to T to avoid the burst/surge release of T systemically. It should be noted that TU exhibits low affinity to the receptor (see also PharmTox review).
- No information is available on the absolute bioavailability of TU from this product. This is not necessarily as patients will be titrated to normal range of T.

What Was Submitted in this NDA?

The sponsor submitted 6 studies in addition to one ongoing long-term safety study. Below is the synopsis of each study with preliminary observations/findings that are pending review and may require further analysis. Therefore, all the findings and conclusions in this memo are included for the filing purpose only and should be considered preliminary until the final reviews and analysis are completed and performed by all members of the review team.

Phase II PK Studies:

Study CLAR-07004 (Pilot Study):

This was a pilot PK study conducted in 12 hypogonadal men in crossover design. The objective of the study was to determine the single day serum PK profile for two oral formulations of T-esters (one T-enanthate (TE) and one T-undecanoate (TU) administered once (QD) and twice-daily (BID). This study used SEDDS formulation for both esters. Subjects received the treatment after either breakfast and/or breakfast and dinner as follows:

Treatment A: 400 mg T (as TE) QD (one dose only after breakfast)
Treatment B: 200 mg T (as TU) QD (one dose only after breakfast)
Treatment C: 200 mg T (as TU) BID (100 mg/dose) (two doses only after breakfast and dinner)
Treatment D: 400 mg T (as TU) BID (200 mg/dose) (two doses only after breakfast and dinner)
Treatment E: 800 mg T (as TE) BID (400 mg/dose) (two doses only after breakfast and dinner)

Based on this study, the following is a summary table for T data:

	A	B	C	D	E
Cavg (ng/dL)	293	246	281	385	316
Cmax (ng/dL)	731	447	470	626	572
	(0-24h)	(0-24h)	(0-12h)	(0-12h)	(0-12h)
	-	-	466	718	523
	-	-	(12-24h)	(12-24h)	(12-24h)

Based on this study, the sponsor concluded that following 200 mg dose, 67% of the subjects achieving a Cavg above 300 ng/dL (lower normal eugonadal limit). In addition, it appears there was no difference in Cmax between the morning and evening doses.

Study CLAR-08005 (Repeat Dose):

This study was designed based on the PK data from the previous study 07004. It was a repeat-dose crossover PK study with food effect examined in one arm. The objective of the study was to assess the acute tolerability and PK of two oral formulations of T-esters (TU, TU + TE) in 29 hypogonadal adult male subjects at 4 study sites. Subject received the four treatments after breakfast or dinner for a total of 29 doses as shown in **Table 08005-1**:

Table 08005-1. Study design (Study 08005).

	Treatment Period 1 (Days 1-7)[a]	**Treatment Period 2 (Days 22-28)[a]**	**Treatment Period 3 (Days 43-50)[b]**	**Treatment Period 4 (Days 64-70)[a]**
Regimen[c]	TU 300 mg BID	TU+TE 400 mg BID	TU 200 mg BID	TU+TE 300 mg BID
Total Dose[c]	600 mg	800 mg	400 mg	600 mg
Total Capsules/Day	6	4	4	4

[a] 24-hour serial blood sampling for serum T, DHT, and TU or TU and TE.

[b] 12-hour serial blood sampling for serum T, DHT, and TU (on 2 days, with and without food).

[c] Doses indicated are in T equivalents. For Periods 1 and 3, each TU capsule contained 158.3 mg TU, which corresponds to 100 mg T equivalents. For Period 2, each TU+TE capsule contained 158.3 mg TU + 138.9 mg TE, which corresponds to 200 mg T equivalents. For Period 4, each TU+TE capsule contained 118.7 mg TU + 104.2 mg TE, which corresponds to 150 mg T equivalents.

It appears that there was dose proportionality in T concentration over the tested doses and also there is correlation between the Cmax and Cavg (**Figure 08005-1**). Furthermore, TU appears to be more efficient than TE in providing adequate serum T when administered as SEDDS formulation (**Table 08005-1**). High fat meal markedly increase both the Cmax and AUC compared to fasting (**Table 08005-2**).

Figure 08005-1. Cmax vs Cavg At Steady-State (Study 08005)

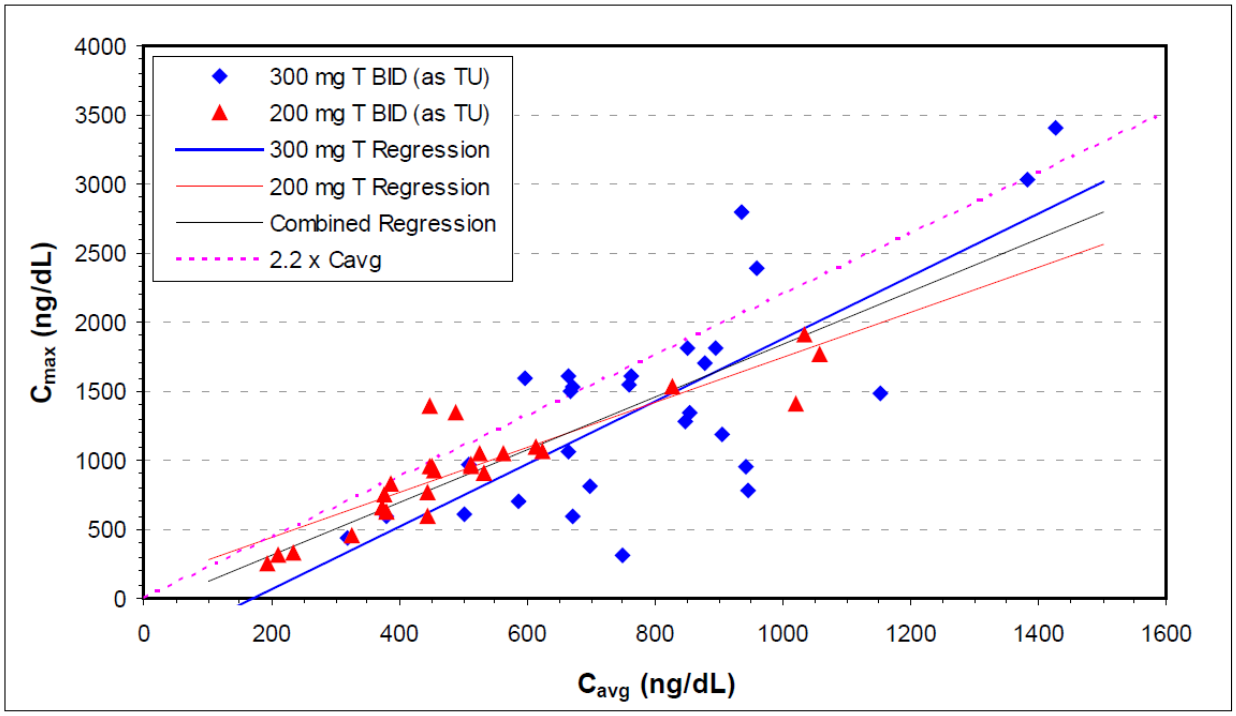


Table 08005-1. Comparison of Steady-State AM ad PM PK of T with BID Dosing (Study 08005)

	Treatment Period 1 300 mg T, as TU, BID		Treatment Period 2 400 mg T as TU+TE, BID		Treatment Period 4 300 mg T as TU+TE, BID	
	AM Dose Mean± SEM	PM Dose Mean± SEM	AM Dose Mean± SEM	PM Dose Mean± SEM	AM Dose Mean± SEM	PM Dose Mean± SEM
C_{max} ng/dL	1410± 146	1441± 118	1184± 122	1078± 90	990± 178	922± 92
T_{max} hr	4.50± 0.39	17.9± 0.5	4.54± 0.58	18.6± 0.6	4.00± 0.55	17.6± 0.6
C_{min} ng/dL	305± 30	324± 36	257± 24	278± 28	207± 22	204± 19
AUC_{0-12} ng•hr/dL	9179± 754	9830± 659	7881± 691	7812± 556	6401± 942	6580± 612
C_{avg} ng/dL	765± 63	819± 55	657± 58	651± 46	533± 78	548± 51
FI ratio	1.37± 0.09	1.36± 0.09	1.35± 0.09	1.20± 0.07	1.33± 0.11	1.27± 0.09
C_{min}/C_{max} ratio	0.256± 0.029	0.243± 0.022	0.254± 0.024	0.280± 0.023	0.274± 0.032	0.259± 0.027

Table 08005-2. Summary of Food-Effect Comparison in Treatment Period 3 (200 mg of T, as TU, BID, Study 08005.

	After High Fat Breakfast		While Fasting		Geometric Mean of Individual Ratios
	Arithmetic Mean	Geometric Mean	Arithmetic Mean	Geometric Mean	
C_{max} (ng/dL)	955	854	394	365	0.426
AUC_{0-12} (ng•hr.dL)	6217	5682	2894	2692	0.471

Administration under fed conditions (high fat breakfast) was used as the reference

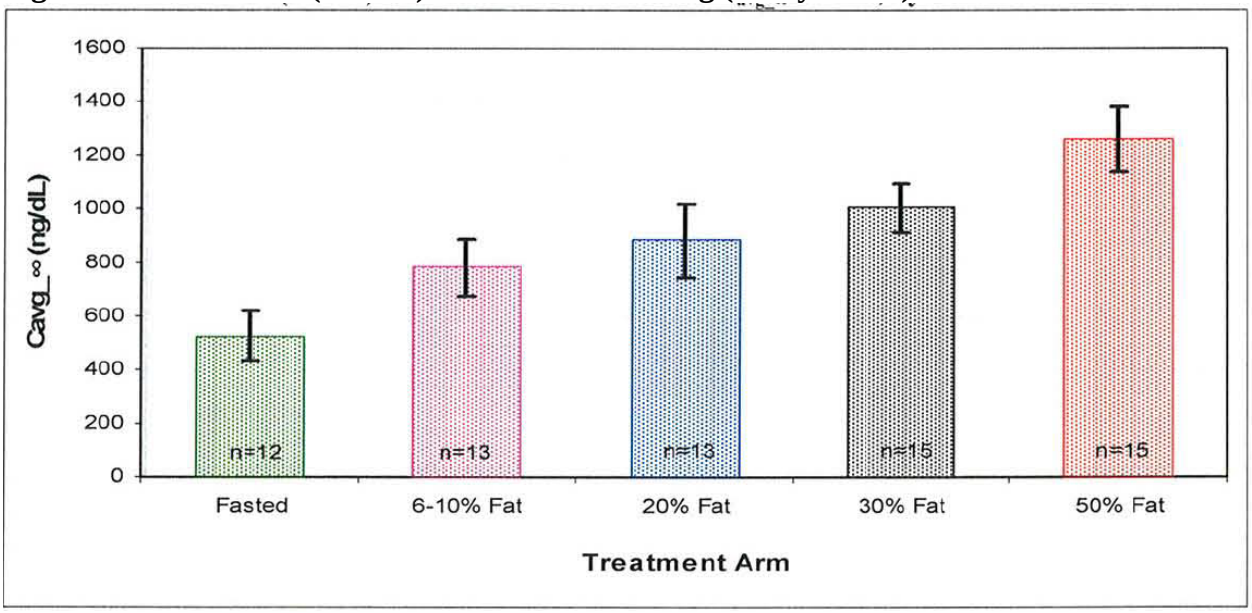
Study CLAR-09008 (Effect of Food):

This study was conducted with food containing various amounts of fat at the maximum recommended dose of 300 mg. The study was conducted as follows:

Treatment A (Fasted): 0% Fat
Treatment B (Very Low Fat): 6-10% Fat
Treatment C (Low Fat): 20% Fat
Treatment D (Normal Diet): 30% Fat
Treatment E (High Fat): 50% Fat

Neither the high-fat meal (50% fat) nor the lower-fat meal (20% fat) showed a significant food effect relative to the normal fat (Western diet) meal (30% fat). In contrast, administering TU while fasting resulted in 50% or less of the cumulative exposure obtained when administered with 20% to 50% fat meals (**Figure 09008-1**). A very-low-fat meal (10% fat) showed a significant food effect relative to the normal meal, but still exceeded the fasting condition by approximately 50%.

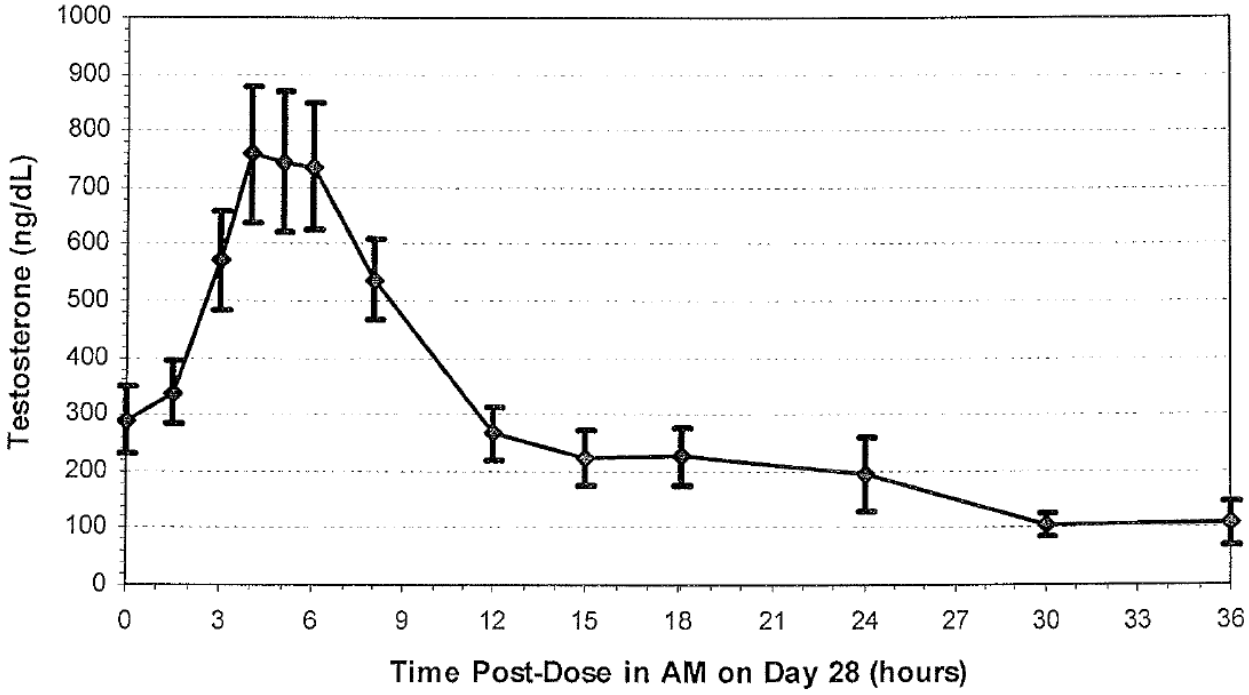
Figure 09008-1. Mean (± SEM) Serum Total T Cavg (Study 09008)



Study CLAR-09009 (Steady State):

The primary objective of this study was to determine the time to reach steady-state in hypogonadal men when TU is administered at a dose of 200 mg BID over 28 days. Prelimiary observation from this study shows that approximately 87% of subjects had Cavg within the targeted/normal range of 300-1000 ng/d. In addition, the Cmax in all subjects was <1800 ng/dL (**Figure 09009-1**). The steady-state for T, DHT, and estradiol reached within the first 7 days of dosing.

Figure 09009-1. Mean (± SEM) Serum T Concentrations After Final Dose (Day 28) of 200 mg BI Dosing (Study 09009).



Phase III Studies:

These are dose-titration studies to assess the safety and efficacy based on both PK and safety evaluation.

Study CLAR-09007 (Dose Titration):

This was the initial study which included an active comparator, AndroGel®, to assess the safety over a one year period. In this study, two parameters were monitored; 1) the average testosterone concentration (Cavg) at the primary efficacy visits (Day 90 or 105) and 2) maximum plasma concentration (Cmax). PK modeling was performed for dose adjustments/ titration using Cavg and Cmax.

This study was conducted in 325 hypogonadal men over 12 weeks therapy at daily doses ranging from 200 mg to 600 mg. TU was administered BID with meals. Dose-titration and adjustment were performed based on serum T concentration assessed at 4-6 h post AM dose. Subjects received the following treatments:

Group A: Oral TU
Initial Dose: 2 x 100 mg capsules BID with food (total daily dose 400 mg)
Group B: Transdermal T-gel (AndroGel®)
Initial Dose: 5 g (T=50 mg) of transdermal 1% Androgel® applied once daily

Titration:

Briefly, on Day 30 (± 3 days), 4-6 hours after the morning dose, serum T sampling was collected. Based on the T concentration in this sample, the need for dose titration was determined. If required, dose titration occurred on Day 42 (± 3 days) for Treatment Period 2 (Days 42 to 90). Those subjects whose dose was titrated on Day 42 were re-evaluated on Day 60 (± 3 days), with dose adjustments made as necessary on Day 74 (±3 days). Serum T sampling was performed on Day 90 (± 3 days), or for Oral TU subjects who had dose titration on Day 74, on Day 105 (± 3 days). If the serum T level was > 1800 ng/dL, the sample was repeated; subjects were to be discontinued if the second assayed T concentration was > 1800 ng/dL.

Group A: Titration Period:

- 1 x 100 mg BID (total daily dose = 200 mg)
- 2 x 150 mg BID (total daily dose = 300 mg
- 2 x 100 mg BID (total daily dose = 400 mg)
- 1 x 100 mg + 150 mg BID (total daily dose = 500 mg)
- 2 x 150 mg BID (total daily dose = 600 mg)

Group B: Titration Period:

- 25 mg = 2.5 g of 1% transdermal gel applied once daily
- 50 mg = 5 g of 1% transdermal gel applied once daily
- 75 mg = 7.5 g of 1% transdermal gel applied once daily
- 100 mg = 10 g of 1% transdermal gel applied once daily

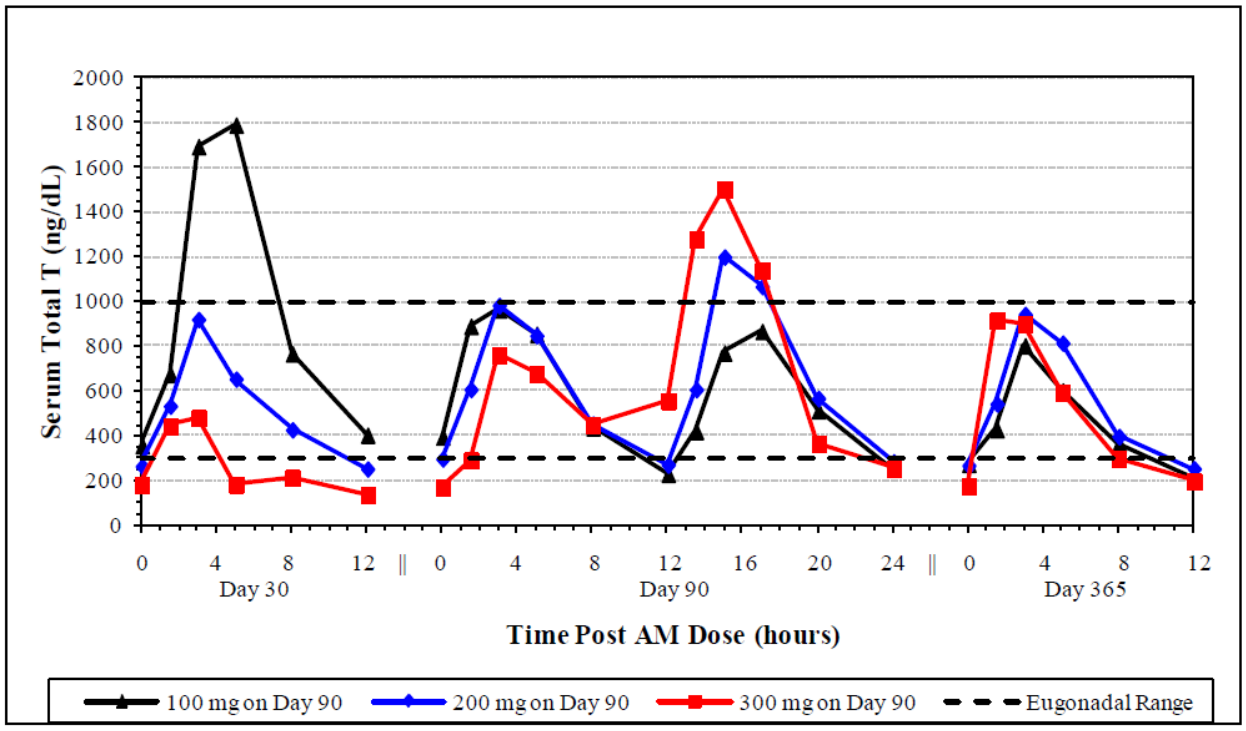
In this study, approximately 84% of the subjects achieved a serum total T C_{avg} within the normal range of 300 to1000 ng/dL (**Table 09007-1**). However, the titration scheme was not optimal in this study. For example, approximately 40% of the oral TU-treated subjects had Cmax values in excess of a 1500 ng/dL which is well above the target of threshold of <15% (**Figure 09007-1**). Similar to the other study, a correlation between Cmax and Cavg was observed. Overall, the steady state exposure remains relatively stable throughout the study.

Table 09007-1. Summary of Success Rate for Obtaining T Cavg Values in Normal Range in Hypogonadal Men (Study 090007).

Observation Day & Time	Oral TU Treatment				Topical T-Gel Treatment			
	Cavg Evaluable	Cavg in 300-1000 ng/dL range		Lower 95% CI	Cavg Evaluable	Cavg in the 300-1000 ng/dL range		Lower 95% CI
	Total	N	%	%	Total	N	%	%
Day 90 Full	146	122	83.6%	76.5%	149	118	79.2%	71.8%
Day 30 AM	155	127	81.9%	NC	156	92	59.0%	NC
Day 90 AM	147	114	77.6%	NC	150	112	74.7%	NC
Day 90 PM	147	117	79.6%	NC	150	117	78.0%	NC
Day 365 AM	127	108	85.0%	NC	131	99	75.6%	NC

NC = Not calculated
Shaded cells indicate rates based on full 24-hour PK observations

Figure 09007-1. Mean T Concentrations Grouped by the Day 90 Titration Defined Dose Study 09007)



Study CLAR-12011 (Dose-Titration optimization):

In this study the dose-titration approach that was used in Study 09007 was revised in which the Cavg was assessed on Day 114. The revised dose-titration algorithm also reduced the frequency of high Cmax values.

The study was conducted in 144 hypogonadal men to determine the efficacy following approximately 114 days of continuous therapy with a revised dosing algorithm. In this study,

efficacy was assessed as the percentage of treated subjects who met the specific endpoint of having their 24-hour C_{avg} of serum total T within the normal range of 300-1000 ng/dL on Day 114. Total daily doses ranged from 200 mg to 500 mg administered BID with meals.

Subjects were instructed to take their study medication within 15 minutes after completion of a meal (i.e., not on an empty stomach). Serial PK samples over 12 h were obtained at Visit 2 (Day 30) and Visit 4 (Day 72). Serial PK samples over 24 h were obtained at Visit 6 (Day 114) (± 3 days). Doses could be titrated at Visit 3 (Day 42) (± 3 days) and/or Visit 5 (Day 84) (± 3 days), if needed, based upon the serum T concentrations obtained at Visit 2 (Day 30) and Visit 4 (Day 72), respectively. The need for dose titration for each subject was determined by the serum T concentration from the sample drawn 3-5 h post AM dose on Visit 2 (Day 30) and Visit 4 (Day 72). All subjects began treatment at an oral dose of 200 mg T BID. The initial dosing and titration were as follows:

First Dose Titrations (Visit 2, Day 30):

If subjects were not within the target range for serum T (250-700 ng/dL) they were titrated as follows:

- T < 250 ng/dL: Dose increased to 250 mg T BID
- T > 700 ng/dL: Dose decreased to 150 mg T BID
- T = 250-700 ng/dL: Dose maintained at 200 mg T BID

Second Dose Titrations (Visit 4, Day 72):

This was divided into three titration levels:

Level I: For subjects whose dose was previously increased to 250 mg T BID, and the resulting serum T at the 3-5 h post-dose time point on Visit 4 (Day 72) was:

- T < 250 ng/dL: Dose increased to 300 mg T BID
- T > 700 ng/dL: Dose decreased to 200 mg T BID
- T = 250-700 ng/dL: Dose remained at 250 mg T BID

Level II: For those whose dose was previously decreased to 150 mg T BID, and the resulting serum T at the 3-5 h post-dose time point was:

- T < 250 ng/dL: Dose increased to 200 mg T BID
- T >700 ng/dL: Dose decreased to 100 mg T BID
- T = 250-700 ng/dL: Dose remained at 150 mg T BID

Level III: For those whose dose was not titrated previously (i.e., remained at 200 mg T BID), and the resulting serum T at the 3-5 h post-dose time was:

- T < 250 ng/dL: Dose increased to 250 mg T BID
- T >700 ng/dL: Dose decreased to 150 mg T BID
- T = 250-700 ng/dL: Dose remained at 200 mg T BID

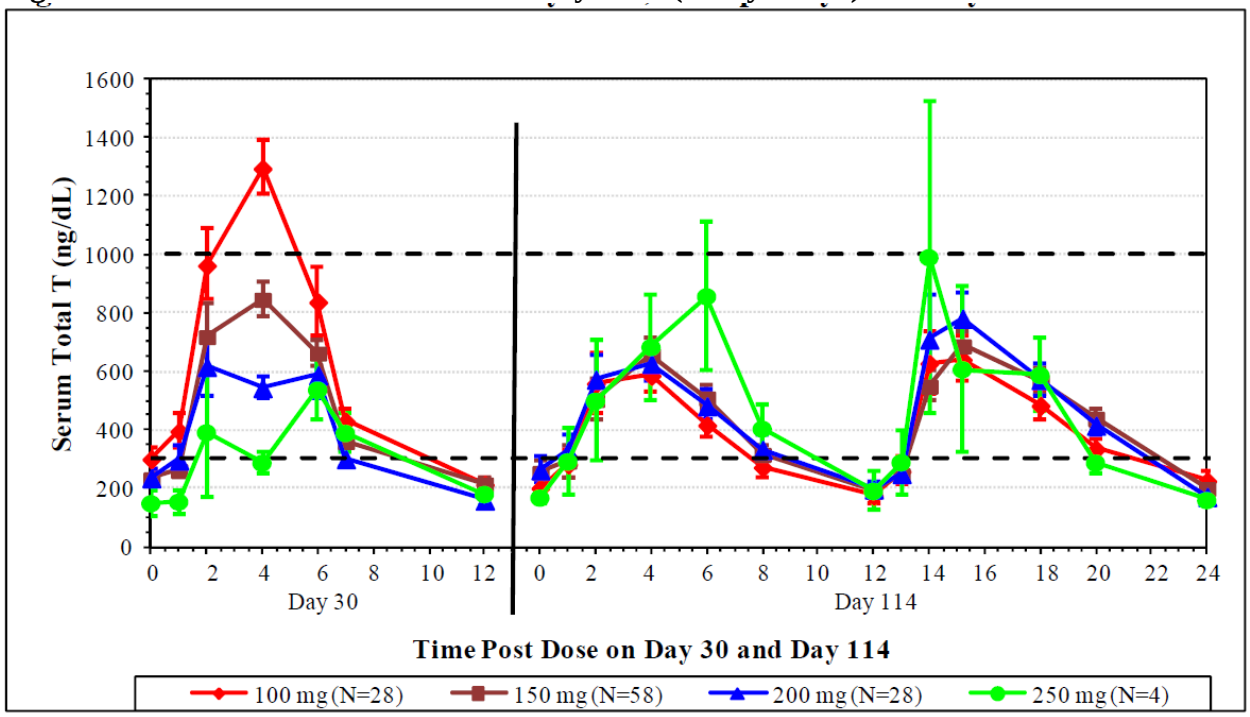
Preliminary observation at this time shows that approximately 75% of subjects achieved a C_{avg} within the normal range (**Table 12011-1**). It should be noted that the critical conclusion drawn by the sponsor from this study is that a single blood time point collected between 3 to 5 hours post dose appears to be the most effective and practical titration method for dose adjustment that provides serum T to be within the target concentration compared to the previous study (**Figure 12011-1 vs Figure 09007-1**).

Table 12011-1. Summary of the Success Rate for Obtaining T Cavg Values in the Normal Range in Hypogonadal Men

Observation Day & Time	Oral TU Treatment			
	Cavg Evaluable Total	Cavg in 300-1000 ng/dL range		Lower 95% CI
		N	%	%
Day 114 Full	116	87	75.0%	66.1%
Day 30 AM	133	114	85.7%	NC
Day 72 AM	130	100	76.9%	NC

NC = Not calculated

Figure 12011-1. Mean T Concentrations by Dose (Study 12011)



Long Term Safety Study:

Study # CLAR-12010: This is a 1-year extension of treatment available to US subjects who completed Study CLAR-09007. The sponsor did not submit the data from this study and is expected to be included in the 120-day safety update.

Safety Data:

The safety and efficacy was primarily based on Phase III studies in 377 subjects. However, the sponsor also included literature data from oral TU marketed outside the US over approximately 30 years by other pharmaceuticals.

Additional parameters:

The ratio of Dihydrotestosterone (DHT) to Testosterone-T (DHT/T) was used in this NDA (pending review).

Pediatric Waiver:

The sponsor is requesting a full waiver from conducting studies in the pediatric population for ages 0 to <18 years of age. The sponsor has submitted a Pediatric Study Plan (PSP) to the IND 78,104 in advance of this NDA (pending review).

Recommendation:

The NDA can be filed from the clinical pharmacology perspective.

Sayed (Sam) Al Habet, R.Ph., Ph.D.

Hae Young Ahn, Ph.D.
Secondary Reviewer Date

4.5 FDA Advisory Committee Clinical Pharmacology Slides (September 18, 2014)

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Overview of Clinical Pharmacology

Joint Meeting of the Bone, Reproductive and Urologic Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee
(September 18, 2014)

Sayed (Sam) Al Habet, R.Ph., Ph.D.,
Senior Clinical Pharmacologist
Office of Clinical Pharmacology (OCP)
Office of Translational Sciences (OTS)

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Outline and Key Review Questions

Topics	Key Questions
Part I Impact of Food: • % of fat • Variability in blood levels	• How should the drug be administered with regard to food?
Part II Exposure: • High exposure of TU, T, and dihydrotestosterone (DHT).	• Is the high exposure a concern?
Part III Titration:	• Is the titration process appropriate?

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What is the Product?

Oral Bioavailability of T:

- **4-7% (based on literature)**

New Oral Formulation:

- Testosterone undecanoate (TU) is a fatty-acid ester prodrug
- Absorption via intestinal lymphatics. A reduced first-pass hepatic effect.
- Hydrolysis by esterases primarily in the blood and liver and some in intestinal walls.

Dosage Strength:

- Liquid filled soft gelatin capsules containing:
  - 100 mg testosterone (T) equivalent to 158.3 mg of testosterone undecanoate (TU)
  - 150 mg testosterone (T) equivalent to 237.46 mg of testosterone undecanoate (TU)

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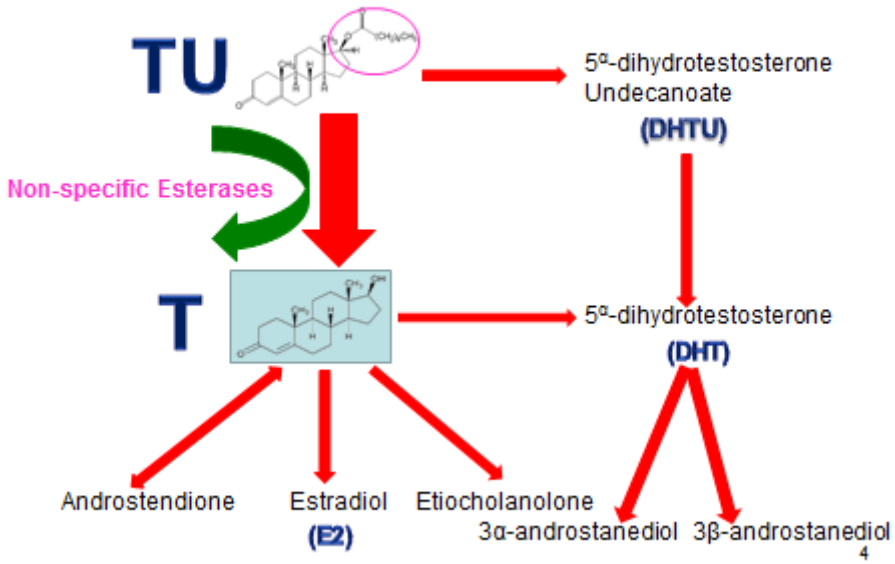
What is the Metabolic Fate of TU?



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Effect of Food Content (Variability)

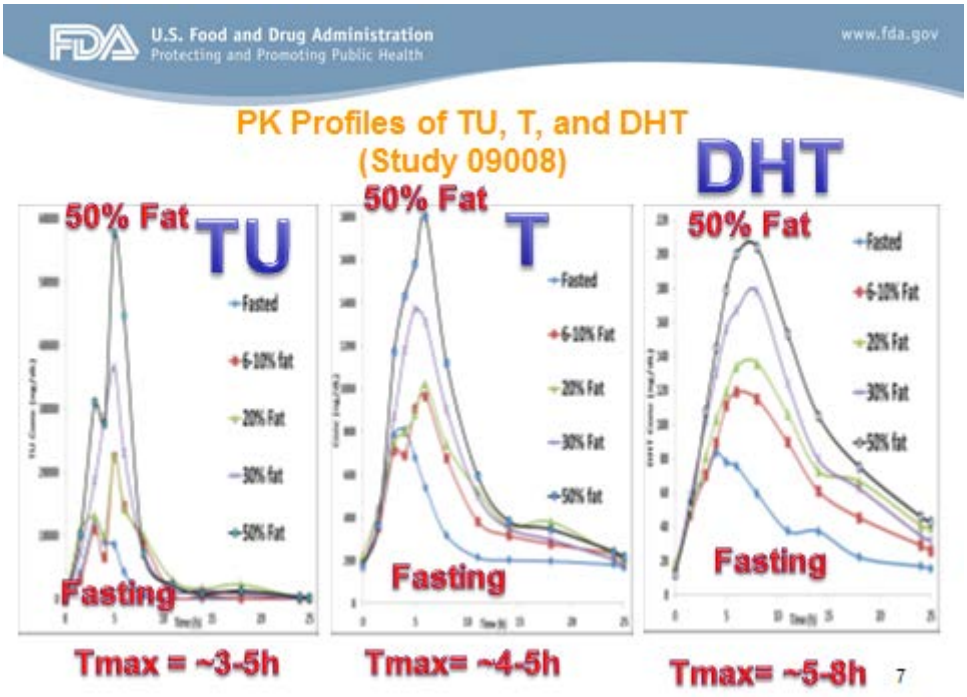
Study Design (Study 09008)

N: 16 men (Crossover)

Dose: single 300 mg T (3 x 100 mg hard Gelatin capsules)

PK Measures: T, TU, and DHT

Treatments	Total Energy (Kcal)	Total Weight (g)	Total Lipid (g)	Total Carbo-hydrate (g)	Total Protein (g)
Fasting	0	0	0	0	0
6-10% Fat	853	662	9	182	27
20% Fat	887	662	20	159	26
30% Fat	894	662	30	139	26
50% Fat	878	662	49	92	25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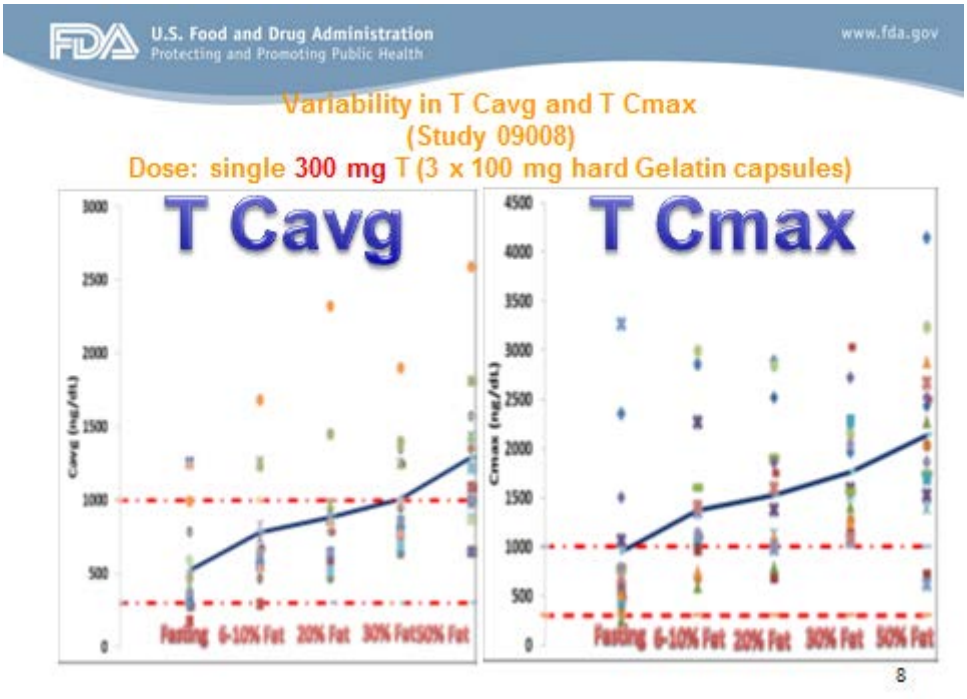
PK Profiles of TU, T, and DHT
(Study 09008)
50% Fat
TU
Fasted
6-10% fat
20% Fat
30% fat
50% Fat
Fasting
Tmax = ~3-5h
50% Fat
T
Fasted
6-10% Fat
20% Fat
30% Fat
50% fat
Fasting
Tmax= ~4-5h
DHT
50% Fat
Fasted
6-10% Fat
20% Fat
30% Fat
50% fat
Fasting
Tmax= ~5-8h
7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Variability in T Cavg and T Cmax
(Study 09008)
Dose: single 300 mg T (3 x 100 mg hard Gelatin capsules)
T Cavg
Cavg (ng/dL)
Fasting
6-10% Fat
20% Fat
30% Fat
50% Fat
T Cmax
Cmax (ng/dL)
Fasting
6-10% Fat
20% Fat
30% Fat
50% Fat
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What is the Effect of Food on Other Oral TU Products Marketed Outside the US ?
Example: Andriol®

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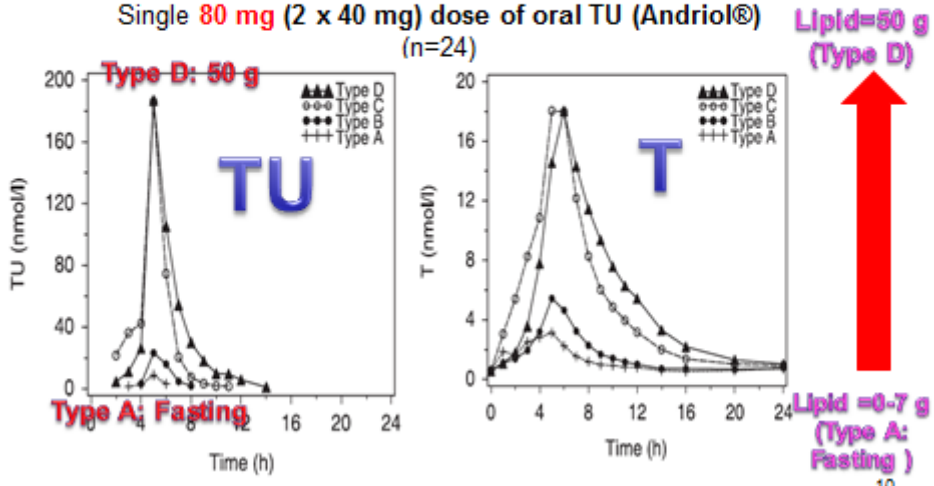
Example: Effect of Food on TU Exposure for Marketed Oral TU Outside the US (Andriol®)

Single 80 mg (2 x 40 mg) dose of oral TU (Andriol®)
(n=24)



Source: Schnabel et al, Clin Endocrinology, 66: 579-585, 2007

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Labeling question: How to be administered

Options	Pros	Cons
Option 1: Fasting	• Better predictability of T Levels	• The dose may need to be increased. • Patients non-compliance increase the risk of high exposure, if given with food with high dose.
Option 2: Irrespective of Food (With or without food)	• More Practical • Convenience • Improve patients compliance	• Complication in the titration process • High day-to-day variability • Unpredictability in T levels
Option 3: Maintain Usual Diet and % Fat	• T level predictable • In alignment with Phase III studies	• **Label must emphasize consistency**

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TU Exposure

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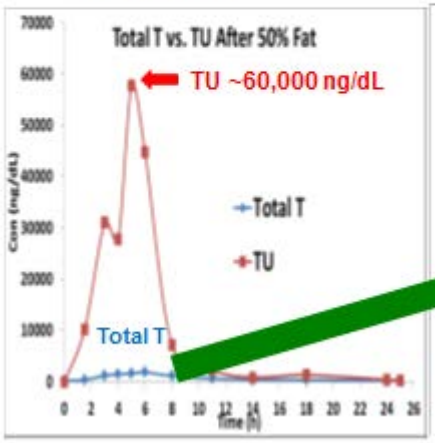
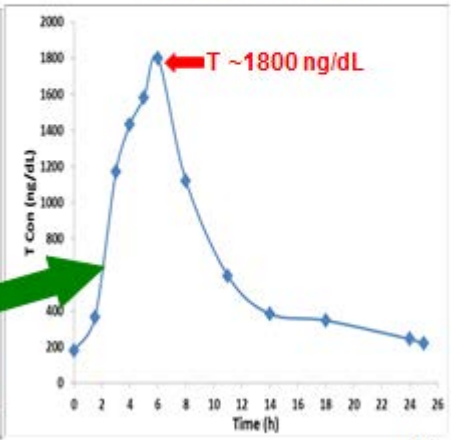
What is the Ratio of TU/T?
Dose: 300 mg with 50% Fat (Study 09008)

One Scale



Expanded Scale



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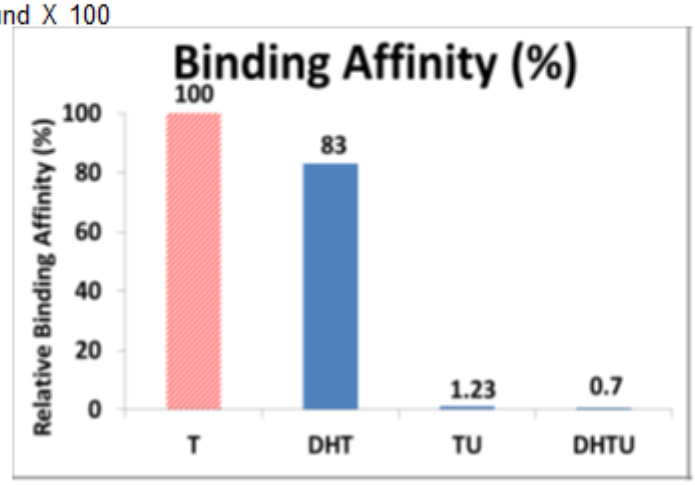
What is the Affinity to Androgenic Receptor?
Source: *In vitro* Polar Screen Study # 013325-02

Relative Binding Affinity = The EC_{50} of T divided by EC_{50} of the test compound X 100



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Exposure and Variability After Oral TU vs. T-gel?
(Phase III Study 09007)

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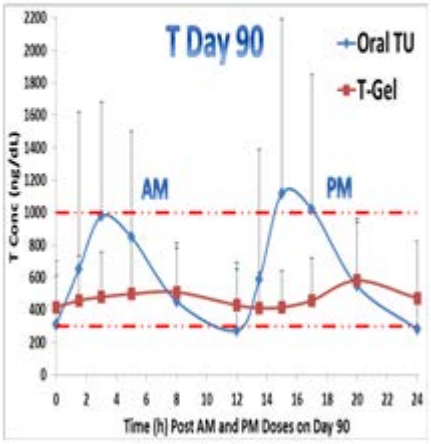
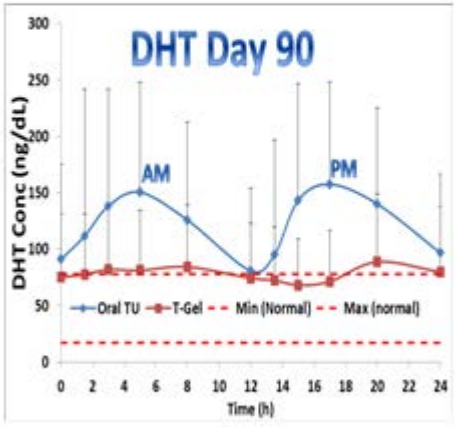
What is the Exposure After Oral TU and T-gel? (Study 09007)





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Titration

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What are the Differences Between Phase III Designs?

Variable	Study 09007 (First Study) N=160 in each arm	Study 12011 (Second Study) N=144
Design	• **Group A** (Oral TU): Starting dose is 200 mg BID (AM and PM) • **Group B** (AndroGel®): Starting 50 mg T QD	• Single Arm (oral TU only) • Starting dose: 200 mg BID
Titration	• Increment or decrement by **100** mg BID	• Increment or decrement by **50 mg** BID
Down Titration	• Based on **T>1100** ng/dL	• Based on **T>700** ng/dL
Time Points	• 4-6 h post AM dose	• 3-5 h post AM dose

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What is the Proposed Titration Algorithm?

Desired T Level = 300 -1000 ng/dL

- Starting dose: 200 mg BID (Min 100 mg BID and max 300 mg BID)
- Based on serum T concentration from a **single** blood draw at **3-5 hours** after the morning dose and at **least 7 days** after treatment or following dose adjustment.

T Levels (ng/dL) @ 3-5 h post dose	Dose Titration (BID)
<250	Increase by 50 mg BID to max of 300 mg BID
250-700	Dose maintained
>700*	Decrease by 50mg BID (min 100 mg BID)

* *If consistently exceeds 700 ng/dL at the lowest daily dose of 100 mg BID, then therapy should be discontinued.*

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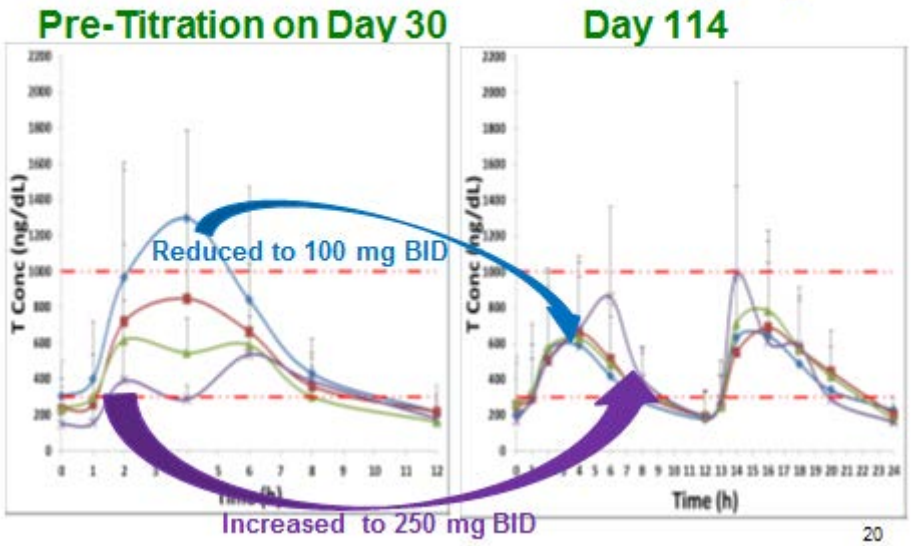
Testosterone PK Profiles After Oral TU (Study 12011)



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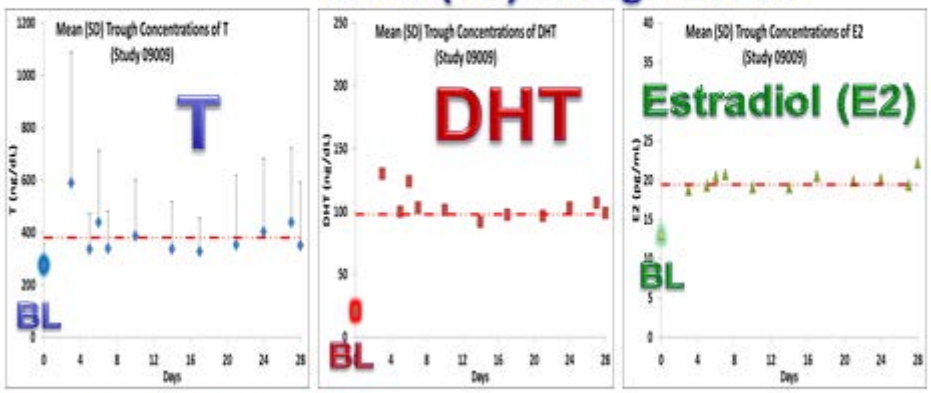
What is the PK at Steady-State for T, DHT, and E2? (Study 09009)

Dose: 200 mg BID X 28 Days

Mean (SD) Trough Levels



BL= baseline

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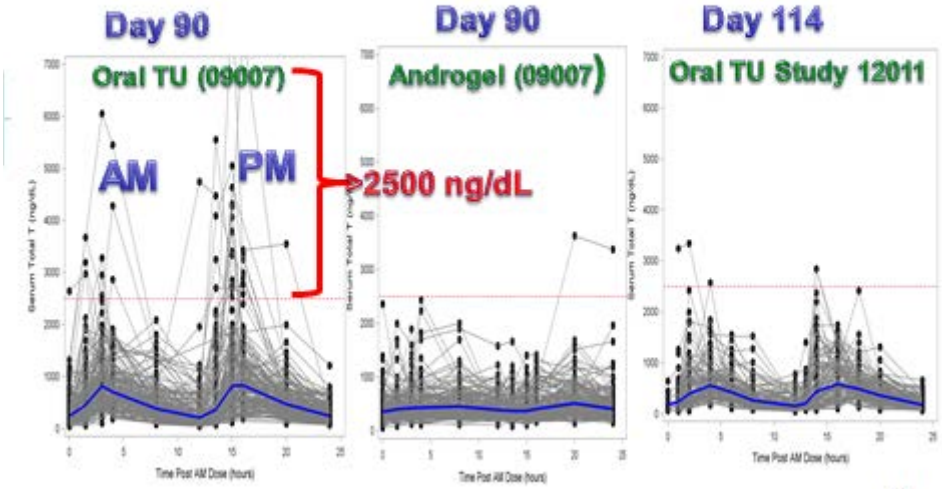
What is the Extent of Variability After Oral TU?



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Summary

- There was high variability in T levels after oral TU administration.
  - Increased absorption and exposure with fat content of meals
  - Possible diurnal and/or meal effect on T levels between PM versus AM.
- To minimize day-to-day variability, patients should consume a steady diet with a relatively consistent % of fat content in meals. In addition, major changes in diet may require re-titration.
- The initial titration by Day 7 at 3-5 hours post AM dose is supported by the PK data.
- There was high TU to T ratio (>20-fold). In addition, compare to T-gel the DHT and other androgens levels were higher after oral TU. The long term clinical impact of such high exposures is unknown at this time.

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

/s/

SAYED AL HABET
10/08/2014

DHANANJAY D MARATHE
10/08/2014

JEFFRY FLORIAN
10/08/2014

EDWARD D BASHAW
10/17/2014
This review is subject to a Supervisory Memo that has been linked to it in DARRTS. Please refer to that memo for final recommendations from the Division of Clinical Pharmacology-3

Memorandum

Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993

DATE: October 17, 2014

From: CAPT Edward D. Bashaw, Pharm.D.
Director, Division of Clinical Pharmacology-3
Office of Clinical Pharmacology
Office of Translational Sciences
US FDA

RE: Supervisory Memo for NDA 206089

This memo serves as a Supervisory Memo for the Clinical Pharmacology review of the NDA 206089 (testosterone undecanoate) written by Sayed Al-Habet, Ph.D. His final review has been placed into the DARRTs archive previously, however, as both secondary reviewer and Division Director, I am exercising my option to issue this memo as I have reservations about the overall structure and content of the recommendations section of the review and specifically the comments in the review with regards to the effect of food and dosing/titration. In addition, I will touch on concerns related to the Analytical Validation section of the review.

Issue 1

Overall Recommendations

The recommendations as provided for in the primary review (Appendix Item 1) are not focused on the Clinical Pharmacology issues so much as they are a list of concerns that were developed at an internal meeting of the review team following the Advisory Committee meeting on this product. The recommendation section, although attempting to be comprehensive does not provide guidance as to how any of these issues are to be addressed, i.e., they provide no recommendations per se for remedial or corrective action. That is not to say that these issues are not in themselves significant, however, they are the subject or reviews by other disciplines that are focused on them. The repeating of these issues in the Clinical Pharmacology Recommendations section is not appropriate as it distracts from the Clinical Pharmacology Recommendations.

The revised recommendation for this NDA is as follows;

> **Recommendation**
> The Division of Clinical Pharmacology-3 recommends that a C/R (complete response) action be issued at this time. The Clinical Pharmacology section of this NDA is not sufficient to provide guidance on dosing instructions with regards to meals or dosing/titration, as outlined below:

Food Effect

In regards to the effect of food the sponsor is advised to undertake a new assessment of the effect of food using "timed food effect trial". Such a trial could utilize a fasted treatment leg and treatment legs where a single dose is administered 1 hr before, 1 hr after, and two hours after a standardized meal. The results of the trial could then be used to design dosing instructions with regards to meals that would be more practical (i.e, reproducible) with unsupervised use.

In addition to the recommended "timed food effect trial" the sponsor is strongly advised, should a new in vivo clinical study be necessary, to use a standardized meal and not a varying diet as was used in the 12011 trial during the pharmacokinetic sampling phase. The use of a non-standardized diet without recording the amounts and types of food consumed (specifically fat content) made any attempt to standardize the results of 12011 futile.

Dosing and Titration

The starting dose and titration schema proposed by the sponsor needs to be re-evaluated. Evaluation of the proposed dosing scheme by the FDA suggest that initiation of therapy at a lower dose (150mg BID) and using a boundary of 300 ng/dL for up-titration rather than 250 ng/dL would enhance the number of subjects within the therapeutic range of 300-1000 ng/dL.

Another strategy that should be considered is the development of a 75mg dosage form. Such a dosage form would allow for a finer control of plasma T (and TU) level by allowing for more dosing flexibility, ie., 100, 150, 175, 200, 225, 250, 275, and 300mg doses would be available instead of 100, 150, 200, 250, and 300mg doses that the100 and 150mg capsules allow for.

ISSUE 2

Variability and Food Effect

As described in the review, the proposed formulation of TU has demonstrated significant variability in the face of meals. The sponsor has conducted a food study (Study 09008) with the earlier hard gelatin capsule formulation (see review from the Office of New Drug Quality Assurance.) The study was conducted with meals of varying fat content ranging from fasted, 6-10%, 20%, 30%, and 50% fat following a single 300mg hard gelatin capsule. The results of this study can be found in the primary review on pages 67-72.

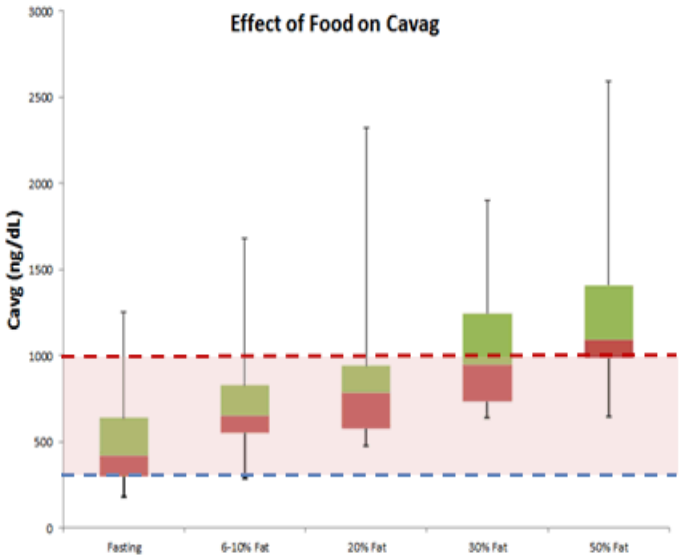
Attached in the Appendix as Item 2 is the summary presented by Dr. Al-Habet along with his interpretation of the data and his summation of the discussion at the aforementioned Advisory Committee.

Although significant discussions have been held on this matter with Dr. Al-Habet, I do not agree with his interpretation of the data, nor his summation of the comments from the Advisory

Committee members. I also do not concur with his conclusion that his "Option 3" which he describes as both the "best option" and "impractical" is one that offers a path forward to the sponsor. As I have already indicated my recommendation for further assessment of the food effect in the revised recommendation section above, I will present the underpinnings of my recommendation below.

Once meals, and specifically fat content was identified as a significant contributor to the observed variability of the proposed TU dosage form, the difficulties associated with assessment of T levels in an uncontrolled setting became quite apparent. T levels, unlike glycosolated hemoglobin (A1C) levels in diabetes management, give no indication as to the previous therapy or meal instruction compliance. At the AC all of the members of the panel were very concerned about the variability and noted that controlling diet in patients would be an impossibility. Even if they "could" at home, the degree of "hidden" fat in prepared meals would upset the plasma levels. An option that the panel did find some favor with was to administer the dosage form in a fasted manner as, at least in that regards; one could expect to get some reproducibility within a patient (i.e. fasting is a reproducible condition). Dr. Al-Habet in his summation dismisses this approach for a variety of reasons including fear that "many patients" would not achieve effective levels, that higher doses would be needed and that patients would learn to use food to modify their absorption causing a higher degree of exposure.

Examination of the dataset for Cavg (or Cmax) shows that in fact the vast majority of the patients could receive effective therapy with a fasted dosing approach. Looking at Cavg data for the 16 subjects in the food effect trial, it is clear that after a single 300mg dose (using the hard gelatin capsule), that the majority of the subjects are within the target range with limited upper range excursions. It is also true that the fasted treatment was more variable, for Cmax, but unlike topical therapies, Cmax for an orally administered product is a transient concentration with little duration at these levels.



Furthermore, as this is a single dose study, it would be expected that due to the effect of accumulation that the levels with repeat dosing would in fact shift higher and bring even more subjects into the effective range. In the same manner it would be expected that the subjects in the other groups would also continue to accumulate drug and a higher percentage of them would exceed the upper threshold. Thus it is unlikely that either "many patients" would fail to achieve effective levels or that higher doses would be needed (especially if the sponsor adds a 75mg dosage form which would allow a finer control). Even if higher doses would be needed in some patients, as patient dosing is individualized this would be a patient management issue.

As for his concern that patients would learn to "modulate" their levels by altering their fat intake, this is a concern for all diets and not just a fasted one. It should also be noted, as was at the AC meeting, that patients cannot determine fat content by looking at meals, nor can one depend upon labeled fat content as a guide due to differing portion sizes and varying styles of meal preparation even in chain restaurants that use "standardized" cooking instructions/portions.

The downside to a fasted recommendation is that while the morning dose can be given fasted "relatively" easily, the second dose presents a timing problem with regards to the evening meal. It is for this reason that I am recommending a timed food effect trial, as described in the recommendations section, to investigate if dosing instructions could be developed to minimize the impact or possibly "modulate" the degree of food effect down to an acceptable level.

ISSSUE 3

Dosing and Titration

I have no issue with the dosing and titration recommendations as developed with by the Pharmacometrics Division in the Office of Clinical Pharmacology. I am including it here as I have singled it out in my introduction as one of the reasons for this memo. My reservation was not with their recommendations per se, but in the way they were portrayed in the original recommendations section in the review. I have no further comment on them and refer to pages 29 and 130-141 of the review for more detail.

ISSUE 4

Analytical Validation

The analytical validation report will require a new review when the NDA is resubmitted. To be clear the data submitted and review with regards to the TU-T conversion is **not** the issue here. Both the evaluation by Dr. Chongwoo Yu, the Office of Scientific Investigation (OSI) and Dr. Al-Habet are all consistent with regards to this.

My concern resides in the fact that at a late date in the review cycle, (month 6) it was discovered that significant information was missing from the analytical validation section of the NDA. An information request was sent to the sponsor on July 25th 2014. The description of the submitted information from Dr. Al-Habet's review is attached as Item 3 in the Appendix.

While acknowledging that the data submission was 6500+ pages, Dr. Al-Habet in his review merely notes the submission of most of this data without providing any independent assessment of the information. A specific example can be found under the entry for the Incurred Sample Reanalysis (ISR) where he states: "The sponsor stated that ISR was conducted in approximately 5% of samples according to the published FDA Guidance." Dr. Al-Habet makes no further mention of the ISR samples, the observed variance or any assessment of the adequacy of their results, just that the sponsor claims to have done 5% of the samples. This in not in keeping with the importance of analytical validation nor the reason for requesting the submission of this information for review in the July Information Request. While acknowledging again the large nature of the submission, a targeted examination of the data should have been undertaken. In the case of the ISR data this is even more important given the role of ISR analysis in resolving the recent (b) (4) analytical validation issues. This information, will need to be fully evaluated in the future in the light of any new trials that are conducted in support of this application.

Appendices (excerpts from Primary Review)

Item 1

1.0 Executive Summary

1.1 Recommendation

From the Clinical Pharmacology perspective, this NDA is **NOT ACCEPTABLE** due to the following deficiencies:

- There was high variability in T levels and other metabolites associated with food intake (fasting versus fed) and % of fat in meals (day-to-day and within day variability). Based on the observed product variability, there is insufficient information at this time to provide labeling in the Dosage and Administration Section for administration of this product with reference to food. Any approach identified by the review team was limited in that substantial variability in product PK would remain and that compliance to the language (administer in a fasting state or to maintain a consistent diet) could not be ensured, which in turn could lead to undesirably high T levels.
- There was high exposure to the parent drug, testosterone undecanoate (TU), and its metabolite dihydro-TU (DHTU). For example the TU exposure was approximately 20 fold higher than T levels. Implications of these metabolite levels on safety cannot be assessed with the available data.
- The pivotal study marginally met the established primary efficacy criteria of 75% of patients falling within the target T Cavg of 300 ng/dL to 1000 ng/dL. However, based on the sensitivity analyses for the missing data, the primary efficacy parameters may become lower than 75%. In addition, the pivotal study had a fraction of subjects with on treatment testosterone (T) Cmax levels exceeding thresholds commonly utilized by the Agency. The observed fraction of Cmax outliers further underscores the variability associated with the product.
- The proposed starting dose should be revisited, particularly in subjects with lower body weight, and considerations should be given to initiating therapy at a lower dose. Baseline bodyweight showed some correlation to exposure, with higher exposures in subjects with low body weights. Such subjects could be initiated at a lower starting dose. A similar position was advocated by Advisory Committee panel members. Additional dosing strengths, including strengths to permit an increment or decrement by 25 mg may also permit more flexibility in dosing at the onset of treatment. However, the proposed product is currently available only in two strengths of 100 mg and 150 mg.
- The titration process should be revisited in a subsequent trial. Specifically, the criteria for up-titration should be increased from the currently selected 250 ng/dL, as these criteria may not identify patients with low C_{avg} for up-titration to achieve T levels within the desired target range of 300-1000 ng/dL.
- There were changes in various cardiovascular (CV) biomarkers, including increase in blood pressure with administration of oral TU relative to baseline in the clinical trials and relative to the control arms. These observations may be associated with higher androgen exposure with oral TU compared to other marketed T products.

1.2 Phase 4 Post-Marketing Commitment (PMC) or Requirement (PMR)

Not applicable at this time.

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ITEM 2, Pages 70-72 of review

Option 1 (Fasting): Since there was relatively some absorption after fasting, then the drug can be given on empty stomach. If so, T level will be relatively predictable with less fluctuation. However, the dose may need to be increased, possibly doubled. That would create another safety issues if the patient do not comply with the instruction and may take the drug with food. Therefore, the T exposure will be markedly increased if inadvertently or even deliberately administered with high dose.

Furthermore, patients will quickly learn the potential effect of fat and may miss use and abuse the drug by deliberately taking it with high fat food to enhance the absorption. This is particularly dangerous if the prescribed dose increased in fasting conditions. Yet, it is recognized that it can also be miss used with any dose.

For this option, patient compliance would be the essence of the successful therapy. Patients may be instructed to specifically take the drug immediately after waking up in the morning and before breakfast. But the evening dose would be challenging, depending on patients personal and work life style.

Based on the PK data, this option can be implanted, but with high risk of over exposure and over dosing, inadvertently or deliberately, if the dose is increased. Also, based on the PK data, if oral TU is administered on empty stomach at the regular dose of 100 to 300 mg BID, the desired T levels of 300-1000 ng/dL will not be achieved in many patients.

Option 2 (irrespective of food): The drug can be given irrespective of food at the same recommended dose (i.e., with or without food). While this may be more practical, convenience, and may increase patient's compliance, the titration process will be more complicated and challenging. In addition, the T levels would be highly fluctuating as in **Option 1**.

Non-compliant patients or those patients who are expected to be non-compliant should start at the lowest dose and then titrate up, if needed. However, those non-compliant patients are expected not to return to the clinic for titration follow up.

Option 3 (maintain usual diet and % fat): In this option the patient must control the % of fat in meals. While this may better predicts and control of T levels and is in some way in alignment with the Phase III studies, patients will have difficulty in assessing fat content in meals.

However, considering everything, the third option appears to be the best option (if not the only option). But the label must clearly emphasize consistency and adherence to the usual diet. If the patient changes diet for example from his/her usual diet to vegetarian diet and vise-versa, patient must undergo new titration process.

Each of the above option has challenges. The key issues are compliance and non-compliance. For example, the issue with options 1 and 2 is that Phase III studies were conducted with food. Therefore, without adequate clinical trial titration data with options 1 and 2, it may be difficult to justify these two options. Option 3 will minimize variability in absorption due to food effect, but as mentioned above, it is difficult and impractical to maintain every day.

Summary of AC Meeting in reference to Food (September 18, 2014):

The above three options were presented at the FDA AC meeting on September 18, 2014. While some members of the panel were stunned with the variability presented at the meeting and others were skeptical about the entire approach. Yet, the committee members and the Agency did not reach consensus on how the drug should be administered with reference to food. Overall, the majority of the committee members voted against the approval of the product.

Conclusion:

At the time of writing this review, no internal consensuses have been reached on what additional studies are needed or how the drug will be administered with respect to food. Based on the internal discussion and the AC outcome, there is no "ideal" option without pros and cons. While the availability of oral TU would provide the convenience of easy oral administration than the gel, nasal, and IM injects, it appears that it is a product with "double-edge sword" due to the inherent wide variability with food, potential for high exposure, and potential for CV risk.

The final point is that whichever option is to be implemented or the hybrid of the three options, patient's compliance is critical for the optimal therapy. Therefore, without additional studies to optimize the administration regimen in reference to food, fat content, and the titration process, from the clinical pharmacology perspective these are considered major deficiencies among others for this product.

ITEM 3, Pages 76 and 77 of the review

Sponsor's Response to the IR Letter Dated July 25, 2014:

On August 6, 2014 the sponsor responded to the above requests and submitted all the requested information totaling 6542 pages of document. The following is a summary of the sponsor's response:

In vitro hydrolysis: Prior to starting clinical studies, the sponsor confirmed that TU would not be hydrolyzed *in vitro* (see also above discussion). The sponsor cited the above literature article by Wang et al and provided supported data. The sponsor demonstrated no impact on measured T concentrations by TU (see detailed discussion of the data below).

Bioanalytical study reports: As requested, the sponsor submitted the bioanalytic study reports for all analytes measured in Studies 09007 and 12011.

Bioanalytical method: The sponsor submitted detailed information on each of the bioanalytical method and the standard operating procedure (SOP) for each analyte including but not limited to sample preparation, HPLC gradient, mass spectrometer conditions as well preparation of calibration standards and quality controls (QCs).

Complete serial chromatograms: The sponsor submitted serial chromatographs from 20 % of the subjects with standards and quality controls for all analytes.

Samples processing and stability: The detailed information on bench-top and processed sample stability were submitted along with the validation Report of each analyte.

Effect of collection tubes: The detailed information on the effect of collection tubes was provided including the validation report of each Analyte.

Incurred sample reanalysis (ISR): The sponsor stated that ISR was conducted in approximately 5 % of samples according to the published FDA Guidance.

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/s/

EDWARD D BASHAW
10/17/2014
This is a Supervisory Memo for the Clinical Pharmacology Review for NDA 206089