Statistical Analysis Plan

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

Protocol No: CLAR-16015
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Compound Name: Testosterone Undecanoate

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Clarus Therapeutics, Inc.
555 Skokie Blvd., Suite 340
Northbrook, IL 60062

Celerion
621 Rose Street
Lincoln, Nebraska 68502
and
100 Alexis-Nihon Boulevard, Suite 360, Montreal, Quebec, H4M 2N8, Canada

Safety Statistical Analysis Plan Signature Page

Clarus Therapeutics, Inc.
555 Skokie Blvd., Suite Suite 340
Northbrook, IL 60062

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Signature:_____ Date:_____

John Brejda, PhD
Senior Biostatistician I, Data Management and Biometrics
Celerion
621 Rose Street
Lincoln, Nebraska 68502

Signature:_____ Date:_____

Mohammad Obaidi, PhD
Senior Scientist, Clinical Pharmacology and Pharmacometrics
Celerion
621 Rose Street
Lincoln, Nebraska 68502

Signature:_____ Date:_____

Theodore Danoff, MD, PhD
Chief Medical Officer and Senior Vice President Clinical and Medical Affairs
Clarus Therapeutics, Inc.
555 Skokie Blvd, Suite 340
Northbrook, IL 60062

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1. INTRODUCTION

The following analysis plan provides the framework for the summarization of the safety and pharmacokinetic data from this study. This document supplements and may replace statistical sections appearing in the protocol

2. OBJECTIVES AND ENDPOINTS

2.1 Primary Objectives and Endpoints

Primary Objectives:

To compare the effect of meals (breakfast) containing various amounts of fat on the PK parameters of Clarus's formulation of oral testosterone undecanoate (TU) at a dose of 237 mg TU (the highest strength capsule being developed by Clarus). To compare maximum A.M. exposure ($C_{max\text{-}am}$) and total A.M. exposure (AUC_{am}, $C_{avg\text{-}am}$) of total testosterone (total T) after consuming various lower and higher fat content breakfasts and fasting versus 30 g fat for breakfast.

Primary Endpoints:

- The following PK parameters for total T will be computed as appropriate: $C_{max\text{-}am}$, $T_{max\text{-}am}$, AUC_{am}, and $C_{avg\text{-}am}$ for the 5 breakfast treatments.

- The 90% confidence intervals (CIs) of the ratios of least-squares means (LSMs) derived from the analyses on the ln-transformed PK parameters $C_{max\text{-}am}$, AUC_{am} and $C_{avg\text{-}am}$ and will be constructed between the treatment of interest (30 gram fat breakfast). The absence of food effect will be concluded if the 90% CIs for the ratios of LSMs (Test Treatment/Reference Treatment) derived from the analyses of ln-transformed $C_{max\text{-}am}$ and AUC_{am} parameters of plasma total T fall within 80.00% and 125.00%. Presence of a food effect will be concluded if the 90% CIs fall outside the range of 70.00% to 143.00%.

2.2 Secondary Objectives and Endpoints:

PK Endpoints and Reference Meals for Comparison

Analyte	PK Time Interval	PK Endpoint	Reference Meal
Total T	pm	$T_{max\text{-}pm}$*, $C_{max\text{-}pm}$, AUC_{pm}, $C_{avg\text{-}pm}$	30 grams fat
Total T	24	$C_{max\text{-}24}$, AUC24, $C_{avg\text{-}24}$	30 grams fat
Total T	am	$T_{max\text{-}am}$*, $C_{max\text{-}am}$, AUC_{am}, $C_{avg\text{-}am}$	15 grams fat
Total T	am	$T_{max\text{-}am}$*, $C_{max\text{-}am}$, AUC_{am}, $C_{avg\text{-}am}$	Fasted
Total T	pm	$T_{max\text{-}pm}$*, $C_{max\text{-}pm}$, AUC_{pm}, $C_{avg\text{-}pm}$	Fasted
Total T	24	$C_{max\text{-}24}$, AUC_{24}, $C_{avg\text{-}24}$	Fasted
DHT	am	$T_{max\text{-}am}$*, $C_{max\text{-}am}$, AUC_{am}	30 grams fat
DHT	pm	$T_{max\text{-}pm}$*, $C_{max\text{-}pm}$, AUC_{pm}	30 grams fat
DHT	24	$C_{max\text{-}24}$, AUC_{24}	30 grams fat
TU	am	$T_{max\text{-}am}$*, $C_{max\text{-}am}$, AUC_{am}	30 grams fat
TU	pm	$T_{max\text{-}pm}$*, $C_{max\text{-}pm}$, AUC_{pm}	30 grams fat
TU	24	$C_{max\text{-}24}$, AUC_{24}	30 grams fat

* will not be used in the statistical comparisons

- The 90% CIs of the ratios of LSMs derived from the analyses on the ln-transformed PK parameters $C_{max\text{-}am}$, $C_{max\text{-}pm}$, C_{max24}, AUC_{am}, AUC_{pm}, AUC_{24}, $C_{avg\text{-}am}$, $C_{avg\text{-}pm}$, and $C_{avg\text{-}24}$ for Total T, DHT(C_{max} and AUC only), and TU(C_{max} and AUC only) will be constructed between the treatments of interest.

- Comparisons between treatments for the above secondary endpoints will be made using the ratios of the LSMs derived from ANOVA of the ln-transformed PK parameters (except for the various T_{max} metrics) for plasma Total T using 30 g fat and 15 g fat breakfast meals as references.

Safety Objective and Endpoints:

To characterize the safety and tolerability of oral TU when consumed with various meals.

Safety endpoints are incidence of treatment emergent adverse events. Other key safety endpoints are change in physical examination findings, change in vital sign measurements, and change in relevant clinical laboratory tests (e.g., hematocrit).

3. STUDY DESIGN

This is a multicenter, Phase 2, repeated, twice daily dose, food effect study in which subjects are randomized to a sequence of meals that vary primarily in fat content (see Tables 3.1 and 3.2 below). Approximately 20 hypogonadal subjects will be enrolled in order to complete approximately 16 subjects. Subjects may be naïve to androgen replacement therapy or washed out of prior androgen replacement therapies as detailed in exclusion criteria.

There will be a Run-In Phase (twice daily dosing with meals) designed to suppress subjects' endogenous testosterone production while allowing the oral TU to reach steady state followed by a PK Phase. Throughout the study, the dose of study drug will be 237 mg TU twice daily, which is the highest strength formulation in development and the starting dose for the ongoing Phase 3 study, CLAR-15012.

After the 14 day Run-In Phase, subjects will be confined in the clinic for approximately 6 consecutive days for evaluations and serial blood draws in the PK Phase. Subjects will present at the clinic on the evening of Day 14 prior to dinner time and will be dosed with oral TU *immediately* prior to a dinner meal. They will remain in the clinic until collection of 24-hour serial sampling following morning dosing in Period 5 of the PK Phase. On each of the PK Phase Periods 1 through 5, the subject will be dosed immediately prior to the breakfast meal (or in the AM with 240 mL of water for the fasting period). The breakfasts will be defined and contain approximately 850 calories with 15 g fat, 30 g fat, or 45 g fat and those meals suggested in the Guidance for Industry on Food-Effect Bioavailability and Fed Bioequivalence Studies (December 2002), namely after an overnight fast or with a high-calorie and high-fat meal (approximately 1000 calories and 50% of the calories from fat). The 15 g, 30 g, and 45 g fat meals are meal options that are incorporated into the ongoing Phase 3 study. Subjects will be randomized to a sequence of the five defined meal plans (including fasting) to be administered on PK Phase Periods 1 through 5 (Days 1 through 5).

Table 3.1 Meals Plans Provided During the PK Phase

Meal Plan A (Fasting) Overnight fast (≥10 hours) Dose oral TU with 240 mL of water Fast additional 4 hours Lunch 30 grams fat Dinner 30 grams fat	**Meal Plan B (15 gm fat)** Overnight fast (≥10 hours) Dose oral TU immediately prior to breakfast Breakfast 15 grams fat Lunch 30 grams fat Dinner 30 grams fat
Meal Plan C (30 gm fat, Reference Meal) Overnight fast (≥10 hours) Dose oral TU immediately prior to breakfast	**Meal Plan D (45 gm fat)** Overnight fast (≥10 hours) Dose oral TU immediately prior to breakfast Breakfast 45 grams fat

Breakfast 30 grams fat Lunch 30 grams fat Dinner 30 grams fat	Lunch 30 grams fat Dinner 30 grams fat
Meal Plan E (FDA high-calorie high-fat) Overnight fast (≥10 hours) Dose oral TU immediately prior to breakfast Breakfast FDA high-fat, high-calorie meal (≈1000 calories, 50% of calories as fat) Lunch 30 grams fat Dinner 30 grams fat	

Table 3.2 Subject Sequence Assignments

	Period 1	Period 2	Period 3	Period 4	Period 5
Sequence 1	A	B	C	D	E
Sequence 2	B	C	E	A	D
Sequence 3	C	E	D	B	A
Sequence 4	D	A	B	E	C
Sequence 5	E	D	A	C	B

The confinement for the PK Phase will begin immediately prior to the evening dose and meal on Run-In Day 14, and will continue through collection of a blood sample 24 hours after the morning dose of the fifth dosing period (Period 5) for a total of approximately 135 hours. During the PK Phase, subjects will have all meals provided, will undergo observed dosing (dosing of study medication taken from site inventory will be observed by site personnel), will have blood samples collected and will have limited activity. During this phase, the subjects must consume their *entire breakfast and dinner meals* and study drug will be administered in the morning and evening (approximately 12 hours apart) immediately before breakfast and dinner.

For all subjects, serial blood samples will be 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 should be performed within ± 10 minutes of the scheduled time points (with the exception of the 0-hour time point which should be performed no more than 5 minutes before oral TU dose administration on each PK Phase Period). The 24-hour PK blood sample on a just completed PK Phase period (Day 1, 2, 3 or 4) will also serve as the predose blood sample for the immediately following morning dose (Day 2, 3, 4 or 5, respectively).

Subjects will be released from the clinic following the 24-hour blood draw and designated end of study activities of the PK Phase, which occurs the morning after the fifth PK Phase study period.

Each subject will participate in the study for approximately 8 weeks, including up to a 28-day Screening Phase, a 14-day out-patient Run-In Phase, and a 6-day in-patient PK Phase, followed by a 5 to 7 day Safety Follow–up Phase to assess safety.

4. ANALYSIS POPULATIONS

4.1 Analysis Populations

PK Population: The PK population shall consist of all subjects in the study who have at least 1 evaluable PK profile (calculable $C_{max\text{-}am}$ and $C_{avg\text{-}am}$) and no significant protocol deviations.

PK Evaluable Population: All subjects in the PK population who comply sufficiently with the protocol and display an evaluable PK profile (e.g., exposure to treatment,

availability of measurements, and absence of major protocol violations). PK evaluable population will be used in the PK parameter summary and statistical analyses. Food effect assessment will be conducted only on data from subjects who complete the study or have sufficient data for a pairwise comparison (i.e. have at completed at least 2 periods, 1 of which must be for Treatment C [30 g fat] or Treatment B [15 g fat], which serve as the reference meals for the primary and secondary comparisons, respectively).

A sensitivity analysis will also be performed on a sub-set of subjects, to be determined by Clarus that will exclude subjects who were determined to not have eaten the majority of the fat containing food in their meal.

Safety Population: All subjects who received at least one dose of the study drug. Safety population will be used in the safety summarizations.

4.2 Preliminary Data and Interim Analysis

No interim analysis is planned for the study.

5. TREATMENT DESCRIPTIONS

Treatments A, B, C, D and E are described as follows:

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

In each treatment arm, the second oral TU dose of the day is administered immediately prior to a dinner containing 30 g fat.

Additional details of each treatment can be found in Table 3.1, Section 3.

6. PHARMACOKINETIC ANALYSIS

Note: PK parameters will not be calculated by Celerion. However, Celerion will complete the statistical analyses of PK parameters and provide the PK tables, listings and figures.

6.1 Measurements and Collection Schedule

Serial blood samples will be collected for total T, dihydrotestosterone (DHT) and TU concentration determinations, for Periods 1 through 5, according to the following schedule: 0 (pre-morning dose), 2, 4, 6, 9, 12, 14, 16, 18, 21 and 24 hours after the

morning dose. The 24 hours sample on Days 1-4 serve as the 0 (pre-morning dose) samples for Days 2-5.

Note: For calculating the PK parameters, the 12-hour time point will be used as the last time point for AM dose and as the predose time point for the PM dose.

Concentrations for total T, DHT and TU will be included in the individual concentration-time plots (based on actual sample times), as well as in the mean concentration-time plots (based on nominal sample times); however, if there are any significant sampling time deviations, additional concentration-time plots of the mean data may be provided.

6.2 Bioanalytical Method

Total T and DHT

Plasma concentrations of total T and DHT will be determined in human NaF+EDTA plasma using liquid-chromatography and tandem-mass spectrometry (LC/MS/MS), as validated at inVentiv Health Clinique, Quebec, Canada. The lower limit of quantitation (LLOQ) for total T and DHT are 10 ng/dL and 5 ng/dL, respectively.

TU

Plasma concentrations of total TU will be determined in human NaF+EDTA plasma using LC/MS/MS as validated at the Los Angeles Biomedical Research Institute (LA Biomed), Torrance, California. The lower limit of quantitation (LLOQ) for TU is 2 ng/mL.

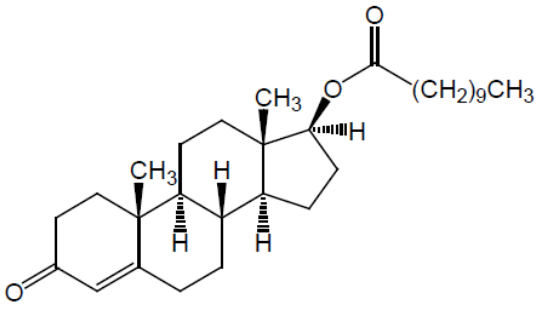
6.3 Investigational Product and PK Analyte Information

Testosterone undecanoate (TU) is currently being developed for the treatment of hypogonadism.

The chemical characteristics of TU are presented below:

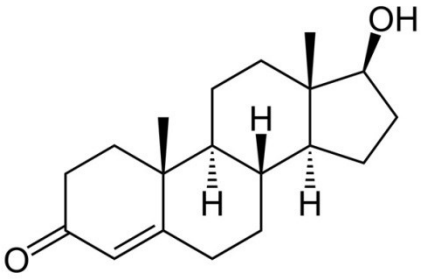
Chemical Name:	17β-undecanoyloxy-androst-4-en-3-one CAS: 549-44-0
Molecular Formula:	$C_{30}H_{48}O_3$
Molecular Weight:	456.7 g/mol

Chemical structure:

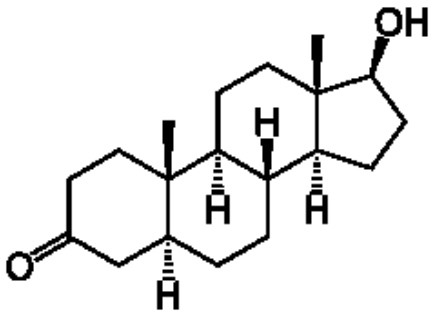


Clarus's formulation of oral TU at a dose of 237 mg TU (the highest strength capsule being developed by Clarus) contains 150 mg T per capsule.

TU is the undecanoate ester of T. T has a molecular weight of 288.42 g/mol and a molecular formula $C_{19}H_{28}O_2$. Its metabolite DHT has a molecular weight of 290.44 g/mol and a molecular formula $C_{19}H_{30}O_2$. Their molecular structures are shown in the following figures:



Testosterone



Dihydrotestosterone

6.4 Pharmacokinetic Concentrations

Plasma concentrations of total T, DHT and TU collected at the times described in Section 6.1, and using the bioanalytical methods described in Section 6.2, will be used for the calculation of the plasma total T, DHT and TU PK parameters, respectively. Only total T PK parameters will be compared using a statistical model for assessment of food effects.

6.5 Noncompartmental Pharmacokinetic Analysis and Parameter Calculation

The appropriate noncompartmental, model-independent PK parameters will be calculated from the plasma total T, DHT, and TU concentration-time data using Microsoft® Excel® 2013. All PK parameters included in the protocol are listed in Table 6.1, and are defined as appropriate for study design.

Table 6.1 Noncompartmental Plasma Pharmacokinetic Parameters to be Calculated

Parameter	Definition	Method of Determination
AUC_{am}	Area under the concentration-time curve over the morning dosing interval	Calculated using the linear trapezoidal method
AUC_{pm}	Area under the concentration-time curve over the evening dosing interval	Calculated using the linear trapezoidal method
AUC_{24}	Area under the concentration-time curve over the combined morning and evening dosing intervals	Calculated using the linear trapezoidal method
$C_{max\text{-}am}$	Maximum measured plasma concentration following the morning dose	Taken directly from the bioanalytical data
$C_{max\text{-}pm}$	Maximum measured plasma concentration following the evening dose	Taken directly from the bioanalytical data
$C_{max\text{-}24}$	Maximum measured plasma concentration over the combined morning and evening dosing intervals	Taken directly from the bioanalytical data
$T_{max\text{-}am}$	Time to reach $C_{max\text{-}am}$. If the maximum value occurs at more than one time point, $T_{max\text{-}am}$ is defined as the first time point with this value	Taken directly from the bioanalytical data
$T_{max\text{-}pm}$	Time to reach $C_{max\text{-}pm}$. If the maximum value occurs at more than one time point, $T_{max\text{-}pm}$ is defined as the first time point with this value	Taken directly from the bioanalytical data
$C_{avg\text{-}am}$	Time-weighted average plasma concentration over the dosing interval following the morning dose	$Cavg-am = \frac{AUCam}{\tau}$ where τ is the anticipated dosing interval for the clinic.

Parameter	Definition	Method of Determination
$C_{avg\text{-}pm}$	Time-weighted average plasma concentration over the dosing interval following the evening dose	$Cavg-pm=\frac{AUCpm}{\tau}$ where τ is the anticipated dosing interval for the clinic.
$C_{avg\text{-}24}$	Time-weighted average plasma concentration over the combined period of the morning and evening dosing intervals.	$Cavg24=\frac{AUC24}{24}$

Additional PK parameters may be computed if deemed appropriate for meeting the objectives of the study.

The primary comparisons of interest will be the total T exposure (maximum and cumulative) over the dosing interval following the morning doses of TU for each specific treatment period.

When sufficient concentration data exist, the analogous PK parameters (AUC_{pm}, $C_{max\text{-}pm}$, $T_{max\text{-}pm}$, and $C_{avg\text{-}pm}$) for total T will be calculated following the evening dose of TU, 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 treatment period). In addition, the morning dose, evening dose, and full day PK parameter versions of C_{max}, T_{max}, and AUC will be calculated for DHT and TU following the doses of TU for each treatment period. Note that T_{max} will not be calculated for the full day.

As the treatment doses will be administered while endogenous T production has been suppressed, the total T values will not be corrected for baseline T concentrations.

Actual sample times will be used in the calculation of PK parameters. If a measurement value is available but the actual time is not captured, the time will be replaced with the nominal time for that visit. Subjects for whom there are insufficient data to calculate PK parameters for an analyte will be included in the concentration tables only and excluded from the statistical analysis of that analyte.

6.6 Handling of Missing Data and BLQ Values

Calculation of PK parameters

For noncompartmental PK parameter calculations, missing concentrations will not be imputed, except when estimation from existing data is supported by standard PK principals as detailed below. A missing concentration value adjacent to the existing C_{max} will make a subject non-evaluable for C_{max}, T_{max}, and AUC calculations. If more than one concentration in sequence is missing, the subject will be considered

non-evaluable for AUCs, unless the missing concentrations are embedded in a series of assay results that are below the limit of quantitation (BLQ).

- Single embedded missing concentrations will be treated as missing and the affected AUCs calculated, if appropriate based on PK principals, by extending the trapezoid to the next existing concentration.
- Missing actual sample collection times may be replaced with nominal scheduled sample collection times based on case-by-case review.
- Leading, trailing and embedded BLQ values will be treated as one-half the lower limit of quantitation (LLOQ/2) for total T and DHT, but as zero (0.0) for TU since TU is not an endogenous molecule.
- A missing predose concentrations (i.e., at T=0 or T=24) may be replaced by a value equal to the morning dose concentration of the preceding or following PK Phase treatment.
- A missing predose concentration prior to the evening TU dose may be estimated by linear or log-linear extrapolation, as appropriate, of the 6 and 9-hour samples if that process is consistent with the observed PK pattern for other subjects when receiving the same treatment.

Summary Statistics

For the calculation of total T and DHT concentration summary statistics, values that are BLQ will be treated as LLOQ/2. For the calculations of TU concentration summary statistics, values that are BLQ will be treated as '0' (zero).

6.7 Data Summarization and Presentation

All total T, DHT and TU PK concentrations and PK parameter descriptive statistics will be generated using SAS® Version 9.3.

For all subjects in the PK Population, plasma total T, DHT and TU concentrations will be listed by subject, and summary statistics, including number of observations (n), arithmetic mean (Mean), standard deviation (SD), coefficient of variation (CV%), standard error of the mean (SEM), minimum, median, and maximum, will be calculated by nominal time point for each treatment separately. Data from excluded subjects will be listed but excluded from the summary statistics and noted as such in the tables. All BLQ values will be presented as "BLQ" in the concentration table listings and footnoted accordingly.

Plasma total T, DHT and TU PK parameters will be listed and summary statistics will be calculated for each treatment separately in the PK Evaluable Population. Summary statistics will include: n, Mean, SD, CV, SEM, minimum, median, maximum, geometric mean (Geom Mean), and geometric CV% (Geom CV%).

Data from excluded subjects will be listed but excluded from the summary statistics and statistical analysis and noted as such in the tables.

The level of precision for each statistic will be presented as follows:

- minimum/maximum in same precision as in bioanalytical data (the bioanalytical data will be rounded to 3 significant figures) or parameter output,
- Mean/median/Geom Mean in one more level of precision than minimum/maximum,
- SD and SEM in one more level of precision than Mean/median,
- CV% and Geom CV% will be presented to 1 decimal place,
- n will be presented as an integer (no decimal place).

Mean (based on nominal time) and individual (based on actual time) concentration time profiles will be presented on linear and semi-log scales for plasma total T, DHT and TU concentrations as appropriate. Linear mean plots will be presented with and without SD.

6.8 Statistical Analysis of PK Parameters

6.8.1 Analysis of Variance

An analysis of variance (ANOVA) will be performed on the natural log (ln)-transformed $C_{max\text{-}am}$, AUC_{am}, and $C_{avg\text{-}am}$. The ANOVA model will include treatment received, sequence, and period as fixed-effects, and subject nested within sequence as a random-effect. A sequence effects will be estimated by testing sequence using subject nested within sequence as the error term at a 10% level of significance. Each ANOVA will include calculation of treatment LSMs as well as the difference between treatment LSMs. The statistical analyses will be done using the following example SAS® code.

```
PROC MIXED;
CLASS Sequence Subject Treatment Period;
MODEL PK_Parameter = Sequence Treatment Period / DDFM=KR;
RANDOM Subject(Sequence);
ESTIMATE “Fasting (A) vs 30 g fat (C)” Treatment 1 0 -1 0 0/CL ALPHA=0.1 E;
ESTIMATE “15 g fat (B) vs 30 g fat (C)” Treatment 0 1 -1 0 0/CL ALPHA=0.1 E;
ESTIMATE “45 g fat (D) vs 30 g fat (C)” Treatment 0 0 -1 1 0/CL ALPHA=0.1 E;
ESTIMATE “high-fat (E) vs 30 g fat (C)” Treatment 0 0 -1 0 1/CL ALPHA=0.1 E;
LSMEANS Treatment/CL;
RUN;
```

6.8.2 Ratios and Confidence Intervals

For the primary comparisons two-way contrasts will be made using the 30 g fat meal as the reference treatment, and the point estimate and 90% CI for the LSM mean

difference in ln-transformed PK parameters $C_{max\text{-}am}$, AUC_{am}, and $C_{avg\text{-}am}$ will be exponentiated to obtain estimates for ratios of geometric LSMs on the original scale. No food effect will be concluded for a contrasted treatment if the 90% CI about the ratio of geometric LSMs of $C_{max\text{-}am}$ and AUC_{am} for that contrast lie totally within the 0.80 to 1.25 interval. Presence of a food effect will be concluded if the 90% CIs fall outside the range of 70.00% to 143.00%.

6.9 Secondary Comparisons

In addition to the primary comparisons as described in Section 6.7, secondary comparisons will be made for total T for $C_{max\text{-}pm}$, AUC_{pm}, C_{max24}, and AUC24. Secondary comparisons with the 15 g fat meal (B) versus the other treatments, and the fasting treatment (A) versus other treatments will be provided to identify the effect of meal type on $C_{max\text{-}am}$, AUC_{am}, and $C_{avg\text{-}am}$ for total T. The following estimate statements will be used with the ANOVA model to calculate the treatment differences for the secondary comparisons (statistical testing will not be completed for fasting comparisons):

Secondary Comparisons:

ESTIMATE “Fasting (A) vs 15 g fat (B)” Treatment 1 -1 0 0 0/CL ALPHA=0.1 E;
ESTIMATE “30 g fat (C) vs 15 g fat (B)” Treatment 0 -1 1 0 0/CL ALPHA=0.1 E;
ESTIMATE “45 g fat (D) vs 15 g fat (B)” Treatment 0 -1 0 1 0/CL ALPHA=0.1 E;
ESTIMATE “high-fat (E) vs 15 g fat (B)” Treatment 0 -1 0 0 1/CL ALPHA=0.1 E;

ESTIMATE “15 g fat (B) vs Fasting (A)” Treatment -1 1 0 0 0/E;
ESTIMATE “30 g fat (C) vs Fasting (A)” Treatment -1 0 1 0 0/E;
ESTIMATE “45 g fat (D) vs Fasting (A)” Treatment -1 0 0 1 0/E;
ESTIMATE “high-fat (E) vs Fasting (A)” Treatment -1 0 0 0 1/E;

Ratios of geometric LSMs will be calculated using the exponentiation of the difference between treatment LSM from the analyses on the ln-transformed $C_{max\text{-}am}$, AUC_{am}, and $C_{avg\text{-}am}$. These ratios will be expressed as a percentage relative to the fasting condition, i.e. the reference treatment (Treatments B and A respectively). CIs will not be calculated for the comparisons with the fasting treatment (A).

Sensitivity Analysis:

A sensitivity analysis will be performed using the same comparisons defined for the primary analysis but with a subset of subjects, determined by Clarus, that exclude subjects who were determined to not have eaten the majority of the fat containing food in their meal.

7. SAFETY

All clinical safety and tolerability data will be listed by subject and assessment time points, including rechecks, unscheduled assessments, and early termination, chronologically.

Continuous safety variables will be summarized using n, arithmetic mean, SD, minimum, median and maximum. Frequency counts will be reported for categorical data when appropriate.

The level of precision for the descriptive statistics will be presented as follows: minimum/maximum in same precision as in the database, mean/median in one more precision level than minimum/maximum, SD in one more precision level than mean/median, and n will be presented as an integer.

Where individual data points are missing because of dropouts or other reasons, the data will be summarized based on reduced denominators.

No inferential statistics are to be performed on safety endpoints.

7.1 Subject Discontinuation

Subjects will be summarized by number of subjects enrolled and randomized, dosed, completed, and discontinued the study. These tabulations include the number of subjects discontinuation by reason specified for discontinuation. In addition, a table presenting dosing status of each subject by treatment will be created.

7.2 Demographics

Descriptive statistics will be calculated for continuous variables (age, weight, height, body mass index [BMI], prostate specific antigen [PSA] International Prostate Symptom Score [I-PSS], and Quality of Life Due to Urinary Symptoms Score). Age will be calculated in years between date of birth and date of informed consent. Frequency counts and corresponding percentages will be provided for categorical variables (gender, race and ethnicity).

7.3 Adverse Events

All adverse events (AEs) occurring during this clinical trial will be coded using the Medical Dictionary for Regulatory Activities (MedDRA®), Version 15.1.

All AEs captured in the database will be listed in by-subject data listings including verbatim term, coded term, treatment, frequency, severity, serious, outcome, action taken and relationship to study medication. However, only treatment-emergent AEs (TEAEs) will be summarized. AEs that occur during the Run-In Phase will be considered to be treatment-emergent.

An AE is considered treatment-emergent if it begins or worsens in severity after the first dose of the study drug. If an AE increases in severity, that AE will be given a resolution date and time and a new record will be initiated with the new severity. If the severity of an AE remains the same or decreases, the AE will be kept open through to resolution and the maximum severity will be recorded.

The number and percentage of subjects with TEAEs will be tabulated by System Organ Class (SOC) and Preferred Term. Summary tables will include number of subjects reporting the AE and as percent of number of subjects dosed, by Phase (Run-In and PK and Follow-Up). Number of TEAEs will be summarized in a similar manner. A summary of the number of subjects with TEAEs will be provided by severity and by relationship to study drug. If for any AE severity and/or relationship to drug is missing, then the least favorable choice(s) (Severe and Definitely) will be assigned for purposes of tabulation and listing. Subjects reporting more than 1 AE for a given MedDRA® preferred term will be counted only once for that term using the most severe incident. Subjects reporting more than 1 type of event within an SOC will be counted only once for that SOC. Incidence of TEAEs, serious TEAEs, TEAEs resulting in discontinuation from study drug, and TEAEs resulting in death will be summarized. Listings will be provided for all AEs, SAEs, and AEs resulting in treatment discontinuation.

7.4 Clinical Laboratory Tests

Blood samples for the clinical safety laboratory tests, including PSA, will be collected at Screening 1, Run-In Phase Day 1, PK Phase Day 1, following the 24-hour PK blood draw on PK Phase Day 6, and 5 to 7 days post last dose during the Safety Follow-Up Phase, if the subject needed to return to the clinic for an in person visit, or at Early Termination from the study. Samples for safety lab tests will be collected in the morning after obtaining vital signs and after overnight fasting, but before meals and study drug administration. Urinalysis will only be assessed at Screening 1.

All out-of-range values for serum chemistry, hematology and urinalysis will be listed by subject. Out-of-range values are considered to be values that are out-of- normal range as defined by the clinical laboratory. The normal range values will be displayed in the data listings along with the Principal Investigator's (PI's) interpretation.

For all serum chemistry and hematology safety laboratory values (including PSA results) that are numeric, descriptive statistics will be presented for each laboratory test by assessment time point. Change from baseline will be summarized in a similar manner. The test results from Screening 1 will serve as the baseline for change from baseline calculations. Rechecks, unscheduled assessments and early termination measurements taken after first dosing will not be used in the summarization. Subjects will only return for clinical lab assessment during the Safety Follow-up Phase if there is a specific need. Therefore, clinical labs will not be summarized for the Safety Follow-up visit. Urinalysis is only assessed at Screening 1. Therefore, change from baseline will not be calculated for urinalysis.

Serum total testosterone assessed at Screening 1 and Screening 2, and DHT assessed at Run-In Phase Day 1 will be listed but not summarized.

7.5 Vital Signs

Vital signs, including systolic and diastolic blood pressure and heart rate will be measured in triplicate at Screening 1, Run-In Phase Day 1, and prior to dosing during the PK Phase on Days 1, 2, 3, 4, 5, and 6, and 5 to 7 days post last dose during the Safety Follow-Up Phase, if a clinical visit is required for the safety follow up, or at Early Termination. The subject should be sitting at rest for at least 5 minutes with his feet resting on the floor and before BP and HR are measured 3 times at 1 to 2 minute intervals. Respiration rate and temperature are only collected during Screening 1 and at Early Termination.

Descriptive statistics (n, mean, SD, median, minimum, and maximum) will be provided for vital sign variables systolic and diastolic blood pressure and heart rate at each assessment time point, including change from baseline. The mean of the triplicate values will be used in the calculation of the summary statistics. The vital signs measurements on Day 1 of the Run-In Phase will serve as the baseline for calculating change from baseline. Rechecks, unscheduled assessments and early termination measurements taken after initial study dosing will not be used in the summarization. Subjects will only return for vital signs assessment during the Safety Follow-up Phase if there is a specific need. Therefore, vital signs will not be summarized for the Safety Follow-up visit. Respiration rate and temperature are only collected at Screening 1 and Early Termination. Therefore, change from baseline will not be calculated for these measurements.

Vital signs will also be displayed in a data listing by subject.

7.6 Concomitant Medications

All prior and concomitant medications recorded during the study will be coded with the WHO Dictionary Version September 2012 and listed. Prior medications are defined as medications documented on the Prior and Concomitant Medications CRF/eCRF as having started and stopped before the first dose of any study drug. Concomitant medications are defined as medications documented on the Prior and Concomitant Medications CRF/eCRF as having started after the start of study drug or having started before the start of study drug and continued on or after the first dose of any study drug. Prior and concomitant medications will be summarized by WHO term in separate tables. All concomitant medications administered will be tabulated in a data listing.

7.7 Physical Examination

A complete physical examination (PE) with a digital rectal examination (DRE) will be performed at Screening 2. A PE may also be completed 5 to 7 days post last dose

during the Safety Follow-Up Phase if needed, or at Early Termination. A brief PE without DRE will be performed on Day 1 prior to dosing during the 14 Day Run-In Phase and prior to departing the clinic following the last PK Phase. For all subjects, a symptom-directed physical examination will be performed when necessary. Any relevant findings from the PI during screening will be reported as medical history. Any significant PE findings after dosing will be recorded as AEs. A by-subject listing will be provided.

8. SUMMARY TABLES AND FIGURES

Summary tables and figures are numbered following the ICH structure but may be renumbered as appropriate during the compilation of the tables and figures for the report. Please note that all safety summary tables will be generated using SAS®.

The following are lists of TFLs numbers and titles that will be included within the report.

8.1 In-text Summary Tables and Figures

The following is a list of table and figure titles that will be included in the text of the report. Tables and figures will be numbered appropriately during compilation of the report.

Section 10:

Table 10-1 Disposition Summary

Table 10-2 Demographic Summary

Section 11:

Tables:

Primary PK Parameters for Total T (C_{max-am}, T_{max-am}, AUC_{am}, and C_{avg-am}) and Secondary PK Parameters for Total T (C_{max-pm}, T_{max-pm}, AUC_{pm}, C_{avg-pm}, C_{max-24}, AUC_{24}, and C_{avg-24})

Table 11-1 Summary of Plasma Total T Pharmacokinetic Parameters Following Treatments A, B, C, D, and E (PK Evaluable Population)

Primary PK Comparison for Total T (C_{max-am}, AUC_{am}, and C_{avg-am})

Table 11-2 Primary Statistical Comparisons of Plasma Total T Pharmacokinetic Parameters Following Treatments A, B, D, and E Versus Treatment C (PK Evaluable Population)

Secondary PK Comparison for Total T (C_{max-am}, AUC_{am}, and C_{avg-am})

Table 11-3 Secondary Statistical Comparisons of Plasma Total T Pharmacokinetic Parameters Following Treatments A, C, D, and E Versus Treatment B

Sensitivity analysis:

Primary PK Parameters (C_{max-am}, AUC_{am}, and C_{avg-am})

Table 11-11 Statistical Comparisons of Plasma Total T Pharmacokinetic Parameters Following Treatments A, B, D, and E Versus Treatment C (A Sub-set of PK Evaluable Population)

Section 12:

Table 12-1 Incidence of Treatment-Emergent Adverse Events by Phase

8.2 Section 14 Summary Tables and Figures

The following is a list of table and figure titles that will be included in Section 14 of the CSR.

14.1 Demographic Data Summary Tables

Table 14.1.1 Summary of Disposition
Table 14.1.2 Disposition of Subjects
Table 14.1.3 Demographic Summary

14.2 Pharmacokinetic Data Summary Tables and Figures

14.2.1 Tables

14.2.1.1 Concentration Tables

Total T

Table 14.2.1.1.1 Plasma Total T Concentrations (ng/dL) Following Administration of 237 mg TU BID Under Fasting Condition for Breakfast (Treatment A) (PK Population)
Table 14.2.1.1.2 Plasma Total T Concentrations (ng/dL) Following Administration of 237 mg TU BID with 15 g fat Breakfast (Treatment B) (PK Population)
Table 14.2.1.1.3 Plasma Total T Concentrations (ng/dL) Following Administration of 237 mg TU BID with 30 g fat Breakfast (Treatment C) (PK Population)
Table 14.2.1.1.4 Plasma Total T Concentrations (ng/dL) Following Administration of 237 mg TU BID with 45 g fat Breakfast (Treatment D) (PK Population)

14.2.1.2 PK Parameter Tables

Total T

Table 14.2.1.2.1 Plasma Total T Pharmacokinetic Parameters Following Administration of 237 mg TU BID Under Fasting Condition for Breakfast (Treatment A) (PK Evaluable Population)

Table 14.2.1.2.2 Plasma Total T Pharmacokinetic Parameters Following Administration of 237 mg TU BID with 15 g fat Breakfast (Treatment B) (PK Evaluable Population)

Table 14.2.1.2.3 Plasma Total T Pharmacokinetic Parameters Following Administration of 237 mg TU BID with 30 g fat Breakfast (Treatment C) (PK Evaluable Population)

Table 14.2.1.2.4 Plasma Total T Pharmacokinetic Parameters Following Administration of 237 mg TU BID with 45 g fat Breakfast (Treatment D) (PK Evaluable Population)

Table 14.2.1.2.5 Plasma Total T Pharmacokinetic Parameters Following Administration of 237 mg TU BID with FDA High-Calorie High-fat Breakfast (Treatment E) (PK Evaluable Population)

DHT

Table 14.2.1.2.6 Plasma DHT Pharmacokinetic Parameters Following Administration of 237 mg TU BID Under Fasting Condition for Breakfast (Treatment A) (PK Evaluable Population)

Table 14.2.1.2.7 Plasma DHT Pharmacokinetic Parameters Following Administration of 237 mg TU BID with 15 g fat Breakfast (Treatment B) (PK Evaluable Population)

Table 14.2.1.2.8 Plasma DHT Pharmacokinetic Parameters Following Administration of 237 mg TU BID with 30 g fat Breakfast (Treatment C) (PK Evaluable Population)

Table 14.2.1.2.9 Plasma DHT Pharmacokinetic Parameters Following Administration of 237 mg TU BID with 45 g fat Breakfast (Treatment D) (PK Evaluable Population)

Table 14.2.1.2.10 Plasma DHT Pharmacokinetic Parameters Following Administration of 237 mg TU BID with FDA High-Calorie High-fat Breakfast (Treatment E) (PK Evaluable Population)

TU

Table 14.2.1.2.11 Plasma TU Pharmacokinetic Parameters Following Administration of 237 mg TU BID Under Fasting Condition for Breakfast (Treatment A) (PK Evaluable Population)

Table 14.2.1.2.12 Plasma TU Pharmacokinetic Parameters Following Administration of 237 mg TU BID with 15 g fat Breakfast (Treatment B) (PK Evaluable Population)

14.2.1.3 Statistical Analyses Tables

Statistical Comparisons of Plasma Total T for Primary PK Parameters ($C_{max\text{-}am}$, AUC_{am}, $C_{avg\text{-}am}$)

Primary Comparisons (Total T versus 30 g fat meal [C]):

Secondary Comparisons (Total T- versus 15 g fat meal [B]):

Table 14.2.1.3.5 Secondary Statistical Comparisons of Plasma Total T Pharmacokinetic Parameters: Treatment A (Test) Versus Treatment B (Reference) (PK Evaluable Population)

Table 14.2.1.3.6 Secondary Statistical Comparisons of Plasma Total T Pharmacokinetic Parameters: Treatment C (Test) Versus Treatment B (Reference) (PK Evaluable Population)

Table 14.2.1.3.7 Secondary Statistical Comparisons of Plasma Total T Pharmacokinetic Parameters: Treatment D (Test) Versus Treatment B (Reference) (PK Evaluable Population)

Table 14.2.1.3.8 Secondary Statistical Comparisons of Plasma Total T Pharmacokinetic Parameters: Treatment E (Test) Versus Treatment B (Reference) (PK Evaluable Population

Secondary Comparisons (Total T – versus fasted state [A]):

Table 14.2.1.3.9 Secondary Statistical Comparisons of Plasma Total T Pharmacokinetic Parameters: Treatment B (Test) Versus Treatment A (Reference) (PK Evaluable Population)

Table 14.2.1.3.10 Secondary Statistical Comparisons of Plasma Total T Pharmacokinetic Parameters: Treatment C (Test) Versus Treatment A (Reference) (PK Evaluable Population)

Table 14.2.1.3.11 Secondary Statistical Comparisons of Plasma Total T Pharmacokinetic Parameters: Treatment D (Test) Versus Treatment A (Reference) (PK Evaluable Population)

Table 14.2.1.3.12 Secondary Statistical Comparisons of Plasma Total T Pharmacokinetic Parameters: Treatment E (Test) Versus Treatment A (Reference) (PK Evaluable Population)

Statistical Comparisons of Plasma Total T for Secondary PK Parameters ($C_{max\text{-}pm}$, AUC_{pm}, $C_{avg\text{-}pm}$, $C_{max\text{-}24}$, and AUC_{24}, $C_{avg\text{-}24}$)

Secondary Comparisons (Total T – versus 30 g fat state[C]):

Table 14.2.1.3.13 Secondary Statistical Comparisons of Plasma Total T Pharmacokinetic Parameters: Treatment A (Test) Versus Treatment C (Reference) (PK Evaluable Population)

Table 14.2.1.3.14 Secondary Statistical Comparisons of Plasma Total T Pharmacokinetic Parameters: Treatment B (Test) Versus Treatment C (Reference) (PK Evaluable Population)

Table 14.2.1.3.15 Secondary Statistical Comparisons of Plasma Total T Pharmacokinetic Parameters: Treatment D (Test) Versus Treatment C (Reference) (PK Evaluable Population)

Table 14.2.1.3.16 Secondary Statistical Comparisons of Plasma Total T Pharmacokinetic Parameters: Treatments E (Test) Versus Treatment C (Reference) (PK Evaluable Population)

Secondary Comparisons (Total T – versus fasted state [A]):

Table 14.2.1.3.17 Secondary Statistical Comparisons of Plasma Total T Pharmacokinetic Parameters: Treatment B (Test) Versus Treatment A (Reference) (PK Evaluable Population)

Table 14.2.1.3.18 Secondary Statistical Comparisons of Plasma Total T Pharmacokinetic Parameters: Treatment C (Test) Versus Treatment A (Reference) (PK Evaluable Population)

Table 14.2.1.3.19 Secondary Statistical Comparisons of Plasma Total T Pharmacokinetic Parameters: Treatment D (Test) Versus Treatment A (Reference) (PK Evaluable Population)

Table 14.2.1.3.20 Secondary Statistical Comparisons of Plasma Total T Pharmacokinetic Parameters: Treatments E (Test) Versus Treatment A (Reference) (PK Evaluable Population)

Statistical Comparisons of Plasma DHT for Secondary PK Parameters ($C_{max\text{-}am}$, AUC_{am}, $C_{max\text{-}pm}$, AUC_{pm}, $C_{max\text{-}24}$, and AUC_{24}):

Secondary Comparisons (DHT):

Table 14.2.1.3.21 Secondary Statistical Comparisons of Plasma DHT Pharmacokinetic Parameters: Treatment A (Test) Versus Treatment C (Reference) (PK Evaluable Population)

Table 14.2.1.3.22 Secondary Statistical Comparisons of Plasma DHT Pharmacokinetic Parameters: Treatment B (Test) Versus Treatment C (Reference) (PK Evaluable Population)

Table 14.2.1.3.23 Secondary Statistical Comparisons of Plasma DHT Pharmacokinetic Parameters: Treatment D (Test) Versus Treatment C (Reference) (PK Evaluable Population)

Table 14.2.1.3.24 Secondary Statistical Comparisons of Plasma DHT Pharmacokinetic Parameters: Treatment E (Test) Versus Treatment C (Reference) (PK Evaluable Population)

Statistical Comparisons of Plasma TU for Secondary PK Parameters ($C_{max\text{-}am}$, AUC_{am}, $C_{max\text{-}pm}$, AUC_{pm}, $C_{max\text{-}24}$, and AUC_{24}):

Secondary Comparisons (TU):

Table 14.2.1.3.25 Secondary Statistical Comparisons of Plasma TU Pharmacokinetic Parameters: Treatment A (Test) Versus Treatment C (Reference) (PK Evaluable Population)

Table 14.2.1.3.26 Secondary Statistical Comparisons of Plasma TU Pharmacokinetic Parameters: Treatment B (Test) Versus Treatment C (Reference) (PK Evaluable Population)

Table 14.2.1.3.27 Secondary Statistical Comparisons of Plasma TU Pharmacokinetic Parameters: Treatment D (Test) Versus Treatment C (Reference) (PK Evaluable Population)

Table 14.2.1.3.28 Secondary Statistical Comparisons of Plasma TU Pharmacokinetic Parameters: Treatment E (Test) Versus Treatment C (Reference) (PK Evaluable Population)

Sensitivity Analysis:

Primary Comparisons:

Statistical Comparisons for Primary PK Parameters ($C_{max\text{-}am}$, AUC_{am}, $C_{avg\text{-}am}$):

Table 14.2.1.4.1 Statistical Comparisons of Plasma Total T Pharmacokinetic Parameters: Treatment A (Test) Versus Treatment C (Reference) (A Sub-Set of PK Evaluable Population)

Table 14.2.1.4.2 Statistical Comparisons of Plasma Total T Pharmacokinetic Parameters: Treatment B (Test) Versus Treatment C (Reference) (A Sub-Set of PK Evaluable Population)

Table 14.2.1.4.3 Statistical Comparisons of Plasma Total T Pharmacokinetic Parameters: Treatment D (Test) Versus Treatment C (Reference) (A Sub-Set of PK Evaluable Population)

Table 14.2.1.4.4 Statistical Comparisons of Plasma Total T Pharmacokinetic Parameters: Treatments E (Test) Versus Treatment C (Reference) (A Sub-Set of PK Evaluable Population)

14.2.2. Figures

14.2.2.1 Concentration Versus Time

Figure 14.2.2.1.1 Mean (SD) Plasma Total T Concentrations Versus Time Following Treatments A, B, C, D, and E (Linear Scale) (PK Population)

Figure 14.2.2.1.2 Mean Plasma Total T Concentrations Versus Time Following Treatments A, B, C, D, and E (Linear Scale) (PK Population)

Figure 14.2.2.1.3 Mean Plasma Total T Concentrations Versus Time Following Treatments A, B, C, D, and E (Semi-Log Scale) (PK Population)

Figure 14.2.2.1.4 Mean (SD) Plasma DHT Concentrations Versus Time Following Treatments A, B, C, D, and E (Linear Scale) (PK Population)

Figure 14.2.2.1.5 Mean Plasma DHT Concentrations Versus Time Following Treatments A, B, C, D, and E (Linear Scale) (PK Population)

Figure 14.2.2.1.6 Mean Plasma DHT Concentrations Versus Time Following Treatments A, B, C, D, and E (Semi-Log Scale) (PK Population)

Figure 14.2.2.1.7 Mean (SD) Plasma TU Concentrations Versus Time Following Treatments A, B, C, D, and E (Linear Scale) (PK Population)

Figure 14.2.2.1.8 Mean Plasma TU Concentrations Versus Time Following Treatments A, B, C, D, and E (Linear Scale) (PK Population)

Figure 14.2.2.1.9 Mean Plasma TU Concentrations Versus Time Following Treatments A, B, C, D, and E (Semi-Log Scale) (PK Population)

Note: every figure will have 5 lines, 1 for each treatment.

14.2.2.2 Food Effect

Total T (Primary PK Parameters):

Figure 14.2.2.2.1 Effect of Food (Treatments A, B, C, D and E) on Plasma Total T Cmax-am (PK Evaluable Population)

Figure 14.2.2.2.2 Effect of Food (Treatments A, B, C, D and E) on Plasma Total T AUCam (PK Evaluable Population)

Figure 14.2.2.2.3 Effect of Food (Treatments A, B, C, D and E) on Plasma Total T Cavg-am (PK Evaluable Population)

DHT (Secondary PK Parameters):

Figure 14.2.2.2.4 Effect of Food (Treatments A, B, C, D and E) on Plasma DHT Cmax-am (PK Evaluable Population)

Figure 14.2.2.2.5 Effect of Food (Treatments A, B, C, D and E) on Plasma DHT AUCam (PK Evaluable Population)

TU (Secondary PK Parameters):

Figure 14.2.2.2.7 Effect of Food (Treatments A, B, C, D and E) on Plasma TU Cmax-am (PK Evaluable Population)

Figure 14.2.2.2.8 Effect of Food (Treatments A, B, C, D and E) on Plasma TU AUCam (PK Evaluable Population)

Note to programmer for Figures 14.2.2.2.1 through to 14.2.2.2.9: these are box plots of total T, DHT, and TU plasma Cmax0-12, and AUC0-12 (including individual values plotted, overlaid with the box plot) under each treatment (Treatments A, B, C, D, E)

14.3 Safety Data Summary Tables

14.3.1 Displays of Adverse Events

Table 14.3.1.1 Treatment-Emergent Adverse Event Frequency by Phase – Number of Subjects Reporting Events (% of Subjects Dosed)

Table 14.3.1.2 Treatment-Emergent Adverse Event Frequency by Phase – Number of Adverse Events (% of Total Adverse Events)

Table 14.3.1.3 Treatment-Emergent Adverse Event Frequency by Severity and Relationship to Drug – Number of Subjects Reporting Events

Table 14.3.1.4 Treatment-Emergent Adverse Event Frequency by Severity and Relationship to Drug – Number of Adverse Events

14.3.2 Listings of Deaths, other Serious and Significant Adverse Events

Table 14.3.2.1 Serious Adverse Events
If no serious adverse event occurred, a statement 'No serious adverse event was reported'

Table 14.3.2.2 Serious Adverse Events Resulting in Discontinuation From Study Drug
If no serious adverse event resulting in discontinuation from study drug occurred, a statement 'No serious adverse event resulting in discontinuation was reported'

Table 14.3.2.3 Serious Adverse Events Resulting in Death
If no serious adverse event resulting in death occurred, a statement 'No serious adverse event resulting in death was reported'

14.3.3. Narratives of Deaths, other Serious and Certain other Significant Adverse Events

Not programmed – included as text in the report

14.3.4. Abnormal Laboratory Value Listing (each subject)

Table 14.3.4.1 Out-of-Range Values and Recheck Results –Chemistry

Table 14.3.4.2 Out-of-Range Values and Recheck Results – Hematology
Table 14.3.4.3 Out-of-Range Values and Recheck Results – Urinalysis

14.3.5. Displays of Other Laboratory, Vital Signs, Physical Examination, and Other Safety Data

Table 14.3.5.1 Clinical Laboratory Summary and Change From Baseline – Chemistry
Table 14.3.5.2 Clinical Laboratory Summary and Change From Baseline – Hematology
Table 14.3.5.3 Clinical Laboratory Summary – Urinalysis
Table 14.3.5.4 Vital Sign Summary
Table 14.3.5.5 Vital Sign Change From Baseline

8.3 Section 16 Data Listings

Data listings are numbered following the ICH structure but may be renumbered as appropriate during the compilation of the tables and figures for the report. The following is a list of appendix numbers and titles that will be included as data listings:

16.1. Study Information

Appendix 16.1.10.1 Clinical Laboratory Reference Ranges

16.2. Subject Data Listings

16.2.1. Subject Discontinuation

Appendix 16.2.1 Subject Disposition

16.2.2. Protocol Deviations

Appendix 16.2.2 Protocol Deviations

16.2.3. Subjects Excluded from Pharmacokinetic Analysis

Appendix 16.2.3 Subjects Excluded from Pharmacokinetic Analysis (PK Population)

Note: Appendices 16.2.2 and 16.2.3 are generated in MS Word for inclusion in the study report.

16.2.4. Demographic Data

Appendix 16.2.4.1 Demographics
Appendix 16.2.4.2.1 Physical Examination (I of II)
Appendix 16.2.4.2.2 Physical Examination (II of II)

Appendix 16.2.4.2.3 Physical Examination Descriptions
Appendix 16.2.4.3 Medical and Surgical History
Appendix 16.2.4.4 Testosterone Replacement Therapy – Screening
Appendix 16.2.4.5 Hypogonadism Signs and Symptoms – Screening
Appendix 16.2.4.6 International Prostate Symptom Score (I-PSS) and Quality of Life Due to Urinary Symptoms Score - Screening

16.2.5. Compliance and Drug Concentration Data

Appendix 16.2.5.2 Subject Eligibility
Appendix 16.2.5.3 Dosing – Run-In Phase Days 1and 14
Appendix 16.2.5.4 Dose Accountability – Run-In Phase, Days 1-14
Appendix 16.2.5.5 Dosing – PK Phase
Appendix 16.2.5.6 Blood Draw Times
Appendix 16.2.5.7 Meal Times
Appendix 16.2.5.8.1 Prior Medications
Appendix 16.2.5.8.2 Concomitant Medications

16.2.6. Individual Pharmacokinetic Response Data

Appendix 16.2.6.1.1-16.2.6.1.X Individual Plasma Total T Concentrations Versus Time (Linear and Semi-Log Scale) Following Treatments A, B, C, D, and E (PK Population)

Appendix 16.2.6.2.1-16.2.6.2.X Individual Plasma DHT Concentrations Versus Time (Linear and Semi-Log Scale) Following Treatments A, B, C, D, and E (PK Population)

Appendix 16.2.6.3.1 16.2.6.3.X Individual Plasma TU Concentrations Versus Time (Linear and Semi-Log Scale) Following Treatments A, B, C, D, and E (PK Population)

Note to programmer: Figures 16.2.6.1-16.2.6.3 are by subject; therefore the number of plots equals the number of subjects for each Appendix.

16.2.7. Individual Adverse Event Listings

Appendix 16.2.7.1 Adverse Events (I of II)
Appendix 16.2.7.2 Adverse Events (II of II)

16.2.8. Individual Laboratory Measurements

Appendix 16.2.8.1 Clinical Laboratory Report - Chemistry

9. TABLE SHELLS

The following table shells provide a framework for the display of data from this study. The shells may change due to unforeseen circumstances. These shells may not be reflective of every aspect of this study, but are intended to show the general layout of the tables that will be presented and included in the final report.

Table 10-1 Disposition Summary

Disposition	Overall
Enrolled and Randomized	X (XX%)
Dosed	X (XX%)
Completed	X (XX%)
Discontinued	X (X%)
<Reason1>	X (X%)
<Reason2>	X (X%)
Source: Table 14.1.1 Program: /CAXXXXX/sas_prg/stsas/intexttest/t_disp.sas DDMMMYYYY HH:MM	

Table 10-2 Demographic Summary

Trait	Category/Statistics	Overall
Gender	Male	X (XXX%)
Race	Asian	X (XX%)
	Black or African American	X (XX%)
	White	X (XX%)
Ethnicity	Hispanic or Latino	X (XXX%)
	Not Hispanic or Latino	X (XXX%)
Age (yrs)	n	X
	Mean	XX.X
	SD	XX.XX
	Minimum	XX
	Median	XX.X
	Maximum	XX
Weight (kg)	n	X
	Mean	XX.XX
	SD	XX.XXX
	Minimum	XX.X
	Median	XX.XX
	Maximum	XX.X
Height (cm)	n	X
	Mean	XXX.X
	SD	XX.XX
	Minimum	XXX
	Median	XXX.X
	Maximum	XXX
PSA (units)	n	X
	Mean	XXX.X
	SD	XX.XX
	Minimum	XXX
	Median	XXX.X
	Maximum	XXX
BMI (kg/m²)	n	X
	Mean	XX.XXX
	SD	X.XXXX
	Minimum	XX.XX
	Median	XX.XXX
	Maximum	XX.XX
I-PSS	n	X
	Mean	XX.XXX
	SD	X.XXXX
	Minimum	XX.XX
	Median	XX.XXX
	Maximum	XX.XX
I-PSS QOL	n	X
	Mean	XX.XXX
	SD	X.XXXX
	Minimum	XX.XX
	Median	XX.XXX
	Maximum	XX.XX

Trait	Category/Statistics	Overall
BMI = Body mass index PSA = Prostate specific antigen I-PSS = International Prostate Symptom Score (Questions 1-7) QOL = Quality of Life Due to Urinary Symptoms Score (Question 8 in I-PSS) Age is calculated at the time of informed consent Source: Table 14.1.3 Program: /CAXXXXX/sas_prg/stsas/intexttest/t_dem.sas DDMMMYYYY HH:MM		

Tables 11-1, 11-7, and 11-9 will be in the following format:

Table 11-X

Summary of Plasma Total T Pharmacokinetic Parameters Following Treatments A, B, C, D, and E (PK Evaluable Population)

	Treatment X		Treatment X	
Pharmacokinetic Parameters	**GM (GCV%)**	**n**	**GM (GCV%)**	**n**
Post-AM Dose				
Param1 (units)	XXX.X (XX.X)	XX	XXX.X (XX.X)	XX
Param2 (units)	XXX.X (XX.X)	XX	XXX.X (XX.X)	XX
Param3 (units)	XXX.X (XX.X)	XX	XXX.X (XX.X)	XX
Param4 (units)	XXX.X (XX.X)	XX	XXX.X (XX.X)	XX

Treatment A: 237 mg TU Administered BID Under Fasting Condition for Breakfast
Treatment B: 237 mg TU Administered BID with 15 g fat for Breakfast
Treatment C: 237 mg TU Administered BID with 30 g fat for Breakfast
Treatment D: 237 mg TU Administered BID with 45 g fat for Breakfast
Treatment E: 237 mg TU Administered BID with FDA High-Calorie, High-fat for Breakfast
n = Number of observations used in the analysis.
Tmax0-12 and Tmax12-24 are presented as Median (Minimum, Maximum).
AUC, Cmax and Cavg are presented as Geometric Mean (GM) and Geometric Coefficient of Variation % (GCV%)
Source: Tables 14.2.1.2.1 through to 14.2.1.2.5, (Table 11-1)Tables 14.2.1.2.6 through to 14.2.1.2.10 (Table 11-7), and Tables 14.2.1.2.11 through to 14.2.1.2.15 (Table 11-9)
Program: /CAXXXXX/sas_prg/pksas/programname.sas DDMMMYYYY HH:MM

Notes for Generating the Actual Table:

Presentation of Data:
Note: ask PKist which subjects to exclude (subjects that did not eat all the fat-containing items of their meal are not part of the PK Evaluable Population)

- The following PK parameters will be presented in Table 11-1,11-5, and 11-6: AUCam (unit), AUCpm (unit), AUC24 (unit), Cmax-am (unit), Cmax-pm (unit), Cmax-24 (unit), Tmax-am (hr), Tmax-pm (hr), Cavg-am (unit), Cavg-pm(unit), and Cavg-24 (unit).
- There will be two columns (GM (GVC%) and n) per Treatment (only 2 in example above; however, there are 5 treatments). The five treatments are as follows:
  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
- n will be presented as an integer (with no decimal).
- Summary statistics will be presented with same precision as defined in post-text shells
- Please use Table ITPar1 internal template.

Program: /CAXXXXX/sas_prg/pksas/adam_intext_pkparam.sas DDMMMYYYY HH:MM

Tables 11-2 through 11-6 and Tables 11-8, and11-10 will be in the following format:

Table 11-X Statistical Comparisons of Plasma Total T Pharmacokinetic Parameters: Treatments <>, <> <> and <> Versus Treatment <> (Reference) (PK Evaluable Population)

Pharmacokinetic Parameters	Treatment A		Treatment B		Treatment C		Treatment D		Treatment E		Intra-Subject CV%
	n	Geometric LSMs	n	Geometric LSMs	n	Geometric LSMs	n	Geometric LSMs	n	Geometric LSMs	
Param 1 (units)	XX	XXX.X	XX	XXX.X	XX	XXX.X	XX	XXX.X	XX	XXX.X	X.XX
Param 2 (units)	XX	XXX.X	XX	XXX.X	XX	XXX.X	XX	XXX.X	XX	XXX.X	X.XX
Param 3 (units)	XX	XXX.X	XX	XXX.X	XX	XXX.X	XX	XXX.X	XX	XXX.X	X.XX

Pharmacokinetic Parameters	Treatment <>/Treatment <>		Treatment <>/Treatment <>		Treatment <>/Treatment <>		Treatment <>/Treatment <>	
	GMR	90% CI	GMR	90% CI	GMR	90% CI	GMR	90% CI
Param 1 (units)	X.XX	X.XX, X.XX	X.XX	X.XX, X.XX	X.XX	X.XX, X.XX	X.XX	X.XX, X.XX
Param 2 (units)	X.XX	X.XX, X.XX	X.XX	X.XX, X.XX	X.XX	X.XX, X.XX	X.XX	X.XX, X.XX
Param 3 (units)	X.XX	X.XX, X.XX	X.XX	X.XX, X.XX	X.XX	X.XX, X.XX	X.XX	X.XX, X.XX

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

Geometric least-squares means (LSMs) are calculated by exponentiating the LSMs derived from the linear mixed-effects model.
Geometric mean ratio (GMR) = 100 x (test/reference)
Intra-subject CV% was calculated as 100 x square root (exp[residual variance]-1).
n = Number of observations used in the analysis.1

Notes for Generating the Actual Table:

Presentation of Data:
Note: ask PKist which subjects to exclude (subjects that did not eat all the fat-containing items of their meal are not part of the PK Evaluable Population)

- The following PK parameters will be presented in Tables 11-2, 11-3, and 11-4: **(C_{max-am}, AUC_{am}, and C_{avg-am}).**
- The following PK parameters will be presented in Tables 11-7, 11-8, and 11-9: **(C_{max-pm}, AUC_{pm}, C_{avg-pm}, C_{max24}, AUC_{24}, and C_{avg-24})**
- n will be presented as an integer (with no decimal);
- All statistics will be presented with same precision as defined in post-text shells
- Treatments for each table, and source tables are the following:
  - Table 11-2: source table 14.2.1.3.1-4
  - Table 11-3: source table 14.2.1.3.5-8
  - Table 11-4: source table 14.2.1.3.9-12
  - Table 11-5: source table 14.2.1.3.13-16
  - Table 11-6: source table 14.2.1.3.17-20
  - Table 11-8: source table 14.2.1.3.21-24
  - Table 11-10: source table 14.2.1.3.25-8
  - Table 11-11: source table 14.2.1.4.1-4
- Please add the respective treatment descriptions for each table, as relevant, from the following:
  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

Programmer's note:

- Please use Table ITPStat1 internal template.
- No changes are made to this table relative to Celerion standard.

Program: /CAXXXXX/sas_prg/pksas/adam_intext_pkparam.sas DDMMMYYYY HH:MM

Table 12-1 Incidence of Treatment-Emergent Adverse Events by Phase

Adverse Events*	Run-In and PK Phase	Follow-Up Phase	Overall
Number of Subjects Enrolled and Randomized	X (100%)	X (100%)	X (100%)
Number of Subjects Dosed	X (100%)	X (100%)	X (100%)
Number of Subjects With Adverse Events	X (XX%)	X (XX%)	X (XX%)
Number of Subjects Without Adverse Events	X (XX%)	X (XX%)	X (XX%)
General disorders and administration site conditions	X (XX%)	X (XX%)	X (XX%)
Vessel puncture site pain	X (XX%)	X (XX%)	X (XX%)
Vessel puncture site reaction	X (XX%)	X (XX%)	X (XX%)

*Adverse events are classified according to MedDRA® Version 15.1
Although a subject may have had 2 or more clinical adverse experiences, the subject is counted only once within a category. The same subject may appear in different categories.

Source: Table 14.3.1.1
Program: /CAXXXXX/sas_prg/stsas/intexttest/t_ae.sas DDMMMYYYY HH:MM

Post-text TFLs will be as follows:

Part 1 of X

Table 14.1.1 Summary of Disposition

Disposition	Overall
Enrolled and Randomized	XX (XX.X%)
Dosed	XX (100%)
Completed Study	XX (XX.X%)
Discontinued Early	XX (XX.X%)
<Reason>	XX (XX.X%)

Program: /CAXXXXX/sas_prg/stsas/tab_PROGRAMNAME.sas DDMMMYYYY HH:MM

Table 14.1.2 Disposition of Subjects

Subject Number	Dosed For PK Phase Period 1	2	3	4	5	Study Completion Status	Date
X	Yes	No	No	No	No	Terminated Study Prematurely	DDMMMYYYY
X	Yes	Yes	Yes	Yes	Yes	Completed Study	DDMMNYYYY
X	Yes	Yes	Yes	Yes	Yes	Completed Study	DDMMMYYYY
X	Yes	Yes	Yes	Yes	Yes	Completed Study	DDMMMYYYY
X	Yes	Yes	Yes	Yes	Yes	Completed Study	DDMMMYYYY
X	Yes	Yes	Yes	Yes	Yes	Completed Study	DDMMMYYYY
X	Yes	Yes	Yes	Yes	Yes	Completed Study	DDMMMYYYY
X	Yes	Yes	Yes	Yes	Yes	Completed Study	DDMMMYYYY
X	Yes	Yes	Yes	Yes	Yes	Completed Study	DDMMMYYYY
X	Yes	Yes	Yes	Yes	Yes	Completed Study	DDMMMYYYY
	XX	XX	XX	XX	XX		

Program: /CAXXXXX/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM

Table 14.1.3 Demographic Summary

Trait		Overall
Gender	Male	X (XX.X%)
Race	XXXXXXXXXXXXXXX	X (XX.X%)
Ethnicity	XXXXXXXXXXXXXXX	X (XX.X%)
Age* (yrs)	n	X
	Mean	X.X
	SD	X.XX
	Minimum	XX
	Median	X.X
	Maximum	XX
Weight (kg)	n	X
	Mean	X.X
	SD	X.XX
	Minimum	XX
	Median	X.X
	Maximum	XX

<Continued with other measures – height, BMI, PSA, I-PSS, I-PSS-QOL>

Note: * Age is calculated from informed consent date.

Program: /CAXXXXX/sas_prg/stsas/tab_PROGRAMNAME.sas DDMMMYYYY HH:MM

Tables 14.2.1.1.1-15 will be formatted as:

Page X of X

Table 14.2.1.1.X Plasma Total <> Concentrations (unit) Following <> Treatment <> (PK Population)

Subject Number	Treatment Sequence	Study Period	Sample Times (hr) Predose	XX	XX	XX	XX	XX	XX	XX	XX
XXX-XXX	XXX	X	BLQ	XX	XX	XX	XX	XX	XX	XX	XX
XXX-XXX	XXX	X	BLQ	XX	XX	XX	XX	XX	XX	XX	XX
XXX-XXX	XXX	X	BLQ	XX	XX	XX	XX	XX	XX	XX	XX
n			XX	XX	XX	XX	XX	XX	XX	XX	XX
Mean			XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X
SD			XX.XX	XX.XX	XX.XX	XX.XX	XX.XX	XX.XX	XX.XX	XX.XX	XX.XX
CV%			.	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X
SEM			XX.XX	XX.XX	XX.XX	XX.XX	XX.XX	XX.XX	XX.XX	XX.XX	XX.XX
Minimum			XX	XX	XX	XX	XX	XX	XX	XX	XX
Median			XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X
Maximum			XX	XX	XX	XX	XX	XX	XX	XX	XX

For the calculation of summary statistics, values that are below the limit of quantitation (BLQ) of <XX> are treated as <0> before the first quantifiable concentration and as missing elsewhere.
. = Value missing or not reportable.

Notes for Generating the Actual Table:

Presentation of Data:

- Concentrations will be presented to same precision as in bio data.
- Summary statistics presentation with respect to the precision of the bio data: n = integer; Mean, Median+1; SD and SEM +2, Min and Max +0, and CV% to 1 decimal
- Tables 14.2.1.1.1 to 14.2.1.1.5 will present Total T concentrations (ng/dL); Tables 14.2.1.1.6 to 14.2.1.1.10 will present DHT concentrations (ng/dL) and Tables 14.2.1.1.11 to 14.2.1.1.15 will present TU concentration (ng/mL).

Programmer Note:

- PK Time points are 0 (predose), 2, 4, 6, 9, 12, 14, 16, 18, 21 and 24 hours post-AM dose. 24 hour time points for PK Period 1, 2,3 and 4 are the same as 0 for PK Period 2,3, 4 and 5.
- Please add the following footnote since sequence will contain these abbreviations:

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

Program: /CAXXXXX/sas_prg/pksas/pk-conc-tables.sas DDMMMYYYY HH:MM
Program: /CAXXXXX/sas_prg/pksas/pk-conc-tables-sig.sas DDMMMYYYY HH:MM

Tables 14.2.1.2.1 through to 14.2.1.2.15 will be formatted as:

Table 14.2.1.2.X Plasma Total T Pharmacokinetic Parameters Following <> Treatment <> (PK Evaluable Population)

Subject Number	Treatment Sequence	Study Period	Parameters: param1 (units)	param2 (units)	param3 (units)	param4 (units)	param5 (units)	param6 (units)
XXX-XXX	XXX	X	XXX	X.XX	XXX	XXX	XX.X	X.XXX
XXX-XXX	XXX	X	XX.X	X.XX	XXX	XXX	XX.X	X.XXX
XXX-XXX	XXX	X	XXX	X.XX	XXX	XXX	XX.X	X.XXX
XXX-XXX	XXX	X	XX.X	X.XX	XXX	XXX	XX.X	X.XXX
XXX-XXX	XXX	X	XX.X	X.XX	XXX	XXX	XX.X	X.XXX
XXX-XXX	XXX	X	X.XX	X.XX	XXX	XXX	XX.X	X.XXX
XXX-XXX	XXX	X	XXX	X.XX	XXX	XXX	XX.X	X.XXX
n			XX	XX	XX	XX	XX	XX
Mean			XXX.X	X.XXX	XXX.X	XXX.X	XX.XX	X.XXXX
SD			XX.XX	XX.XX	XX.XX	XX.XX	XX.XX	XX.XX
CV%			.	XX.X	XX.X	XX.X	XX.X	XX.X
SEM			XX.XX	XX.XX	XX.XX	XX.XX	XX.XX	XX.XX
Minimum			XX.X	X.XX	XXX	XXX	XX.X	X.XXX
Median			XX.XX	X.XXX	XXX.X	XXX.X	XX.XX	X.XXXX
Maximum			XXX	X.XX	XXX	XXX	XX.X	X.XXX
Geom Mean			XXX.X	X.XXX	XXX.X	XXX.X	XX.XX	X.XXXX
Geom CV%			XX.X	XX.X	XX.X	XX.X	XX.X	XX.X

. = Value missing or not reportable.

Notes for Generating the Actual Table:

Presentation of Data:

Note: ask PKist which subjects to exclude (subjects that did not eat all the fat-containing items of their meal are not part of the PK Evaluable Population)

- PK Parameters will be presented in the following order: AUC0-12 (unit), AUC12-24 (unit), AUC24 (unit), Cmax0-12 (unit), Cmax12-24 (unit), Cmax24 (unit), Tmax0-12 (hr), Tmax12-24 (hr), Cavg0-12 (unit), Cavg12-24(unit), and Cavg0-24 (unit)..
- Please add the following footer:
  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
- n will be presented as an integer (with no decimal);
- Parameter values for exposure based parameters (i.e. AUCs, Cmax, Cavg) will be presented with 3 significant figures.
- Summary statistics for exposure parameters will be presented as: Mean, Median, Geom Mean +1; SD and SEM +2, Min and Max +0.
- Values for Tmax and its summary statistics of Mean, SD, SEM, Minimum, Median, Maximum and Geom Mean, will be presented
- CV% and Geom CV% for all parameters will be presented with 1 decimal

Program: **/CAXXXXX/sas_prg/pksas/**pk-tables.sas DDMMMYYYY HH:MM
Program: **/CAXXXXX/sas_prg/pksas/**adam_pkparam.sas DDMMMYYYY HH:MM

Tables 14.2.1.3.1 through to 14.2.1.3.28 and Tables 14.2.1.4.1-4 will have the following format:

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Table 14.2.1.3.X Statistical Comparisons of Plasma Total T Pharmacokinetic Parameters: Treatment <> (Test) Versus Treatment <> (Reference) Conditions (PK Evaluable Population)

		Treatment ----- Geometric LSMs -----				Geometric Mean	Confidence Intervals	Intra-subject
Parameter	(unit)	<>	(n)	<>	(n)	Ratio	(90% Confidence)	CV%
Param1	(unit)	X.XX	(n)	X.XX	(n)	X.XX	XX.XX - XXX.XX	X.XX
Param2	(unit)	X.XX	(n)	X.XX	(n)	X.XX	XX.XX - XXX.XX	X.XX
Param3	(unit)	X.XX	(n)	X.XX	(n)	X.XX	XX.XX - XXX.XX	X.XX

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

Parameters were ln-transformed prior to analysis.
Geometric least-squares means (LSMs) are calculated by exponentiating the LSMs from the linear mixed-effects model.
Geometric Mean Ratio = exp(test-reference)
Intra-subject CV (%CV) = 100 x square root(exp[MSE]-1)]
MSE = Residual variance from the linear mixed-effects model.
n = Number of observations used in the analysis.

Notes for Generating the Actual Table:

Presentation of Data:

- PK Parameters are:
  Tables 14.2.1.3.1-12: Cmax-am, AUCam, Cavg-am
  Tables 14.2.1.3.13-20: Cmax-pm, AUCpm, Cavg-pm, Cmax-24, and AUC24, Cavg-24
  Tables 14.2.1.3.21-24: Cmax-am, AUCam, Cmax-pm, AUCpm, Cmax-24, and AUC24

```
    Tables 14.2.1.3.25-28:  Cmax-am, AUCam, Cmax-pm, AUCpm, Cmax-24, and AUC24
    Tables 14.2.1.4.1-4: Cmax-am, AUCam, Cavg-am
•   Geometric LSMs be presented to same precision as Mean in the PK parameter table CPPar1,
•   Geometric Mean Ratio, 90% CI and intra-subject CV% will be presented to 2 decimal places.
Program:  /CAXXXXX/sas_prg/pksas/stats-tables-mixed.sas     DDMMMYYYY  HH:MM
```

Table 14.3.1.1 Treatment-Emergent Adverse Event Frequency by Phase - Number of Subjects Reporting Events (% of Subjects Dosed)

Adverse Event*	Run-In and PK Phase	Follow-Up Phase	Total
Number Enrolled/ Randomized			
Number of Subjects Dosed	XX (XXX%)	XX (XXX%)	XX (XXX%)
Number of Subjects With TE Adverse Events	X (XX%)	X (XX%)	X (XX%)
Number of Subjects Without TE Adverse Events	XX (XX%)	XX (XX%)	XX (XX%)
Nervous system disorders	X (X%)	X (X%)	X (X%)
Dizziness	X (X%)	X (X%)	X (X%)
Headache	X (X%)	X (X%)	X (X%)
Presyncope	X (X%)	X (X%)	X (X%)
Respiratory, thoracic and mediastinal disorders	X (X%)	X (X%)	X (X%)
Dry throat	X (X%)	X (X%)	X (X%)
Oropharyngeal pain	X (X%)	X (X%)	X (X%)
Sinus congestion	X (X%)	X (X%)	X (X%)
Sneezing	X (X%)	X (X%)	X (X%)
General disorders and administration site conditions	X (X%)	X (X%)	X (X%)
Fatigue	X (X%)	X (X%)	X (X%)
Thirst	X (X%)	X (X%)	X (X%)

Note: * Adverse events are classified according to MedDRA Version 15.1.

Program: /CAXXXXX/sas_prg/stsas/tab_PROGRAMNAME.sas DDMMMYYYY HH:MM

Table 14.3.1.2 Treatment-Emergent Adverse Event Frequency by Phase - Number of Adverse Events (% of Total Adverse Events)

Adverse Event*	Run-In and PK Phase	Follow-Up Phase	Total
Number of Adverse Events	X (XXX%)	X (XXX%)	X (XXX%)
Nervous system disorders	X (X%)	X (X%)	X (X%)
Dizziness	X (X%)	X (X%)	X (X%)
Headache	X (X%)	X (X%)	X (X%)
Presyncope	X (X%)	X (X%)	X (X%)
Respiratory, thoracic and mediastinal disorders	X (X%)	X (X%)	X (X%)
Dry throat	X (X%)	X (X%)	X (X%)
Oropharyngeal pain	X (X%)	X (X%)	X (X%)
Sinus congestion	X (X%)	X (X%)	X (X%)
Sneezing	X (X%)	X (X%)	X (X%)
General disorders and administration site conditions	X (X%)	X (X%)	X (X%)
Fatigue	X (X%)	X (X%)	X (X%)
Thirst	X (X%)	X (X%)	X (X%)

Note: * Adverse events are classified according to MedDRA Version 15.1.

Program: /CAXXXXX/sas_prg/stsas/tab_PROGRAMNAME.sas DDMMMYYYY HH:MM

Table 14.3.1.3 Treatment-Emergent Adverse Event Frequency by Severity and Relationship to Drug
Number of Subjects Reporting Events

						Relationship to Study Drug				
		Number of Subjects with	Severity/Intensity			Definitely Not	Probably Not	Possibly	Probably	
Adverse Event*	Phase	Adverse Events	Mild	Moderate	Severe	Related	Related	Related	Related	Definitely
Dizziness	Run-In and PK	X	X	X	X	X	X	X	X	X
	Follow-Up	X	X	X	X	X	X	X	X	X
Dry eye	Follow-Up	X	X	X	X	X	X	X	X	X
Dry mouth	XXXXXXXXXXXX	X	X	X	X	X	X	X	X	X
Ear pain	XXXXXXXXXXXX	X	X	X	X	X	X	X	X	X
	XXXXXXXXXXXX	X	X	X	X	X	X	X	X	X
Fatigue	XXXXXXXXXXXX	X	X	X	X	X	X	X	X	X
Headache	XXXXXXXXXXXX	X	X	X	X	X	X	X	X	X
Hyperhidrosis	XXXXXXXXXXXX	X	X	X	X	X	X	X	X	X
Run-In and PK	XX	XX	X	X	X	X	X	X	X	X
Follow-UP	XX	XX	X	X	X	X	X	X	X	X
Overall	XX	XX	X	X	X	X	X	X	X	X

Note: * Adverse events are classified according to MedDRA Version 15.1
When a subject experienced the same AE at more than one level of severity during a treatment period, the AE with the maximum severity was counted. When a subject experienced the same AE at more than one level of drug relationship during a treatment period, the most related AE was counted.

Program: /CAXXXXX/sas_prg/stsas/tab_PROGRAMNAME.sas DDMMMYYYY HH:MM

Table 14.3.1.4 Treatment-Emergent Adverse Event Frequency by Severity and Relationship to Drug
Number of Adverse Events

Adverse Event*	Phase	Number of Subjects with Adverse Events	Severity/Intensity			Relationship to Study Drug				
			Mild	Moderate	Severe	Definitely Not Related	Probably Not Related	Possibly Related	Probably Related	Definitely
Dizziness	Run-In and PK	X	X	X	X	X	X	X	X	X
	Follow-Up	X	X	X	X	X	X	X	X	X
Dry eye	Follow-Up	X	X	X	X	X	X	X	X	X
Dry mouth	XXXXXXXXXXXX	X	X	X	X	X	X	X	X	X
Ear pain	XXXXXXXXXXXX	X	X	X	X	X	X	X	X	X
	XXXXXXXXXXXX	X	X	X	X	X	X	X	X	X
Fatigue	XXXXXXXXXXXX	X	X	X	X	X	X	X	X	X
Headache	XXXXXXXXXXXX	X	X	X	X	X	X	X	X	X
Hyperhidrosis	XXXXXXXXXXXX	X	X	X	X	X	X	X	X	X
Run-In and PK	XX	XX	X	X	X	X	X	X	X	X
Follow-UP	XX	XX	X	X	X	X	X	X	X	X
Overall	XX	XX	X	X	X	X	X	X	X	X

Note: * Adverse events are classified according to MedDRA Version 15.1

Program: /AAXXXXX/sas_prg/stsas/tab_PROGRAMNAME.sas DDMMMYYYY HH:MM

Tables 14.3.2.1 through 14.3.2.3 will have the following format.

Table 14.3.2.1 Serious Adverse Event

Subject Number	Dosing Day	TE?^	Adverse Event* >Preferred Term >>System Organ Class	Onset Date	Onset Time	Frequency	Severity/ Intensity	Serious	Outcome	Action Taken	Relationship to Study Drug
X	1	Yes	XXXXXXXXXXXXX >XXXXXXXXXXXXX >>XXXXXXXXXXXXXXXXX	DDMMMYYYY	X:XX	Intermittent	Severe	Is life threatening	Unchanged	XXXXXX	XXXXXXXXX

Programmer Note: *if there are no SAEs reported, this table will just show the statement that "No serious adverse event is reported.".*

Note: * Adverse events are classified according to MedDRA Version 15.1.

Program : /CAXXXXX/ECR/sas_prg/stsas/tab/PROGRAMNAME.sas DDMMMYYYY HH:MM

Tables 14.3.4.1 through 14.3.4.3 will have the following format.

Page 1 of X

Table 14.3.4.1 Out-of-Range Values and Recheck Results - Chemistry

Subject Number	Age#	Study Phase	Day	Date	Parameter	Units	Normal Range	Test Value	PI Interpretation
XXX-XXX	XX	Screen		DDMMMYYYY	XXXXX	XXXX	XX-XX	XXXXX	Not clinically significant
		X	XX	DDMMMYYYY	XXXXX	XXXX	XX-XX	XXXXX	XXXXXXXXXXXXXXXXXXXXXXXXX

Programmer Note: Replace Parameter with actual lab tests in the study.

Note: # Age is calculated from the date of informed consent.

Program: /CAXXXXX/sas_prg/stsas/tab_PROGRAMNAME.sas DDMMMYYYY HH:MM

Tables 14.3.5.1 through 14.3.5.3 will have the following format.

Table 14.3.5.1 Clinical Laboratory Summary and Change From Baseline - Chemistry

Laboratory Test (units)	Study Phase	Day	Statistic		Change From Baseline
Calcium (mg/dL)	Screening 1		n	XX	
			Mean	X.XX	
			SD	X.XXX	
			Minimum	X.X	
			Median	X.XX	
			Maximum	XX.X	
	Run-In Phase	1	n	XX	XX
			Mean	X.XX	X.XX
			SD	X.XXX	X.XXX
			Minimum	X.X	X.X
			Median	X.XX	X.XX
			Maximum	XX.X	XX.X
	PK Phase	1	n	XX	XX
			Mean	X.XX	X.XX
			SD	X.XXX	X.XXX
			Minimum	X.X	X.X
			Median	X.XX	X.XX
			Maximum	XX.X	XX.X

Programmer Note: Laboratory tests will be performed at Run-In Phase Day 1, PK Phase Day 1, following the 24-hour PK blood draw on PK Phase Day 6, and 5 to 7 days post last dose during the Safety Follow-Up Phase, if the subject needed to return to the clinic for an in person visit, or at Early Termination from the study. Screening 1 values will serve as baseline. Subjects will only return for clinical lab assessment during the Safety Follow-up Phase if there is a specific need. Therefore, clinical labs will not be summarized for the Safety Follow-up visit.

Note: Refer to Appendix 16.1.10.1 for normal ranges for the laboratory tests.

Program: /AAXXXXX/sas_prg/stsas/tab_PROGRAMNAME.sas DDMMMYYYY HH:MM

Table 14.3.5.4 Vital Sign Summary

Measurement (units)	Study Phase	Day	Statistic	
Systolic Blood Pressure (mmHg)	Screening 1		n	XX
			Mean	X.XX
			SD	X.XXX
			Minimum	X.X
			Median	X.XX
			Maximum	XX.X
	Run-In Phase	1	n	XX
			Mean	X.XX
			SD	X.XXX
			Minimum	X.X
			Median	X.XX
			Maximum	XX.X
	PK Phase	1	n	XX
			Mean	X.XX
			SD	X.XXX
			Minimum	X.X
			Median	X.XX
			Maximum	XX.X

Programmer Note: Blood pressure and heart rate will be measured at Screening 1, Run-In Phase Day 1, and prior to dosing during the PK Phase on Days 1, 2, 3, 4, 5, and 6, and 5 to 7 days post last dose during the Safety Follow-Up Phase, if a clinical visit is required for the safety follow up, or at Early Termination. Respiration rate and temperature will be measured only at Screening 1 and Early Termination. Therefore, no post-dose summaries will be provided for respiration and temperature. Subjects will only return for vital signs assessment during the Safety Follow-up Phase if there is a specific need. Therefore, vital signs will not be summarized for the Safety Follow-up visit.

Program: /AAXXXXX/sas_prg/stsas/tab_PROGRAMNAME.sas DDMMMYYYY HH:MM

Table 14.3.5.5 Vital Sign Change From Baseline

Measurement (units)	Statistic	Change From Baseline*						
		Run-In Day 1	PK Phase Day 1	PK Phase Day 2	PK Phase Day 3	PK Phase Day 4	PK Phase Day 5	PK Phase Day 6
Systolic Blood Pressure (mmHg)	n	XX	XX	XX	XX	XX	XX	XX
	Mean	X.XX	X.XX	X.XX	X.XX	X.XX	X.XX	X.XX
	SD	X.XXX	X.XXX	X.XXX	X.XXX	X.XXX	X.XXX	X.XXX
	Minimum	X.X	X.X	X.X	X.X	X.X	X.X	X.X
	Median	X.XX	X.XX	X.XX	X.XX	X.XX	X.XX	X.XX
	Maximum	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X

Programmer Note: Blood pressure and heart rate will be measured at Screening 1, Run-In Phase Day 1, and prior to dosing during the PK Phase on Days 1, 2, 3, 4, 5, and 6, and 5 to 7 days post last dose during the Safety Follow-Up Phase, if a clinical visit is required for the safety follow up, or at Early Termination. Respiration rate and temperature will be measured only at Screening 1 and Early Termination. Therefore, no post-dose summaries will be provided for respiration and temperature. Subjects will only return for vital signs assessment during the Safety Follow-up Phase if there is a specific need. Therefore, change from baseline will not be calculated for the Safety Follow-up visit.

Note: * Baseline is the average of the triplicate values, including rechecks, measured at Predose Day 1 of the Run-In Phase

Program: /AAXXXXX/sas_prg/stsas/tab_PROGRAMNAME.sas DDMMMYYYY HH:MM

10. LISTING SHELLS

The following listing shells provide a framework for the display of data from this study. The shells may change due to unforeseen circumstances. These shells may not be reflective of every aspect of this study, but are intended to show the general layout of the listings that will be presented and included in the final report.

Appendix 16.1.10.1 Clinical Laboratory Reference Ranges

Laboratory Group	Test Name	Gender	Age Category	Normal Range	Unit
Chemistry	Test Name	XXXXXX	XX	XX – XX	units
	Test Name	XXXXXX	XX	XX – XX	units
	Test Name	XXXXXX	XX	XX – XX	units
	Test Name	XXXXXX	XX	XX – XX	units
	Test Name	XXXXXX	XX	XX – XX	units
	Test Name	XXXXXX	XX	XX – XX	units
Hematology	Test Name	XXXXXX	XX	XX – XX	units
	Test Name	XXXXXX	XX	XX – XX	units
	Test Name	XXXXXX	XX	XX – XX	units
	Test Name	XXXXXX	XX	XX – XX	units
	Test Name	XXXXXX	XX	XX – XX	units

Note to Programmer: Two labs were used in this study so please prepare a separate set of reference ranges for each lab.

<similar for remaining Laboratory Groups and Test Names>

Program: /CAXXXXX/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM

Appendix 16.2.1 Subject Disposition

Site-Subject Number	Study Phase	Date	Completed Study?	Reason for Discontinuation
XXX-XXX	Post	DDMMMYYYY	No	Personal Reason
XXX-XXX	Post	DDMMMYYYY	Yes	
XXX-XXX	Post	DDMMMYYYY	Yes	
XXX-XXX	Post	DDMMMYYYY	Yes	
XXX-XXX	Post	DDMMMYYYY	Yes	
XXX-XXX	Post	DDMMMYYYY	Yes	
XXX-XXX	Post	DDMMMYYYY	Yes	
XXX-XXX	Post	DDMMMYYYY	Yes	

Program: /CAXXXXX/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM

Appendix 16.2.4.1 Demographics

Site-Subject Number	Date Of Birth	Age* (yrs)	Gender	Race	Ethnicity	Height (cm)	Weight (kg)	Body Mass Index (kg/m^2)	PSA	I-PSS Score	I-PSS QOL Score	Informed Consent Date
XXX-XXX	DDMMMYYYY	XX	Male	AAAAAAAA	AAAAAAAAAA	XXX	XX.XX	XX.XX	XX.X	XX.XX	X	DDMMMYYYY
XXX-XXX	DDMMMYYYY	XX	Male	AAAAAAAA	AAAAAAAAAA	XXX	XX.XX	XX.XX	XX.X	XX.XX	X	DDMMMYYYY
XXX-XXX	DDMMMYYYY	XX	Male	AAAAAAAA	AAAAAAAAAA	XXX	XX.XX	XX.XX	XX.X	XX.XX	X	DDMMMYYYY
XXX-XXX	DDMMMYYYY	XX	Male	AAAAAAAA	AAAAAAAAAA	XXX	XX.XX	XX.XX	XX.X	XX.XX	X	DDMMMYYYY
XXX-XXX	DDMMMYYYY	XX	Male	AAAAAAAA	AAAAAAAAAA	XXX	XX.XX	XX.XX	XX.X	XX.XX	X	DDMMMYYYY
XXX-XXX	DDMMMYYYY	XX	Male	AAAAAAAA	AAAAAAAAAA	XXX	XX.XX	XX.XX	XX.X	XX.XX	X	DDMMMYYYY
XXX-XXX	DDMMMYYYY	XX	Male	AAAAAAAA	AAAAAAAAAA	XXX	XX.XX	XX.XX	XX.X	XX.XX	X	DDMMMYYYY

Note: * Age will be calculated in years between date of birth and informed consent date.
PSA = Prostate specific antigen
I-PSS = International Prostate Symptom Score
QOL = Quality of Life Score

Program: /CAXXXXX/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM

Appendix 16.2.4.2.1 Physical Examination (I of II)

Site-Subject Number	Study Phase	Date	Was PE Performed?	HEENT	Skin/Mucosa	Chest	Lungs	Abdomen	Extremities
XXX-XXX	Screening 2	DDMMMYYYY	NA	NORMAL	ABNORMAL*	NORMAL	NORMAL	NORMAL	NORMAL
	Run-In, Day 1	DDMMMYYYY	Yes	UNCHANGED	UNCHANGED	CHANGED*	UNCHANGED	UNCHANGED	UNCHANGED
	PK Phase Day 6	DDMMMYYYY	Yes	UNCHANGED	UNCHANGED	UNCHANGED	UNCHANGED	UNCHANGED	UNCHANGED

Note: HEENT = Head, Eyes, Ears, Nose, Throat
* = See Appendix 16.2.4.2.3. Physical Examination Descriptions.

Program: /AAXXXXX/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM

Appendix 16.2.4.2.2 Physical Examination (II of II)

Site-Subject Number	Study Phase	Date	Was PE Performed?	Lymph Nodes	Neuro-logical	Musculo-skeletal	Urinary	Rectal	Other	Specify
XXX-XXX	Screening 2	DDMMMYYYY	NA	NORMAL	ABNORMAL*	NORMAL	NORMAL	NORMAL		
	Run-In Day 1	DDMMMYYYY	Yes	UNCHANGED	UNCHANGED	CHANGED*	UNCHANGED		NORMAL	XXXXXXXXXXXX
	PK Phase Day 6	DDMMMYYYY	Yes	UNCHANGED	UNCHANGED	UNCHANGED	UNCHANGED			

Note: * = See Appendix 16.2.4.2.3. Physical Examination Descriptions.

Program: /AAXXXXX/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM

Appendix 16.2.4.2.3 Physical Examination Descriptions

Site-Subject Number	Study Phase	Date	Result	System	Description or Comment
XXX-XXX	Screening 2	DDMMMYYYY	ABNORMAL	Skin	RIGHT CHEST SCAR-NCS
XXX-XXX	Screening 2	DDMMMYYYY	ABNORMAL	Skin	ABDOMINAL SCAR-NCS
XXX-XXX	Screening 2	DDMMMYYYY	ABNORMAL	Skin	ABDOMINAL SCAR-NCS
XXX-XXX	Screening 2	DDMMMYYYY	ABNORMAL	Skin	ABDOMINAL SCAR-NCS
XXX-XXX	Screening 2	DDMMMYYYY	ABNORMAL	Back	MILD SCOLIOSIS-NCS

Note: HEENT = Head, Eyes, Ears, Nose, Throat.
Program: /AAXXXXX/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM

Appendix 16.2.4.3 Medical and Surgical History

Site-Subject Number	Any History?	Date Start	Date End	Ongoing?	Description
XXX-XXX	YES	DDMMMYYYY		YES	XXXXXXX XXXXXX XXXXXXXX
		DDMMMYYYY	DDMMMYYYY	NO	XXXXXXX XXXXXX XXXXXXXX
XXX-XXX	YES	DDMMMYYYY	DDMMMYYYY	NO	XXXXXXX XXXXXX XXXXXXXX

Note: NA = Not Applicable

Program: /CAXXXXX/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM

Appendix 16.2.4.4 Testosterone Replacement Therapy - Screening

Site-Subject Number	Received Prior Therapy?	Medication	Date Start	Date End	Dose	Unit	Frequency	Route
XXX-XXX	Yes	XXXXXX XXXXX	DDMMMYYYY	DDMMMYYYY	XXXX	XXXX	XXXXX	Oral
XXX-XXX	No							

Program: /CAXXXXX/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM

Appendix 16.2.4.5 Hypogonadism Signs and Symptoms - Screening

Site-Subject Number	Date	Signs and Symptoms	Response
XXX-XXX	DDMMMYYY	Incomplete sexual development, eunochoidism	Yes
		Reduced sexual desire (libido) and activity	Yes
		Decreased spontaneous erections	Yes
		XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX	Yes

Note to programmer: There are 18 signs and symptoms to list for each subject in the CRF. But in this listing present only those which are responded to with YES.

Program: /CAXXXXX/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM

Appendix 16.2.4.6 International Prostate Symptom Score (I-PSS) and Quality of Life Due to Urinary Symptoms Score - Screening

Site-Subject Number	Date	Symptom	Score
XXX-XXX	DDMMMYYY	1. Over the past month, how often have you had a sensation of not emptying your bladder completely after you finished urinating?	X
		2. Over the past month, how often have you had to urinate again less than two hours after you finished urinating?	X
		3. Over the past month, how often have you found you stopped and started again several times when you urinated?	X
		4. Over the past month, how often have you found it difficult to postpone urination?	X
		5. Over the past month, how often have you had a weak urinary stream?	X
		6. Over the past month, how often have you had to push or strain to begin urination?	X
		7. Over the past month, how many times did you most typically get up to urinate from the time you went to bed at night until the time you got up in the morning?	X
		Total I-PSS Score	XX
		8. If you were to spend the rest of your life with your urinary condition just the way it is now, how would you feel about that?	X

Note: The Total I-PSS score is the sum of the first 7 questions.

Program: /CAXXXXX/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM

Appendix 16.2.5.2 Subject Eligibility

Site-Subject Number	Study Phase	Did subject meet all eligibility criteria?	Criterion Not Met*	Specify
XXX-XXX	Screening 1	Yes		
	Screening 2	No	EXCLUSION X	XXXXXXXXXXXXXXX XXXX
XXX-XXX	Screening 1	Yes		
	Screening 2	Yes		

Program: /CAXXXXX/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM

Appendix 16.2.5.3 Dosing - Run-In Phase Days 1 and 14

Site-Subject Number	Day	Time-point	Administered?	Date	Time	Compound
XXX-XXX	1	AM	Yes	DDMMMYYYY	HH:MM	XXXXXXXXX
	14	PM	Yes	DDMMMYYYY	HH:MM	XXXXXXXXX

Program: /CAXXXXX/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM

Appendix 16.2.5.4 Dose Accountability – Run-In Phase Days 1-14

Site-Subject Number	Day	Date	AM Time		PM Time		Capsules	
			Dosing	Meal	Dosing	Meal	Dispensed	Returned
XXX-XXX	1	DDMMMYYYY			HH:MM	HH:MM	XX	
	2	DDMMMYYYY	HH:MM	HH:MM	HH:MM	HH:MM		
	3	DDMMMYYYY	HH:MM	HH:MM	HH:MM	HH:MM		
	4	DDMMMYYYY	HH:MM	HH:MM	HH:MM	HH:MM		
	5	DDMMMYYYY	HH:MM	HH:MM	HH:MM	HH:MM		
	6	DDMMMYYYY	HH:MM	HH:MM	HH:MM	HH:MM		
	7	DDMMMYYYY	HH:MM	HH:MM	HH:MM	HH:MM		
	8	DDMMMYYYY	HH:MM	HH:MM	HH:MM	HH:MM		
	9	DDMMMYYYY	HH:MM	HH:MM	HH:MM	HH:MM		
	10	DDMMMYYYY	HH:MM	HH:MM	HH:MM	HH:MM		
	11	DDMMMYYYY	HH:MM	HH:MM	HH:MM	HH:MM		
	12	DDMMMYYYY	HH:MM	HH:MM	HH:MM	HH:MM		
	13	DDMMMYYYY	HH:MM	HH:MM	HH:MM	HH:MM		
	14	DDMMMYYYY	HH:MM	HH:MM				XX

Program: /CAXXXXX/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM

Appendix 16.2.5.5 Dosing – PK Phase

Site-Subject Number	Time-point	Dose Administered?	Date	Time	Compound
XXX-XXX	AM	Yes	DDMMMYYYY	HH:MM	XXXXXXXXX
	PM	Yes	DDMMMYYYY	HH:MM	XXXXXXXXX

Program: /CAXXXXX/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM

Appendix 16.2.5.6 Blood Draw Times

Site-Subject Number	Study Phase	Day	Hour	Date	Time	Bioassay	Comments
XXX-XXX	X	XX	-X.XX	DDMMMYYYY	XX:XX	XXXXXXXXXX	
			X.XX	DDMMMYYYY	XX:XX	XXXXXXXXXX	
			X.XX	DDMMMYYYY	XX:XX	XXXXXXXXXX	

Program: /CAXXXXX/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM

Appendix 16.2.5.7 Meal Times

Site-Subject Number	Study Phase	Day	Meal Plan	Event	Date	Start Time	Stop Time	Entire Mean Consumed?	Comments
XXX-XXX	PK Phase	X	X	Breakfast	DDMMMYYYY	XX:XX:XX	XX:XX:XX	Yes	
				Dinner	DDMMMYYYY	XX:XX:XX	XX:XX:XX	Yes	
			X	Breakfast	DDMMMYYYY	XX:XX:XX	XX:XX:XX	No	75%
				Dinner	DDMMMYYYY	XX:XX:XX	XX:XX:XX	Yes	
			X	Breakfast	DDMMMYYYY	XX:XX:XX	XX:XX:XX	Yes	
				Dinner	DDMMMYYYY	XX:XX:XX	XX:XX:XX	Yes	

Note to Programmer: If the subject received Meal Plan A (fasting for breakfast) the Start Time, Stop Time, and Entire Mean Consumed? will be blank.

Meal Plan
A: Fasting condition for breakfast
B: 15 g fat breakfast
C: 30 g fat breakfast
D: 45 g fat breakfast
E: FDA high-calorie, high-fat breakfast

Program: /CAXXXXX/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM

Appendix 16.2.5.8.1 Prior Medications

Site-Subject Number	Any Med?	Medication (WHO* Term)	Indication	Dose	Unit	Route	Frequency	Start Date	Start Time	Stop Time	Stop Date	Continuing?
XXX-XXX	No	None										
XXX-XXX	Yes	ACETAMINOPHEN (ACETAMINOPHEN)	Toothache	620	MG	ORAL	Once	DDMMMYYYY	HH:MM	DDMMMYYYY	HH:MM	No

Note: Prior medications include any medication begun prior to first dose of study medication.
Prior medications are coded with the WHO Dictionary Version SEP2012

Program: /AAXXXXX/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM

Appendix 16.2.5.8.2 Concomitant Medications

Site-Subject Number	Any Med?	Medication (WHO* Term)	Indication	Associated AE Number	Dose	Unit	Route	Frequency	Start Date	Start Time	Stop Time	Stop Date	Continuing Medication?
XXX-XXX	No	None											
XXX-XXX	Yes	ACETAMINOPHEN (ACETAMINOPHEN)	Toothache	XXXXXXXXX	620	MG	ORAL	Once	DDMMMYYYY	HH:MM	DDMMMYYYY	HH:MM	No

Note: Concomitant medications are coded with the WHO Dictionary Version SEP2012

Program: /AAXXXXX/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM

Appendix 16.2.7.1 Adverse Events (I of II)

Site-Subject Number	Study Phase	Day	TE?^	Adverse Event*	Preferred Term	Time From Last Dose (DD:HH:MM)	Onset Date	Onset Time	Resolved Date	Resolved Time	Duration (DD:HH:MM)
XXX-XXX				None							
	X	XX	Yes	XXXXXXXXXXXX	XXXXXXXXX XXXXXXX	XX:XX:XX	DDMMMYYYY	X:XX	DDMMMYYYY	X:XX	XX:XX:XX

Note: ^ = Abbreviation for treatment-emergent. An AE is considered treatment-emergent if it begins or worsens in severity after the first dose of the study drug.
* = Adverse events are classified according to MedDRA Version 15.1.

Program: /AAXXXXX/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM

Appendix 16.2.7.2 Adverse Events (II of II)

Site-Subject Number	Study Phase	Day	Adverse Event	Onset Date	Onset Time	Frequency	Severity	Serious	Outcome	Relationship to Study Drug	Action Taken
XXX-XXX			None								
	X	XX	XXXXXXXXXXXXXXXXX	DDMMMYYYY	XX:XX	Intermittent	Mild	Yes/No	Resolved	XXXXXXXX	None

Note: ^ = Abbreviation for treatment-emergent. An AE is considered treatment-emergent if it begins or worsens in severity after the first dose of the study drug.
* = Adverse events are classified according to MedDRA Version 15.1.

Program: /CAXXXXX/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM

Appendices 16.2.8.1 to 16.2.8.3 will have the following format.

Appendix 16.2.8.1 Clinical Laboratory Report - Chemistry

Site-Subject Number	Age	Study Phase	Day	Date	Parameter1 < Range> (Unit)	Parameter2 < Range> (Unit)	Parameter3 < Range> (Unit)	Parameter4 < Range> (Unit)	Parameter5 < Range> (Unit)	Parameter6 < Range> (Unit)
XXX-XXX	XX	Screen		DDMMMYYYY	XX HN	XX	XX	XX	XX	XX
	XX	Post	XX	DDMMMYYYY	XX LY	XX	XX	XX	XX	XX

Programmer Note: Replace Parameter1, 2 etc. with actual lab tests in the study. Sort unscheduled assessment and early term chronologically with other scheduled assessments and rechecks. Recheck should be sorted with the scheduled timepoint the recheck is for.

Program: /AAXXXXX/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM

Appendix 16.2.8.4 Clinical Laboratory Report – Total Testosterone and DHT

Site-Subject Number	Age	Study Phase	Day	Date	Total Testosterone (Unit)	Dihydro-testosterone (Unit)
XXX-XXX	XX	Screening 1		DDMMMYYYY	XXX	
		Screening 2		DDMMMYYYY	XXX	
		Run-In	1	DDMMMYYYY	XXX	XXX

Programmer Note: Replace Parameter1, 2 etc. with actual lab tests in the study. Sort unscheduled assessment and early term chronologically with other scheduled assessments and rechecks. Recheck should be sorted with the scheduled timepoint the recheck is for.

Program: /AAXXXXX/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM

Appendix 16.2.8.5 Clinical Laboratory Report - Comments

Site-Subject Number	Study Phase	Day	Date	Department	Test	Result	Unit	Comment
XXX-XXX	X	XX	DDMMMYYYY	Serum Chemistry	Calcium	XXX	mg/dL	Not significant in the context of this study.

Program: /CAXXXXX/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM

Appendix 16.2.8.6 Vital Signs

Site-Subject Number	Study Phase	Day	Date	Time	Blood Pressure (mmHg) Arm	Blood Pressure (mmHg) Systolic/Diastolic	Heart rate (bpm)	Respiration (rpm)	Temperature (°C)	Height (cm)	Weight (kg)	BMI (kg/cm2)
XXX-XXX	Screening 1		DDMMMYYYY	XX:XX	Left	XXX/ XX	XX	XX	XX.X	XXX.X	XXX.X	XXX.X
			DDMMMYYYY	XX:XX	Left	XXX/ XX	XX					
			DDMMMYYYY	XX:XX	Left	XXX/ XX	XX					
	Run-In	1	DDMMMYYYY	XX:XX	Left	XXX/ XX	XX					
			DDMMMYYYY	XX:XX	Left	XXX/ XX	XX					
			DDMMMYYYY	XX:XX	Left	XXX/ XX	XX					
	PK Phase	1	DDMMMYYYY	XX:XX	XXXX	XXX/ XX	XX					
			DDMMMYYYY	XX:XX	XXXX	XXX/ XX	XX					
			DDMMMYYYY	XX:XX	XXXX	XXX/ XX	XX					

Programmer note: Sort unscheduled assessment and early term chronologically with other scheduled assessments.

Program: /CAXXXXX/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM

Appendix 16.2.8.7 Vital Signs – Average of Triplicate Values

Site-Subject Number	Study Phase	Day	Date	Time	Blood Pressure (mmHg) Arm	Blood Pressure (mmHg) Systolic/Diastolic	Heart rate (bpm)
XXX-XXX	Screening 1		DDMMMYYYY	XX:XX	Left	XXX/ XX	XX
	Run-In	1	DDMMMYYYY	XX:XX	Left	XXX/ XX	XX
	PK Phase	1	DDMMMYYYY	XX:XX	XXXX	XXX/ XX	XX
	PK Phase	2	DDMMMYYYY	XX:XX	XXXX	XXX/ XX	XX
	PK Phase	3	DDMMMYYYY	XX:XX	XXXX	XXX/ XX	XX
	PK Phase	4	DDMMMYYYY	XX:XX	XXXX	XXX/ XX	XX
	PK Phase	5	DDMMMYYYY	XX:XX	XXXX	XXX/ XX	XX
	PK Phase	6	DDMMMYYYY	XX:XX	XXXX	XXX/ XX	XX

Programmer note: Sort unscheduled assessment and early term chronologically with other scheduled assessments.

Program: /CAXXXXX/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM

Appendix 16.2.8.8 Phone Call – Safety Follow-Up Phase

Site-Subject Number	Date	Was phone call made?	Has subject experienced any clinically significant changes in health?	Comments
XXX-XXX	DDMMMYYY	No, subject returned for follow-up visit	Yes/No	

Program: /AAXXXXX/sas_prg/stsas/lis_PROGRAMNAME.sas DDMMMYYYY HH:MM

Appendix 16.2.8.9 Study Completion/Early Termination

Site-Subject Number	Subject Complete Study	Competion/ Discontinuation Date	Date of Last Dose	Reason
XXX-XXX	Yes	DDMMMYYYY	DDMMMYYYY	
XXX-XXX	No	DDMMMTTTT	DDMMMYYYY	XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX

Appendix 16.2.8.10 General Comments

Site-Subject Number	Any Comments?	Date	Page #	Comment
XXX-XXX	None			
XXX-XXX		DDMMMYYYY	XX	XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX
XXX-XXX		DDMMMYYYY	XX	XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX