1.0 TITLE PAGE

Clinical Study Protocol: LPCN 1021-18-001

Ambulatory Blood Pressure Monitoring in Oral Testosterone Undecanoate (TU, LPCN 1021) Treated Hypogonadal Men.

Investigational Product	:	Testosterone Undecanoate (TU, LPCN 1021)
Date of Protocol	:	19 February 2019
FDA IND No.	:	106476
Development Phase	:	Phase 3
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
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Protocol Version	:	06

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2.0 SUMMARY OF CHANGES TO PROTOCOL VERSION 2

Version 02 of the LPCN 1021-18-001 study protocol was developed to make the following changes to the study:

- Added sexual desire and sexual distress questions to pre-treatment and post-treatment phases of the study.
- Clarified that subjects with chronic conditions requiring medication should be under stable treatment, with the same medication and dosage for at least 3 months prior to dosing.
- Added a list of prohibited concomitant medications.
- Clarified that a digital rectal exam (DRE) is not part of screening procedures.
- Clarified that adverse events will be collected from the time of informed consent.
- Adopted the changes from Protocol Clarification Letter 1
    - Screens for Drugs of Abuse and Alcohol: A urine drug and alcohol screen will be performed at Visit 2, and not as part of study exit.
    - Screening Procedures (Visits 1 and 2): Vital signs (single measurement of body temperature, triplicate measurement of pulse rate, systolic and diastolic blood pressure) will be performed at Visit 2 of Screening, not at Visit 1 of Screening.
    - Vital Signs: Vital signs (single measurement of body temperature, triplicate measurement of pulse rate, systolic and diastolic blood pressure) will be performed at Visit 2, Visit 3, Visit 5 and study exit, not at Visit 1 and Visit 4.
    - Ambulatory Blood Pressure Monitoring: Clarified the ambulatory blood pressure monitoring (ABPM) Data Criteria.
- Minor editorial changes for protocol consistency.

3.0 SUMMARY OF CHANGES TO PROTOCOL VERSION 3

Version 03 of the LPCN 1021-18-001 study protocol was developed to make the following changes to the study:

- The study size was increased to 140 subjects.
- The duration of treatment increased to 4 months, with ABPM measurements at baseline and 4 months. A study drug resupply was added to accommodate the updated study duration.
- Added a blood draw at the end of study for pharmacokinetic sampling.
- Added exclusion criteria for subjects with screening systolic BP or diastolic BP above 160 mmHg or 100 mmHg, respectively.
- Added instruction for sites to ask each subject if he found the baseline ABPM measurement tolerable, and if he is willing to complete the ABPM measurements after 4 months.
- Duration of confinement at Visit 5 increased from about 33 hours to up to 45 hours.
- Statistical section added with calculation of ability of the study to identify changes in BP that can be ruled out based on the new sample size.

4.0 SUMMARY OF CHANGES TO PROTOCOL VERSION 4

Version 04 of the LPCN 1021-18-001 study protocol was developed to make the following changes to the study:

- The timing of the Visit 5 ambulatory blood pressure monitoring (ABPM) measurement was changed from Day 120 to Day 107. Subjects will be instructed to continue taking study medication after Visit 5 to provide the option for subjects to repeat the ABPM measurement if there are issues with the Visit 5 ABPM reading.
- Added Visit 6 to schedule the exit procedures that were formerly performed at Visit 5.
- Additional tests were added to assess subjects at baseline (prior to Visit 4) and post-treatment (following Visit 5):
    - Added baseline Magnetic Resonance Imaging-Proton Density Fat Fraction (MRI-PDFF) between Visit 2 and Visit 4, and a post-treatment MRI-PDFF between Visit 5 and Visit 6 (study exit).
    - Added additional clinical laboratories tests at baseline Visit 2 and Visit 6.
- Added instruction for sites to query subjects on specific aspects of their Medical History (smoking status and history of hypertension).
- Minor editorial changes for protocol consistency.

5.0 SUMMARY OF CHANGES TO PROTOCOL VERSION 5

Version 05 of the LPCN 1021-18-001 study protocol was developed to make the following changes to the study:

- Added an interim MRI-PDFF (MRI-2) between Visit 4 and Visit 5, to occur between Day 56 and Day 76, inclusive.
- Minor editorial changes for protocol consistency.

6.0 SUMMARY OF CHANGES TO PROTOCOL VERSION 6

Version 06 of the LPCN 1021-18-001 study protocol was developed to make the following changes to the study:

- The primary endpoint of the study was changed from change in average daytime systolic blood pressure to change in average 24-hour systolic blood pressure based on the recent Food and Drug Administration (FDA) public workshop on ambulatory blood pressure monitoring studies ("Evaluating the Pressor Effects of Drugs and Ambulatory Blood Pressure Monitoring Studies"). The public workshop noted that the primary endpoint for ABPM studies should be the change in 24-hour average blood pressure.
- Changed the Development Phase of the study protocol from Phase 1 to Phase 3. The FDA's Division of Bone, Reproductive and Urologic Products noted that although Protocol LPCN 1021-18-001 listed the Development Phase of the study as Phase 1, the study design is not consistent with the definition of a Phase 1 study in 21 CFR Part 312.21. The Division requested that Lipocine change the designated Development Phase to be consistent with the CFR. Based on the CFR study descriptions, the Development Phase for Protocol LPCN 1021-18-001 was changed to Phase 3.
- Minor editorial changes for protocol consistency.

7.0 SYNOPSIS

Sponsor : Lipocine Inc.

Protocol Number : LPCN 1021-18-001

Study Drug Name : Testosterone Undecanoate Capsule

Phase of Development : Phase 3

Active Ingredient : Testosterone Undecanoate

Protocol Title:

Ambulatory Blood Pressure Monitoring in Oral Testosterone Undecanoate (TU, LPCN 1021) Treated Hypogonadal Men.

Objective: To assess average daytime (7:00 AM to 11:00 PM), nighttime (11:00 PM to 7:00 AM), and average 24-hour blood pressure (BP) and pulse rate (PR) by ambulatory blood pressure monitoring (ABPM) at baseline (Visit 3) and post-treatment (Visit 5).

Study Population: Hypogonadal males, aged 18–80 years (inclusive).

Number of Subjects: 140

Study Endpoints:

Primary Endpoint:

The primary endpoint is the change in ABPM-measured average 24-hour systolic BP from Visit 3 to Visit 5.

Other Measures:

Change in average daytime and nighttime systolic BP assessed by ABPM from Visit 3 to Visit 5.

Change in average daytime, nighttime, and average 24-hour diastolic BP and PR assessed by ABPM from Visit 3 to Visit 5.

Change in morning systolic and diastolic BP and PR measured in triplicate at the clinic ("Clinic BP and PR") from Visit 3 to Visit 5.

Change in patient reported sexual desire and sexual distress from baseline to Visit 5.

Change in Magnetic Resonance Imaging-Proton Density Fat Fraction (MRI-PDFF) from MRI-1 (baseline) to MRI-2 (interim) and to MRI-3 (post-treatment) in all subjects with baseline, interim, and post-treatment MRI-PDFF measurements, those with a MRI-PDFF measurement of >5% at baseline, and those with a MRI-PDFF measurements of >10% at baseline.

Methodology:

This is an open-label, multicenter, single arm study evaluating the BP changes from baseline (Visit 3) to post-treatment (Visit 5) assessed by ABPM in LPCN 1021 treated adult hypogonadal male subjects.

The study is comprised of six scheduled visits: Visit 1 and 2 are for screening, Visit 3 is scheduled on Day -4 (±2 day) to assess subject's baseline BP and PR via ABPM. Visit 4 is to enroll subjects, and to provide subjects with study medication for the start of dosing. Visit 5 is to assess subject's post-treatment BP and PR via ABPM. Visit 6 is to perform exit procedures.

There are two confinement visits during the study of approximately 30 hours each (prior to start of the dosing and at the end of the study). The study visits are described below.

Visit 1 & 2: Subjects will undergo a screening period to complete the pre-study examinations and to confirm their hypogonadal status. Serum total testosterone (T) below lab normal range 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.

MRI-1 (Window: any time between Visit 2 and Visit 4): The MRI-1 baseline MRI-PDFF measurement will be performed between Visit 2 and Visit 4 in a subset of study subjects (approximately 20 or more subjects). Following confirmation of a subject's hypogonadal status at Visit 2, sites will schedule a MRI-1 at a local MRI facility for the subject. MRI-1 will be performed for all subjects reaching Visit 4 after implementation of Protocol Version 04 until target enrollment is reached. MRI-1 will not be performed for subjects who have already progressed past Visit 4 at the time of Version 04 implementation.

Visit 3: The morning of Visit 3 (Day -4), hypogonadal men meeting the inclusion criteria and none of the exclusion criteria will be confined for approximately 26 hours in the clinic for BP assessments by ABPM. In the morning, about 2 hours prior to start of the ABPM, sites will measure each subject's vital signs (oral temperature, Clinic BP and PR), with the subject seated at rest with back support for at least 10 minutes prior to vital sign measurement. Following this measurement, subjects will be started on the 24-hour ABPM portion of the study, starting at 7:00 AM. During the 24-hour ABPM portion of the study, the site will provide the subject with a meal, and then affix a validated, 510(k) cleared, portable ABPM device to the subject's arm; the device will record the subject's BP and PR over 24-hours. At the end of confinement period, sites will upload the ABPM data from the device to the web upload, and a central reader will evaluate if a subject's ABPM data are valid based on the ABPM Data Criteria provided in Section Ambulatory Blood Pressure Monitoring. Subjects with valid recorded ABPM data will proceed to Visit 4; subjects who do not have valid ABPM data may choose to repeat Visit 3 or they will not be enrolled into the study. Further, subjects will be asked if they are able to tolerate the ABPM component of the study and if they are willing to complete another 24 hour ABPM visit.

Visit 4: Subjects with valid ABPM data will return to the clinic for study enrollment. The morning (6 – 10 AM) of Visit 4 (Day 1 of treatment), eligible subjects will return to the clinic, where staff will dispense study drug.

Investigation Drug Product Resupply (Day 60; Window Day 30 to Day 60): subjects will return to the clinic for a resupply of study drug. Sites will record the day of the study drug resupply, and batch number of the study drug provided to the subject.

MRI-2 (Window: any time between Day 56 and Day 76, inclusive): The MRI-2 interim MRI-PDFF measurement will be performed between Visit 4 and Visit 5 in subjects who had a baseline MRI-PDFF measurement (MRI-1). Sites will schedule MRI-2 at the same local MRI facility that performed the subject's MRI-1.

Visit 5: The Visit 5 (Day 107, window ± 7 days) schedule involves collecting a blood sample, providing meals to subjects, dosing the study medication and ABPM measurements.

The visit starts on Day 106 with confinement lasting for up to 45 hours. Subjects will enter the clinic on Day 106 after taking their study medication in the morning. The site will collect a single blood sample from the subjects (at approximately 3 hours post-morning dose on Day 106). Following the blood sample collection, subjects will remain at the site until completion of ABPM on Day 108 (on site duration: ~45 hours). For subjects who are not able to remain in the site for the 45-hour duration, blood sample may be collected at approximately 3 hours after the evening dose of Day 106 (on site duration at least 33 hours).

On the morning of Day 107 prior to start of the ABPM, vital signs (oral temperature, Clinic BP and PR) will be measured when seated at rest with back support for 10 minutes. Subjects will then be provided with the study medication approximately 30 minutes after a meal. Following the administration of study drug, subjects will be started on the 24-hour ABPM portion of the study, starting at 7:00 AM. For the 24-hour ABPM portion of the study, the site will affix a validated, 510(k) cleared portable ABPM device to the subject's arm; the device will record the subject's BP and PR over 24-hours. During the ABPM confinement visit, the subjects will be administered study drug every 12 hours with meal (evening of Day 106, morning and evening of Day 107, morning of Day 108 prior to exiting site). Following the 24-hour ABPM period, subjects will exit the clinic. All subjects will be instructed to continue taking their study medication. Subjects with valid recorded ABPM data at Visit 5 will proceed to Visit 6 for exit procedures after completing the MRI-2 measurement described below; subjects who do not have valid ABPM data may choose to repeat Visit 5.

MRI-3 (Window: any time between Visit 5 and Visit 6): Following the second ABPM measurement at Visit 5, subjects who had a baseline MRI-PDFF measurement (MRI-1) will have a post-treatment MRI-PDFF (MRI-3). Sites will schedule MRI-3 at the same local MRI facility that performed the subject's MRI-1.

Visit 6: The Visit 6 (Day 110, window ± 10 days) schedule involves exit procedures, including return of study medication, vital signs measurement (oral temperature, Clinic BP and PR), a

blood sample for clinical laboratory tests, adverse event (AE) reporting, and a review of the subject's Medical History, including specific querying if the subject has a history of diabetes, hypertension (never diagnosed, diagnosed but treated, diagnosed but not treated), and the subject's smoking status (never smoked, former smoker, current smoker) to ensure that this information is included in the subject's Medical History. Sites will collect the blood sample for clinical laboratory tests in the morning prior to meals and study drug administration.

The total duration of the study will be approximately 110 days not including the screening period.

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 lab normal value (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.
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 baseline 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 abnormal laboratory value, in the opinion of the investigator, in serum chemistry, hematology, or urinalysis including but not limited to:
    a. 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 > 4 ng/mL

g. Prolactin > 17.7 ng/mL.

3. Clinically significant findings in the pre-study examinations including abnormal breast examination requiring follow-up.
4. Subjects with screening systolic BP or diastolic BP above 160 mmHg or 100 mmHg, respectively.
5. Subjects with symptoms of moderate to severe benign prostatic hyperplasia.
6. History of seizures or convulsions occurring after age 5, including alcohol or drug withdrawal seizures.
7. History of gastric surgery, cholecystectomy, vagotomy, bowel resection or any surgical procedure that might interfere with gastrointestinal motility, pH or absorption.
8. History of any clinically significant illness, infection, or surgical procedure within 1 month prior to study drug administration.
9. Known tolerability issues with ABPM devices.
10. History of stroke, myocardial infarction, transient ischemic attack, or acute coronary syndrome within the past 5 years.
11. History of long QT syndrome (or QTcB > 450) or unexplained sudden death (including cardiac death) or history of long QT syndrome in a first degree relative (parent, sibling, or child).
12. Subjects who are not on stable dose of current medication (no changes in medication in the last 3 months).
13. History of current or suspected prostate or breast cancer.
14. History of untreated obstructive sleep apnea or not compliant with sleep apnea treatment.
15. 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.
16. 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. A list of prohibited medications is provided in Appendix C.
17. Use of any investigational drug within 5 half-lives of the last dose in the past 6 months prior to Study Day –2 without principal investigator and/or sponsor approval.
18. 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.

19. Subject who is not willing to use adequate contraception for the duration of the study.
20. Any contraindications to a MRI scan (i.e. subjects with non-removable ferromagnetic implants, pacemakers, aneurysm clips or other foreign bodies), and/or subjects with claustrophobic symptoms and/or inability to fit into an MRI scanner.
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 (exact reason should be specified by the investigator).

Investigational Product: Testosterone Undecanoate (TU) Oral Capsules, 112.5 mg TU per capsule.

Doses: The study involves a 225 mg dose of LPCN 1021. The dose is administered as 225 mg TU (two capsules of 112.5 mg) twice daily (BID) approximately 12 hours apart with meal (total daily dose of 450 mg taken as 225 mg in the morning and 225 mg in the evening).

Administration Route: Oral.

Study Duration: Study duration will be up to 110 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.
- Significant noncompliance with the protocol requirements.
- Lost to follow-up.

Criteria for Evaluation:

Changes from baseline in average daytime, average night time and average 24-hour BP as measured by ABPM in LPCN 1021 treated subjects. If the upper limit of the two-sided 95% confidence interval (CI) for the change from baseline in average 24-hour systolic BP is ≤ 4.9 mmHg, the change will be considered as not clinically significant.

Statistical Methods: Statistical analyses will be described in the statistical analysis plan (SAP).

8.0 LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

8.1. Abbreviations

AE	Adverse event
ALT (SGPT)	Alanine aminotransferase (serum glutamic pyruvic transaminase)
ABPM	Ambulatory blood pressure monitoring
AST (SGOT)	Aspartate aminotransferase (serum glutamic oxaloacetic transaminase)
BID	Twice daily
BMI	Body mass index
BP	Blood pressure
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

9.0 TABLE OF CONTENTS

10.0 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."[1] 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.[2] 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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[1] 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

[2] 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.[3]

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.[4]

The LPCN 1021 clinical development program included eight Phase 1 studies and three Phase 3 studies. In previous clinical studies (Study LPCN 1021-05-001 and Study LPCN 1021-09-001), various oral TU 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 Study LPCN 1021-13-001 provides safety, efficacy, and pharmacokinetic for a titrated dose of LPCN 1021 as a T replacement therapy in men with primary and secondary hypogonadism. Results indicate that a starting dose of 225 mg BID, with titration to 150 mg or 300 mg LPCN 1021 based on a pharmacokinetic algorithm, was effective in restoring T levels of hypogonadal men to the eugonadal range when taken with a meal.

The Phase 3 Study LPCN 1021-16-002 provides safety, efficacy, and pharmacokinetic data for a fixed dose of LPCN 1021 as a T replacement therapy in men with primary and secondary hypogonadism. Results indicate that a twice daily fixed dose of 225 mg taken with a meal is

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[3] 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.

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

effective in restoring T levels of hypogonadal men to the eugonadal range.

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

11.0 STUDY OBJECTIVES

11.1. Primary Objective

To assess average daytime (7:00 AM to 11:00 PM), nighttime (11:00 PM to 7:00 AM), and average 24-hour BP and PR by ABPM at baseline (Visit 3) and post-treatment (Visit 5).

11.2. Study Endpoints

11.2.1. Primary Endpoint

The primary endpoint is the change in ABPM-measured average 24-hour systolic BP from Visit 3 to Visit 5.

11.2.2. Other Measures

Change in average daytime and nighttime systolic BP assessed by ABPM from Visit 3 to Visit 5.

Change in average daytime, nighttime, and average 24-hour diastolic BP and PR assessed by ABPM from Visit 3 to Visit 5.

Change in morning systolic and diastolic BP and PR measured in triplicate at the clinic ("Clinic BP and PR") from Visit 3 to Visit 5.

Change in patient reported sexual desire and sexual distress from baseline to Visit 5.

Change in Magnetic Resonance Imaging-Proton Density Fat Fraction (MRI-PDFF) from MRI-1 (baseline) to MRI-2 (interim) and to MRI-3 (post-treatment) in all subjects with baseline, interim, and post-treatment MRI-PDFF measurements, those with a MRI-PDFF measurement of >5% at baseline, and those with a MRI-PDFF measurements of >10% at baseline.

12.0 INVESTIGATIONAL PLAN

12.1. Overall Study Design

This is an open-label, multicenter, single arm study evaluating the BP changes from baseline (Visit 3) to post-treatment (Visit 5) assessed by ABPM in LPCN 1021 treated adult hypogonadal male subjects.

The study is comprised of six scheduled visits: Visit 1 and 2 are for screening, Visit 3 is scheduled on Day -4 (±2 day) to assess subject's baseline BP and PR via ABPM. Visit 4 is to

enroll subjects, and to provide subjects with study medication for the start of dosing. Visit 5 is to assess subject's post-treatment BP and PR via ABPM. Visit 6 is to perform exit visit procedures.

There are two confinement visits during the study, one prior to start of the dosing and another at the end of the study. The study visits are described below.

Visit 1 & 2: Subjects will undergo a screening period to complete the pre-study examinations and to confirm their hypogonadal status. Serum total testosterone (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. At the end of Visit 2, sites will provide subjects with a 7-day sexual desire question printout, with instructions to answer the question each day for 7 days leading up to Visit 3. Sites will remind subjects to complete the sexual desire question printout when scheduling Visit 3 for eligible subjects; ineligible subjects will be informed that they will not be able to participate in the study, and they do not need complete the printout.

MRI-1 (Window: between Visit 2 and Visit 4): The MRI-1 baseline MRI-PDFF measurement will be performed between Visit 2 and Visit 4 in a subset of study subjects (approximately 20 or more subjects). Following confirmation of a subject's hypogonadal status at Visit 2, sites will schedule MRI-1 at a local MRI facility for the subject. A local MRI facility capable of performing the MRI-PDFF test will be pre-identified by the Medpace Core Lab within the geographic location of the site. Alternatively, if the site has a preferred MRI facility, the site can use their preferred facility following confirmation by the Medpace Core Lab.

MRI-1 will be performed for all subjects reaching Visit 4 after implementation of Protocol Version 04 until target enrollment is reached. MRI-1 will not be performed for subjects who have already progressed past Visit 4 at the time of Version 04 implementation.

Visit 3: The morning of Visit 3 (Day -4), hypogonadal men meeting the inclusion criteria and none of the exclusion criteria will be confined for approximately 26 hours in the clinic for BP assessments by ABPM. Upon clinic entry, sites will collect the 7-day sexual desire question printout from subjects and give subjects a sexual distress question printout to answer. About 2 hours prior to start of the ABPM, vital sign measurements will be recorded to include oral temperature, Clinic BP PR. For proper measurement of Clinic BP and PR, the following procedures should be followed:

- An appropriately sized cuff for the size of the subject's arm circumference should be utilized to minimize inaccurate readings.
- No smoking or exercise for at least 30 minutes before a blood pressure measurement
- Subjects should sit in a chair with a back support and the arm supported at heart level with feet flat on the floor. The subject should void prior to the measurement.
- Blood pressure and PR will be measured in triplicate over a minimum of approximately 10 minutes after the subject has rested in a sitting position for at least 10 minutes. The three measurements will each be recorded in the CRF and a mean value for that visit will be calculated.

Following this measurement, subjects will be started on the 24-hour ABPM portion of the study, starting at 7:00 AM. During the 24-hour ABPM portion of the study, the site will provide the subject with a meal, and then affix a validated, 510(k) cleared portable ABPM device to the subject's arm; the device will record the subject's BP and PR over 24-hours. Sites will set the ABPM device to record BP and PR every 15 minutes during daytime hours (7 AM to 11 PM), and every 20 minutes during nighttime hours (11 PM to 7 AM). At the end of confinement period, sites will upload the ABPM data from the device to the web upload, and a central reader will evaluate if a subject's ABPM data are valid based on the ABPM Data Criteria provided in Section Ambulatory Blood Pressure Monitoring. Subjects with valid ABPM data will proceed to Visit 4; subjects who do not have valid ABPM data may choose to repeat Visit 3 or they will not be enrolled into the study. Subjects will be asked if they were able to tolerate the ABPM component of the study and if they are willing to participate in the ABPM visit at the end of the study.

Visit 4: Subjects with valid ABPM data will return to the clinic for study enrollment. The morning (6 – 10 AM) of Visit 4 (Day 1 of treatment), eligible subjects will return to the clinic, where staff will dispense study drug. At the end of the visit, sites will provide subjects with a 7-day sexual desire question printout, with instructions to answer the question each day for 7 days leading up to Visit 5. Sites will contact subjects 7 days in advance of Visit 5 to remind subjects to complete the sexual desire question printout.

Investigation Drug Product Resupply (Day 60; Window Day 30 to Day 60): subjects will return to the clinic for a resupply of study drug. Sites will record the day of the study drug resupply, and batch number of the study drug provided to the subject.

MRI-2 (Window: any time between Day 56 to Day 76, inclusive): The MRI-2 interim MRI-PDFF measurement will be performed between Visit 4 and Visit 5 in subjects who had a baseline MRI-PDFF measurement (MRI-1). Sites will schedule MRI-2 at the same local MRI facility that performed the subject's MRI-1.

The Visit 5 (Day 107, window ± 7 days) schedule involves collecting a blood sample, providing meals to subject, dosing the study medication and ABPM measurements.

The visit starts on Day 106 with confinement lasting for up to 45 hours. Subjects will enter the clinic on Day 106 after taking their study medication in the morning. The site will collect a single blood sample from the subjects (at approximately 3 hours post-morning dose on Day 106). Following the blood sample collection, subjects will remain at the site until completion of ABPM on Day 108 (confinement duration of about 45 hours). For subjects who are not able to remain in the site for the 45-hour duration, blood sample may be collected at approximately 3 hours after the evening dose of Day 106 (confinement duration of at least 33 hours).

Sites will collect the 7-day sexual desire question printout from subjects and give subjects a sexual distress question printout to answer. Then, on the morning of Day 107, prior to start of the ABPM, vital signs (oral temperature, Clinic BP and PR) will be measured. Subjects will then be provided with the study medication approximately 30 minutes after a meal. Following the

administration of study drug, subjects will be started on the 24-hour ABPM portion of the study, starting at 7:00 AM. During the 24-hour ABPM portion of the study, the site will affix a valid, 510(k) cleared portable ABPM device to the subject's arm; the device will record the subject's BP and PR over 24-hours. Sites will set the ABPM device to record BP and PR every 15 minutes during daytime hours (7 AM to 11 PM), and every 20 minutes during nighttime hours (11 PM to 7 AM). During the ABPM confinement visit, the subjects will be administered study drug every 12 hours with a meal (evening of Day 106, morning and evening of Day 107, morning of Day 108 prior to exiting site). Following the 24-hour ABPM portion of the study, the subjects will exit the clinic. All subjects will be instructed to continue taking their study medication. Subjects with valid recorded ABPM data at Visit 5 will proceed to Visit 6 for exit procedures after completing the MRI-2 measurement described below; subjects who do not have valid ABPM data may choose to repeat Visit 5.

MRI-3 (Window: between Visit 5 and Visit 6): Following the second ABPM measurement at Visit 5, subjects who had the MRI-1 baseline MRI-PDFF will have a post-treatment MRI-PDFF, MRI-3. Sites will schedule MRI-3 at the same local MRI facility that performed the subject's MRI-1.

Visit 6: The Visit 6 (Day 110, window ± 10 days) schedule involves exit procedures including weight measurement, physical exam, vital signs, return of study medication, a blood sample for clinical laboratory tests, review of concomitant medication, AE reporting, and a review of the subject's Medical History, including specific querying if the subject has a history of diabetes, hypertension (never diagnosed, diagnosed but treated, diagnosed but not treated), and the subject's smoking status (never smoked, former smoker, current smoker) to ensure that this information is included in the subject's Medical History. Sites will collect the blood sample for clinical laboratory tests in the morning prior to meals; the subject will not take study drug the morning of Visit 6.

The total duration of the study will be approximately 110 days not including the screening period.

12.2. Selection of Study Population

Subjects will undergo screening procedures within approximately 60 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.

12.2.1. 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 lab normal range (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.
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 baseline serum T samples to determine study eligibility.
6. Judged to be in good general health as determined by the investigator at screening.

12.2.2. 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 abnormal laboratory value, in the opinion of the investigator, in serum chemistry, hematology, or urinalysis including but not limited to:
    a. 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 > 4 ng/mL
    g. Prolactin > 17.7 ng/mL.
3. Clinically significant findings in the pre-study examinations including abnormal breast examination requiring follow-up.
4. Subjects with screening systolic BP or diastolic BP above 160 mmHg or 100 mmHg, respectively.
5. Subjects with symptoms of moderate to severe benign prostatic hyperplasia.
6. History of seizures or convulsions occurring after age 5, including alcohol or drug withdrawal seizures.
7. History of gastric surgery, cholecystectomy, vagotomy, bowel resection or any surgical procedure that might interfere with gastrointestinal motility, pH or absorption.
8. History of any clinically significant illness, infection, or surgical procedure within 1 month prior to study drug administration.

9. Known tolerability issues with ABPM devices.
10. History of stroke, myocardial infarction, transient ischemic attack, or acute coronary syndrome within the past 5 years.
11. History of long QT syndrome (or QTcB > 450) or unexplained sudden death (including cardiac death) or history of long QT syndrome in a first degree relative (parent, sibling, or child).
12. Subjects who are not on stable dose of current medication (no changes in medication in the last 3 months).
13. History of current or suspected prostate or breast cancer.
14. History of untreated obstructive sleep apnea or not compliant with sleep apnea treatment.
15. 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.
16. 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. A list of prohibited medications is provided in Appendix C.
17. Use of any investigational drug within 5 half-lives of the last dose in the past 6 months prior to Study Day –2 without principal investigator and/or sponsor approval.
18. 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.
19. Subject who is not willing to use adequate contraception for the duration of the study.
20. Any contraindications to a MRI scan (i.e. subjects with non-removable ferromagnetic implants, pacemakers, aneurysm clips or other foreign bodies), and/or subjects with claustrophobic symptoms and/or inability to fit into an MRI scanner.
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 (exact reason should be specified by the investigator).

13.0 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).

13.1. Screening Procedures (Visits 1 and 2)

Screening procedures will be performed within approximately 60 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: informed consent, demographic data, medical and medication histories, physical examination and the first screening testosterone sample.

In Visit 2, sites will perform sampling for additional laboratory analysis including a second screening testosterone sample, electrocardiogram, a blood sample for clinical laboratory tests, and drug and alcohol screen. At the end of the visit, sites will provide subjects with a 7-day sexual desire question printout, with instructions to answer the question each day for 7 days leading up to Visit 3 (sites will collect at Visit 3). Sites will remind subjects to complete the sexual desire question printout when scheduling Visit 3 for eligible subjects; ineligible subjects will be informed that they will not be able to participate in the study, and they do not need complete the printout.

13.2. MRI-1 (Window: between Visit 2 and Visit 4)

The MRI-1 baseline MRI-PDFF measurement will be performed between Visit 2 and Visit 4 in a subset of study subjects (approximately 20 or more subjects). Following confirmation of a subject's hypogonadal status at Visit 2, sites will schedule MRI-1 at a local MRI facility for the subject. A local MRI facility capable of performing the MRI-PDFF test will be pre-identified by the Medpace Core Lab within the geographic location of the site. Alternatively, if the site has a preferred MRI facility, the site can use their preferred facility following confirmation by the Medpace Core Lab.

MRI-1 will be performed for all subjects reaching Visit 4 after implementation of Protocol Version 04 until target enrollment is reached. MRI-1 will not be performed for subjects who have already progressed past Visit 4 at the time of Version 04 implementation.

13.3. Baseline ABPM (Visit 3)

Hypogonadal men meeting the inclusion criteria and none of the exclusion criteria will be return to the clinic on the morning of Day -4 (±2) for a confinement visit of approximately 26 hours. During this confinement visit, subjects will have their BP measured by ABPM for 24 hours starting at 7:00 AM. Upon clinic entry, sites will collect the 7-day sexual desire question printout from subjects and give subjects a sexual distress question printout. In the morning, prior to start of the ABPM, vital signs (oral temperature, Clinic BP and PR) will be measured. Following this measurement, subjects will be started on the 24-hour ABPM portion of the study

starting at 7:00 AM. The site will provide the subject with a meal, and then affix a validated, 510(k) cleared portable ABPM device to the arm of the subject, and the device will record BP and PR for 24-hours. At the end of confinement period, sites will upload the ABPM data from the device to the web upload, and a central reader will evaluate if subjects had valid ABPM results. For the 24-hour ABPM results to qualify as valid, the data must meet ABPM Data Criteria provided in Section Ambulatory Blood Pressure Monitoring.

Subjects with valid 24-hour ABPM results proceed to study enrollment (Visit 4). Subjects who do not have valid ABPM data based on the ABPM criteria can choose to repeat Visit 3 or they will not be enrolled into the study. Subject will be asked by the clinic staff if the subject was able to tolerate the ABPM component of the study and if they are able to participate in the ABPM visit at the end of the study.

13.4. Treatment Phase (Visit 4 through Visit 6)

Treatment Phase of the study consists of approximately 107 days starting at Visit 4 and ending at Visit 5.

Visit 4: Sites will enroll subjects with valid 24-hour ABPM data from Visit 3 into the study. The morning of study Visit 4 (Day 1 of treatment), eligible subjects will return to the clinic. Sites will dispense study drug, review the concomitant medications of the subject, review any AEs. Sites will instruct subjects to take LPCN 1021 225 mg twice daily, with a meal (approximately 30 minutes following meal), for 107 days (± 7 days). Sites will schedule subjects for the confinement visit (Visit 5, starting on Day 106). At the end of the visit, sites will provide subjects with a 7-day sexual desire question printout, with instructions to answer the question each day for 7 days leading up to Visit 5. Sites will contact subjects 7 days in advance of Visit 5 to remind them to answer the question as instructed.

Investigation Drug Product Resupply (Day 60; Window Day 30 to Day 60): subjects will return to the clinic for a resupply of study drug. Sites will record the day of the study drug resupply, and batch number of the study drug provided to the subject.

MRI-2 (Window: any time between Day 56 to Day 76, inclusive): The MRI-2 interim MRI-PDFF measurement will be performed between Visit 4 and Visit 5 in subjects who had a baseline MRI-PDFF measurement (MRI-1). Sites will schedule MRI-2 at the same local MRI facility that performed the subject's MRI-1.

The Visit 5 (Day 107, window ± 7 days) schedule involves collecting a blood sample, providing meals to subject, dosing the study medication and ABPM measurements.

The visit starts on Day 106 with confinement lasting for up to 45 hours. Subjects will enter the clinic on Day 106 after taking their study medication in the morning. The site will collect a single blood sample from the subjects (at approximately 3 hours post-morning dose on Day 106). Following the blood sample collection, subjects will remain at the site until completion of ABPM on Day 108 (on site duration: ~45 hours). For subjects who are not able to remain in the

site for the 45-hour duration, blood sample may be collected at approximately 3 hours after the evening dose of Day 106 (on site duration at least 33 hours).

Sites will collect the 7-day sexual desire question printout from the subjects, and the subjects will be given a question to assess their sexual distress. On the morning of Day 107, prior to start of the ABPM, vital signs (oral temperature, Clinic BP and PR) will be measured. Subjects will then be provided with the study medication approximately 30 minutes after a meal. Following the administration of study drug, subjects will be started on the 24-hour ABPM portion of the study starting at 7:00 AM. During the 24-hour ABPM portion of the study, the site will affix a valid, 510(k) cleared portable ABPM device to the subject's arm; the device will record the subject's BP and PR over 24-hours. During the ABPM confinement visit, the subjects will be administered study drug every 12 hours with meal (evening of Day 106, morning and evening of Day 107, morning of Day 108 prior to exiting site). At the end of 24-hours, subjects will exit the clinic. Clinic staff will return study medication to the subject and instruct the subject to continue taking their study medication until Visit 6. Subjects with valid recorded ABPM data at Visit 5 will proceed to Visit 6 for exit procedures after completing the MRI-2 measurement described below; subjects who do not have valid ABPM data may choose to repeat Visit 5.

MRI-3 (Window: between Visit 5 and Visit 6): Following the second ABPM measurement at Visit 5, subjects who had the MRI-1 baseline MRI-PDFF will have a post-treatment MRI-PDFF, MRI-3. Sites will schedule a MRI-PDFF measurement at the same local MRI facility that performed the baseline MRI-PDFF.

Visit 6: The Visit 6 (Day 110, window ± 10 days) schedule involves exit procedures including weight measurement, physical exam, vital signs, return of study medication, a blood sample for clinical laboratory tests, review of concomitant medication, AE reporting, and a review of the subject's Medical History, including specific querying if the subject has a history of diabetes, hypertension (never diagnosed, diagnosed but treated, diagnosed but not treated), and the subject's smoking status (never smoked, former smoker, current smoker) to ensure that this information is included in the subject's Medical History. Sites will collect the blood sample for clinical laboratory tests in the morning prior to meals; the subject will not take study drug the morning of Visit 6.

13.5. Clinical Procedures

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

13.5.1.1. 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). 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 with a chronic condition requiring medication must:

- Be under stable treatment, with the same medication and dosage for at least 3 months prior to first dosing.
- Have no expected change to medication planned throughout the study.
- The subject's medication should have no interaction with the pharmacokinetics of the study drug or the bioanalytical methods.

Concomitant Medication for Hypertension

Given that the objective of this study is to assess changes in blood pressure after LPCN 1021 treatment, sites should document the medical and medication history associated with hypertension. Subjects should be queried on medication for hypertension, start date, current medication, last change in medication prior to the start of the study. During the study, changes in hypertensive medication should be driven only by the requirement due to change in hypertensive status. Any such changes should be documented with a reason for change.

Any addition of medication should be documented including the indication for which the medication was added. This will be coded per WhoDrug dictionary.

13.5.1.2. Electrocardiogram

An electrocardiogram will be performed at the screening to identify, and subsequently exclude, subjects with long QT syndrome. Subjects with QTcB > 450 msec will not be enrolled into the trial.

13.5.1.3. 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. Any changes during the study will be documented. Subject's height and weight will be used to calculate BMI.

13.5.1.4. Vital Signs

Sites will measure oral temperature (single measurement), and Clinic BP and PR on Visit 3, Visit 5, and at Visit 6/study exit. Vital signs must be measured after the subject has been sitting at rest for at least 10 minutes with a back support, using automated digital blood pressure devices (the device used should be current with respect to calibration, the exact make and model of the device used to record blood pressure should be documented). The average of the three BP and PR measurements will be used in statistical analyses.

13.5.1.5. Ambulatory Blood Pressure Monitoring

Sites will measure subject ABPM on Visit 3 and Visit 5. Sites will affix a validated, 510(k) cleared portable ABPM device to the arm of the subject, and the device will record BP and PR. Sites will set the ABPM device to record BP and PR every 15 minutes during daytime hours (7 AM to 11 PM), and every 20 minutes during nighttime hours (11 PM to 7 AM). At the end of 24-hours, sites will evaluate if subjects had valid ABPM results. Site staff will be trained in the usage of the device. At the end of the 24-hour measurements, sites will upload the data to a central web upload tool. A central reader of the data will qualify the data as valid or not. If data are not valid at Visit 3 or Visit 5, a repeat measurement may be allowed at the discretion of study medical monitor. For the 24-hour ABPM results to qualify as valid, the data must meet the following ABPM Data Criteria:

- Minimum of 1 valid reading per hour, including during sleep.
- Valid data for at least 22 out of 24 hours in the day.

13.5.1.6. Clinical Laboratory Tests

13.5.1.6.1. Hematology, Chemistries, and Urinalysis

For all subjects, blood samples will be taken at screening Visit 2 (refer to Table 1 and Appendix A) for clinical laboratory tests (hematology, clinical chemistry, and hormones). Sites will collect samples for serum chemistry tests in the morning prior to meals.

Table 1: Listing of Clinical Laboratory Tests for all Subjects at Visit 2

Hematology	Clinical Chemistry	Hormones
Hematocrit Hemoglobin	Creatinine Bilirubin Serum glutamic-pyruvic transaminase (SGPT/ALT) Serum glutamic-oxaloacetic transaminase (SGOT/AST)	Prolactin Prostate specific antigen

For subjects reaching Visit 2 after Protocol Version 04, additional clinical laboratory tests (refer

to Table 2) will be performed at Visit 2. The additional tests will be performed for all subjects reaching Visit 2 following the implementation of Protocol Version 04 until target enrollment is reached.

Table 2: Listing of Additional Clinical Laboratory Tests for Subjects for Reaching Visit 2 after Protocol Version 04

Clinical Chemistry	Hematology/Coagulation
Albumin Alkaline phosphatase (ALP) Blood urea nitrogen (BUN) Gamma-glutamyltransferase (GGT) Cholesterol Triglycerides High density lipoprotein (HDL) cholesterol Low density lipoprotein (LDL) cholesterol Free fatty acid	Prothrombin time (PT) and international normalized ratio (INR) Hemoglobin A1C (HBA1C)

For all subjects, blood samples will be taken at screening Visit 6 (refer to Table 3 and Appendix A) for clinical laboratory tests. Sites will collect samples for serum chemistry tests in the morning prior to meals.

Table 3: Listing of Clinical Laboratory Tests for Subjects at Visit 6

Clinical Chemistry	Hematology/Coagulation
Creatinine Bilirubin Serum glutamic-pyruvic transaminase (SGPT/ALT) Serum glutamic-oxaloacetic transaminase (SGOT/AST) Albumin Alkaline phosphatase (ALP) Blood urea nitrogen (BUN) Gamma-glutamyltransferase (GGT) Cholesterol Triglycerides High density lipoprotein (HDL) cholesterol Low density lipoprotein (LDL) cholesterol Free fatty acid	Prothrombin time (PT) and international normalized ratio (INR) Hemoglobin A1C (HBA1C)

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.

13.5.1.6.2. Residual Serum Sample Testing Performed by Medpace

For subjects who progressed past Visit 2 prior to Protocol Version 04, the following additional

tests will be performed by Medpace using residual serum sample (no additional blood sampling is required by study sites).

Table 4: Listing of Clinical Laboratory Tests Performed on Residual Serum Sample

Clinical Chemistry
Albumin
Alkaline phosphatase (ALP)
Blood urea nitrogen (BUN)
Gamma-glutamyltransferase (GGT)
Cholesterol
Triglycerides
High density lipoprotein (HDL) cholesterol
Low density lipoprotein (LDL) cholesterol

13.5.1.6.3. Screens for Drugs of Abuse and Alcohol

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

13.5.1.6.4. Prostate-Specific Antigen (PSA)

Sites will collect samples for PSA at screening. A digital rectal exam (DRE) is not part of screening procedures. If the investigator conducts a DRE outside of protocol requirement, the PSA samples should be collected prior to the DRE.

13.5.1.6.5. Serum Testosterone

At screening, serum total T must be below lab normal range based on two 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. Refer to the Schedule of Events (Appendix A) for sample collection days and times.

13.5.1.6.6. Blood Sample Collection – Serum TU

On Day 106 (approximately 3 hours post-morning dose on Day 106), when subjects enter the clinic, a single blood sample of 8 mL blood will be collected in a serum separator tube (gold top tube), at approximately 3 hours post-morning dose on Day 106. For subjects who are not able to remain in the site for the 45-hour duration, blood sample may be collected at approximately 3 hours after the evening dose.

The collected sample will be processed for serum separation and stored at -20°C. The samples will be shipped in dry ice to PPD bioanalytical laboratory. The serum samples will be analyzed for TU levels.

13.5.1.7. Confinement

There are two confinement visits for each subject. During Visit 3 and Visit 5, subjects will return to the clinic for 24-hour ABPM. During the confinement, sites will provide meals and snacks to subjects; during confinement visits. Also, the study drug administration during Visit 5 confinement will be carried out by the site. Strenuous activity during confinement will not be permitted.

13.5.1.8. Meals and Dietary Requirements

Throughout the study, subjects will be advised to maintain a diet that 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.

13.5.1.9. Patient Reported Sexual Desire and Distress

Subjects will be asked two questions to assess the patient reported outcomes before and after treatment:

(A) Sexual desire: Seven-day questionnaire

(B) Sexual distress: One day questionnaire

For the sexual desire question, sites will give subjects a printout of a sexual desire question (provided in Appendix D) repeated on 7 pages at Visit 2, with instructions to answer the question each day for 7 days. Sites will remind subjects to complete the sexual desire question printout when scheduling Visit 3 for eligible subjects; ineligible subjects will be informed that they will not be able to participate in the study, and they do not need complete the printout. Sites will collect the printout from the subjects upon entry for Visit 3.

For the sexual distress question, sites will provide subjects with a printout of a question to assess sexual distress (provided in Appendix D) upon clinic entry at Visit 3.

Subjects will be asked the same two questions at the end of treatment. For the sexual desire question, sites will give subjects a printout of the sexual desire question (provided in Appendix D) repeated on 7 pages at Visit 4, with instructions to answer the question each day for 7 days leading up to Visit 5. Sites will contact subject's 7 days in advance of Visit 5 to remind them to answer the sexual desire question. Sites will collect the printout from the subjects upon entry for Visit 5. For the sexual distress question, sites will provide subjects with a printout of a question

to assess sexual distress (provided in Appendix D) upon clinic entry at Visit 5.

13.5.1.10. Magnetic Resonance Imaging-Proton Density Fat Fraction (MRI-PDFF)

A MRI-PDFF measurement will be performed at baseline between Visit 2 and Visit 4 (MRI-1), at an interim point between Day 56 and Day 76, inclusive, (MRI-2) and post-treatment between Visit 5 and Visit 6 (MRI-3). MRI-1 will be performed for all subjects reaching Visit 4 after implementation of Protocol Version 04 until target enrollment is reached (approximately 20 or more subjects). MRI-1 will not be performed for subjects who have already progressed past Visit 4 at the time of Version 04 implementation. The MRI-2 and MRI-3 measurements will be performed for all subjects who complete MRI-1.

13.6. DOSAGE ADMINISTRATION

All subjects will receive 225 mg BID (two capsules of 112.5 mg) taken twice daily (total daily dose of 450 mg taken as 225 mg in the morning and 225 mg in the evening), approximately 12 hours apart, approximately 30 minutes after morning and evening meals, with water.

13.7. 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.
- 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. For consent withdrawn subjects, sites should query the specific reason for withdrawal and document it. For subjects who are lost to follow-up sites should make at least three documented attempts to contact the subject prior to terminating from study. 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.

13.7.1. Exit Evaluation

Exit evaluation occurs during Visit 6 for subjects who complete the study. For subjects who withdraw from the study or discontinued early exit evaluation should be conducted.

13.8. 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.

13.9. Drug Product

LPCN 1021 is gelatin capsule product that will be provided as 112.5 mg TU per capsule.

13.9.1. Packaging and Labeling

LPCN 1021 will be provided in high-density polyethylene (HDPE) bottles containing 120 capsules in each bottle. 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.

13.9.2. 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.

13.9.3. 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.

13.10. 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.

14.0 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.

14.1. 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.

14.2. 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.

14.3. 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.

14.4. 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.

14.5. 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 completion of the last visit after the last dose of study drug will be collected, whether solicited or spontaneously reported by the subject.

14.6. Serious Adverse Event Reporting

In the event of an SAE in the subject, 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

14.7. Pregnancy Reporting

In the event of a pregnancy in a subject's partner, the investigator will notify the sponsor or representative within 24 hours of the site being made aware of the pregnancy.

15.0 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
Dr. Nachiappan (Chidu) Chidambaram, PhD
nc@lipocine.com
(801) 534-6807

Alternate Contact
Dr. Anthony DelConte,
ad@lipocine.com
(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.

16.0 STATISTICAL ANALYSIS

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

16.1. Determination of Sample Size

The final sample size of 135 was chosen for the study based on the recommendations of FDA. This sample size is higher than the originally proposed 75 subject sample size and should meet the scientific objective of ruling out a change from baseline of 4.9 mmHg.

16.2. Study Populations

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

Safety Set (SS): The safety set includes all subjects who received a dose of study drug. All safety analyses will be conducted in the SS.

Full Analysis Set (FAS): The FAS consists of all subjects enrolled into the study with valid ABPM data at Visit 3 and Visit 5. All analyses of blood pressure will be conducted in the FAS.

16.3. 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 [%]), minimum, maximum, and median) of Clinic BP and PR measurements will be summarized descriptively for all subjects who were dosed (SS population).

Descriptive statistics (arithmetic and geometric means, SD, CV [%], minimum, maximum, and median) of daytime (7:00 AM to 11:00 PM), nighttime (11:00 PM to 7:00 AM), and 24-hour ABPM parameters (heart rate, systolic blood pressure, and diastolic blood pressure) from Visit 3 and Visit 5 will be summarized descriptively for all subjects who were dosed and have valid

ABPM data (FAS population).

In addition, the following analyses and data presentation will be included:

- Central tendency analysis and outlier analysis for the 24-hour average and for the hourly average. Outliers will be defined in the SAP (i.e., systolic BP exceeding 160 mmHg or a change in systolic BP > 20 mmHg, or a diastolic BP exceeding 100 mmHg or a change in diastolic BP > 15 mmHg).
- Graphical display of hourly ABPM averages that include standard deviation bars for both systolic BP and diastolic BP at baseline and at endpoint (mid-trial data optional).
- Cumulative distribution curves of 24-hour average systolic BP and diastolic BP at baseline and at each of the timepoints in which ABPM studies are performed.
- Forest plots of daytime, nighttime, and 24-hour change from baseline with 95% confidence interval displays for systolic BP and diastolic BP.

Sensitivity analyses: 1) the above four sub-bullets grouped for subjects without hypertension, with hypertension untreated, and with hypertension treated; 2) the above four sub-bullets for subjects with/without diabetes mellitus.

A complete description of the statistical analyses to be performed will be presented in the SAP.

16.4. Endpoint Analysis

Details of the analyses to be performed will be described in detail in the SAP. Study primary endpoints are briefly discussed below. Primary endpoint analysis will be performed using data from all subjects with valid ABPM data at baseline (Visit 3) and post-treatment (Visit 5).

The objective of the study is to rule out a clinically meaningful increase in 24-hour average systolic BP, as measured by ABPM. The primary endpoint is the change from Visit 3 to Visit 5 of the average 24-hour systolic BP. If the upper limit of the two-sided 95% CI for the change from Visit 3 to Visit 5 in average 24-hour systolic BP is ≤ 4.9 mm Hg, then the change will be considered not clinically significant.

16.5. Other Safety Endpoints

Other key safety endpoints are AEs and physical examination.

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. Listings will be provided for all AEs, SAEs, AEs resulting in discontinuation, and target AEs.

17.0 ETHICS

17.1. 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.

17.2. 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.

17.3. 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.

18.0 SOURCE DOCUMENTS AND CASE REPORT FORM

COMPLETION

18.1. 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.

18.2. 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. 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.

19.0 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.

20.0 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.

21.0 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	*MRI-PDFF* *Baseline* Visit 3		Visit 4	Investigational Drug Resupply	*MRI-PDFF* *Interim*	Visit 5					*MRI-PDFF* *Post- Treatment*	Visit 6 Exit[1]
Day (Relative to start of dosing)	**Screen**	**Screen**	**Screen (Day -4 [±2 day]) Time relative to ABPM on morning of Day -4**		**Day 1**	**Day 60 (Window Day 30 to Day 60)**	*(Window Day 56 to Day 76)*	**Day 107 (Window: ± 7 days) Time relative to time of dosing on morning of Day 107.**					*(Window Between Visit 5 and Visit 6)*	**Day 110 (Window: ± 10 days)**
Time on the Day			**-2 hour**	**0 to 24 hour**				**-21 hour**	**-12 hour**	**0 hour**	**12 hour**	**24 hour**		
Informed consent	✓													
Inclusion/exclusion	✓	✓												
Height, Weight, body mass index (BMI)[2]	✓		✓											✓
Medical history[3]							✓							
Physical examination	✓													✓
Electrocardiogram		✓												
Vital signs (Clinic BP and PR, and oral temperature)			✓							✓				✓
24-hour Ambulatory BP Measurement				✓							✓			
Sample collection														
Serum Testosterone (6-10 AM)	✓	✓												
Study clinical laboratory tests (all subjects)		✓												✓
Additional clinical laboratory tests (subset of study subjects)		✓												✓
Drug screen		✓												
AE Reporting							✓							
Blood sample collection for TU measurement[4]								✓						
Prior and Concomitant medication[5]	✓	✓	✓		✓			✓						✓
Confinement begins			✓					✓						
Study enrollment					✓									
Study drug dispensed					✓	✓						✓		
Study drug returned								✓						✓
Meal provided				✓					✓	✓	✓	✓		
Study drug administered									✓	✓	✓	✓		
Sexual distress question upon clinic entry			✓					✓						
Collect sexual desire question printout (completed for 7 days prior to visit)			✓					✓						
MRI-PDFF measurement			**MRI-1***				**MRI-2***						**MRI-3***	

* Schedule the MRI-1 baseline MRI-PDFF any time between Visit 2 and Visit 4. Schedule the MRI-2 interim MRI-PDFF any time between Day 56 and Day 76, inclusive. Schedule the MRI-3 post-treatment MRI-PDFF to occur any time between Visit 5 and Visit 6.

[1] Study exit can be conducted at Visit 6 or when subject discontinues the study
[2] Height and BMI at screening only
[3] Medical history for the past 5 years will be collected at screening, changes will be documented at subsequent visits
[4] Blood sample collected ~ 3 hours post-morning dose on Day 106. For subjects who cannot come post-morning dose, sample ~3 hours post-evening dose may be collected.
[5] Full medication history will be collected at screening; changes will be documented at subsequent visits

Appendix B. INVESTIGATOR'S AGREEMENT

Study Title: Ambulatory Blood Pressure Monitoring in Oral Testosterone Undecanoate (TU, LPCN 1021) Treated Hypogonadal Men.

Study Number: LPCN 1021-18-001

Final Date: 19 February 2019

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)

Appendix C. LPCN 1021-PROHIBITED CONCOMITANT MEDICATIONS

Concurrent treatment with medications that may impact the absorption, distribution, metabolism or excretion of TU or place the subject at risk for treatment with testosterone within 30 days prior to study drug administration and through the end of the study without sponsor approval. Examples of prohibited concurrent medications include lipase inhibitors, saw palmetto, androgenic or androgenic-modifying supplements, anti-androgens, estrogens, oral CYP3A4 inducers or inhibitors, and long-acting opioid analgesics. All such medications, including but not limited to those listed below, are prohibited without sponsor approval.

1. Medications that affect SHBG metabolism (levels)
   - Phenobarbital
   - Phenytoin (Dilantin)
   - Carbamazepine (Tegretol)
   - Spironolactone (Aldactone)
   - Flutamide (Drogenil)
   - Cyproterone acetate (Androcur)
   - Ketoconazole (Nizoral)
2. Medications that affect Prolactin metabolism (levels)
   - Risperidone (Risperdal)
   - Olanzapine (Zyprexa)
   - Clozapine (Clozaril)
   - Haloperidol (Haldol)
   - Ramelton (Rozerem)
   - Methyldopa (Aldomet)
   - Reserpine
3. Androgenic and androgenic modifying supplements (may include other supplements)
   - Saw palmetto
   - ZMA (zinc monomethionine aspartate)
   - NatraSterone (Natural Anabolic Androgen)
   - Natadrol
4. GnRH (Gonadotropin-releasing hormone) analogues
   - Leuprolide (Lupron)
   - Buserelin (Suprefact)
   - Decapeptyl
   - Clomiphene citrate (Clomid)
   - Tamoxifen citrate (Nolvadex)
   - Valproic acid
5. Other Antiandrogens
   - Casodex (bicalutamide)
   - Eulexin (flutamide)
   - Nilandron (nilutamide)
   - Xtandi (enzalutamide)
   - Goserelin
   - Abarelix
   - Flutamide

- Nilutamide
- Bicalutamide
- Cyproterone acetate
- Medroxyprogesterone
- Spironolactone

6. Opioid analgetics-

Any of various sedative narcotics containing opium or one or more of its natural or synthetic derivatives.

- Heroin
- Methadone
- Opium

7. Lipase inhibitors

- Orlistat (alli, Xenical)

8. Estrogens

- Amnestrogen® (esterified estrogens)
- Cenestin® (conjugated synthetic A estrogens)
- Enjuvia® (conjugated synthetic B estrogens)
- Estrace® Tablets (estradiol)
- Estratab® (esterified estrogens)
- Evex® (esterified estrogens)
- Femogen® (esterified estrogens)
- Menest® (esterified estrogens)
- Ogen® Tablets (estropipate)
- Ortho-est® (estropipate)
- Premarin® Tablets (conjugated estrogens)
- Covaryx® (containing Esterified Estrogens, Methyltestosterone)
- Essian® (containing Esterified Estrogens, Methyltestosterone)
- Estratest® (containing Esterified Estrogens, Methyltestosterone)
- Femtest® (containing Esterified Estrogens, Methyltestosterone)
- Menogen® (containing Esterified Estrogens, Methyltestosterone)
- Menrium® (containing Chlordiazepoxide, Esterified Estrogens)¶
- Milprem® (containing Conjugated Estrogens, Meprobamate)¶
- PMB® (containing Conjugated Estrogens, Meprobamate)¶
- Premarin® with Methyltestosterone (containing Conjugated Estrogens, Methyltestosterone)
- Syntest® (containing Esterified Estrogens, Methyltestosterone)

9. CYP3A4 inhibitors

- Clarithromycin
- Clotrimazole
- Delavirdine
- Diltiazem
- Erythromycin
- Fluconazole
- Fluvoxamine
- Itraconazole
- Ketoconazole
- Lorazepam
- Nefazodone

- Nelfinavir
- Quinupristin/dalfopristin (Synercid)
- Ritonavir (Norvir)
- Saquinavir (Invirase)
- Troleandomycin (TAO)
- Verapamil (Isoptin, Verelan, Verelan PM, Calan, Bosoptin, Covera-HS)
- Indinavir (Crixivan)

10. CYP3A4 inducers
    - Carbamazepine (Carbatrol, Epitol, Equetro, Tegretol, mazepine, Carbamaz, CBZ)
    - Dexamethasone (Decadron)
    - Efavirenz (Sustiva, Stocrin, Efavir, EFV)
    - Nevirapine (Viramune)
    - Oxcarbazepine (Trileptal)
    - Phenobarbital
    - Phenytoin
    - Primidone
    - Rifampin
    - St. John's wort (Hypericum perforatum)
    - Troglitazone (Rezulin, Resulin, Romozin, Noscal)
11. Medications that may impact absorption, distribution, metabolism or excretion of TU
    - Atropine
    - Activated charcoal
    - Lactulose,
    - Sodium phosphate
    - Sodium biphosphate
    - Magnesium sulfate
    - Magnesium hydroxide
    - Bisacodyl
    - Phenolphthalein
    - Castor oil
    - Petroleum products
    - Acepromazine
    - Ipecac syrup
    - Magnesium hydroxide
    - Aluminum/magnesium hydroxide
12. 5 alpha-reductace inhibitors
    - Finasteride
    - Dutasteride
    - Bexlosteride
    - Epristeride
    - Izonsteride
    - Lapisteride
    - Turosteride

Appendix D. SEXUAL DESIRE AND DISTRESS QUESTIONS

PROVIDE A 7-PAGE PRINTOUT OF THE FOLLOWING QUESTION FOR SUBJECTS TO COMPLETE PRIOR TO VISIT 3 AND VISIT 5.

Sexual Desire Question: Daily Rating

Instructions: Please read the item below carefully and circle the number that best describes how you feel. Circle only one number.

How would you rate your level (degree) of sexual desire today?

0	1	2	3	4	5
None at all	Very low	Low	Moderate	High	Very high

PROVIDE A SINGLE PAGE PRINTOUT OF THE FOLLOWING QUESTION FOR SUBJECTS TO COMPLETE AT VISIT 3 AND VISIT 5.

Sexual Distress Question: Weekly Rating

Instructions: Please read the item below carefully and circle the number that best describes how you feel. Circle only one number. Rate how much the problem listed below has bothered you **over the past 7 days**, including today.

How often did you feel: Bothered by low sexual desire?

	0	1	2	3	4
Past 7 Days	Never	Rarely	Occasionally	Frequently	Always