CLINICAL STUDY PROTOCOL

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 Number:	CLAR-16015
IND Number	78,104
Investigational Product:	Testosterone Undecanoate
Phase:	Phase 2
Sponsor:	Clarus Therapeutics, Inc. 555 Skokie Blvd., Suite 340 Northbrook, IL 60062 United States
Contract Research Organization:	Celerion Applied Translational Medicine 621 Rose Street Lincoln, Nebraska 68502 United States
Protocol Date:	15 Sep 2016
Protocol Version:	Version 1.0

1 PROTOCOL APPROVAL SIGNATURES

Protocol Title: A Phase 2 Study of the Effect of Meals with Various Amounts of Fat Given Immediately After Dosing on the Pharmacokinetics of an Oral Testosterone Undecanoate in Hypogonadal Men

Protocol Number: CLAR-16015

This study will be conducted in compliance with the clinical study protocol (and amendments), International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guidelines for current Good Clinical Practice and applicable regulatory requirements.

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2 STUDY INFORMATION

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3 SYNOPSIS

Sponsor: Clarus Therapeutics, Inc.	**Protocol No**.: CLAR-16015
Study Drug Name: Testosterone Undecanoate Oral Capsule	**Phase of Development**: Phase 2
Active Ingredient: Testosterone Undecanoate	**Date of Protocol Synopsis**: 15 September 2016
Protocol Title: A Phase 2 Study of the Effect of Meals with Various Amounts of Fat Given Immediately After Dosing on the Pharmacokinetics of an Oral Testosterone Undecanoate	
Objectives: **Primary Objective**: • The objective of the study is to determine the effect of meals (breakfast) containing various amounts of fat on the pharmacokinetics of Clarus's formulation of oral TU at a dose of 237 mg TU (the highest strength capsule being developed by Clarus). **Safety Objective**: • To characterize the safety and tolerability of oral TU when consumed with various meals.	
Study Sites: Two centers in the United States	
Study Population: Hypogonadal men aged 18 to 65 years (inclusive), and legally able to give informed consent, as applicable by law.	
Number of Subjects: Approximately 20 subjects.	
Methodology: This is a Phase 2, open-label, randomized, cross over, pharmacokinetic study. Subjects will initially be dosed for 2 weeks (Run-In Phase) to allow suppression of endogenous testosterone production, while allowing the oral TU to reach steady state. The subjects will then be confined to a clinical unit in which they undergo the PK Phase of the study. During the PK Phase of the study, subjects will undergo a five-period cross-over in which oral TU is dosed twice daily. Subjects will dose in the morning and in the evening immediately prior to protocol-defined meals. The protocol-defined breakfasts will contain various levels of fat including 15 g, 30 g, 45 g, a breakfast consistent with the fat and calorie content of the high-fat breakfast consistent with recommendations in the Guidance for Industry on Food-Effect Bioavailability and Fed Bioequivalence Studies (December 2002), or while fasting (with no meal until 4 hours post-dose). Subjects will be randomized to a designated sequence of the protocol-defined breakfasts, or the fasted state. The subjects will be required to consume the entire breakfast within 20 minutes during the PK Phase. The protocol-defined evening meal will be required to be consumed within 20 minutes. The 5 meal periods will occur on sequential days. Approximately twenty (20) subjects will be enrolled in order to ensure completion of 16 subjects.	

Main Criteria for Inclusion/Exclusion

Main Inclusion Criteria

The main inclusion criteria include:

- **S**ubject must be a man 18 to 65 years of age, inclusive and legally able to give informed consent, as applicable by law, with a clinical diagnosis of hypogonadism (signs/symptoms consistent with hypogonadism for testosterone naïve subjects and history of signs/symptoms for subjects who have received prior treatment) and 2 morning total T values of <300 ng/dL (between 6:00 and 10:00 AM drawn on 2 separate days [approximately 7±2 days apart]).
- Subject must have adequate venous access in the left or right arm to allow collection of a number of blood samples via a venous cannula.
- Subject must be naïve to androgen-replacement therapy **or** washed out of prior androgen replacement therapies (wash out durations specified in exclusion criterion 1); that is, be willing to cease current T treatment, or currently not be taking T treatment.
- Subject on replacement therapy for hypopituitarism or multiple endocrine deficiencies must be on stable doses of thyroid hormone and adrenal replacement hormones for at least 14 days before Screen 1.
- Subject must be willing to eat entire protocol defined breakfasts and dinners.

Main Exclusion Criteria

Subject will be excluded if 1 or more of the main exclusion is applicable:

- Received oral topical (eg, gel or patch), intranasal, or buccal T therapy within the previous 2 weeks, intramuscular T injection of short-acting duration (eg, T enanthate, T cypionate) within the previous 4 weeks, intramuscular T injection of long-acting duration (eg, AVEED®) within the previous 20 weeks, or T implantable pellets (Testopel®) within the previous 6 months.
- Has an intercurrent disease deemed clinically significant in the opinion of the investigator of any type; in particular, liver, kidney, uncontrolled or poorly controlled heart disease, including hypertension, congestive heart failure or coronary heart disease, or psychiatric-illness, including severe depression.
- Has had a recent (within 2 years) history of stroke, transient ischemic attack, or acute coronary event.
- Has had a recent (within 2 years) history of angina or stent (coronary or carotid) placement.
- Has a mean of the triplicate assessments of systolic BP (sBP) > 150 mm Hg and/or diastolic BP (dBP) > 90 mm Hg at screening (if prescribed antihypertensives, subject should be taking medications on the day of the screening visit with a sip of water). Subjects < 60 years of age and prescribed antihypertensives will be excluded if the mean of the triplicate assessment of sBP > 140 mm Hg and/or dBP > 90 mm Hg at screening.
- If receiving antihypertensive medications, has been on a stable dose for < 3 months.
- Has an abnormal prostate DRE (palpable nodules), elevated PSA (serum PSA > 4.0 ng/mL), International Prostate Symptom Score (I-PSS) > 19 points at screening, and/or history of, or current or suspected, prostate cancer.
- Has a history of, or current or suspected breast cancer.
- Current use of the following groups of drugs that affect T levels, T metabolism or levels of T metabolites, namely antiandrogens, 5 alpha reductase inhibitors (eg, dutasteride, finasteride), estrogens, long-acting opioid analgesics (eg, methadone hydrochloride, buprenorphine hydrochloride) or human growth hormone (HGH).

Investigational Product: Testosterone Undecanoate Oral Capsule

Doses: During the Run In phase, the dose will be 237 mg TU BID (approximately 12 hours apart) with breakfast and dinner meals. During the PK Phase, the dose will be 237 mg BID immediately prior to the protocol defined breakfast (or fasting) and protocol defined dinner. The 237 mg dose is a soft-gel capsule which is the largest dose strength being developed.

Administration Route: Oral

Duration of Study Participation:

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.

Endpoints:

Pharmacokinetic Endpoint:

The testosterone pharmacokinetics associated with each breakfast diet (fasting, 15 g fat, 30 g fat, 45 g fat and a high fat meal) will be evaluated using non-compartmental pharmacokinetic analysis. The parameters C_{max}, T_{max}, AUC_{12} and C_{avg} will be derived using the assay results for total T. The concentrations and pharmacokinetic parameters for the individuals will be listed, along with descriptive statistics. 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. Comparisons will be made between the C_{max} and AUC_{12} and C_{avg} values obtained for each treatment, after log transformations. The 30 g fat breakfast treatment ("normal" fat content for the US population) will serve as the reference treatment in the comparisons to identify the effects of the different meals on the relative bioavailability of T.

Safety Endpoints:

Treatment emergent adverse events

Pharmacokinetic Variables:

Pharmacokinetic variables to be calculated include total T C_{max}, time to maximum concentration (T_{max}), area under the plasma concentration time-curve over the post-breakfast dosing interval (AUC_{12}) and C_{avg} over the dosing interval.

Safety Variables:

Safety variables include: adverse events, routine vital sign measurements (including cuff measured sBP and dBP), physical examination findings, clinical laboratory tests.

Statistical Methods:

For all subjects enrolled in the study, descriptive tabular and/or graphical summarizations will be generated, if applicable. Continuous variables will be presented using descriptive statistics: number of observations (n), mean, standard deviation, standard error of the mean, median, and minimum and maximum values. Categorical values will be summarized with counts and percentages.

All collected data will be presented in listings

Pharmacokinetics

Pharmacokinetic parameters will be summarized for each meal treatment. Non-compartmental analysis of the total T concentrations measured on the treatment days will be used to calculate PK parameters, including C_{max}, T_{max}, AUC and C_{avg} for each breakfast diet option. Actual sample collection times will be used for PK parameter determinations; summary listings and tables will be organized by nominal (scheduled) sample collection time.

Safety

Adverse events will be summarized and tabulated by system organ class and preferred term.

Physical examination and results will be summarized.

Observed values and changes from baseline in vital sign measurements, including sBP, dBP, heart rate (HR), will be summarized.

Observed values and changes from baseline in laboratory test results will be summarized. Laboratory tests will be performed at screening and following the Day 5 24 hour PK sample.

Date of Protocol: 15 September 2016

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5 LIST OF ABBREVIATIONS

AE	adverse event
ALT	alanine aminotransferase
ANOVA	Analysis of variance
AST	aspartate aminotransferase
AUC	area under plasma concentration-time curve
AUC_{12}	area under the plasma concentration-time curve over the 12-hour dosing interval
AUC_{24}	area under the plasma concentration-time curve over the 24-hour dosing interval following the AM dose
BID	twice daily
BLQ	below the limit of quantitation
BMI	body mass index
BP	blood pressure
C_{avg}	average concentration
CI	confidence interval
C_{max}	maximum concentration
C_{max1}	C_{max} values associated with oral TU morning dose
C_{max2}	C_{max} values associated with oral TU evening dose
CRF	case report form
CV	cardiovascular
dBP	diastolic blood pressure
DHT	dihydrotestosterone
DRE	digital rectal examination
E_2	estradiol
eCRF	electronic case report form
EDTA	Ethylenediaminetetraacetic acid
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
HCT	hematocrit
HDL	high-density lipoprotein
HR	heart rate
ICF	informed consent form
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
I-PSS	International Prostate Symptom Score
IRB	institutional review board
ITT	intent-to-treat
LH	luteinizing hormone
LLOQ	lower limit of quantitation
LS	least square
MedDRA	Medical Dictionary for Regulatory Activities
mm Hg	millimeters of mercury

NaF	sodium fluoride
PDQ	Psychosexual Daily Questionnaire
PK	pharmacokinetic(s)
PSA	prostate-specific antigen
SAE	serious adverse event
sBP	systolic blood pressure
SHBG	sex-hormone binding globulin
SOC	system organ class
T	testosterone
TEAE	treatment-emergent adverse event
T_{max}	time to maximum concentration
TRT	testosterone replacement therapy
TU	testosterone undecanoate
ULN	upper limits of normal
WHO	World Health Organization

6 INTRODUCTION

The Endocrine Society defines hypogonadism as a clinical syndrome that results from failure of the testes to produce physiological levels of testosterone (T) (androgen deficiency) and a normal number of spermatozoa because of disruption of 1 or more levels of hypothalamic pituitary-testicular axis.[2] Hypogonadism may result from a genetic abnormality or may occur secondary to a chronic disease or from certain drug therapies. Clinical findings in adult men with the androgen deficiency component of hypogonadism are non-specific. The signs and symptoms suggestive of androgen deficiency include reduced sexual desire (libido); decreased spontaneous erections; breast discomfort and/or gynecomastia; low bone mineral density; dysthymia; decreased energy and/or motivation; reduced muscle bulk; and increased body fat.

Testosterone is an endogenous androgen that is produced in men by Leydig cells under the influence of luteinizing hormone (LH) secreted by the pituitary gland. In normal men, the average daily production of T is approximately 7 mg. Testosterone in circulation is primarily bound to sex-hormone binding globulin (SHBG) and albumin. Equilibrium exists between bound and unbound T such that only 1 to 3% of the total circulating T is free. Total T levels (serum or plasma) typically range between 300 and 1000 ng/dL in eugonadal men.[3]

Testosterone, in addition to being directly responsible for certain actions, serves as a precursor to 2 active metabolites, namely, dihydrotestosterone (DHT) and estradiol (E_2). Dihydrotestosterone is formed by the intracellular action of 5α-reductase on T within target tissues (eg, muscle, prostate). Testosterone and DHT exert their pharmacological activity in androgen-sensitive target tissue by binding with the androgen receptor. At physiologic levels, the action of T and DHT differs. Although both androgens bind to the same receptor, the T-receptor complex regulates gonadotropin secretion and is responsible for Wolffian duct stimulation during sexual development. In contrast, the DHT-receptor complex is responsible for external virilization during fetal development and DHT is the primary androgen responsible for sexual maturation and adult male sexual activity. Which androgen is responsible for the control of spermatogenesis is poorly understood.[4]

Testosterone deficiency is characterized by abnormally low levels of circulating T. There are a variety of causes of male hypogonadism but essentially all of these fall into 1 of 2 categories: primary hypogonadism (resulting from a defect of androgen production/secretion at the testicular level) and secondary hypogonadism (resulting from a defect in gonadotropin production/secretion at the hypothalamic-pituitary level). In primary hypogonadism, gonadotropin (ie, LH and follicle-stimulating hormone [FSH]) levels are abnormally high because the negative feedback action of T to suppress secretion is absent. Conversely, secondary hypogonadism is associated with low gonadotropin levels. Some hypogonadal states may involve a defect at more than 1 physiological

level. Regardless of the cause, adult male hypogonadism is generally associated with a constellation of symptoms, often composed of diminished libido, depressed mood, decreased muscle strength, increased fat mass and reduced energy. Testosterone deficiency is also a risk factor for osteoporosis and has recently been implicated as a potential risk factor in coronary artery disease.[5,6]

The goal of T replacement therapy (TRT) is to restore T levels to the eugonadal range and thereby restore normal male secondary sexual characteristics and behavior and to mimic the somatic action of T (eg, hemoglobin, muscle mass, nitrogen balance, bone mineral density). Several pharmacologic preparations of T (or active derivatives or pro-drugs) have been developed and approved for androgen-replacement therapy. These products can be divided into 5 main categories: oral androgens (eg, methyltestosterone, T undecanoate [TU; not currently available in the United States]); intramuscular T-esters (eg, T-enanthate, T-cypionate, TU); transdermal T preparations (T-gels, T-solutions, and non-scrotal T-patches); a buccal T delivery system; and an intranasal T delivery system.

The use of oral TU for TRT is not new. A non-self-emulsifying drug delivery system oral TU formulation containing 40 mg of TU dissolved in oleic acid is approved and has been available for use for decades in over 80 countries around the world (including Canada and most countries in Europe) but not in the United Stated. Following administration, the oral TU dose undergoes entero-lymphatic absorption from the gut, bypassing the portal circulation and thereby circumventing first-pass hepatic metabolism. The pharmacokinetic (PK) profile of this TU formulation is highly variable and, consequently, this TU formulation has generally not been regarded as optimal for the treatment of male hypogonadism.[7]

Clarus Therapeutics, Inc. (Clarus) is developing a unique oral TU formulation for TRT in hypogonadal men. Testosterone undecanoate (TU) is an extremely lipophilic T-ester, much more lipophilic than T, and thus is recognized by the small intestine as a fat. Accordingly, most of an orally absorbed TU dose is absorbed via the intestinal lymphatics thus avoiding first-pass hepatic metabolism. Clarus's TU is formulated in a lipid matrix that contains other lipophilic substances and an emulsifier and is administered in a soft-gel capsule. All the excipients in the TU formulation are commonly used in the pharmaceutical and/or food industry and pose no known health risks. This orally administered TU formulation constitutes a self-emulsifying drug delivery system designed to promote the solubility, absorption, and subsequent bioavailability of TU. Once absorbed, non-specific esterases cleave the fatty acid chain to yield T that provides the androgenic activity of this formulation.

Clarus has evaluated its oral TU formulation in 5 Phase 2 studies and 2 Phase 3 studies. In repeat-dose Phase 2 studies, the serum concentrations of T, DHT, and E_2 reached steady-state by the

seventh day of dosing. In a single-dose, 5-period study of the effect of food with various levels of fat, in which the meal was consumed before dosing, demonstrated that the formulation can be taken across the spectrum of low-normal-high fat meals but bioavailability was substantially reduced when the formulation was taken in the fasted state. Increasing fat in the diet increases the bioavailability of T, with a high-fat meal (50% of calories of the approximately 1000 calorie meal as fat) resulting in about a 31% higher exposure compared to a standard (30% fat) meal. The formulation should not be taken in a fasted state, since fasting results in about a 40% reduction in absorption compared with a meal that has 30% of its calories as fat. In that study, a high dose of oral TU, 474 mg, was evaluated.

Another phase 2 open-label, single oral TU dose study was conducted in eight (8) hypogonadal men at a single study site. Each participant received a single oral TU dose of 316 mg TU (two 158 mg TU capsules) immediately prior to a standardized breakfast meal comprised of 25 to 30 % of calories as fat. Subjects were asked to consume the entire breakfast meal in no more than 30 minutes. Blood samples were collected into four different types of tubes, Plain, with no additives, NaF +EDTA, NaF + Oxalate, and NaF containing tubes at pre-dose, and hourly for 12 hours post-dose. This study was performed, in part, to confirm and expand the findings published by Lachance et al[7]. which demonstrated that when oral TU is administered to hypogonadal men, conversion of TU to T continues after blood collection unless the action of non-specific esterases is inhibited at the time blood is drawn for measurement of T. Preliminary review of the data indicate an increased conversion of TU to T at every post dose time point for results collected in plain tubes as compared to those tubes containing an esterase inhibitor (tubes containing sodium fluoride). Final analyses of this study are not yet available.

In Phase 3, the formulation was initially evaluated in a 12-month, randomized, active-controlled, dose-titration study (CLAR-09007; N=325). The study initiated subjects on oral TU at 316 mg TU twice daily (BID) after meals. The meals at PK visits approximated the average fat content of the American male diet with about 30 g of fat. Unlike a food effect study, the subjects were not required to consume the whole meal. Only those subjects requiring dose titration on Day 30, based on a single time point (4 to 6 hours after dose) serum T determination, had an opportunity for a second titration on Day 60. Subjects who did not require dose titration at Day 30 continued on the 316 mg TU BID dose to Day 90, without additional assessments of serum T levels. On Day 90, 87.2% of subjects on oral TU achieved a serum T average concentration (C_{avg}) in the eugonadal range (ie, 300 to 1000 ng/dL), meeting the primary efficacy endpoint of the study; however, roughly one-quarter of subjects on oral TU had serum T maximum concentrations (C_{max}) that fell outside the targets for C_{max} set by the Food and Drug Association (FDA). Approximately 14% of subjects had a C_{max} >2500 ng/dL and 13% had a C_{max} of 1800 to 2500 ng/dL. The safety profile of the oral TU group was similar to that of the active comparator group (AndroGel® 1%). In Study

CLAR-09007, the incidence of any adverse event (AE), any serious AE (SAE), and any AE leading to discontinuation of study drug for oral TU-treated patients was 68.3%, 6.8%, and 5.0%, respectively, as compared with 62.5%, 3.8%, and 3.1% in patients who received AndroGel. Some of the differences in the AE profile, such as the incidence of edema, and an increase in mean Day 90 baseline systolic blood pressure (sBP)/diastolic blood pressure (dBP) of 2.6/2 mm Hg may have been related to the higher T exposure in the subjects who received oral TU, with the Day 90 serum T C_{avg} (standard deviation) in the oral TU group of 628 (343) ng/dL compared with 485 (220) ng/dL in the AndroGel group.

The results of CLAR-09007 study led Clarus to develop a revised dose-titration algorithm and test it in a second Phase 3 trial. This trial (CLAR-12011) was a single-arm, 114-day dose-titration study. Like CLAR-09007, subjects were initiated on oral TU at a dose of 316 mg TU BID, but in this trial all subjects had 2 opportunities to undergo dose titration. Subjects in CLAR-12011 took their dose within 15 minutes of consuming meals. Subjects were provided with meal options which were similar to that used in the previous Phase 3 trial. Titration decisions were based on a serum T concentration drawn 3 to 5 hours post-dose, and the T concentration upon which dose reduction occurred was lower than that used in CLAR-09007 study. On Day 114, 75.0% of subjects on oral TU achieved a T C_{avg} in the eugonadal range (ie, 300 to 1000 ng/dL), meeting the primary efficacy endpoint of the study. The frequency of high C_{max} values was substantially decreased. Approximately 3% of subjects had a C_{max} > 2500 ng/dL and 6% had a C_{max} of 1800 to 2500 ng/dL. The FDA has set targets for T C_{max} > 2500 ng/dL at 0% of subjects and 5% of subjects with a T C_{max} of 1800 to 2500 ng/dL. The incidence of any AE, any SAE, and any AE leading to discontinuation of study drug was 48.6%, 1.4%, and 2.1%, respectively. No AE could be directly associated with an elevated T C_{max}. The mean change in baseline sBP/dBP at Day 114 was 0.1/0.5 mm Hg, which was less than seen in the previous study and may reflect the lower mean T C_{avg} 422 ng/dL (standard deviation 171) in study CLAR-12011. Approximately 75% of CLAR-12011 subjects had a final dose that was lower than the starting dose; therefore, a lower starting dose was studied in the next Phase 3 study, CLAR-15012.

Currently ongoing, CLAR-15012 is a multicenter, Phase 3, randomized, open-label, active-comparator group, efficacy (based on C_{avg} of T), and safety study in adult hypogonadal male subjects. Enrollment into the study is based on selection criteria designed to be the general population of hypogonadal men. Subject's study drug dose is determined by a dose-titration algorithm that bases dose-titration decisions on total T C_{avg}. Subjects may be naïve to androgen replacement therapy or washed out of prior androgen replacement therapies. A total of about 550 subjects were screened in order to enroll 222 subjects, which meets both scientific and regulatory objectives. Subjects who meet all eligibility criteria were randomly assigned in a 3:1 ratio such that 166 subjects were assigned to the oral TU treatment arm and 56 subjects were assigned to receive

Axiron, an active comparator which is a prescribed topical T replacement product. Treatment lasts approximately 3.5 months, including up to a 21 day Screening Phase (Screen 1, Screen 2, and Screen 3 visits), a 70-day Titration Phase, a 35 day Maintenance Phase, and an end-of-study visit, Visit 7 Day 105 (± 3 days). As the study is ongoing, results are not yet available.

The Investigator's Brochure presents a full discussion of the pre-clinical toxicology, metabolism, pharmacology, and results in humans.[9]

7 STUDY OBJECTIVES

7.1 Primary Objective

To determine the effect of meals (breakfast) containing various amounts of fat on the pharmacokinetics of Clarus's formulation of oral TU at a dose of 237 mg TU (the highest strength capsule being developed by Clarus).

7.2 Safety Objective

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

8 INVESTIGATIONAL PLAN

8.1 Overall Study Design and Plan: Description

This will be 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. 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).

Meal plans provided during PK Phase are as follows:

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 Breakfast 30 grams fat Lunch 30 grams fat Dinner 30 grams fat	**Meal Plan D (45 gm fat)** Overnight fast (≥10 hours) Dose oral TU immediately prior to breakfast Breakfast 45 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	

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 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 taking 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 administered no more than 5 minutes before oral TU dose administration on each PK Phase Period).

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.

8.2 Discussion of Study Design

This will be a Phase 2 open-label, food effect study in adult hypogonadal male subjects. Enrollment into the study will be based on selection criteria designed to sample the general population of hypogonadal men. The study includes an up to 28-day Screening Phase, a 14 day outpatient Run-in Phase, followed by an in-patient PK Phase (6 days), and then a Follow up Phase.

The primary objective of the study is to determine the effect of meals (breakfast) containing various amounts of fat on the pharmacokinetics of Clarus's formulation of oral TU at a dose of 237 mg TU. The period associated with the randomly assigned 30 g fat breakfast meal will be considered the reference period.

8.2.1 Anticipated Benefits

This study only requires short term exposure to testosterone, yet the management of hypogonadism requires chronic therapy; therefore, participants in this study will not get therapeutic benefit for their hypogonadism. However, the subjects may benefit from the screening evaluation as it may identify health issues that require further follow up. Chronic treatment with TRT may provide a wide range of benefits for men with hypogonadism, including improvement in libido and sexual function, increased bone density, increased muscle mass, decreased adiposity, and increased quality of life. The goal of TRT is to restore T levels to the eugonadal range and thereby restore normal male secondary sexual characteristics and behavior and to mimic the somatic action of T (eg, hemoglobin, muscle mass, nitrogen balance, bone mineral density). Several pharmacologic preparations of T (or T pro-drugs) have been developed and approved for TRT.

8.2.2 Anticipated Risks

This study will only require short term exposure to testosterone, so any androgen associated risk is expected to be minimal. In addition, screening criteria are designed to identify subjects who are at high risk and exclude them from participating in the study. Clarus's oral TU has been dosed for up to 2 years in Phase 3 studies with a well-tolerated safety profile, which is comparable to that of a commonly prescribed topical TRT, AndroGel. The dose used in this study is lower than the dose that most subjects were exposed to in the Phase 3 studies. Both Phase 3 studies dosed subjects for

the first 21 days of treatment at a dose level of 316 mg BID, but this study will dose subjects for less than 21 days at 237 mg BID, which should add a further margin of safety.

Androgens are contraindicated in men with carcinoma of the breast and known or suspected carcinoma of the prostate. In men receiving androgen-replacement therapy, surveillance for prostate cancer should be consistent with practices for eugonadal men. Geriatric subjects treated with androgens may be at an increased risk for the development of prostatic hyperplasia and prostatic carcinoma. Potential study participants will be screened by history, physical exam including digital rectal exam and lab testing [prostate-specific antigen (PSA)], in order to identify subjects who are at higher risk.

Other potential side effects with androgen therapy include gynecomastia and edema with or without congestive heart failure in subjects with pre-existing cardiac, renal, or hepatic disease. Oral therapy with high doses of 17-α–alkylated androgens (eg, methyltestosterone) has been associated with serious hepatic effects that can have life-threatening or fatal complications, although liver toxicity has not been observed following the oral administration of natural T or T esters including TU.

Long-term clinical safety trials have not been conducted to assess the cardiovascular (CV) outcomes of TRT in men. To date, epidemiologic studies and randomized controlled trials have been inconclusive for determining whether or not the incidence of major adverse CV events, such as non-fatal myocardial infarction, non-fatal stroke, and CV death, is higher in men who use T compared to non-users. Some studies, but not all, have reported an increased risk of major adverse CV events in association with use of TRT in men. Subjects should be informed of this possible risk. There have been post-marketing reports of venous thromboembolic events, including deep vein thrombosis and pulmonary embolism, in subjects using T products. All subjects who report symptoms of pain, edema, warmth, and erythema in the lower extremities should be evaluated for deep vein thrombosis and those who present with acute shortness of breath should be evaluated for pulmonary infarction. If a venous thromboembolic event is suspected, treatment should be discontinued and appropriate workup and management initiated.

The total volume of blood to be collected from each subject during the study will not exceed approximately 500 mL, the volume of a routine blood donation, with possible reduction in hemoglobin and hematocrit.

8.2.3 Dose Rationale

Subjects enrolled in the CLAR-16015 will receive 237 mg capsules of oral TU. The 237 mg TU capsule is the highest dose strength in development by Clarus. The FDA food effect guidance indicates that the food effect study should investigate the highest dosage strength to be marketed.

8.3 Selection of Study Population

Adult hypogonadal male subjects will be eligible for enrollment in the study based on the inclusion and exclusion criteria listed below. Subjects will undergo screening procedures up to 28 days before the start of study drug treatment.

8.3.1 Inclusion Criteria

To be eligible for study entry subjects must satisfy all of the following criteria:

1. Man 18 to 65 years of age, inclusive, with a clinical diagnosis of hypogonadism (signs/symptoms consistent with hypogonadism for testosterone naïve subjects and history of signs/symptoms for subjects who have received prior treatment) as well as testosterone levels consistent with hypogonadism as defined by 2 morning total T values of <300 ng/dL (between 6:00 and 10:00 AM drawn on 2 separate days [approximately 7 (±2) days apart].

2. Adequate venous access in the left or right arm to allow collection of a number of blood samples via a venous cannula.

3. Must be naïve to androgen-replacement therapy **or** washed out of prior androgen-replacement therapies; that is, be willing to cease current T treatment or currently not be taking T treatment, (washout durations specified in exclusion criterion #1). Subjects must remain off all forms of T, except for dispensed study drug, throughout the entire study.

4. Subjects on replacement therapy for hypopituitarism or multiple endocrine deficiencies must be on stable doses of thyroid hormone and adrenal replacement hormones for at least 14 days before Screen 1.

5. Has voluntarily given written informed consent to participate in this study.

8.3.2 Exclusion Criteria

Subjects will be excluded from the study if 1 or more of the following criterion is applicable:

1. Received oral topical (eg, gel or patch), intranasal, or buccal T therapy within the previous 2 weeks, intramuscular T injection of short-acting duration (eg, T enanthate, T cypionate) within the previous 4 weeks, intramuscular T injection of long-acting duration (eg, AVEED) within the previous 20 weeks, or T implantable pellets (Testopel®) within the previous 6 months.

2. Has an intercurrent disease deemed clinically significant in the opinion of the investigator of any type; in particular, liver, kidney, uncontrolled or poorly controlled heart disease, including hypertension, congestive heart failure or coronary heart disease, or psychiatric-illness, including severe depression.

3. Has had a recent (within 2 years) history of stroke, transient ischemic attack, or acute coronary event.

4. Has a mean of the triplicate assessment of sBP > 150 mm Hg and/or dBP > 90 mm Hg at screening (if prescribed antihypertensives, subject should be taking medications on the day of the screening visit with a sip of water). Subjects < 60 years of age and prescribed antihypertensives will be excluded if the mean of the triplicate assessment of sBP > 140 mm Hg and/or dBP > 90 mm Hg at screening.

5. Has had recent (within 2 years) history of angina or stent (coronary or carotid) placement.

6. Has untreated, severe obstructive sleep apnea.

7. Has clinically significant abnormal laboratory values, including serum transaminases > 2 × upper limits of normal (ULN), serum bilirubin > 1.5 × ULN and serum creatinine > 1.5 × ULN.

8. Has a hematocrit (HCT) value of < 35% or > 48%.

9. Has a history of polycythemia, either idiopathic or associated with TRT treatment.

10. Is a diabetic subject with a glycosylated hemoglobin > 8.5%.

11. Has a body mass index (BMI) ≥ 38 kg/m^2.

12. Has been on stable doses of antihypertensive medication for < 3 months.

13. Has an abnormal prostate digital rectal examination [(DRE); palpable nodules], elevated PSA (serum PSA > 4.0 ng/mL), I-PSS > 19 points at screening, and/or history of, or current or suspected, prostate cancer.

14. Has a history of, or current or suspected, breast cancer.

15. Has a history of abnormal bleeding tendencies or thrombophlebitis unrelated to venipuncture or intravenous cannulation within the previous 2 years.

16. Use of dietary supplements such as saw palmetto or phytoestrogens and any dietary supplements that may increase total T, such as androstenedione or dehydroepiandrosterone within the previous 4 weeks.

17. Has known malabsorption syndrome and/or current treatment with oral lipase inhibitors (eg, orlistat [Xenical®]) and/or bile acid-binding resins (eg, cholestyramine [Questran®], colestipol [Colestid®]) or treatments that promote gastric emptying (eg, metoclopramide [Reglan®]).

18. Inability to observe all rules and smoking restrictions in place at the clinical facility during confinement.

19. Has history of abuse of alcohol or any drug substance within the previous 2 years.

20. Poor compliance or unlikely to keep clinic appointments and remain for entire confinement period.

21. Has received any drug as part of another research study within 30 days of initial dose administration in this study.

22. Donated blood (≥ 500 mL) within the 12-week period before the initial study dose.

23. Current use of the following groups of drugs that effect T levels, T metabolism or levels of T metabolites, namely antiandrogens, 5-alpha-reductase inhibitors (eg, dutasteride, finasteride), estrogens, long-acting opioid analgesics (eg, methadone hydrochloride, buprenorphine hydrochloride) or human growth hormone (HGH).

24. Unwilling or unable to follow the dietary requirements for this study.

8.3.3 Number of Planned Subjects

Two study centers in the United States will participate in the study. The plan is to enroll approximately 20 subjects in the study.

8.3.4 Subject Discontinuation From Therapy or Assessments

Subjects may stop study drug for any of the following reasons:

- Subject request.
- Use of non-permitted concurrent therapy as assessed by the medical monitor and sponsor.
- Non-compliance with the study drug or study schedule.
- Lost to follow-up.
- Occurrence of AEs not compatible with the continuation of subject participation in the study, in the investigator's opinion, or unacceptable to the subject to continue.
- Investigator request.
- Significant intercurrent illness.
- Sponsor request.

Subjects may withdraw from the study (study drug and assessments) at any time without prejudice to further treatment (withdrawal of consent). Efforts should be made to determine why the subject is withdrawing. The subject will be asked about the reason(s) for withdrawal and the presence of any adverse events (AEs) and the reason(s) will be documented in the case report form (CRF/eCRF).

Reasonable efforts will be made to contact subjects who are lost to follow-up. These efforts must be documented in the subject's file.

The sponsor has the right to terminate the study at any time. In this event, the investigators will be informed of the reason for study termination.

8.3.4.1 Withdrawal Procedures

Subjects may withdraw from the study at any time without prejudice to further treatment. If possible, the subject will be seen by an investigator and undergo the safety follow-up assessments and procedures (Appendix A). If the subject cannot be seen in person, phone/email/other follow-up should be attempted to ascertain the reason for withdrawal. Adverse events should be followed for 7 days after the last dose of study drug, and all remaining study drug should be returned by the subject.

8.4 Investigational Product – Oral Testosterone Undecanoate

8.4.1 Investigational Product Administered

Subjects in the study will receive orally administered TU 237 mg BID for 14 (±2) days during the Run-In Phase and throughout Days 1 through 5 of the PK Phase.

8.4.2 Identity of Investigational Product

Oral TU capsules are soft-gel capsules. The capsules will be manufactured in accordance with current Good Manufacturing Practice regulations by Catalent Pharma Solutions (St. Petersburg, FL). The soft-gel capsules will be manufactured with 237.46 mg TU, which will nominally be referred to as 237 mg TU capsules. The 237 mg TU capsules are orange opaque in color and are equivalent to 150 mg T per capsule. Testosterone undecanoate will be solubilized in a proprietary mixture of lipid excipients and emulsifiers that are generally regarded as safe and/or commonly used by the pharmaceutical and food industries.

Subjects will receive 237 mg TU BID for 14 (±2) days leading up to the 6 day PK Phase. Doses of TU are to be taken BID with meals (breakfast and dinner), approximately 12 hours apart. The capsules are to be taken **immediately** before the start of the meal.

During the PK Phase, the subjects will take a single 237 mg TU capsule immediately before the protocol-defined breakfast and again immediately before the protocol-defined evening meal. Subjects should consume their entire morning and evening meals within 20 minutes. Subjects will consume a standardized mid-day meal during PK Phase. Snacks may be provided to subjects only after the mid-day meal.

8.4.3 Investigational Product Storage and Disposal

The TU capsules will be packaged in a high-density polyethylene safety bottle that should be stored in a dry place at room temperature (25°C or 77°F). Excursions are permitted to 15°C to 30°C (59°F to 86°F).

Testosterone and related substances like TU are Schedule III non-narcotic, controlled substances. These study drugs must be stored at the site in a securely locked, substantially constructed cabinet or other substantially constructed enclosure with limited access to prevent theft or diversion of the drug into illegal channels of distribution.

Subjects must be instructed to ensure that all study drugs be kept out of reach of children.

Study site Standard Operating Procedures will be followed for the disposal of the study formulation upon approval of the Sponsor or designee.

8.4.4 Packaging and Labeling

The study drug is for investigational use only and is to be used only within the context of this study. The study drug supplied for this study must be maintained under adequate security and stored under the conditions specified on the label until dispensed for subject use or returned to the sponsor.

The clinical study labeling was done by Catalent Pharma Solutions, Philadelphia, PA and an over label specific to this study, CLAR-16015, will be applied to all investigational product prior to study start at each center by a Clarus representative. All packaging and labeling operations will be performed according to Good Manufacturing Practice for Medicinal Products and the relevant regulatory requirements.

The TU soft-gel capsules are packaged in high-density polyethylene bottles (120 capsules per bottle).

8.4.5 Study Drug Dosing During Run-In Phase and PK Phase

Subjects will self-administer 237 mg oral TU BID for a 14 day Run-in Phase. Subjects will be asked to record their morning and evening doses every day during the Run-In Phase. The evening of Day 14 (±2) subjects will report to the clinic or Phase 1 unit before their PM dose and dinner to begin the PK Phase. Subjects will take their PM dose on Day 14 from the same bottle that was dispensed on Dosing Day 1. Following that dose, study drug will be collected and accountability will be performed. Subjects will take their study dose immediately prior to the protocol-defined dinner meal provided. During the entire PK Phase of the study, subjects will be confined to the clinic/unit and will be administered 237 mg TU immediately prior to the protocol-defined breakfast, and immediately prior to the protocol-defined dinner. During the PK Phase Periods 1 through 5, site personnel will administer all study drug from site inventory.

In the event of a missed dose during the Run-In Phase, the missed dose will be documented and the subject will wait until it is time to take the next dose of study drug, in keeping with the scheduled dosing regimen.

During the PK Phase if the subject's AM or PM dose is missed, he may be asked to repeat that study day including the assigned protocol-defined meals and serial sampling for 12 – 24 hours.

Per protocol, the 24 hour blood collection time point also serves as the time 0 for the next day's serial sampling. However, if the dose-associated meal is not ready to be served at the 24 hour time point (ie., time 0) a window of up to one hour is acceptable and the sample collection clock for that dose (time 0) begins with the actual time of the dose. This may require that the 24-hour sample from the previous dose does not serve as time 0 for the following dose.

8.4.6 Blinding and Randomization

This is an open-label study. Subjects will be randomly assigned to one of the five sequences (shown below) of breakfast meals where the sequences follows a Latin square design for a 5 period cross-over study.

1. ABCDE
2. BCEAD
3. CEDBA
4. DABEC
5. EDACB

8.4.7 Prior and Concomitant Therapy

If any medication or nutritional supplement is taken, the name, dose, route, frequency of dosing, and reason for use will be recorded on the concomitant medication page in the CRF/eCRF. Subjects will be asked about their treatment history for hypogonadism and the start and stop dates for their most recent TRT. In addition, start dates for the use of any medications for hypertension, taken > 3 months within screening will be recorded in the CRF/eCRF.

Eligible subjects must have a screening mean sBP < 150 mm Hg and/or dBP < 90 mm Hg. Subjects taking prescribed antihypertensives should be taking medications on the day of the screening visit with sips of water; the medication should be noted as a prior medication. Subjects < 60 years of age and prescribed antihypertensives will be excluded if the mean of the triplicate assessment of sBP > 140 mm Hg and/or dBP > 90 mm Hg at screening. Any increase in the dose of the antihypertensive medication or any need to add new antihypertensive medications should be considered an AE and recorded in the CRF/eCRF.

8.4.7.1 Prohibited Medication/Therapy

Subjects must remain off <u>all forms of T</u> except for study drug throughout the entire study. Use of dietary supplements such as saw palmetto or phytoestrogens as well as any dietary supplements that may affect total T levels such as androstenedione or dehydroepiandrosterone during the study is not permitted. Use of antiandrogens, 5-alpha-reductase inhibitors (eg, dutasteride, finasteride),

estrogens or long-acting opioid analgesics (eg, methadone hydrochloride, buprenorphine hydrochloride) are not permitted during the study.

8.4.7.2 Other Restrictions

During the Run-In Phase subjects will be advised to avoid taking oral study drug while fasting (ie, "on an empty stomach"). Subjects should take the oral TU *immediately* before the breakfast and dinner meals. While in the clinic or Phase 1 unit during the PK Phase, subjects will be required to consume the entire protocol-defined breakfast and dinner meals within 20 minutes after taking oral TU.

Subjects will be asked to refrain from consuming grapefruit, grapefruit juice, or grapefruit supplements while on study drug.

Subjects will be asked to observe all rules and smoking restrictions in place at the clinical facility during confinement.

8.4.8 Treatment Compliance

Subjects will return their unused study medication and compliance with study drug will be assessed on Day 14 of the Run-In Phase following the PM dose. Significant non-compliance with treatment during the Run-in Phase (<80% or > 120% compliant) will be documented as a protocol deviation. During the PK Phase dosing administration will be observed and compliance assessed. Any deviation from the prescribed dosage regimen will be recorded. In cases of significant non-compliance, a subject may be discontinued from the study at the investigator's and sponsor's discretion.

9 TIMING OF STUDY PROCEDURES

Subjects will provide written informed consent before any study-related procedures are performed.

9.1 Screening Phase

9.1.1 Screen 1 Day -28 to -7

Screening of all subjects will be performed up to 28 days of the initial dose of study drug to assess subject eligibility. After the subject provides signed informed consent, the procedures of the Screen 1 visit will include:

- Assess for eligibility (against the inclusion and exclusion criteria)
- Record medical history, including concomitant illnesses/diseases. The subject's medical history (key events) will be recorded on the Medical History CRF/eCRF. If a clinical event concerns a chronic disorder, which means it started in the past and it is still present at the screening visit, it should also be recorded on the Medical History CRF/eCRF.
- Record concomitant medications. Medication use (prescription and/or over-the-counter, including vitamins and herbal supplements) from 3 months before study drug administration through the end of the study will be recorded on the Concomitant Medication eCRF. If a subject reports taking any over-the-counter or prescription medications, vitamins and/or herbal supplement or if administration becomes necessary from 3 months before study drug administration through the end of the study, the name of the medication, dosage information including dose, route, frequency, date(s) of administration including start and end dates, and reason for use must be recorded. For any medications taken after study drug administration and through the end of the study, the subject may continue to participate in the study only after the investigator agrees the subject may continue.
- Subjects will be asked about their treatment history for hypogonadism and the start and stop dates of their most recent TRT.
- Record demographic data, such as ethnic origin, and date of birth.
- Obtain height, weight and BMI.
- Record vital signs (sitting BP and heart rate [HR] in triplicate). If the subject is taking antihypertensives, then these medications should be taken on the morning of the visit with sips of water.

- Ensure adequate venous access in the left or right arm to allow collection of a number of blood samples via a venous cannula.
- Collect samples for hematology, clinical chemistry, and urine dipstick after subjects have fasted overnight. Eligibility laboratory tests will include complete blood count, chemistry panel, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, bilirubin, creatinine, lipids, and albumin.
- Obtain PSA
- A glycosylated hemoglobin test will be performed for diabetic subjects only.
- Obtain blood sample for total T determination between 6:00 and 10:00 AM.

9.1.2 Screen 2 approximately 7 (±2) days post Screen 1

The Screen 2 visit should occur between 6:00 and 10:00 AM, approximately 7 (2±) days after the Screen 1 visit, and after results from the Screen 1 total T value have been received. Subjects should return for the Screen 2 visit only if the Screen 1 visit total T is < 300 ng/dL and no exclusionary values for safety are identified. No rescreening will be allowed for T levels ≥ 300 ng/dL.

The Screen 2 assessments include:

- Assess for eligibility (against the inclusion and exclusion criteria).
- Record any changes in prior and concomitant medications.
- Perform a physical examination (including DRE).
- Obtain blood sample for the second total T determination approximately 7 days after the initial sample, between 6:00 and 10:00 AM.
- Review for AEs.

9.2 Run-In and PK Phases

9.2.1 Run-In Phase (14±2 Days)

During the Run-In Phase, subjects will be instructed to take study drug BID just before the morning (breakfast) and evening (dinner) meals approximately 12 hours apart, which will suppress subjects' endogenous testosterone production while allowing the oral TU to reach steady state.

9.2.2 Run-In Phase Dosing Day 1

Once it has been confirmed the subject's total T values at the Screen 1 and Screen 2 visits meet eligibility criteria (morning total T values of <300 ng/dL [obtained between 6:00 and 10:00 am] drawn on 2 separate days approximately 7 (±2) days apart), the subject will be asked to return to the clinic for Run-In Dosing Day 1 prior to breakfast (ie, overnight fast). No rescreening will be allowed for total T levels ≥ 300 ng/dL. Study center personnel will review prior and concomitant medications.

The following Run-In Dosing Day 1 procedures should be performed pre-dose:

- Assess for eligibility (against the inclusion and exclusion criteria) and if the subject meets eligibility
- Collect safety laboratory tests after an overnight fast.
- Collect pre-dose blood samples for T, DHT and TU concentrations.
- Record vital signs [sitting BP and heart rate (HR) in triplicate]. Obtain vital signs prior to blood draws.
- Perform a brief physical examination.
- Dispense one bottle of 237 mg capsules and instruct subject to take first dose *immediately* prior to the breakfast, which will be provided at the clinic. Document in drug accountability record.
- Instruct subjects to take study medication twice-daily *immediately* before breakfast and dinner meals each day. Subjects will be instructed to maintain their regular diet throughout the Run-In Phase.
- Instruct subjects to bring all study drug with them to the clinic the evening of Run-In Dosing Day 14 (±2) prior to the evening dose and meal.
- Assess for AEs and changes in concomitant medications.

9.2.3 Run-In Phase, Dosing Day 14 (±2)

Subjects should not take their PM dose or eat before arrival at the overnight clinic in the evening of Run-In Phase Dosing Day 14. Vital sign measurements will be obtained (sitting BP and HR in triplicate) prior to blood draws. Site personnel will confirm that each subject has taken his dose of

concomitant medications (with sips of water) and morning dose of study medication. Subjects will be administered their evening dose of study medication *immediately* prior to the provided, protocol-defined evening meal at the clinic. Site personnel will document any changes in concomitant medications and assess any previous and/ or new AEs, collect study medication and complete drug accountability and determine adequate treatment compliance to proceed with the in-patient PK Phase (>80% compliance). Subjects will take their study dose immediately prior to the protocol-defined meal provided at the Clinic. Study drug accountability will be performed following the PM dose.

9.2.4 PK Phase/Periods 1, 2, 3, 4, and 5

Each participating site will receive a bottle containing 120 capsules of 237 mg TU from which to dispense study medication to subjects during Periods 1 through 5 of the PK Phase.

Vital sign measurements will be obtained (sitting BP and HR in triplicate) and site personnel will confirm that each subject has taken his dose of concomitant medications (with sips of water). Blood samples for hematology and clinical chemistry will be collected prior to breakfast. Subjects will be administered their morning dose immediately prior to the protocol-defined breakfast, except for fasting period. Study personnel will provide 1 of 4 defined breakfasts or a 240 mL glass of water (for the fasting treatment) on Periods 1 through 5. Study personnel will provide standardized lunch and protocol-defined dinner meals. Subjects will be instructed to consume *entire breakfast and dinner meals within 20 minutes*. Subjects will be administered their evening dose immediately prior to the protocol-defined dinner. Subjects should not consume food within 10 hours prior to the next morning dose during the PK Phase.

Serial blood samples will be collected over 24 hours. Samples will be collected as follows:, 0 (pre-morning dose), 2, 4, 6, 9, 12, 14, 16, 18, 21, and 24 hours after morning dose (serial sampling times are relative to the AM dose). The 24-hour sample collection following dosing on Days 1, 2, 3, and 4 will also serve as the 0 (pre-dose) samples on Days 2, 3, 4, and 5, respectively. Blood sample collection should be performed within ±10 minutes of the scheduled time points (with the exception of the 0-hour time point for each treatment during the PK Phase which should be collected within 5 minutes before oral TU dose administration. Dose administration, meal times and sample collection times will be recorded.

The subject will be asked to consume the *entire* breakfast (except during fasting Period) and dinner meals within 20 minutes. If unable to consume the entire meal, the subject will return any unconsumed portion of the meal to the site personnel who record the unconsumed portion. In addition to PK blood sampling, the subject will be assessed for AEs. Subjects will be instructed to take their concomitant medications every morning before breakfast (or fasting). Subjects should

maintain their current prescribed concomitant medication schedule. Strenuous activity during confinement will not be permitted.

9.2.5 PK Phase on Day 6 (Discharge from Unit)

Subjects will be released from the clinic after the 24-hour blood draw following the 5th treatment period of the PK Phase (ie. PK Day 6). Vital signs will be measured (sBP, dBP, HR in triplicate) at least 30 minutes prior to collecting the final PK sample. Complete fasting safety laboratory tests will be obtained at the time of the 24 hour PK sample. A brief physical exam will be performed and AEs will be assessed. Subjects will be provided with a non-protocol defined morning meal before being discharged from the unit.

9.2.6 Safety Follow-up Phase (5 to 7 days post last-dose)

Subjects should be contacted (or seen if necessary) 5 to 7 days after their final dose to assess the following:

- Report of an AE that requires further evaluation.
- Repeat of an abnormal laboratory value or for a laboratory result that requires additional follow up.
- Repeat complete blood count for any subject with an elevated HCT value over 54% on PK Phase Period 5. Elevated HCT will be followed to resolution.
- Subject may be contacted by telephone for this safety assessment if no follow up laboratory work or assessment of adverse events is required.

9.3 Early Withdrawal Visit

Subjects who withdraw from treatment or the study will be asked to undergo the early withdrawal assessments and procedures including a physical examination, vital sign measurements (sitting BP and HR in triplicate), review for concomitant medications, AEs, and drug accountability, and if possible, blood samples for complete safety laboratory tests. Subjects should return all study drugs.

9.4 PK Phase Meals

Subjects will be admitted to the clinic the evening of Run-in Phase Dosing Day 14 (±2). Subjects will be provided all meals during the PK Phase and will be confined in the clinic. The protocol defined breakfast must follow the exact order of the randomly assign sequence (see Section 8.4.6). The subjects will take a single 237 mg TU capsule immediately before the protocol-defined breakfast and again immediately before the protocol-defined evening meal (See Appendix D for all protocol-defined meals). Subjects will be asked to consume their *entire* protocol-defined breakfast and dinner meals within 20 minutes. Subjects will be provided with standardized mid-day during the PK Phase. Subjects will be offered a selection of protocol-defined lunch and dinner meals (included in Appendix D). Subjects may select any meal from those available and described in the protocol-defined lunch and dinner list, but must be served and consume the assigned breakfast meal according to the randomly assigned sequence. Meals will be scheduled at the same time on each day of the PK Phase. Doses of study drug will be administered **immediately** before breakfast and dinner. The subject will fast, except for water, until 4 hours post-AM dose when he can eat lunch. Water is allowed as desired except for one hour before and after the protocol-defined meals.

9.5 Duration of Subject Participation

The duration of subject participation in the study will be up to approximately 56 days (approximately 8 weeks), including

- Up to a 28-day Screening Phase;
- A 14-day Run-In Phase; and
- A 6-day PK Phase; and
- A 5 to 7-Day Safety Follow up Phase.

10 PHARMACOKINETICS AND SAFETY VARIABLES

10.1 Pharmacokinetic Variables

Serial blood sampling for total T, DHT and TU will be collected throughout PK Phase Periods 1 through 5. Samples will be collected at the following times: 0, 2, 4, 6, 9, 12, 14, 18, 21 and 24 hours post the AM dose on each day that a treatment (meal type) is administered.

The concentrations of total T, DHT and TU collected following each of the defined breakfast meals will be analyzed to derive the PK parameters of C_{max}, time to maximum concentration (T_{max}), area under the plasma concentration-time curve over the 12-hour dosing interval (AUC_{12}) following the AM dose.

The time of dose administration and the timing of each blood sample collection will be recorded to the minute (nominal scheduled time points are listed in Table 1). 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 within 5 minutes before oral TU dose administration on each PK Phase treatment day).

Table 1 Timing of Blood Samples

Study Visit	Analytes	Blood Samples Assay Time Points*
PK Phase Period 1/ Day 1	Total T, DHT and TU	0 (pre-morning dose), 2, 4, 6, 9, 12, 14, 16, 18, 21, and 24 hours after morning dose
PK Phase Period 2/ Day 2	Total T, DHT and TU	0 (pre-morning dose), 2, 4, 6, 9, 12, 14, 16, 18, 21, and 24 hours after morning dose
PK Phase Period 3/ Day 3	Total T, DHT and TU	0 (pre-morning dose), 2, 4, 6, 9, 12, 14, 16, 18, 21, and 24 hours after morning dose
PK Phase Period 4/ Day 4	Total T, DHT and TU	0 (pre-morning dose), 2, 4, 6, 9, 12, 14, 16, 18, 21, and 24 hours after morning dose
PK Phase Period 5/ Day 5	Total T, DHT and TU	0 (pre-morning dose), 2, 4, 6, 9, 12, 14, 16, 18, 21, and 24 hours after morning dose

*The 24 hours sample on Days 1-4 serve as the 0 hour samples for Days 2-5.

Note: Blood samples for Total T, DHT and TU determination are collected in tubes containing sodium fluoride and EDTA (NaF-EDTA).

A certified laboratory will process samples and provide results for the hormone assays throughout the study. The certified study laboratory will provide information for sample collection and shipment and contact information in the Laboratory Manual.

10.2 Safety Variables

10.2.1 Adverse Events

The investigator will monitor each subject for clinical and laboratory evidence of AEs on a routine basis throughout the study. The investigator will assess and record any AE in detail including the date of onset, event diagnosis (if known) or sign/symptom, severity, time course, duration, outcome, relationship of the AE to study drug, and any action(s) taken. For serious AEs not considered "related" to study drug, the investigator will provide an “Other” cause of the event. For AEs to be considered intermittent, the events must be of similar nature and severity. Adverse events, whether in response to a query, observed by site personnel, or reported spontaneously by the subject will be recorded. All AEs will be followed to a satisfactory resolution.

10.2.1.1 Adverse Event Definition

An AE is defined as any untoward medical occurrence in a clinical study subject administered a medicinal product that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not it is related to the medicinal (investigational) product. This includes an exacerbation of pre-existing conditions or events, intercurrent illnesses, drug interaction or the significant worsening of the indication under investigation that is not recorded elsewhere in the CRF/eCRF under specific efficacy assessments. Anticipated fluctuations of pre-existing conditions, including the disease under study, that do not represent a clinically significant exacerbation or worsening need not be considered AEs.

The investigator is responsible for documenting all AEs that occur during the study. Adverse events will be elicited by asking the subject a non-leading question, for example, “Have you experienced any new or changed symptoms since we last asked/since your last visit?” Adverse events should be reported on the appropriate page of the CRF/eCRF.

10.2.1.2 Assessment of Severity

Each AE will be assigned a category by the investigator as follows:

Mild:	An AE that is easily tolerated by the subject, causes minimal discomfort, and does not interfere with everyday activities.
Moderate:	An AE that is sufficiently discomforting to interfere with normal everyday activities; intervention may be needed.
Severe:	An AE that prevents normal everyday activities; treatment or other intervention usually needed.

If there is a change in severity of an AE, it must be recorded as a separate event.

10.2.1.3 Assessment of Causality

Every effort will be made by the investigator to assess the relationship of the AE, if any, to the study drug. Causality should be assessed using the categories presented in the following table:

Definitely not related:	Clinical event with an incompatible time relationship to study drug administration, and that could be explained by underlying disease or other drugs or chemicals or is incontrovertibly not related to the study drug.
Probably not related:	Clinical event whose time relationship to study drug administration makes a causal connection improbable, but that could plausibly be explained by underlying disease or other drugs or chemicals.
Possibly related:	Clinical event with a reasonable time relationship to study drug administration, but that could also be explained by concurrent disease or other drugs or chemicals.
Probably related:	Clinical event with a reasonable time relationship to study drug administration, and is unlikely to be attributed to concurrent disease or other drugs or chemicals.
Definitely:	Clinical event with plausible time relationship to study drug administration, and that cannot be explained by concurrent disease or other drugs or chemicals

10.2.1.4 Action Taken

The investigator will describe the action taken in the appropriate section of the CRF/eCRF, as follows:

- Drug withdrawn
- Drug interrupted
- Other, specify

10.2.1.5 Follow-up of Adverse Events

All investigators should follow up subjects with AEs until the event is resolved or until, in the opinion of the investigator, the event is stabilized or determined to be chronic. Details of AE resolution must be documented in the CRF/eCRF.

Any open AEs at the end of the study should be followed up for 7 days after the subject receives the last dose of study drug, and any spontaneous AEs that occur during this time should be reported according to the procedures outlined above.

Pregnancy

Subjects will be instructed that known or suspected pregnancy occurring during the study, in female partners of study subjects, should be confirmed and reported to the investigator. The investigator should also be notified of pregnancy occurring during the study but confirmed after completion of the study. In the event that a female partner of a study subject is subsequently found to be pregnant, any pregnancy will be followed to term, and the status of mother and child will be reported to the sponsor after delivery.

10.2.1.6 Documentation and Reporting of Adverse Events

AEs should be reported and documented in accordance with the procedures outlined below. All AEs occurring during the study must be documented on the relevant CRF/eCRF pages. The following data should be documented for each AE:

- Description of the symptom event
- Classification as “serious” or “not serious”
- Severity
- Date of first occurrence and date of resolution (if applicable)
- If the date of first occurrence is on or after date of initial dosing, the AE is regarded as “treatment emergent”.
- Action taken
- Causal relationship
- Outcome of event (unknown, recovered, not yet recovered, recovered with sequelae, death [with date and cause reported])

10.2.2 Serious Adverse Events (SAE)

10.2.2.1 Serious Adverse Event Definition

An SAE is any untoward medical occurrence or effect that, at any dose,

- Results in death.
- Is life threatening (an AE is life threatening if the subject was at immediate risk of death from the event as it occurred, ie, it does not include a reaction that might have caused death if it had occurred in a more serious form).
- Requires or prolongs inpatient hospitalization. (Complications occurring during hospitalization are AEs and are SAEs if they cause prolongation of the current hospitalization. Hospitalization for elective treatment of a pre-existing non-worsening condition is not, however, considered an AE. The details of such hospitalizations must be recorded on the medical history or physical examination page of the eCRF).
- Results in persistent or significant disability/incapacity. (An AE is incapacitating or disabling if it results in a substantial and/or permanent disruption of the subject's ability to carry out normal life functions).
- Results in a congenital anomaly/birth defect of an offspring or a female partner or a study subject.

In addition, medical and scientific judgment is required to decide if prompt notification is required in situations other than those defined for SAEs above. This may include any event that the investigator regards as serious that did not strictly meet the criteria above but may have jeopardized the subject or required intervention to prevent one of the outcomes listed above, or that would suggest any significant hazard, contraindication, side effect, or precaution that may be associated with the use of the investigational product.

10.2.2.2 Reporting of Serious Adverse Events

Any SAE must be reported by the investigator if it occurs during the clinical study or within 7 days of receiving the study drug, whether or not the SAE is considered to be related to the investigational product. An SAE report consists of the SAE form, the AE form, and the concomitant medication form. A copy of these forms must be faxed **within 24 hours** for the attention of the product safety scientist at:

The investigator should not wait to receive additional information to document fully the event before notification of a SAE, though additional information may be requested. Where applicable, information from relevant laboratory results, hospital case records, and autopsy reports should be obtained.

Instances of death, congenital abnormality, or an event that is of such clinical concern as to influence the overall assessment of safety, if brought to the attention of the investigator at any time after cessation of study drug administration and linked by the investigator to this study, should be reported to the study monitor.

The sponsor will promptly notify all relevant investigators and the regulatory authorities of findings that could adversely affect the safety of subjects, impact on the conduct of the study or alter the institutional review board (IRB) approval/favorable opinion of the study. The sponsor, will expedite the reporting to all concerned investigators, to the IRBs, where required, and to the regulatory authorities of all adverse reactions that are both serious and unexpected.

10.2.3 Clinical Laboratory

The hematology and clinical chemistry laboratory analyses will be performed by certified laboratories. Reference ranges will be supplied by each laboratory and used by the investigator to assess the laboratory data for clinical significance and pathological changes.

10.2.3.1 Hematology, Chemistry, and Urine Dipstick

Blood samples for the clinical safety laboratory tests will be collected at Screening 1 and on PK Phase Period 5 (refer to Schedule of Assessments Table in Appendix A). Samples for serum chemistry tests will be collected in the morning after obtaining vital signs and after overnight fasting, but before meals and study drug administration. The test results from screening will serve as the baseline for future clinical assessments.

Certified laboratories will process and provide results for the tests conducted at screening and throughout the study. The certified study laboratories for sample shipment and contact information are provided in the Laboratory Manual.

Table 2 Listing of Clinical Laboratory Tests

Hematology	Clinical Chemistry	Urine Dipstick
Hematocrit Hemoglobin Red blood cell (RBC) count White blood cell (WBC) count Neutrophils bands (if detected) Lymphocytes Monocytes Basophils (if detected) Eosinophils (if detected) Absolute platelet count Mean corpuscular hemoglobin (MCH) Mean corpuscular volume (MCV) Mean corpuscular hemoglobin concentration (MCHC)	Serum glutamic-pyruvic transaminase (SGPT/ALT) Serum glutamic-oxaloacetic transaminase (SGOT/AST) (screening) Alkaline phosphatase Sodium Potassium Bicarbonate Glucose Calcium Total Cholesterol Triglycerides Chloride High-density lipoprotein (HDL) cholesterol Low-density lipoprotein (LDL) cholesterol Bilirubin (screening) Glycosylated hemoglobin (screening) Creatinine Albumin	Leukocytes Nitrite Specific gravity Ketones pH Protein Blood (hemoglobin) Glucose Urobilinogen Bilirubin

Any laboratory test value obtained during the treatment phases that falls outside the reference range that the investigator considers to be clinically significant will be repeated to verify the out-of-range value and will be followed to a satisfactory clinical resolution. Investigators may consider laboratory abnormalities which are considered clinically significant to be AEs. A laboratory test value that requires a subject to be discontinued from the study or requires a subject to receive treatment will be recorded as an AE. Clinical laboratory testing must be performed by appropriately credentialed laboratory.

10.2.3.2 Prostate-Specific Antigen

Blood samples for PSA will be collected at Screening 1 and PK Phase Period 5 prior to discharge from the clinical facility. The blood sample must be collected before a DRE (if a DRE is also performed).

10.2.4 Vital Sign Measurements

Body temperature, BP and HR will be measured at screening and daily during the PK Phase. (see Appendix A). The vital sign measurements at screening will serve as the baseline measurements for clinical assessments. The subject should be sitting at rest for at least 5 minutes with his feet resting on the floor and before the BP and HR being measured 3 times at 1 to 2 minute intervals.

Blood pressure should be obtained prior to blood draws and measured by an automated, oscillometric device in the non-dominant arm, using a cuff that is appropriate for the size of the arm (during the course of the study, the same size cuff for the subject should be used). Study center personnel should ensure that there has been no recent caffeine or cigarette exposure (within 30 minutes of reading) and that the subject's bladder is empty. During BP measurements, the arm should be supported so that the bottom of the cuff is at the height of the heart (1 to 2 cm above the elbow). The cuff bladder (the part that inflates) should encircle at least 80% of the arm, if in doubt a larger cuff should be used. Whenever possible, the cuff should be in contact with skin, or very light clothing. Neither the subject nor the person measuring the BP should talk during the BP assessment. Study center personnel should explain the need to remain silent for accurate readings in advance.

10.2.5 Physical Examination

A complete physical examination will be performed at Screen 2. A brief examination will be performed at the conclusion of PK Phase Period 5 and will include at minimum examination of head/eyes/ears/nose/throat. Height and weight will be measured at screening only. The subject will wear lightweight clothing and no shoes. Subject's height and weight will be used to calculate BMI.

For all subjects, a symptom-directed physical examination will be performed when necessary. Any relevant findings from the physical examination during screening will be recorded on the Medical History CRF/eCRF (for findings from the past). Any significant physical examination findings after dosing will be recorded as AEs.

10.2.6 International Prostate Symptom Score (I-PSS)

The I-PSS, a validated questionnaire used to assess the severity and impact of urinary symptoms, will be used to exclude subjects with moderate to severe symptoms of benign prostate hypertrophy (Appendix C). Subjects will complete the I-PSS provided by the sponsor as defined in the Schedule of Assessments Table (Appendix A). The screening I-PSS score (total I-PSS) must be ≤ 19 to meet eligibility requirements. The I-PSS questionnaire will be repeated for early withdrawal subjects.

10.3 Handling and Processing of PK Blood Sample Collections

Results from a recent study evaluating the degradation of TU to T in conditions typically used in clinical studies showed that for subjects receiving oral TU, the analysis of T in blood collected in red top tubes to separate serum causes overestimation of T exposure. This overestimation occurs because of the *ex vivo* conversion of TU to T by non-specific esterases in blood. *Ex vivo* conversion can be minimized by collecting blood into tubes that contain the esterase inhibitor

sodium fluoride (NaF), by immediately placing the samples on ice after collection, and by processing the samples at 4°C. Therefore analysis of T and TU in plasma, combined with the addition of NaF in the sample collection tube as an esterase inhibitor is being used in this study.[10]

The total volume of blood to be collected from each subject during the study will not exceed approximately 500 mL. Details on the handling and processing of samples are provided in the Laboratory Manual.

10.4 Appropriateness of Measurements

The PK and safety assessments planned for this study are widely used and generally recognized as reliable, accurate, and relevant for a pharmacokinetics and tolerability study.

11 STATISTICAL METHODS

11.1 Statistical and Analytical Plans

The PK, and safety variables and associated analyses are described in this section.

General methodology will include descriptive tabular and/or graphical summarizations by meal type at each dosing session of the PK Phase. Continuous variables will be presented using the descriptive statistics of number of observations (n), mean, standard deviation, standard error of the mean, median, minimum, and maximum values. Categorical values will be summarized with counts and percentages.

All collected data will be presented in listings.

11.2 Pharmacokinetic Endpoints

The pharmacokinetics of total T will be assessed by using noncompartmental analysis to analyze the total T concentrations from PK samples collected during each of the 5 treatment periods within the PK Phase of the study. The primary comparison of interest will be the dosing interval following the five protocol defined breakfasts (AM dose). The total T PK parameters to be assessed within each relevant dosing interval will be peak concentration (C_{max}), the time of peak concentration (T_{max}), the area under the curve over the dosing interval (AUC_{12}) and the time-weighted average total T concentration (C_{avg}). Also to be calculated, when sufficient concentration data exist, will be the analogous parameters for the dosage interval following the PM dose of TU during each of the 5 treatment periods within the PK Phase, and the analogous PK parameters (C_{max}, T_{max}, AUC_{24} and C_{avg}) for the combined 24-hour period that includes both the AM and the PM doses of TU for each specific treatment period.

The concentrations and pharmacokinetic parameters for the individual subjects will be listed, and tabular summaries provided by treatment, along with appropriate descriptive statistics.

The 30 gram fat breakfast treatment will serve as the reference meal in the comparisons to identify the effect of meal type on C_{max}, AUC_{12} and C_{avg} for total T. Subjects must have consumed the reference meal containing 30 g fat and at least one other treatment meal during the PK Phase, and to be evaluable for at least C_{max} or AUC_{12} with respect to those minimum two meals in order to be included in the PK population.

An analysis of variance (ANOVA) will be performed on the natural logarithms of C_{max}, AUC_{12} and C_{avg} with treatment received, sequence, and period as fixed effects and subject as a random effect within sequence. Treatment carryover effects will be estimated by testing sequence using subjects within sequence as the error term. Two-way contrasts will be made using the 30 g fat meal as the

reference treatment, and the point estimate and 90% confidence interval (CI) for the least squares (LS) mean difference in PK parameters on the log scale between the contrasted treatments will be exponentiated to obtain estimates for ratios of LS geometric means on the original scale. No food effect will be concluded for a contrasted treatment if the 90% CI about the ratio of LS geometric means of C_{max} and AUC_{12} for that contrast lie totally within the 0.80 to 1.25 interval.

11.3 Safety Endpoints

11.3.1 Systolic Blood Pressure

Observed values in vital sign measurements, including sBP, dBP, HR, and changes from baseline in sBP, dBP, and HR will be summarized at each scheduled collection visit.

11.3.2 Other Safety Endpoints

Other key safety endpoints are:

- Incidence of AEs
- Change in physical examination findings
- Change in vital sign measurements
- Change in clinical laboratory tests, including hematocrit, and PSA.

All safety endpoints will be analyzed using the safety population except if otherwise defined..

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 15.1. An AE is considered treatment-emergent if it begins or worsens in severity after the first dose of randomized study drug. The number and percentage of subjects with treatment emergent adverse events (TEAEs) will be tabulated by system organ class (SOC) and preferred term. 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.

Physical examination and results will be summarized at each scheduled visit.

Laboratory tests will be performed at screening 1 and at Day 6 and will be summarized are noted in Section 10.2.3.

11.4 Other Variables

11.4.1 Demographic and Other Baseline Characteristics

Descriptive statistical methods will be used to tabulate and summarize demographics and baseline characteristics (age [years], race, ethnicity, height, weight, body mass index, I-PSS, etc.).

11.4.2 Study Drug Exposure and Compliance

Duration of treatment in days will be summarized for all subjects. The number of subjects who required termination of study drug treatment will be summarized.

Compliance will be calculated as the actual number divided by the expected number of dosages.

11.4.3 Medical and Medication History

Medications and a complete medical history will be obtained at screening. These will serve as the baseline for future clinical assessments.

11.4.4 Prior and Concomitant Medications

Prior and concomitant medications will be coded using the September 2012 World Health Organization (WHO) Drug Dictionary. Prior medications will be 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 will be 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 in separate tables.

All concomitant medications administered will be tabulated in a data listing.

11.5 Handling of Missing Data

Missing PK concentrations will not be imputed. A missing concentration value adjacent to the existing C_{max} will make a subject non-evaluable for C_{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 by extending the trapezoid to the next existing concentration. Leading,

trailing and embedded BLQ values will be treated as 0.5 x lower limit of quantitation (LLOQ) for T. Missing actual sample collection times may be replaced with nominal scheduled sample collection times based on case-by-case review.

11.6 Sample Size

Approximately 20 hypogonadal subjects will be enrolled at two to three study centers. This number is based on the following considerations and assumptions:

If 20 subjects are enrolled, approximately 16 subjects are expected to complete the PK Phase.

11.7 Protocol Deviations

The investigator should not implement any deviation from the protocol without prior review and agreement by the sponsor and in accordance with the IRB and local regulations, except when necessary to eliminate an immediate hazard to study subjects. When a deviation from the protocol is deemed necessary for an individual subject, the investigator must alert one of the following people:

Primary Contact	**Alternate Contact**
Theodore Danoff, MD, PhD Clarus Therapeutics, Inc. 555 Skokie Blvd., Suite 340 Northbrook, IL 60062 United States (mobile) +1 215 219-7446 (office) +1 847 562-4300	Cheryl Demos Fludas Clarus Therapeutics, Inc. 555 Skokie Blvd., Suite 340 Northbrook, IL 60062 United States (office) + 847 562-4300

Such contact must be made as soon as possible to permit a review by the investigator/sponsor to determine the impact of the deviation on the subject and/or the study. Any significant protocol deviations affecting subject eligibility and/or safety must be reviewed and/or approved by the IRB, as applicable, before implementation.

Deviations will be listed in the clinical study report.

12 QUALITY ASSURANCE AND QUALITY CONTROL

12.1 Audit and Inspection

Study centers and study documentation may be subject to Quality Assurance audit during the course of the study by the sponsor or its nominated representative. In addition, inspections may be conducted by regulatory authorities at their discretion.

12.2 Monitoring

Data for each subject will be recorded on a CRF/eCRF. Data collection must be completed for each subject who signs an informed consent form (ICF) and is administered study drug.

In accordance with current Good Clinical Practice and International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guidelines, the study monitor will carry out source document verification at regular intervals to ensure that the data collected in the CRF/eCRF are accurate and reliable.

The investigator must permit the monitor, the IRB, the sponsor's internal auditors, and representatives from regulatory authorities direct access to all study-related documents and pertinent hospital or medical records for confirmation of data contained within the DRF/eCRFs.

12.3 Data Management and Coding

Data Management and coding activities include setting up a relevant database and data transfer mechanisms, along with appropriate validation of data and resolution of queries.

Study centers will enter data directly onto a paper CRF/eCRF for entry into a secure data base. All data must be verifiable against source documents at the study center. Data recorded directly on the CRF/eCRF will be identified and the CRF/eCRF will be considered the source document.

Medical coding will use MedDRA version 15.1 for concomitant diseases and AEs and WHODrug dictionary dated September 2012 for concomitant diseases and AEs and WHODrug for medications.

Missing or inconsistent data will be queried in writing to the investigator for clarification. Subsequent modifications to the database will be documented.

13 RECORDS AND SUPPLIES

13.1 Drug Accountability

On receipt of the study drug, the investigator (or deputy) will conduct an inventory of the supplies and verify that study drug supplies are received intact and in the correct amounts. The investigator will retain a copy of this receipt at the study center and return the original receipt to the study monitor. The monitor may check the study supplies at each study center at any time during the study.

It is the responsibility of the study monitor to ensure that the investigator (or deputy) has correctly documented the amount of the study drug received, dispensed, and returned on the dispensing log that will be provided and that the drug is stored properly. A full drug accountability log will be maintained at the study center at all times. The study monitor will perform an inventory of study drug at the close-out visit to the study center. All discrepancies must be accounted for and documented.

14 ETHICS

14.1 Institutional Review Board

Before initiation of the study at each study center, the protocol, the ICF, other written material given to the subjects, and any other relevant study documentation will be submitted to the appropriate IRB. Written approval of the study and all relevant study information must be obtained before the study center can be initiated or the study drug is released to the investigator. Any necessary extensions or renewals of IRB approval must be obtained for changes to the study such as amendments to the protocol, the ICF or other study documentation. The written approval of the IRB together with the approved ICF must be filed in the study files.

The investigator will report promptly to the IRB any new information that may adversely affect the safety of the subjects or the conduct of the study. The investigator will submit written summaries of the study status to the IRB as required. On completion of the study, the IRB will be notified that the study has ended.

14.2 Regulatory Authorities

Relevant study documentation will be submitted to the regulatory authorities, according to local/national requirements, for review and approval before the beginning of the study. On completion of the study, the regulatory authorities will be notified that the study has ended.

14.3 Ethical Conduct of the Study

The investigators and all parties involved in this study should conduct the study in adherence to the ethical principles based on the Declaration of Helsinki, Good Clinical Practice (GCP), ICH guidelines, and the applicable national and local laws and regulatory requirements.

14.4 Informed Consent

The process of obtaining informed consent must be in accordance with applicable regulatory requirement(s) and must adhere to GCP.

The investigator is responsible for ensuring that no subject undergoes any study-related examination or activity before that subject has given written informed consent to participate in the study.

The investigator or designated personnel will inform the subject of the objectives, methods, anticipated benefits and potential risks and inconveniences of the study. The subject should be given every opportunity to ask for clarification of any points he does not understand and, if necessary, ask for more information. At the end of the interview, the subject will be given ample

time to consider the study. Subjects will be required to sign and date the ICF. After signatures are obtained, the ICF will be kept and archived by the investigator in the investigator's study file. A signed and dated copy of the subject ICF will be provided to the subject or their authorized representative.

It should be emphasized that the subject may refuse to enter the study or to withdraw from the study at any time, without consequences for their further care or penalty or loss of benefits to which the subject is otherwise entitled. Subjects who refuse to give or who withdraw written informed consent should not be included or continue in the study.

If new information becomes available that may be relevant to the subject's willingness to continue participation in the study, a new ICF will be approved by the IRB(s) (and regulatory authorities, if required). The study subjects will be informed about this new information and re consent will be obtained.

14.5 Subject Confidentiality

Monitors, auditors, and other authorized agents of the sponsor and/or its designee, the IRB(s) approving this research, and the US FDA, as well as that of any other applicable agency(ies), will be granted direct access to the study subjects' original medical records for verification of clinical study procedures and/or data, without violating the confidentiality of the subjects to the extent permitted by the law and regulations. In any presentations of the results of this study or in publications, the subjects' identity will remain confidential.

All personal data collected and processed for the purposes of this study should be managed by the investigator and his/her staff with adequate precautions to ensure confidentiality of those data, and in accordance with the Health Insurance Portability and Accountability Act[10], applicable to national and/or local laws and regulations on personal data protection.

15 REPORTING AND PUBLICATION, INCLUDING ARCHIVING

Essential documents are those that individually and collectively permit evaluation of the study and quality of the data produced. After completion of the study (end of study defined as the date of the last visit of the last subject), all documents and data relating to the study will be kept in an orderly manner by the investigator in a secure study file. This file will be available for inspection by the sponsor or its representatives. Essential documents should be retained for 2 years after the final marketing approval in an International Conference on Harmonization (ICH) region or for at least 2 years since the discontinuation of clinical development of the investigational product. The sponsor is responsible for informing the study center when these documents no longer need to be retained. The investigator must contact the sponsor before destroying any study related documentation. In addition, all subject medical records and other source documentation will be kept for the maximum time permitted by the hospital, institution, or medical practice.

The sponsor intends to work with investigators to collectively publish results of the study in a peer-reviewed medical journal where authorship generally will follow level of participation in the study. Furthermore, the sponsor must review and approve any results of the study or abstracts for professional meetings prepared by the investigator(s). Published data must not compromise the objectives of the study. Data from individual study centers in multicenter studies will not be published separately.

16 REFERENCES

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Appendices

Appendix A. SCHEDULE OF ASSESSMENTS

Table 3 Schedule of Assessments

Activity	Screening Phase		Treatment Phase							Safety Follow-Up Phase
	Screen 1	Screen 2	14 (±2) Day Run-In Phase		PK Phase					Phone or Clinic Visit [a]
	Day -28 to -21	Approx 7 (±2) days post Screen 1	Dosing Day 1	Dosing Day 14	Period 1/ Day 1 Dosing Day 15	Period 2/ Day 2 Dosing Day 16	Period 3/ Day 3 Dosing Day 17	Period 4/ Day 4 Dosing Day 18	Period 5[e]/ Day 5-6 Dosing Day 19	5 to 7 Days post Last Dose
Informed consent	X									
Inclusion/Exclusion Review	X	X	X							
Medical History Review	X									
Prior & Concomitant Meds	X	X	X	X	X	X	X	X	X	X
Physical Examination with DRE		X								X[b]
Brief Physical Examination			X						X[f]	
Weight, Height, and BMI	X									
Adverse Event Assessment		X	X	X	X	X	X	X	X	X
Vital Signs (triplicate sitting BP & HR)	X		X		X	X	X	X	X	X[b]
Complete Safety Lab (fasting) (Period 5 labs will be drawn at the 24-hour post AM dose)	X				X				X	X[b]
Urine Dipstick	X									
Serum Total Testosterone (T) between 6:00 and 10:00 AM (7±2 days apart)	X	X								

Activity	Screening Phase		Treatment Phase							Safety Follow-Up Phase
	Screen 1	Screen 2	14 (±2) Day Run-In Phase		PK Phase					Phone or Clinic Visit [a]
	Day -28 to -21	Approx 7 (±2) days post Screen 1	Dosing Day 1	Dosing Day 14	Period 1/ Day 1	Period 2/ Day 2	Period 3/ Day 3	Period 4/ Day 4	Period 5[e]/ Day 5-6	5 to 7 Days post Last Dose
					Dosing Day 15	Dosing Day 16	Dosing Day 17	Dosing Day 18	Dosing Day 19	
PSA (Period 5 PSA will be drawn at the 24-hour post AM dose)	X								X	
Study Meal Administration			X[c]	X[c]	X	X	X	X	X	
Pre-dose Total T and DHT between 6:00 and 10:00 AM			X							
Serial PK Sampling Total T, DHT and TU					X[d]	X[d]	X[d]	X[d]	X[d]	
I-PSS	X									
Dispense Bottle of Study Drug			X							
Dosing instructions given for BID dosing for Run-In Phase -- Day 1 PM Dose to Day 14 AM. Doses will be self-administered at home immediately prior to breakfast and dinner meals			X							
In clinic Study Drug Administered AM			X[c]		X	X	X	X	X	
In clinic Study Drug Administered PM				X[c]	X	X	X	X	X	
Study Drug Accountability				X	X	X	X	X	X	

[a] A visit done by telephone is acceptable if follow-up for safety issues (i.e. abnormal lab result, or adverse event) is not needed.
[b] Collect sample or complete procedure if abnormal at Period 5 or needed as follow-up for a safety concern.
[c] Subjects will take their AM dose on Day 1 and PM dose on Day 14 in the clinic with meals provided. The doses will be dispensed from the bottle that was dispensed on Dosing Day 1. Subjects will take their study dose immediately prior to the protocol-defined meal provided at the Clinic. Study drug accountability will be performed following the PM dose on Day 14.
[d] Blood samples for total T: Subjects will have 4 NaF-EDTA-containing tubes (for plasma) collected. Samples will be collected as follows: 0 (pre-morning dose), 2, 4, 6, 9, 12, 14, 16, 18, 21, and 24 hours after morning dose. The 24-hour PK sample for Day 1, 2, 3, and 4 will also serve as the 0 (pre-dose) PK sample for Day 2, 3, 4, and 5, respectively. Samples following pre-morning dose must be drawn within 10 minutes of the nominal time relative to the AM dose taken each Period.
[e] A brief physical examination will be performed and subjects will depart clinic the following morning on Day 6. No study medication will be administered after PK Phase Period 5.

Appendix B. INVESTIGATOR SIGNATURE PAGE

Investigator Signature Page

Protocol Title: A Phase 2 Study of the Effect of Meals with Various Amounts of Fat Given Immediately After Dosing on the Pharmacokinetics of an Oral Testosterone Undecanoate in Hypogonadal

Protocol Number: CLAR-16015

Confidentiality and cGCP Compliance Statement

I, the undersigned, have reviewed this protocol (and amendments), including appendices, and I will conduct the study as described in compliance with this protocol (and amendments), GCP, and relevant ICH guidelines.

Once the protocol has been approved by the IRB, I will not modify this protocol without obtaining prior approval of Clarus Therapeutics, Inc. and of the IRB. I will submit the protocol amendments and/or any ICF modifications to Clarus Therapeutics, Inc. and IRB, and approval will be obtained before any amendments are implemented.

I understand that all information obtained during the conduct of the study with regard to the subjects' state of health will be regarded as confidential. No subjects' names will be disclosed. All subjects will be identified by assigned numbers on all CRF/eCRFs, laboratory samples, or source documents forwarded to the sponsor. Clinical information may be reviewed by the sponsor or its agents or regulatory agencies. Agreement must be obtained from the subject before disclosure of subject information to a third party.

Information developed in this clinical study may be disclosed by Clarus Therapeutics, Inc., to other clinical investigators, regulatory agencies, or other health authority or government agencies as required.

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Investigator Signature Date

_____

Printed Name

_____

Institution

Appendix C. INTERNATIONAL PROSTATE SYMPTOM SCORE (I-PSS)

International Prostate Symptom Score
(I-PSS)

INTERNATIONAL PROSTATE SYMPTOM SCORE (I-PSS)

		Not at all	Less Than 1 Time in 5	Less Than Half the Time	About Half the Time	More Than Half the Time	Almost Always
1	Over the past month, how often have you had a sensation of not emptying your bladder completely after you finished urinating?	0	1	2	3	4	5
2	Over the past month, how often have you had to urinate again less than two hours after you finished urinating?	0	1	2	3	4	5
3	Over the past month, how often have you found you stopped and started again several times when you urinated?	0	1	2	3	4	5
4	Over the past month, how often have you found it difficult to postpone urination?	0	1	2	3	4	5
5	Over the past month, how often have you had a weak urinary stream?	0	1	2	3	4	5
6	Over the past month, how often have you had to push or strain to begin urination?	0	1	2	3	4	5
		None	1 time	2 times	3 times	4 times	5 or more times
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?	0	1	2	3	4	5

Total I-PSS Score S =

(I-PSS continued)

QUALITY OF LIFE DUE TO URINARY SYMPTOMS

		Delighted	Pleased	Mostly Satisfied	Mixed About Equally Satisfied and Dissatisfied	Mostly Dissatisfied	Unhappy	Terrible
1	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?	0	1	2	3	4	5	6

Quality of life assessment index L =

Appendix D. PROTOCOL DEFINED MEALS

Diet Meal Plan B 15 g Fat Breakfast							
Meal	Food Description	Amount	Measure	Energy	Protein	Fat	Carbohydrate
15 g Fat Breakfast 1	KELLOGG'S FROSTED FLAKES	60	gram	221.4	2.38	1.01	53.52
	Milk, lowfat, fluid, 1% milkfat, with added vitamin A and vitamin D	0.75	1 cup	76.86	6.17	1.78	9.13
	Nature Valley Protein Chewy Bar	1	counted prepackage	190	10	12	14
	Apple juice, canned or bottled, unsweetened	8	1 fl oz	114.08	0.25	0.32	28.02
	Chobani non fat fruit yogurt (150 gr)	1	counted prepackage	120	12	0	19
	Motts Cinnamon Applesauce sweetened	1	counted prepackage	100	0	0	25
			Actual	822.34	30.79	15.11	148.68
			Goal	850.0	31.9	15.0	146.9
15 g Fat Breakfast 2	Thomas 100% Whole Wheat Bagel (95gr)	95	gram	240	11	1.5	45
	Butter, salted	10	gram	71.7	0.09	8.11	0.01
	Motts Cinnamon Applesauce sweetened	226	gram	200	0	0	50
	Weight Watchers Smart Ones Ham and Cheese Scramble	1	counted pre	180	19	6	13
	Ocean Spray Cranberry Cocktail Drink, 5.5 fl oz, 48 Count	2	counted pre	160	0	0	38
			Actual	851.7	30.08	15.61	146.01
			Goal	850.0	31.9	15.0	146.9

Diet Meal Plan C 30 g Fat Breakfast							
Meal	Food Description	Amount	Measure	Energy	Protein	Fat	Carbohydrate
30 g Fat Breakfast 1	Jimmy Dean Bacon, Egg and Cheese Sandwich biscuit 3.6 oz	1	counted prepackage	330	10	20	27
	Belvita Breakfast biscuit Nabisco 50g cinnamon brown sugar	1	counted prepackage	225	4.1	8	35.3
	Chobani non fat fruit yogurt (150 gr)	1	counted prepackage	120	12	0	19
	Milk, chocolate, fluid, commercial, lowfat, with added vitamin A and vitamin D	1	1 cup	177.5	8.1	2.5	31.5
			Actual	852.5	34.2	30.5	112.8
			Goal	850.0	31.9	30.0	113.1
30 g Fat Breakfast 2	Thomas 100% Whole Wheat Bagel (95gr)	1	counted prepackage	240	11	1.5	45
	Butter, salted	15	gram	107.55	0.13	12.17	0.01
	Egg, whole, cooked, hard-boiled	1	1 large	77.5	6.29	5.3	0.56
	Bacon, fully cooked, pork (9 gr/sl)	30	gram	140.4	10.18	10.53	0.51
	Motts Cinnamon Applesauce sweetened	1	counted prepackage	100	0	0	25
	Apple juice, canned or bottled, unsweetened	13.5	1 fl oz	192.51	0.42	0.54	47.29
			Actual	857.96	28.01	30.04	118.37
			Goal	850.0	31.9	30.0	113.1

Diet Meal Plan D 45 g Fat Breakfast							
Meal	Food Description	Amount	Measure	Energy	Protein	Fat	Carbohydrate
45 g Fat Breakfast 1	Jimmy Dean sausage Egg Cheese croissant	1	counted prepackage	410	12	28	27
	Cheese, mozzarella, part skim milk, low moisture	1	1 oz	85.62	7.36	5.68	1.09
	Nature Valley Protein Chewy Bar	1	counted prepackage	190	10	12	14
	Ocean Spray Cranberry Cocktail Drink, 5.5 fl oz, 48 Count	2	counted prepackage	160	0	0	38
			Actual	845.6	29.4	45.7	80.1
			Goal	850.0	31.9	45.0	79.4
45 g Fat Breakfast 2	Butter, salted	10	gram	71.7	0.09	8.11	0.01
	Weight Watchers Smart Ones Ham and Cheese Scramble	1	counted prepackage	180	19	6	13
	Croissants, butter, large (67g)	2	1 croissant, large	544.04	10.99	28.14	61.37
	Candies, milk chocolate	9.1	gram	48.69	0.7	2.7	5.41
			Actual	844.42	30.77	44.95	79.78
			Goal	850.0	31.9	45.0	79.4

Diet Meal Plan E (FDA Guideline Meal) 55 g Fat Breakfast							
Meal	Food Description	Amount	Measure	Energy	Protein	Fat	Carbohydrate
55 g Fat Breakfast - Per FDA Guidelines for Food Effect	Oreida Tater Tots (approximately 15 pieces)	140	gram	260.47	3.26	13.02	32.56
	Commercially prepared sliced bread (38 gr/sl) - Buttered toast	76	gram	191.52	9.46	2.66	32.46
	Butter, salted (used for toast and eggs)	20	gram	143.4	0.17	16.22	0.01
	Bacon, fully cooked, pork (9 gr/sl)	18	gram	84.24	6.11	6.32	0.31
	Egg, whole (fried in butter or scrambled with butter added)	2	1 large	143	12.56	9.51	0.72
	Milk, whole, 3.25% milkfat, with added vitamin D	8	1 fl oz	148.84	7.69	7.93	11.71
			Actual	971.47	39.24	55.66	77.77
			Goal	1000.0	37.5	55.6	87.5

Diet Lunch and Dinner Plan for A, B, C, D and E. Subjects may choose any lunch and dinner option listed below in any combination. Subjects must be instructed to consume entire dinner meals.							
Meal	Food Description	Amount	Measure	Energy	Protein	Fat	Carbohydrate
Lunch or Dinner Option 1 Total	amy's bowl brocolli and cheddar bake 9.5 oz	1	counted prepackage	427	16.5	20.6	44.9
	Lays potato chips 1 oz	1	counted prepackage	153	1.28	10.07	15
	Chobani non fat fruit yogurt (150 gr)	1	counted prepackage	120	12	0	19
	Ocean Spray Cranberry Cocktail Drink, 5.5 fl oz, 48 Count	1	counted prepackage	80	0	0	19
			Actual	780	29.78	30.67	97.9
			Goal	775.0	29.1	30.0	97.2
lunch or Dinner Option 2 Total	amy's bowls mexican casserole 9.5 oz	1	counted prepackage	380	12	16	48
	Candies, milk chocolate (Hersey Kiss 4.55 gr/kiss)	18.2	gram	97.37	1.39	5.4	10.81
	Ocean Spray Cranberry Cocktail Drink, 5.5 fl oz, 48 Count	1	counted prepackage	80	0	0	19
	Chobani non fat fruit yogurt (150 gr)	1	counted prepackage	120	12	0	19
	Cheese, colby	1	1 oz	111.7	6.74	9.1	0.73
			Actual	789.07	32.13	30.5	97.54
			Goal	775.0	29.1	30.0	97.2
Lunch or Dinner Option 3 Total	amy's bowl pesto tortellini 9.5 oz	1	counted prepackage	440	17	20	50
	Applesauce, canned, unsweetened	113	gram	47.46	0.19	0.11	12.74
	Chobani non fat fruit yogurt (150 gr)	1	counted prepackage	120	12	0	19
	Lays potato chips 1 oz	1	counted prepackage	153	1.28	10.07	15
			Actual	760.46	30.47	30.18	96.74
			Goal	775.0	29.1	30.0	97.2

Meal	Food Description	Amount	Measure	Energy	Protein	Fat	Carbohydrate
Lunch or dinner Option 4 (no yogurt) Total	Marie Callender Grilled Chicken alfredo bake 369g	1	counted prepackage	480	28	21	45
	Candies, milk chocolate (Hersey Kiss 4.55 gr/kiss)	27.3	gram	146.05	2.09	8.1	16.22
	Orange juice, canned, unsweetened	10	1 fl oz	146.17	2.11	0.47	34.24
			Actual	772.22	32.2	29.56	95.46
			Goal	775.0	29.1	30.0	97.2
Lunch or dinner Option 5 Total	Lays potato chips 1 oz	1	counted prepackage	153	1.28	10.07	15
	Nature Valley Protein Chewy Bar	1	counted prepackage	190	10	12	14
	Apple juice, canned or bottled, unsweetened	4	1 fl oz	57.04	0.12	0.16	14.01
	Lean Cuisine Craveables Four Cheese Pizza	1	counted prepackage	380	19	7	60
			Actual	780.04	30.4	29.23	103.01
			Goal	775.0	29.1	30.0	97.2

FDA High Fat Breakfast (50%; 55 gr) " Meal Plan E"									
Calories	Protein g	Fat g	Carb g	Protein calories	Fat calories	Carb calories	% Protein	% fat	% Carb
2400	90	115	251.25	360	1035	1005	15	43.125	41.875
1000	37.5	55.56	87.5	150	500	350	15	50	35
775	29.1	30.0	97.2	116.3	270.0	388.7	15.0	34.8	50.2
775	29.1	30.0	97.2	116.3	270.0	388.7	15.0	34.8	50.2

45 g Fat "Meal Plan D"									
Calories	Protein g	Fat g	Carb g	Protein calories	Fat calories	Carb calories	% Protein	% fat	% Carb
2400	90.0	105.0	273.8	360.0	945.0	1095.0	15.0	39.4	45.6
850	31.9	45.0	79.4	127.5	405.0	317.5	15.0	47.6	37.4
775	29.1	30.0	97.2	116.3	270.0	388.8	15.0	34.8	50.2
775	29.1	30.0	97.2	116.3	270.0	388.8	15.0	34.8	50.2

30 g Fat "Meal Plan C"									
Calories	Protein g	Fat g	Carb g	Protein calories	Fat calories	Carb calories	% Protein	% fat	% Carb
2400	90.0	90.0	307.5	360.0	810.0	1230.0	15.0	33.8	51.3
850	31.9	30.0	113.1	127.5	270.0	452.5	15.0	31.8	53.2
775	29.1	30.0	97.2	116.3	270.0	388.8	15.0	34.8	50.2
775	29.1	30.0	97.2	116.3	270.0	388.8	15.0	34.8	50.2

15 g Fat "Meal Plan B"									
Calories	Protein g	Fat g	Carb g	Protein calories	Fat calories	Carb calories	% Protein	% fat	% Carb
2400	90.0	75.0	341.3	360.0	675.0	1365.0	15.0	28.1	56.9
850	31.9	15.0	146.9	127.5	135.0	587.5	15.0	15.9	69.1
775	29.1	30.0	97.2	116.3	270.0	388.8	15.0	34.8	50.2
775	29.1	30.0	97.2	116.3	270.0	388.8	15.0	34.8	50.2

Fasting "Meal Plan A"									
Calories	Protein g	Fat g	Carb g	Protein calories	Fat calories	Carb calories	% Protein	% fat	% Carb
775	29.1	30.0	97.2	116.3	270.0	388.8	15.0	34.8	50.2
775	29.1	30.0	97.2	116.3	270.0	388.8	15.0	34.8	50.2

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 and with a high-calorie and high-fat meal (approximately 1000 calories and 50% of the calories from fat).