1.0 TITLE PAGE

Clinical Study Protocol: LPCN 1021-16-003

Dosing Flexibility Study of Oral Testosterone Undecanoate (TU, LPCN 1021) in Hypogonadal Men.

Investigational Product	:	Testosterone Undecanoate (TU, LPCN 1021)
Date of Protocol	:	March 7, 2017
FDA IND No.	:	106476
Development Phase	:	Phase 1
Indication	:	Testosterone replacement therapy in adult, 18 years or older, males for conditions associated with a deficiency or absence of endogenous testosterone – primary hypogonadism (congenital or acquired) or secondary hypogonadism (congenital or acquired)
Investigator	:	Multi-Center, US
Sponsor	:	Lipocine Inc. 675 Arapeen Drive, Suite 202, Salt Lake City, Utah – 84108 Tel: +1-801-994-7383 Fax: +1-801-994-7388
Sponsor / Emergency Contact	:	Nachiappan Chidambaram 675 Arapeen Drive, Suite 202, Salt Lake City, Utah – 84108 Tel: +1-801-994-7383, Ext 2188 Fax: +1-801-994-7388 Email: nc@lipocine.com
Protocol Version	:	02
Amendments	:	N/A

Confidentiality Statement

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2.0 SUMMARY OF CHANGES TO PROTOCOL IN VERSION 02

Version 02 of the LPCN 1021-16-003 study protocol was developed to make the following changes to the study:

- Added a pre-dose blood draw the morning of Day 24 (Visit 5) to measure pre-dose testosterone concentrations for subjects at selected sites. Selected sites will receive a notification letter requesting that they perform the additional blood draw on Day 24. The schedule of events was updated accordingly.
- Restricted the pre-dose blood draw the Day of 23 (Visit 4) to apply only to subjects at selected sites. Selected sites will receive a notification letter requesting that they perform Visit 4.
- Updated the schedule of events to clarify that adverse events will be collected starting at Visit 1.
- Minor editorial changes for protocol consistency.

3.0 SYNOPSIS

Sponsor : Lipocine Inc.

Protocol Number : LPCN 1021-16-003

Study Drug Name : Testosterone Undecanoate Capsule

Phase of Development : Phase 1

Active Ingredient : Testosterone Undecanoate

Date of Protocol Synopsis : March 7, 2017

Protocol Title:

Dosing Flexibility Study of Oral Testosterone Undecanoate (TU, LPCN 1021) in Hypogonadal Men.

Objectives:

Primary Objective: To validate an alternate dosing regimen of LPCN 1021 to achieve therapeutic concentrations of T in Hypogonadal Men.

Secondary Objectives: To assess safety and tolerability of LPCN 1021.

Study Population: Hypogonadal males, aged 18–80 years (inclusive), with onset of hypogonadism diagnosed at age < 65 years.

Number of Subjects: 100

Study Endpoints:

Primary Endpoint:

To determine the proportion of LPCN 1021-treated subjects who achieve a 24-hour average serum total testosterone (T) concentration [Cavg (0-24)] within the lab determined normal range starting on Day 24.

Secondary Endpoints:

To determine the proportion of T Cmax below 1500 ng/dL, T Cmax between 1800 and 2500 ng/dL, and T Cmax > 2500 ng/dL in subjects treated with LPCN 1021 starting on Day 24.

Testosterone Cmax is defined as the maximum serum T concentration that occurs in the dosing interval. Starting the afternoon of Day 24, all Cmax values that occur following afternoon, evening and morning doses will be used to compute the proportions.

Additional Evaluation:

To determine the proportion of T 24-hour Cmax below 1500 ng/dL, T Cmax between 1800 and 2500 ng/dL, and T Cmax > 2500 ng/dL in subjects treated with LPCN 1021 starting on Day 24. The T 24-hour Cmax is defined as the maximum serum T concentration that occurs in a 24-hour period.

Methodology:

This is a multicenter, open-label, one treatment study evaluating the efficacy of LPCN 1021 in adult hypogonadal male subjects.

The study is comprised of five scheduled visits:

- Visit 1 and 2 are for screening.
- Visit 3 is scheduled on Day 1 of the study for the start of dosing.
- Visit 4 is a pre-dose blood draw to measure pre-dose testosterone concentrations.
- Visit 5 is for confinement of subjects for intensive pharmacokinetic (PK) sampling.

Visit 1 & 2: Subjects will undergo a screening period to complete the pre-study examinations and to confirm their hypogonadal status. Serum total T below 300 ng/dL based on two consecutive blood samples obtained between 6 and 10 AM, on two separate days at approximately the same time of day (following an appropriate washout of current androgen replacement therapy if required) will be used for screening T levels.

Visit 3: A total of 100 hypogonadal men meeting inclusion criteria and none of the exclusion criteria will be enrolled to the study and assigned to receive 150 mg of LPCN 1021 three times a day for about 24 days (window of 20 to 28 days).

Visit 4 This visit is to be carried out by selected sites that receive a notification letter requesting that they perform Visit 4 (Refer to Selected Sites: Subject Pre-Dose Blood Draws).

Visit 5: Starting the evening of Day 23, subjects will undergo confinement lasting for about 42 hours. Subjects will enter the clinic on the evening of Day 23 (approximately 18 hours prior to the anticipated dosing on the afternoon of Day 24) and will remain confined until the 24-hour blood draw on Day 25 is completed. There is one confinement visit in the study. Subjects will be exited from the study on Day 25.

On Day 23, subjects will arrive at the clinic after taking their evening dose at home with dinner. The subects will receive their morning dose with breakfast at the clinic on Day 24. Following the administration of the afternoon dose with lunch on Day 24 (refer to Section 9.4.1.8), intensive PK sampling will be carried out for up to 24 hours post afternoon dose. Blood samples will be obtained at 0 (pre-dose), 2, 4, 5, 6, 7, 8, 10, 12, 13, 14, 15, 16, 18, 20, 21, 22, 23 and 24 hours relative to afternoon dose. Safety assessments will be carried out periodically during the

study, and at exit. The total duration of the study will be about 25 days not including the screening period.

Selected Sites: Subject Pre-Dose Blood Draws:

Please Note: These steps are to be carried out by selected sites that receive a notification letter requesting that they perform pre-dose blood draws at Visit 4 and as part of Visit 5.

Visit 4: The morning of Day 23, subjects at selected sites will return to the clinic for pre-dose blood draws to measure pre-dose T concentrations. Subjects will leave the clinic after blood draw.

Visit 5: The morning of Day 24, subjects at selected sites will have a pre-dose blood draw to measure pre-dose T concentrations.

Inclusion Criteria

A subject will be eligible for study participation if he meets the following criteria.

1. Voluntarily sign and date the study consent form(s) which have been approved by an Institutional Review Board (IRB). Written consent must be obtained prior to the initiation of any study procedures.
2. Male between 18 and 80 years of age, inclusive, with documented onset of hypogonadism prior to age 65.
3. Subjects should be diagnosed to be primary (congenital or acquired) or secondary hypogonadal (congenital or acquired).
4. Serum total T below 300 ng/dL based on 2 consecutive blood samples obtained between 6 and 10 AM, on two separate days at approximately the same time of day (between 6 and 10 AM), following an appropriate washout of current androgen replacement therapy.
5. Naïve to androgen replacement or has discontinued current treatment and completed adequate washout of prior androgen therapy. Washout must be completed prior to collection of serum T samples to determine study eligibility.
6. Judged to be in good general health as determined by the investigator at screening.

Exclusion Criteria

A subject will not be eligible for study participation if he meets any of the following criteria.

1. History of significant sensitivity or allergy to androgens, or product excipients.
2. Clinically significant findings in the pre-study examinations including abnormal breast examination requiring follow-up.

3. Abnormal prostate digital rectal examination (DRE) with palpable nodule(s).
4. Subjects with symptoms of moderate to severe benign prostatic hyperplasia.
5. Clinically significant abnormal laboratory value, in the opinion of the investigator, in serum chemistry, hematology, or urinalysis including but not limited to:
    a. Baseline hemoglobin < 11.5 g/dL or > 16.5 g/dL
    b. Hematocrit < 35% or > 54%
    c. Serum transaminases > 2.5 times upper limit of normal
    d. Serum bilirubin > 2.0 mg/dL
    e. Creatinine > 2.0 mg/dL
    f. PSA > 2 ng/mL
    g. Prolactin > 17.7 ng/mL.
6. Positive test result for hepatitis A virus immunoglobulin M (HAV-IgM), hepatitis B surface antigen (HBsAg) or hepatitis C virus antibody (HCV Ab) or human immunodeficiency virus antibodies (HIV Ab).
7. History of seizures or convulsions occurring after age 5, including alcohol or drug withdrawal seizures.
8. History of gastric surgery, cholecystectomy, vagotomy, bowel resection or any surgical procedure that might interfere with gastrointestinal motility, pH or absorption.
9. History of any clinically significant illness, infection, or surgical procedure within 1 month prior to study drug administration.
10. History of stroke or myocardial infarction within the past 5 years.
11. History of or current or suspected prostate or breast cancer.
12. History of untreated and severe obstructive sleep apnea.
13. Active alcohol or any drug substance abuse, or history of abuse that will interfere with the subject's ability to participate in the study in the judgement of the investigator.
14. History of long QT syndrome (QTc > 450) or unexplained sudden death in a first degree relative (parent, sibling, or child).
15. Use of known inhibitors (e.g., ketoconazole) or inducers (e.g., dexamethasone, phenytoin, rifampin, carbamazepine) of cytochrome P450 3A (CYP3A) within 30 days prior to study drug administration and through the end of the study.
16. Use of any investigational drug within 5 half-lives of the last dose prior to Study Day –2 without principal investigator and/or sponsor approval.
17. Receipt of any investigational drug by injection within 30 days or 10 half-lives (whichever is longer) prior to study drug administration without principal investigator

and/or sponsor approval.

18. Subjects who are not on stable dose of current medication.
19. Donation or loss of 550 mL or more blood volume (including plasmapheresis) or receipt of a transfusion of any blood product within 3 months prior to the start of treatment.
20. Inadequate venous access for collection of serial blood samples required for pharmacokinetic profiles.
21. Inability to understand and provide written informed consent for the study.
22. Considered by the investigator or the sponsor-designated physician, for any reason, that the subject is an unsuitable candidate to receive LPCN 1021 (when investigator criteria is used, exact reason should be specified).
23. Subject who is not willing to use adequate contraception for the duration of the study.

Investigational Product: Testosterone Undecanoate Oral Capsules, 75 mg TU per capsule.

Doses: The study involves a dose of 150 mg LPCN 1021. The dose is administered as 150 mg TU (2 capsules of 75 mg) three times a day (TID) with a meal (total daily dose of 450 mg taken as 150 mg after breakfast, 150 mg after lunch and 150 mg after dinner).

Administration Route: Oral.

Reference Therapy: Not applicable.

Study Duration: Study duration will be up to 25 days excluding screening.

Stopping Criteria:

All subjects are free to withdraw from the study at any time during the study. In addition, subjects may be withdrawn from the study at the discretion of the investigator if they meet any of the following criteria:

- Any event, in the judgment of the investigator, where continuation of the subject in the trial could put the subject at health risk.
- Increase in hematocrit to > 54%, PSA > 4 ng/mL
- Significant noncompliance with the protocol requirements.
- Lost to follow-up.

Criteria for Evaluation:

The pharmacokinetics of T, dihydrotestosterone (DHT), TU, dihydrotestosterone undecanoate (DHTU) and estradiol (E2) will be assessed starting on Day 24.

Safety and tolerability of LPCN 1021 will be reported over the duration of treatment for the following parameters:

- Change from baseline in physical examinations and laboratory parameters (i.e., chemistries, hematology, hematocrit, lipids, PSA).
- Incidence of AEs.

Statistical Methods: Statistical analyses will be described in the Protocol and SAP.

4.0 LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

4.1. Abbreviations

AE	Adverse event
ALT (SGPT)	Alanine aminotransferase (serum glutamic pyruvic transaminase)
AST (SGOT)	Aspartate aminotransferase (serum glutamic oxaloacetic transaminase)
BID	Twice daily
BMI	Body mass index
BPH	Benign prostate hypertrophy
BUN	Blood urea nitrogen
CI	Confidence interval
CRF	Case Report Form
CRO	Clinical research organization
DEA	Drug Enforcement Agency
DHT	Dihydrotestosterone
DHTU	Dihydrotestosterone undecanoate
E2	Estradiol
ECG	Electrocardiogram
EDC	Electronic data capture
eCRF	Electronic Case Report Form
FAS	Full analysis set
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
HAV-IgM	Hepatitis A virus immunoglobulin M
HBsAg	Hepatitis B surface antigen
HCT	Hematocrit
HCV Ab	Hepatitis C virus antibody
HDL	High-density lipoprotein
HDPE	High-density polyethylene
Hgb	Hemoglobin
HIV Ab	Human immunodeficiency virus antibodies
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
I-PSS	International Prostate Symptom Score
IRB	Institutional Review Board
LDL	Low-density lipoprotein
LH	Luteinizing hormone
MedDRA	Medical Dictionary for Regulatory Activities
PD	Pharmacodynamic
PI	Principal investigator

PK	Pharmacokinetic
PSA	Prostate-specific antigen
RBC	Red blood cell
SAE	Serious adverse event
SAP	Statistical analysis plan
SHBG	Sex hormone binding globulin
SOC	System organ class
WBC	White blood cell
T	Testosterone
TU	Testosterone undecanoate
TID	Three times daily

4.2. Pharmacokinetic and Statistical Abbreviations

AUC	Area under the serum concentration-time curve
AUC_t	Area under the serum concentration-time curve from time zero to time of last measurable concentration
C_{avg}	Average serum concentration
C_{max}	Maximum observed serum concentration
$C_{max-tau}$	The maximum serum concentration that occurs in the dosing interval
T_{max}	Time to maximum observed serum concentration

5.0 TABLE OF CONTENTS

6.0 INTRODUCTION

LPCN 1021 (TU) is an oral capsule developed for use in the proposed indication of replacement therapy in males for conditions associated with a deficiency or absence of endogenous T due to primary or hypogonadotropic hypogonadism.

Testosterone is an endogenous androgen that is responsible for normal growth and development of the male sex organs and for maintenance of secondary sex characteristics. Testosterone has effects that include the growth and maturation of the prostate, seminal vesicles, penis, and scrotum; the development of male hair distribution, such as facial, pubic, chest, and axillary hair; laryngeal enlargement; vocal cord thickening; alterations in body musculature; and fat distribution. Dihydrotestosterone is another androgen endogenously produced in the body. Testosterone and DHT are necessary for the normal development of secondary sex characteristics.

The Endocrine Society defines hypogonadism in men as "a clinical syndrome that results from failure of the testis to produce physiological levels of T (androgen deficiency) and a normal number of spermatozoa due to disruption of one or more levels of the hypothalamic pituitary-testicular axis."[i] Male hypogonadism, a clinical syndrome resulting from insufficient secretion of T, has two main etiologies. Primary hypogonadism is caused by defects of the gonads, such as Klinefelter's Syndrome or Leydig cell aplasia, whereas secondary hypogonadism is the failure of the hypothalamus (or pituitary) to produce sufficient gonadotropins (i.e., follicle stimulating hormone [FSH] and luteinizing hormone [LH]). The 2010 Endocrine Society guidelines recommends replacement therapy for symptomatic men with androgen deficiency to induce and maintain secondary sex characteristics and to improve bone mineral density, sexual function, sense of well-being, and muscle mass and strength.

There are various routes of T preparation administration available in the US. Each of the routes of delivery and formulations are approved to provide T replacement therapy, although each has unique pharmacokinetic properties, limitations, risks, and safety concerns.

Oral administration of native T generally results in low bioavailability as it is extensively metabolized through pre-systemic first-pass metabolism.[ii] The only oral product currently used is a 17-α-alkyl androgens (methyl testosterone), and this product has been associated with serious hepatic adverse effects including life-threatening or fatal complications.

To date, there is no FDA approved oral T replacement therapy product that is not 17-α-alkylated. Availability of an oral product may confer benefits over existing T replacement products

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[i] Bhasin S, Cunningham G, Hayes F, Matsumoto AM, Snyder PJ, Swerdloff RS, et al. Testosterone therapy in men with androgen deficiency syndromes: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab 2010;95(6):2536-59

[ii] Daggett PR, Wheeler MJ, Nabarro JD. Oral testosterone, a reappraisal. Horm Res 1978;9(3):121-9.

including absence of transfer risk, absence of the need for transdermal application, absence of application site reactions or need for self-injections/doctor's office visit for injections, and an improved safety profile compared with 17-α-alkylated androgens.[iii]

LPCN 1021 is an oral capsule product 112.5 mg of TU employing a proprietary formulation composed of lipids. LPCN 1021 oral product is designed to enable absorption of TU via the intestinal lymphatic pathway. Testosterone undecanoate, is a straight chain fatty acid ester of T, which is not alkylated at the 17-alpha position. Testosterone undecanoate is converted to T by non-specific esterases that are abundantly present in the body. Currently, TU is available as an injectable product in the US (brand name, Aveed®). Oral TU is not available in the US, but has been marketed for more than 20 years outside of the US and is available in more than 80 countries, including Canada (as Andriol), for the treatment of male hypogonadism.[iv]

The LPCN 1021 clinical development program included eight Phase 1 studies and one Phase 3 study. In previous clinical studies (Study LPCN 1021-05-001 and Study LPCN 1021-09-001), various oral T undecanoate formulations were evaluated. All formulations increased T concentrations in postmenopausal female and hypogonadal male subjects. Two formulations (07 and 10) were further evaluated in a single ascending dose study in hypogonadal males (Study S361.1.001). Single doses administered ranged from 75 mg to 225 mg, and all doses for both formulations achieved T C_{max} values at or slightly above the eugonadal range. In a multiple ascending dose study (Study M12-778), LPCN 1021 was administered at doses ranging from 75 to 300 mg as a single dose on Day 1 and twice daily from Day 2 to 14 or 28 days with a normal-fat diet.

Effect of food and food-fat content were evaluated on LPCN 1021 product in a clinical study LPCN 1021-14-001. Food affects the rate and extent of TU absorption from the LPCN 1021 drug product with higher absorption occurring when the product is taken with food compared to fasting. However, systemic exposure of T following administration of LPCN 1021 with varying fat contents was evaluated and the data demonstrated that there was no significant influence of varying fat content on T levels.

The Phase 3 clinical study, LPCN 1021-13-001, provides safety, efficacy, and pharmacokinetic data relating to the use of twice daily dosing of LPCN 1021 for T replacement therapy in men with primary and secondary hypogonadism. Results indicate that eugonadal range levels can be achieved with a dose of 225 mg BID taken with a meal; a 225 mg BID dose will be evaluated in the clinical study LPCN 1021-16-002.

The LPCN 1021-16-003 study will evaluate a 150 mg dose three times daily (BID), with a meal.

[iii] Lowdell CP, Murray-Lyon IM. Reversal of liver damage due to long-term methyltestosterone and safety of non-17-a-alkylated androgens. Brit Med J 1985;291(6496):637.

iv Andriol product information. Available at: http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=a9758bea-b15b-42e5-938c-03e3f042b290. Accessed on 08 August 2015

Based on simulated data, 150 mg TID will result in T in the eugonadal range.

Further discussion of the preclinical toxicology, metabolism, and pharmacology can be found in the Investigator's Brochure.

7.0 STUDY OBJECTIVES

7.1. Primary Objective

To validate an alternate dosing regimen of LPCN 1021 to achieve therapeutic concentrations of T in Hypogonadal Men.

7.2. Secondary Objectives

To assess safety and tolerability of LPCN 1021.

7.3. Study Endpoints:

7.3.1. Primary Endpoint:

To determine the proportion of LPCN 1021-treated subjects who achieve a 24-hour average serum total testosterone concentration [Cavg (0-24)] within the lab determined normal range starting on Day 24.

7.3.2. Secondary Endpoint:

To determine the proportion of T Cmax below 1500 ng/dL, T Cmax between 1800 and 2500 ng/dL, and T Cmax > 2500 ng/dL in subjects treated with LPCN 1021 starting on Day 24.

T Cmax is defined as the maximum serum T concentration that occurs in the dosing interval. Starting on Day 24, all T Cmax values that occur following afternoon, evening and morning, doses will be used to compute the proportions.

Additional Evaluation:

To determine the proportion of T 24-hour Cmax below 1500 ng/dL, T Cmax between 1800 and 2500 ng/dL, and T Cmax > 2500 ng/dL in subjects treated with LPCN 1021 starting on Day 24. The T 24-hour Cmax is defined as the maximum serum T concentration that occurs in a 24-hour period.

8.0 INVESTIGATIONAL PLAN

8.1. Overall Study Design

This is a multicenter, open-label, one treatment study evaluating the efficacy of LPCN 1021 in adult hypogonadal male subjects. Subjects may be naive to T treatment or may enroll after stopping current treatment and completing an adequate washout period.

The study is comprised of five scheduled visits:

- Visit 1 and 2 are for screening.
- Visit 3 is scheduled on Day 1 of the study for the start of dosing.
- Visit 4 is a pre-dose blood draw to measure pre-dose testosterone concentrations.
- Visit 5 is for confinement of subjects for intensive pharmacokinetic (PK) sampling.

Visit 1 & 2: Subjects will undergo a screening period to complete the pre-study examinations and to confirm their hypogonadal status. Serum total T below 300 ng/dL based on two consecutive blood samples obtained between 6 and 10 AM, on two separate days at approximately the same time of day, following an appropriate washout of current androgen replacement therapy will be used for screening T levels.

Visit 3: A total of 100 hypogonadal men meeting inclusion criteria and none of the exclusion criteria will be enrolled to the study and assigned to receive 150 mg of LPCN 1021 three times a day for about 24 days (window of 20 to 28 days).

Visit 4: This visit is to be carried out by selected sites that receive a notification letter requesting that they perform Visit 4 (Refer to Selected Sites: Subject Pre-Dose Blood Draws).

Visit 5: Starting the evening of Day 23, subjects will undergo confinement lasting for about 42 hours. Subjects will enter the clinic on the evening of Day 23 (approximately 18 hours prior to anticipated dosing on the afternoon of Day 24) and will remain confined until the 24-hour blood draw on Day 25 is completed. There is one confinement visit in the study. Subjects will be exited from the study on Day 25.

On Day 23, subjects will arrive at the clinic after taking their evening dose at home with dinner. The subects will receive their morning dose after breakfast at the clinic on Day 24. Following the administration of the afternoon dose after lunch on Day 24 (refer to Section 9.4.1.8), intensive PK sampling will be carried out for up to 24 hours post afternoon dose. Blood samples will be obtained at 0 (pre-dose), 2, 4, 5, 6, 7, 8, 10, 12, 13, 14, 15, 16, 18, 20, 21, 22, 23 and 24 hours relative to the afternoon dose. Safety assessments will be carried out periodically during the study, and at exit. The total duration of the study will be about 25 days not including the screening period.

Selected Sites: Subject Pre-Dose Blood Draws:

Please Note: These steps are to be carried out by selected sites that receive a notification letter requesting that they perform pre-dose blood draws at Visit 4 and as part of Visit 5.

Visit 4: The morning of Day 23, subjects at selected sites will return to the clinic for pre-dose blood draws to measure pre-dose T concentrations. Subjects will leave the clinic after blood draw.

Visit 5: The morning of Day 24, subjects at selected sites will have a pre-dose blood draw to measure pre-dose T concentrations.

8.2. Selection of Study Population

Subjects will undergo screening procedures approximately 30 days prior to the start of treatment. Adult hypogonadal male subjects will be eligible for enrollment in the study based on the following inclusion and exclusion criteria.

8.2.1. Inclusion Criteria

A subject will be eligible for study participation if he meets the following criteria:

1. Voluntarily sign and date the study consent form(s) which have been approved by an Institutional Review Board (IRB). Written consent must be obtained prior to the initiation of any study procedures.
2. Male between 18 and 80 years of age, inclusive, with documented onset of hypogonadism prior to age 65.
3. Subjects should be diagnosed to be primary (congenital or acquired) or secondary hypogonadal (congenital or acquired).
4. Serum total T below 300 ng/dL based on 2 consecutive blood samples obtained between 6 and 10 AM, on two separate days at approximately the same time of day (between 6 and 10 AM), following an appropriate washout of current androgen replacement therapy.
5. Naïve to androgen replacement or has discontinued current treatment and completed adequate washout of prior androgen therapy. Washout must be completed prior to collection of serum T samples to determine study eligibility.
6. Judged to be in good general health as determined by the investigator at screening.

8.2.2. Exclusion Criteria

A subject will not be eligible for study participation if he meets any of the following criteria.

1. History of significant sensitivity or allergy to androgens, or product excipients.

2. Clinically significant findings in the pre-study examinations including abnormal breast examination requiring follow-up.
3. Abnormal prostate digital rectal examination (DRE) with palpable nodule(s).
4. Subjects with symptoms of moderate to severe benign prostatic hyperplasia.
5. Clinically significant abnormal laboratory value, in the opinion of the investigator, in serum chemistry, hematology, or urinalysis including but not limited to:
    a. Baseline hemoglobin < 11.5 g/dL or > 16.5 g/dL
    b. Hematocrit < 35% or > 54%
    c. Serum transaminases > 2.5 times upper limit of normal
    d. Serum bilirubin > 2.0 mg/dL
    e. Creatinine > 2.0 mg/dL
    f. PSA > 2 ng/mL
    g. Prolactin > 17.7 ng/mL
6. Positive test result for hepatitis A virus immunoglobulin M (HAV-IgM), hepatitis B surface antigen (HBsAg) or hepatitis C virus antibody (HCV Ab) or human immunodeficiency virus antibodies (HIV Ab).
7. History of seizures or convulsions occurring after age 5, including alcohol or drug withdrawal seizures.
8. History of gastric surgery, cholecystectomy, vagotomy, bowel resection or any surgical procedure that might interfere with gastrointestinal motility, pH or absorption.
9. History of any clinically significant illness, infection, or surgical procedure within 1 month prior to study drug administration.
10. History of stroke or myocardial infarction within the past 5 years.
11. History of or current or suspected prostate or breast cancer.
12. History of untreated and severe obstructive sleep apnea.
13. Active alcohol or any drug substance abuse or history of abuse that will interfere with the subject's ability to participate in the study in the judgement of the investigator.
14. History of long QT syndrome (QTc >450) or unexplained sudden death in a first degree relative (parent, sibling, or child).
15. Use of known inhibitors (e.g., ketoconazole) or inducers (e.g., dexamethasone, phenytoin, rifampin, carbamazepine) of cytochrome P450 3A (CYP3A) within 30 days prior to study drug administration and through the end of the study.
16. Use of any investigational drug within 5 half-lives of the last dose prior to Study Day –2 without principal investigator and/or sponsor approval.
17. Receipt of any investigational drug by injection within 30 days or 10 half-lives (whichever is longer) prior to study drug administration without principal investigator

and/or sponsor approval.

18. Subjects who are not on stable dose of current medication.
19. Donation or loss of 550 mL or more blood volume (including plasmapheresis) or receipt of a transfusion of any blood product within 3 months prior to the start of treatment.
20. Inadequate venous access for collection of serial blood samples required for pharmacokinetic profiles.
21. Inability to understand and provide written informed consent for the study.
22. Considered by the investigator or the sponsor-designated physician, for any reason, that the subject is an unsuitable candidate to receive LPCN 1021 (when investigator criteria is used, exact reason should be specified).
23. Subject who is not willing to use adequate contraception for the duration of the study.

9.0 STUDY PROCEDURES

The following study procedures will be performed periodically during the study. Please refer to the schedule of events for the study schedule (Appendix A).

9.1. Screening Procedures

Screening procedures will be performed within 30 days preceding study drug administration. Subjects must provide written informed consent prior to initiation of any screening procedures. The consent to perform some general screening procedures may be obtained on a consent document other than the Informed Consent Form (ICF) specific to the study. The study-specific ICF must be signed and dated by the subject before participation to study-specific procedures.

Screening procedures will be conducted over two scheduled visits Visit 1 and Visit 2. Visit 1 screening procedures will include: demographic data, medical and medication histories, physical examination (including digital rectal examination, breast and testicular exams), vital signs, oral temperature and the first screening Testosterone sample.

In the Second Screening Visit sampling for additional laboratory analysis will be carried out and will include second screening testosterone sample, electrocardiogram, hematology, coagulation (PT/INR and aPTT), biochemistry (including prolactin, PSA), HIV, hepatitis B and C tests, urinalysis and urine drug and alcohol screen. In addition, baseline endocrinology assessments at Visit 2 include follicle simulating hormone (FSH), luteinizing hormone (LH), estradiol (E2), sex hormone binding globulin (SHBG), and DHT. Cosyntropin stimulation testing will be performed on a subset of approximately 50 subjects.

9.2. Randomization and Blinding

This is an open-label, single arm study. There is no randomization and study treatment is neither blinded to the subject or investigator's staff.

9.3. Treatment Phase

Treatment Phase of the study consists of approximately 25 days starting with Visit 3, and ending in Visit 5.

Visit 3: Once subjects are enrolled into the study, they will come to the site where adequate quantities study drug will be dispensed. This will be the Day 1 of treatment. Subjects will be advised to take the study medication three times daily, at approximately 30 minutes following a meal. Subjects will be scheduled to return to the clinic on Day 23 (Visit 4 and Visit 5).

Visit 4: The morning of Day 23, subjects will have pre-dose blood draws to measure pre-dose testosterone concentrations.

Visit 5 is a confinement visit with intensive PK blood sampling starting on Day 24. It starts the day before and ends following 24th hour blood sample next day. This confinement visits lasts for about 42 hours. The permitted window for this visit to begin is Day 20 to Day 28.

During the confinement visit, meals and study drug administration on the morning, afternoon and evening of Day 24, and the morning of Day 25 will be carried out at the site. On Day 24, following study drug administration after lunch, intensive blood samples will be obtained for PK analysis. Subjects will be exited from the study confinement and study following 24th hour blood sampling and exit procedures.

9.4. Clinical Procedures

The following sections help define the requirements of medical / clinical information to be obtained as a part of the study.

9.4.1.1. Medical and Medication History

The subject's medical history (key events) during the past 5 years will be obtained and recorded on the Medical History Electronic Case Report Form (eCRF). All subjects entering the study should have diagnosis of primary or secondary hypogonadism. Any new information / changes should be documented during the study. 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 eCRF.

All subjects should be instructed to use adequate contraception for the duration of the study, acceptable methods of birth control include the following methods: abstinence, barrier methods, hormonal contraception, intrauterine devices, fallopian tube occlusion devices, and sterilization either of the male or female partner.

Medication use (prescription or over-the-counter, including vitamins and herbal supplements) from 3 months prior to study drug administration through the end of the study will be recorded in the 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 prior to 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.

Subjects participating in the trial should be naive to androgen replacement or has discontinued current therapy and completed an adequate washout. Recommended adequate washout is 12 weeks following intramuscular androgen injections; 4 weeks following topical or buccal androgens; 3 weeks following oral androgens, or, in the judgement of the investigator, the subject has had an adequate washout window to be eligible.

Subjects who have been under stable treatment with the same medication for at least 3 months for a stable chronic condition, with no change in dosage for at least 14 days before the first dosing, and no expected change throughout the study, and for which there is no interaction with the pharmacokinetics of the study drug or the bioanalytical methods, will be eligible for the.

9.4.1.2. Electrocardiogram

An electrocardiogram will be performed at the screening to identify, and subsequently exclude, subjects with long QT syndrome.

9.4.1.3. Physical Examination

A physical examination will be performed at screening and exit. The examination will include at minimum an examination of head/eyes/ears/nose/throat, breast, testicular exams and digital rectal exam (DRE) of prostate. Any changes during the study will be documented. Subject's height and weight will be used to calculate BMI.

9.4.1.4. Vital Signs

Body temperature, systolic and diastolic blood pressure, respiratory rate and pulse rate will be measured at screening, confinement visit and at the end of the study. The vital sign measurements at screening will serve as the baseline measurements for clinical assessments. Vital signs must be measured after the subject has been sitting at rest for at least 5 minutes.

9.4.1.5. Clinical Laboratory Tests

9.4.1.5.1. Hematology, Chemistries, and Urinalysis

Blood samples for the clinical laboratory tests will be performed screening and end of the study (refer Table 1 and Appendix A). Samples for serum chemistry tests will be collected in the morning prior to meals and study drug administration. The test results from screening will serve as the baseline for future clinical assessments.

Clinical laboratory testing must be performed by appropriately credentialed laboratories. Certified central 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 will be provided in lab manual.

Table 1: Listing of Clinical Laboratory Tests

Hematology	**Clinical Chemistry**	**Urinalysis**
Hematocrit	Blood urea nitrogen (BUN)	Specific gravity
Hemoglobin	Creatinine	Ketones
Red blood cell (RBC) count	Total bilirubin	pH
White blood cell (WBC) count	Serum glutamic-pyruvic transaminase (SGPT/ALT)	Protein
Neutrophils bands (if detected)	Serum glutamic-oxaloacetic transaminase (SGOT/AST)	Blood
Lymphocytes	Alkaline phosphatase	Glucose
Monocytes	Sodium potassium	Urobilinogen
Basophils (if detected)	Calcium	Bilirubin
Eosinophils (if detected)	Inorganic phosphorus	
Absolute platelet count	Uric acid	
Mean corpuscular hemoglobin (MCH)	Cholesterol	
Mean corpuscular volume (MCV)	Total protein	
Mean corpuscular hemoglobin concentration (MCHC)	Triglycerides	
Prothrombin time (PT)	Albumin	
Activated partial thromboplastin time (aPTT)	Chloride	
	High density lipoprotein (HDL) cholesterol	
	Low density lipoprotein (LDL) cholesterol	
	Magnesium	
	Gamma-glutamyl transpeptidase (GGTP)	

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.

9.4.1.5.2. Screening for Hepatitis

HAV-IgM, HBsAg and HCV Ab tests will be performed at screening. The hepatitis test panel will be performed by a certified laboratory. Some states might require facilities that perform this testing to report the name of anyone who tests positive for hepatitis B or hepatitis C antibodies.

9.4.1.5.3. Screening for HIV

Subjects will have blood tested by a certified laboratory for the presence of HIV antibodies at screening. Only those subjects negative for the presence of antibodies will be allowed to enroll in the study. The results of the HIV antibodies testing will be retained by the study site under confidential restriction. However, some states might require facilities that perform this testing to report the names of anyone who tests positive for HIV antibodies.

9.4.1.5.4. Urine Screens for Drugs of Abuse and Alcohol

A urine screen for drugs of abuse and alcohol will be performed at screening and exit. The panel for drugs of abuse will minimally include cannabinoids, opiates, barbiturates, amphetamines, cocaine, and benzodiazepines. Analyses will be performed by a certified laboratory.

9.4.1.5.5. Endocrinology Assessments

The sex hormone binding globulin (SHBG), follicle-stimulating hormone (FSH), luteinizing hormone (LH) and prolactin will be performed at screening and exit.

9.4.1.5.6. Cosyntropin Stimulation Test

During screening Visit 2, a Cosyntropin stimulation test will be performed on 50 subjects. Subjects who have the Cosyntropin stimulation test at screening who are subsequently enrolled and complete the study will have the test repeated at Visit 5, or exit, which ever comes first.

Cosyntropin stimulation testing will be conducted after obtaining a control blood sample for cortisol measurement. Refer to product label of Cosyntropin for exact dosage and administration instructions.

9.4.1.5.7. Prostate-Specific Antigen (PSA)

Samples for PSA (prior to DRE if applicable) will be collected at screening and end of the study.

9.4.1.5.8. Serum Testosterone and Related Hormones

At screening, serum total T must be below 300 ng/dL based on 2 consecutive blood samples obtained between 6 and 10 AM, on two separate days at approximately the same time of day, following washout of any prior androgen replacement therapy. The analytical method used to assess screening testosterone will be the same method as used for pharmacokinetic analysis. In addition, a blood sample for determination of baseline serum hormones (E2, and DHT) will be collected at screening. Refer to the Schedule of Events (Appendix A) for sample collection days and times.

9.4.1.6. Blood Samples for Pharmacokinetic Analyses

On the day of confinement, the timing of blood collections will take priority over all other scheduled study activities except for dosing. Intensive pharmacokinetic sampling will be done as follows. A total of 12 mL whole blood will be collected for the PK analysis.

- 0 (pre-dose), 2, 4, 5, 6, 7, 8, 10, 12, 13, 14, 15, 16, 18, 20, 21, 22, 23 and 24 hours relative to afternoon dose.

A total of 19 blood samples, 228 mL of blood will be collected per subject. The time that each blood sample is collected will be recorded to the minute. Blood sample collection should be performed within ± 10 minutes of the scheduled time points (with the exception of the 0-hour time point). Details on the handling and processing of samples are provided in the laboratory manual.

9.4.1.7. Confinement:

There is one confinement visit for each subject on Day 24 (20 to 28 days). Subjects will be admitted to the clinic approximately 18 hours prior to the afternoon dose on Day 24 and remain confined for approximately 42 hoursThe subects will the receive their morning dose after breakfast at the clinic. Following the administration of the afternoon dose after lunch on Day 24, serial blood samples will be drawn for approximately 24 hours after the afternoon dose. Subjects will be released from the clinic 24 hours after the afternoon dose blood draw. Strenuous activity during confinement will not be permitted.

Selected Subjects Pre-Dose Blood Draws:

Please Note: This step is to be carried out by selected sites that receive a notification letter requesting that they perform pre-dose blood draws at Visit 4 and as part of Visit 5.

Visit 4: The morning of Day 23, subjects for selected sites will return to the clinic for pre-dose blood draws to measure pre-dose T concentrations and subjects will leave the clinic after blood draw.

Visit 5: The morning of Day 24, subjects for selected sites will have a pre-dose blood draw to measure pre-dose T concentrations.

9.4.1.8. Meals and Dietary Requirements

Throughout the study, subjects will be advised to maintain a standard diet which provides a total daily caloric content of approximately 2400 calories (total per day).

During the confinement periods, the subjects will be provided with meals. Breakfast, lunch, a snack, and dinner will be provided during confinement. Subjects with special meal requirements may be accommodated accordingly at the clinic. Study medication in the morning and evening will be administered 30 minutes after the meal. Alcohol is prohibited during the confinement, and caffeine intake should be limited. Administration of water with meals is permitted.

9.4.2. Dosage Administration and Titration

All subjects will receive 150 mg TID (two capsules of 75 mg) taken three times daily with a meal (total daily dose of 450 mg taken as 150 mg after breakfast, 150 mg after lunch and 150 mg after dinner), approximately 30 minutes after the meal, with water.

9.5. Subject Discontinuation

All the subjects are free to withdraw from the study at any time; additionally, subjects may be withdrawn from the study at the discretion of the investigator if they meet any of the following criteria:

- Any event, in the judgment of the investigator, where continuation of the subject in the trial could put the subject at health risk.
- Increase in hematocrit to > 54%, PSA > 4 ng/mL.
- Significant noncompliance with the protocol requirements.
- Lost to follow-up.

Subjects who withdraw from the study will not be replaced. In the event that a subject withdraws or is discontinued from the study, the reason(s) for the discontinuation from the study will be recorded and the study exit evaluation should be performed. If a subject is discontinued from the study with an ongoing AE or an unresolved laboratory result that is significantly outside of the reference range, the investigator will attempt to provide follow-up until a satisfactory clinical resolution of the laboratory result or AE is achieved.

9.5.1. Exit Evaluation

Exit evaluation is the same as Day 25 procedures (24 hours from afternoon dose of Day 24) for subjects who complete the study. For subjects who withdraw from the study or discontinued early exit evaluation should be conducted.

9.6. Study Discontinuation

The sponsor may terminate this study prematurely, either in its entirety or at any study site, for reasonable cause provided that written notice is submitted in advance of the intended termination. The investigator may also terminate the study at his/her site for reasonable cause, after providing written notice to sponsor in advance of the intended termination. Advance notice is not required by either party if the study is stopped due to safety concerns. If Lipocine terminates the study for safety reasons, Lipocine will immediately notify the investigators.

9.7. Drug Product

LPCN 1021 is gelatin capsule product that will be provided as 75 mg TU per capsule.

9.7.1. Packaging and Labeling

LPCN 1021 will be provided in high-density polyethylene (HDPE) bottles containing 120 capsules in each bottle (two bottles will be provided to each subject). Each HDPE bottle will be labeled with the information required by regulatory authorities. Adequate supplies of study

drug will be provided to the study center.

9.7.2. Storage and Disposition of Study Drug

The study drug must be stored at room temperature 15°C to 25°C (59°F to 77°F). LPCN 1021 capsules are listed as Drug Enforcement Administration (DEA) Schedule CIII drugs in the United States and must be handled according to applicable federal and local regulations. The study drugs are for investigational use only and are 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 sponsor.

9.7.3. Treatment Compliance and Drug Accountability

The investigator or his/her designated and qualified representatives will dispense study drug only to subjects enrolled in the study in accordance with the protocol. The study drug must not be used for reasons other than that described in the protocol. During the confinement periods for LPCN 1021-treated subjects, study-site personnel will ensure ingestion of each dose. Subjects must return all unused medication and empty bottles to the study center. The number of capsules returned will be counted and entered into the eCRF. Treatment compliance is calculated as follows:

% compliance = [(number of capsules dispensed – number of capsules returned)/ number of capsules expected to be used] * 100

The investigator must agree to comply with all applicable DEA laws and regulations regarding controlled substances as outlined in 21 CFR 1300-1321.

A current (running) and accurate inventory of study drug will be kept by the investigator and will include shipping invoices and the date on which study drug is dispensed to the subject. An overall accountability of the study drug will be performed and verified by sponsor monitor throughout the study and at the study site closeout visit. Upon completion or premature discontinuation of the study, all original containers (empty or containing unused study drug) will be returned to sponsor (or a designee), according to instructions from sponsor and according to local regulations. Labels must remain attached to the containers.

9.8. MISSED DOSE

Subjects who miss a dose and recall the missed dose within 4 hours of their usual dose time should take their dose with a meal. If more than 4 hours have elapsed after their usual dosing time, they should skip that dose and resume their normal schedule with the following dose.

10.0 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.

10.1. Definition of an Adverse Event

An AE is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not the event is considered causally related to the use of the product.

Such an event can result from use of the drug as stipulated in the protocol or labeling, as well as from accidental or intentional overdose, drug abuse, or drug withdrawal. Any worsening of a pre-existing condition or illness is considered an AE. Worsening in severity of a reported AE should be reported as a new AE. Laboratory abnormalities and changes in vital signs are AEs only if they result in discontinuation from the study, necessitate therapeutic medical intervention, and/or if the investigator considers them to be AEs.

10.2. Serious Adverse Events

If an AE meets any of the following criteria, it is to be reported to the sponsor/PI as an SAE within 24 hours of the site being made aware of the SAE:

Event	Description of Event
Death of Subject	An event that results in the death of a subject.
Life-Threatening	An event that, in the opinion of the investigator, would have resulted in immediate fatality if medical intervention had not been taken. This does not include an event that would have been fatal if it had occurred in a more severe form.
Hospitalization or Prolongation of Hospitalization	An event that results in an admission to the hospital for any length of time or prolongs the subject's hospital stay. This does not include an emergency room visit or admission to an outpatient facility.
Congenital Anomaly	An anomaly detected at or after birth, or any anomaly that results in fetal loss in the female partner of a study subject.

Persistent or Significant Disability/Incapacity	An event that results in a condition that substantially interferes with the activities of daily living of a study subject. Disability is not intended to include experiences of relatively minor medical significance such as headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle).
Important Medical Event Requiring Medical or Surgical Intervention to Prevent Serious Outcome	An important medical event that may not be immediately life-threatening or result in death or hospitalization, but based on medical judgment may jeopardize the subject and may require medical or surgical intervention to prevent any of the outcomes listed above (i.e., death of subject, life-threatening, hospitalization, prolongation of hospitalization, congenital anomaly, or persistent or significant disability/incapacity). Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

For SAEs with the outcome of death, the date and cause of death will be recorded on the appropriate eCRF.

10.3. Adverse Event Severity

The investigator will use the following definitions to rate the severity of each AE:

Mild	The AE is transient and easily tolerated by the subject.
Moderate	The AE causes the subject discomfort and interrupts the subject's usual activities.
Severe	The AE causes considerable interference with the subject's usual activities and may be incapacitating or life-threatening.

10.4. Relationship to Study Drug

The investigator will use the following definitions to assess the relationship of the AE to the use of study drug:

Related	An AE where there is evidence to suggest a causal relationship between the study drug and the AE.
Not Related	An AE where there is no evidence to suggest a causal relationship between the study drug and the AE.

For causality assessments, events assessed as having a reasonable possibility of being related to the study drug will be considered “related”. Events assessed as having no reasonable possibility of being related to study drug will be considered “not related”. If an investigator's opinion of no reasonable possibility of being related to study drug is given, an “other” cause of event must be provided by the investigator for the SAE.

10.5. Adverse Event Collection Period

All AEs in the subject and pregnancies that occur in subject's partner reported from the time of informed consent until 30 days after last dose of study drug will be collected, whether solicited or spontaneously reported by the subject.

10.6. Adverse Event Reporting

In the event of an SAE in the subject or pregnancy in subject partner, whether related to study drug or not, the investigator will notify the sponsor or representative within 24 hours of the site being made aware of the SAE. For SAE Reporting or subject safety concerns, please contact:

Anthony DelConte, MD, Office: 610-660-3182, Mobile: 862-432-9036, E-mail: ad@lipocine.com

11.0 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 the following contact(s):

Primary Contact	**Alternate Contact**
Dr. Nachiappan (Chidu) Chidambaram, PhD	Dr. Anthony DelConte,
nc@lipocine.com	ad@lipocine.com
(801) 534-6807	(862) 432-9036

Such contact must be made as soon as possible to permit a review by the 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, prior to implementation.

12.0 STATISTICAL ANALYSIS

The primary and secondary endpoints and associated analyses are described in this section. Details of the analyses to be performed will be given in a statistical analysis plan

12.1. Study Populations

Statistical analyses will be performed on the full analysis set (FAS), pharmacokinetic set (PK set), and safety set.

Safety Set (SS): The safety set includes all subjects who were randomized and received a dose of study drug.

Full Analysis Set (FAS): The FAS consists of all subjects enrolled into the study with at least one post baseline efficacy variable data point (Cmax or Cavg).

Pharmacokinetic Set (PK set): The PK set consists of subjects in FAS who complete the study without major protocol deviations.

12.2. Pharmacokinetic Analyses

The following pharmacokinetic parameters will be calculated by standard non-compartmental methods for T, DHT, TU, and DHTU:

- AUC0-24: area under the concentration-time curve from time zero to the 24 hours.
- Cavg0-24: average concentration from 0 to 24 hours obtained by dividing AUC0-24 /24.
- Cmax: maximum concentration following administration of LPCN 1021 prior to next dose.
- 24-hour Cmax: maximum concentration occurring in a 24-hour interval

Pharmacokinetic parameters will be calculated based on serum concentrations as appropriate. Additional analysis includes estimating the duration for which a subject's serum T concentration levels exceed 1500 ng/dL, 1800 ng/dL and 2500 ng/dL. A comprehensive listing of the serum hormone concentrations measured during the study confinement periods will be presented. Individual and treatment overall, will be presented.

12.3. Primary Endpoint

The primary endpoint will be the percentage of LPCN 1021-treated subjects who achieve a 24-hour average serum T concentration within the lab determined normal range upon completion of 24 days of treatment. The target minimum acceptable percentage is 75%. A 95%, 2-sided, binomial confidence interval surrounding the point estimate must have a lower bound of ≥ 65%. The analysis will be done using all treated subjects, with missing data handled by imputation.

12.4. Secondary Endpoints

The secondary endpoints will be based on the proportion of T Cmax below 1500 ng/dL, T Cmax between 1800 and 2500 ng/dL, and T Cmax > 2500 ng/dL in subjects treated with LPCN 1021 for 24 days.

T Cmax is defined as the maximum serum T concentration that occurs in the dosing interval. Starting on Day 24, all Cmax values that occur following morning, afternoon and evening doses will be used to compute the proportions.

Testosterone Cmax must be 1) ≤ 1500 ng/dL in ≥ 85% of all subjects, 2) between 1800 and 2500 ng/dL in ≤ 5% of subjects, and 3) > 2500 ng/dL in no subjects treated.

The analysis will be done using all treated subjects.

Additional Evaluation:

To determine the proportion of T 24-hour Cmax below 1500 ng/dL, T Cmax between 1800 and 2500 ng/dL, and T Cmax > 2500 ng/dL in subjects treated with LPCN 1021 starting on Day 24. The T 24-hour Cmax is defined as the maximum serum T concentration that occurs in a 24-hour period.

Testosterone 24-hour Cmax must be 1) ≤ 1500 ng/dL in ≥ 85% of all subjects, 2) between 1800 and 2500 ng/dL in ≤ 5% of subjects, and 3) > 2500 ng/dL in no subjects treated.

The analysis will be done using all treated subjects.

12.5. Safety Endpoints

Key safety endpoints are AEs, physical examination, clinical laboratory tests and vital signs.

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). An AE is considered treatment emergent if the event begins or worsens in severity after initiation of treatment. The number and percentage of subjects with treatment-emergent AEs will be tabulated by system organ class (SOC) and preferred term. A summary of the number of subjects with treatment-emergent AEs will be provided by severity and by relationship to study drug. 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 a SOC will be counted only once for that SOC. Incidence of treatment-emergent AEs, serious treatment-emergent AEs, treatment-emergent AEs resulting in discontinuation, and target treatment-emergent AEs (e.g., elevated PSA, elevated hematocrit, elevated LDL) will be summarized. Listings will be provided for all AEs, SAEs, AEs resulting in discontinuation, and target AEs.

12.6. Statistical Analysis

Demographic parameters will be summarized descriptively. Treatment-emergent AEs will be summarized descriptively for all subjects who were dosed (safety population).

Descriptive statistics (arithmetic and geometric means, standard deviation (SD), coefficient of variation (CV [%]), min., max., and median) of the serum concentrations versus time will be presented for the pharmacokinetic parameters.

A complete description of the statistical analyses to be performed will be presented in a Statistical Analysis Plan (SAP) as a separate document.

12.7. Determination of Sample Size

Sample size for the study was based on the primary endpoint, the incidence and binomial confidence interval for the percentage of subjects achieving serum T concentrations within the normal range. In previous multiple dose clinical studies with LPCN 1021 (Study LPCN 1021-13-001 and M12-778), subjects were administered with 150 mg, 225 mg and 300 mg LPCN 1021 twice daily. In the LPCN 1021-13-001 study, 86% of subjects administered LPCN 1021 225 mg BID would have achieved the primary efficacy endpoint (e.g., ≥ 75% of subjects have normal T concentrations) based on a post-hoc analysis of Week 3 data. Assuming similar efficacy in the current study, a sample size of 11 subjects would meet the 95 % CI lower bound of ≥ 65%. Simulations of 150 mg TID administration based on additional analsysis of the M12-778 150 mg BID data suggested that more than 86 % of subjects would have achieved Cavg0-24 within the normal range. Based on the recommedations of the Food and Drug Administration (FDA), a sample size of 100 subjects was selected.

13.0 ETHICS

13.1. Institutional Review Board (IRB)

Good Clinical Practice (GCP) requires that the clinical protocol, any protocol amendments, the Investigator's Brochure, the informed consent and all other forms of subject information related to the study (e.g., advertisements used to recruit subjects) and any other necessary documents be reviewed by an IRB. The IRB will review the ethical, scientific and medical appropriateness of the study before it is conducted. IRB approval of the protocol, informed consent and subject information and/or advertising, as relevant, will be obtained prior to the authorization of drug shipment to a study site. Any amendments to the protocol will require IRB approval prior to implementation of any changes made to the study design. The investigator will be required to submit, maintain and archive study essential documents according to International Conference on Harmonization (ICH).

Serious adverse events that meet the reporting criteria, as dictated by local regulations, will be reported to both IRB and Regulatory Agencies as required by local regulations. During the conduct of the study, the investigator should promptly provide written reports (e.g., ICH Expedited Reports or any additional reports required by local regulations) to the IRB of any changes that affect the conduct of the study and/or increase the risk to subjects. Written documentation of the submission to the IRB should also be provided to sponsor/PI.

13.2. Ethical Conduct of the Study

The study will be conducted in accordance with the protocol, ICH GCP guidelines, applicable regulations and guidelines governing clinical study conduct and ethical principles that have their origin in the Declaration of Helsinki. Responsibilities of the clinical investigator are specified in Appendix B.

13.3. Subject Information and Consent

Prior to the initiation of any screening or study-specific procedures, the investigator or his/her representative will explain the nature of the study to the subject and answer all questions regarding this study. Each informed consent will be reviewed, signed and dated by the subject, the person who administered the informed consent, and any other signatories according to local requirements. A copy of each informed consent will be given to the subject and each original will be placed in the subject's medical record. An entry must also be made in the subject's dated source documents to confirm that informed consent was obtained prior to any study-related procedures and that the subject received a signed copy.

14.0 SOURCE DOCUMENTS AND CASE REPORT FORM COMPLETION

14.1. Source Documents

Source documents are defined as original documents, data and records. These may include hospital records, clinical and office charts, laboratory data/information, subject questionnaires or evaluation checklists, pharmacy dispensing and other records, recorded data from automated instruments, microfiches, photographic negatives, microfilm or magnetic media, and/or x-rays. Source document data may be transcribed onto eCRFs as required. Data collected during this study must be recorded on the appropriate source document.

The investigator/institution will permit study-related monitoring, audits, IRB review, and regulatory inspection(s), providing direct access to source data documents.

14.2. Case Report Forms

Case report forms (CRF) must be completed for each subject who receives study medication in this study. These forms will be used to transmit information collected during the study to sponsor/PI and regulatory authorities, as applicable. The CRF data for this study will be collected with an electronic data capture (eEDC) system (e.g., Rave, Medidata). The EDC system and the study-specific eCRFs will comply with Title 21 CFR Part 11. The documentation related to the validation of the EDC system is available through the system vendor, while the validation of the study-specific eCRFs will be conducted by the clinical research organization (CRO) and will be maintained in the Trial Master File at the CRO.

The investigator will document subject data in his/her own subject files. These subject files will serve as source data for the study. All eCRF data required by this protocol will be recorded by investigative site personnel in the EDC system. All data entered into the eCRF will be supported by source documentation.

The investigator or an authorized member of the investigator's staff will make any necessary corrections to the eCRF. All change information, including the date and person performing the corrections, will be available via the audit trail, which is part of the EDC system. For any

correction, a reason for the alteration will be provided. The eCRFs will be reviewed periodically for completeness, legibility, and acceptability by CRO personnel (or their representatives). The CRO (or their representatives) will also be allowed access to all source documents pertinent to the study in order to verify eCRF entries. The investigator will review the eCRFs for completeness and accuracy and provide his or her electronic signature and date to eCRFs as evidence thereof.

The CRO will provide access to the EDC system for the duration of the trial through a password-protected method of internet access. Such access will be removed from investigator sites at the end of the site's participation in the study. Data from the EDC system will be archived on appropriate data media (e.g., CD-ROM) and provided to the investigator at that time as a durable record of the site's eCRF data. It will be possible for the investigator to make paper printouts from that media.

15.0 DATA QUALITY ASSURANCE

Prior to enrolling any subject in the study, an initiation meeting will be held with CRO personnel, the investigator(s), and the study coordinators/project manager(s). This meeting will include a detailed discussion and review of the protocol and essential documents, performance of study procedures, eCRF completion and specimen collection methods.

The CRO monitor will monitor the study site throughout the study. Source document verification will be performed. A quality assurance check will be performed to ensure that the investigator is complying with the protocol and regulations. In addition, after the eCRFs are submitted, a review of the data will be conducted by a representative at CRO.

Computer logic checks will be run to identify such items as inconsistent study dates. Any necessary corrections will be made to the database via the eCRF.

Routine hematology, serum chemistry, and urinalysis tests will be conducted using a certified clinical laboratory. Laboratory reference ranges will be obtained prior to the initiation of the study. A review of all laboratory results will be conducted by the CRO monitor, the investigator and other appropriate personnel from CRO.

16.0 USE OF INFORMATION

All information concerning LPCN 1021 and Lipocine operations, such as Lipocine patent applications, formulas, manufacturing processes, basic scientific data, or formulation information, supplied by Lipocine and not previously published is considered confidential information.

The information developed during the conduct of this clinical study is also considered confidential and will be used by Lipocine in connection with the development of LPCN 1021. This information may be disclosed as deemed necessary by Lipocine to other clinical investigators, other pharmaceutical companies, and to governmental agencies. To allow for the

use of the information derived from this clinical study and to ensure complete and thorough analysis, the investigator is obligated to provide Lipocine with complete test results and all data developed in this study and to provide direct access to source data/documents for study-related monitoring, audits, IRB review, and regulatory inspection.

This confidential information shall remain the sole property of Lipocine, shall not be disclosed to others without the written consent of Lipocine, and shall not be used except in the performance of this study. The investigator will maintain a confidential subject identification code list of all subjects enrolled in the study, including each subject's name, subject number, address, phone number and emergency contact information. This list will be maintained at the study site with other study records under adequate security and restricted access, and will not be retrieved by Lipocine/CRO.

17.0 COMPLETION OF THE STUDY

The investigator will provide a final report to the IRB following conclusion of the study, and will forward a copy of this report to Lipocine or their representative.

The investigator must retain any records related to the study according to local requirements. If the investigator is not able to retain the records, he/she must notify Lipocine/CRO to arrange alternative archiving options. The end of study is defined as the date of the last subject's last visit. If, on the date of the last subject’s last visit, the subject is experiencing an ongoing AE, the event will be followed until satisfactory resolution occurs.

Appendix A. SCHEDULE OF EVENTS:

Visit	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5 (Confinement Visit)																									Exit[1]
Day			Day1	Day 23	Day 24 (Window: 20 to 28 days); Time relative to time of dosing on Day 24 afternoon																									Day 25
Time				0	-18	-~6 to 8	0	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	
Informed consent	✓																													
Inclusion/exclusion	✓	✓																												
Height, Weight, BMI[3]	✓				✓																									✓
Medical history[4]	✓		✓		✓																									
Physical examination	✓																													✓
Electrocardiogram		✓																												
Vital signs	✓						✓																							✓
Sample collection[10]																														
Screening T Measurements	✓	✓																												
Hematology		✓																												✓
Serum chemistry including PSA		✓																												✓
Serum hormones (E2, DHT)		✓																												
Urine analysis		✓																												✓
Drug screen and Serology[5]		✓																												
LH, FSH, SHBG		✓																												✓
Cosyntropin[9]		✓				✓																								
Selected Sites: subject pre-dose sample				✓		✓																								
PK sampling[6,11,12]							✓	✓		✓	✓	✓	✓	✓		✓		✓	✓	✓	✓	✓		✓		✓	✓	✓	✓	✓	
AE Reporting	✓	✓	✓	✓														✓												
Medication reporting[7]	✓	✓		✓														✓												
Meal administration & record						✓	✓							✓								✓								
Snack administration									✓																	✓				
Confinement begin[2]					✓																									
Study drug administration[8]						✓	✓							✓								✓								
Study drug dispensed			✓																											
Study drug returned					✓																									

1. Study exit can be conducted at 24-hour time-point (up to 2 hours later) on Day 24 or when subject discontinues the study.
2. Confinement begins in the evening on the day before intensive PK
3. Height and BMI at screening only.
4. Medical history for the past 5 years at screening, anything changed basis at subsequent visits.
5. Serology includes HIV, Hepatitis A, B and C.
6. Sample at T=0 will be taken prior to dose administration (up to about 45 minutes' prior to AM dose)
7. Prior medication history at screening and anything changed basis at subsequent visits.
8. Study drug to be administered approximately 30 minutes after administration of meals
9. At Visit 2, 50 subjects will have a Cosyntropin stimulation test performed. Subjects who have the Cosyntropin stimulation test at screening who are subsequently enrolled and complete the study will have the test repeated at the confinement visit or exit, whichever comes earlier.
10. Listing of clinical laboratory tests provided in Table 1.
11. On Visit 4, a single blood draw will be performed to evaluate pre-dose T concentration for subjects at selected sites.
12. The morning of Day 24, a pre-dose blood draw will be performed to evaluate pre-dose T concentration for subjects at selected sites.

Appendix B. INVESTIGATOR'S AGREEMENT

Study Title: Dosing Flexibility Study of Oral Testosterone Undecanoate (TU, LPCN 1021) in Hypogonadal Men

Study Number: LPCN 1021-16-003

Final Date:

Clinical research studies sponsored by Lipocine are subject to the Good Clinical Practices (GCP) and local regulations and guidelines governing the study at the site location. In signing below, the investigator is agreeing to the following:

1. Conducting the study in accordance with the current protocol, making changes to a protocol only after obtaining approval from Lipocine, except when necessary to protect the safety, rights or welfare of subjects.
2. Personally conducting or supervising the described investigation(s).
3. Informing all subjects, or persons used as controls, that the drugs are being used for investigational purposes and complying with the requirements relating to informed consent and institutional review board [IRB] review and approval of the protocol and amendments).
4. Reporting adverse experiences that occur in the course of the investigation(s) to Lipocine/ PI and the site director.
5. Reading the information in the Investigator's Brochure/safety material provided, including the instructions for use and the potential risks and side effects of the investigational product(s).
6. Informing all associates, colleagues, and employees assisting in the conduct of the study about their obligations in meeting the above commitments.
7. Maintaining adequate and accurate records of the conduct of the study, making those records available for inspection by representatives of Lipocine/CRO and/or the appropriate regulatory agency, and retaining all study-related documents until notification from Lipocine.
8. Maintaining records demonstrating that an ethics committee reviewed and approved the initial clinical investigation and all amendments.
9. Reporting promptly, all changes in the research activity and all unanticipated problems involving risks to human subjects or others, to the appropriate individuals (e.g., coordinating investigator, institution director) and/or directly to the ethics committees and Lipocine/PI.
10. Following the protocol and not make any changes in the research without ethics committee approval, except where necessary to eliminate apparent immediate hazards to human subjects

I have read the protocol described above. I agree to comply with all applicable regulations and to conduct the study as described in the protocol.

1. I have received and reviewed the Investigator's Brochure for LPCN 1021.
2. I have read this protocol and agree that the study is ethical.
3. I agree to conduct the study as outlined in the protocol and in accordance with all applicable regulations and guidelines. I will not deviate from the protocol without prior written approval from the sponsor or designee.
4. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

Signature of the Investigator

Date

Name of the Investigator (Printed or Typed)