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STATISTICAL ANALYSIS PLAN

Investigational Product	:	Testosterone Undecanoate (TU, LPCN 1021)
Clinical Study Protocol	:	LPCN 1021-18-001
Protocol Title	:	Ambulatory Blood Pressure Monitoring in Oral Testosterone Undecanoate (TU, LPCN 1021) Treated Hypogonadal Men
Date of SAP	:	January 23, 2019
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)
Protocol Version	:	Version 6
SAP Version	:	02
Previous Version (# and Date)	:	01, September 15, 2018

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1. SUMMARY OF CHANGES

The purpose of LPCN 1021-18-001 Statistical Analysis Plan Version 2 is to incorporate changes summarized below:

- The primary endpoint of the study was changed from change in average daytime blood 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.
- Added change in daytime systolic blood pressure to the secondary endpoints, and revised secondary endpoints for consistency.
- Added details for blood pressure analysis.
- Added details for subgroup analysis.
- Changed the Development Phase 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.
- Updated to reflect other changes made to Protocol LPCN 1021-18-001.
- Minor editorial changes for consistency.

2. TABLE OF CONTENTS

3. LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

3.1. Abbreviations

AE	Adverse event
ABPM	Ambulatory blood pressure monitoring
AUC	Area under the curve
BMI	Body mass index
BP	Blood pressure
CI	Confidence interval
CRO	Clinical research organization
DBP	Diastolic blood pressure
eCRF	Electronic Case Report Form
FAS	Full analysis set
HDL	High-density lipoprotein
ICH	International Conference on Harmonization
IRB	Institutional Review Board
LDL	Low-density lipoprotein
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic Resonance Imaging
MRI-PDFF	Magnetic Resonance Imaging-Proton Density Fat Fraction
PK	Pharmacokinetic
PR	Pulse rate
PSA	Prostate-specific antigen
SAE	Serious adverse event
SAP	Statistical analysis plan
SBP	Systolic blood pressure
SOC	System organ class
SS	Safety Set
T	Testosterone
TU	Testosterone undecanoate

3.2.

4. INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to ensure that the data listings, summary tables and figures which will be produced, and the statistical methodologies that will be used, are complete and appropriate to allow valid conclusions regarding the study objectives in accordance with the study protocol.

4.1. Responsibilities

Study conduct, data management, statistical analyses, and the production and quality control of all tables, figures and listings are the responsibilities of Medpace and Softworld, as assigned.

4.2. Timings of Analyses

The final analysis is planned after all subjects have completed Visit 6 or discontinued early from the study.

5. BRIEF DESCRIPTION

This is an open-label, multicenter, single arm study evaluating the blood pressure (BP) changes from baseline (Visit 3) to post-treatment (Visit 5)assessed by ambulatory blood pressure monitoring (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 pulse rate (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 Magnetic Resonance Imaging-Proton Density Fat Fraction (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 Data Validity. 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-3 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.

5.1. Selection of Study Population

Subjects will undergo screening procedures 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.

5.1.1. 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 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.

5.1.2. 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. Prostate-specific antigen (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).

5.1.3. 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.

5.2. 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.

Assuming that the true standard deviation of the change from baseline is equal to 9.0, and that the assumed true mean increase from baseline is equal to zero, a sample size of 135 subjects provides the study with 90% power to detect an increase of 3.58 mmHg (based on the upper limit of the two-sided 95% CI).

5.3. Treatment Assignment & Blinding

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

5.4. Administration of Study Medication

The study involves only a 225 mg dose option for LPCN 1021. The dose is administered as 225 mg testosterone undecanoate (TU) (2 capsules of 112.5 mg) twice daily (BID) approximately 12 hours apart (total daily dose of 450 mg taken as 225 mg in the morning and 225 mg in the evening).

5.5. Study Procedures

The schedule of events is provided in Appendix A of the protocol.

6. ANALYSIS SETS

Statistical analyses will be performed on the following analysis sets.

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.

Pharmacokinetic Set (PK): The PK set consists of all subjects enrolled into the study with valid serum concentration data at Visit 5.

MRI- Full Analysis Set (MRI-FAS): The MRI-FAS consists of all subjects enrolled into the study after the Protocol version 4 was implemented with valid MRI-PDFF data at baseline and end of the study.

7. ENDPOINTS

7.1. Efficacy Endpoint

7.2. Primary Efficacy Endpoint

The objective of the study is to rule out a clinically meaningful increase in 24-hour systolic blood pressure (SBP), as measured by ABPM.

The primary endpoint is the change from Visit 3 to Visit 5 of the weighted average 24-hour SBP. If the upper limit of the two-sided 95% CI for the change from Visit 3 to Visit 5 in weighted average 24-hourSBP is ≤ 4.9 mmHg, then the change will be considered not clinically significant.

The primary analysis will be done using the FAS.

7.3. Secondary Efficacy Endpoints

- Change in weighted average daytime and nighttime SBP, weighted average daytime diastolic blood pressure (DBP), weighted average nighttime DBP, and weighted average 24-hour DBP assessed by ABPM from Visit 3 to Visit 5.
- Change in hourly average daytime and nighttime SBP, hourly average 24-hour SBP, hourly average daytime DBP, hourly average nighttime DBP, and hourly average 24-hour DBP assessed by ABPM from Visit 3 to Visit 5.
- Change in mean average daytime and nighttime SBP, mean average 24-hour SBP, mean average daytime DBP, mean average nighttime DBP, and mean average 24-hour DBP assessed by ABPM from Visit 3 to Visit 5.
- Change in dip from Visit 3 to Visit 5.
- Change in weighted average daytime, nighttime, and24-hour 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.

7.4. Additional Evaluations

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

- Change and percent Change in MRI-PDFF to MRI-2 (interim) and to MRI-3 (post-treatment) in all subjects with baseline, interim, and post-treatment MRI-PDFF measurements, those with MRI-PDFF measurement of >5% at baseline, and those with a MRI-PDFF measurements of >10% at baseline.

7.5. Efficacy Endpoints Calculation

7.5.1. ABPM Data Validity

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.

7.5.2. ABPM Data Selection

Systolic BP, diastolic BP, pulse rate and mean arterial pressure values will be obtained every 15 minutes during the day and every 20 minutes during the night. 24-hour ABPM measurements will be selected as stated below, assuming a 24-hour biological cycle:

(1) If the first measurement starts at 7 AM on ABPM Day 1, select all measurements between 7 AM on ABPM Day 1 and 6:59 AM on ABPM Day 2.

(2) If the last measurement ends before 7 AM on ABPM Day 2 (eg. 6:30 AM), all measurements in the 24-hour interval prior to the last measurement will be selected, eg. 6 AM on ABPM Day 1 to 5:59 AM on ABPM Day 2.

(3) If the last measurement ends after 7 AM on ABPM Day 2, select all measurements between 7 AM on ABPM Day 1 and 6:59 AM on ABPM Day 2.

Generally, we will select the measurements from the whole hour, if this results in less than 24-hour measurements, we will select partial hour. For example, if the last measurement ends at 6:30 AM on ABPM Day 2, and the first measurement is from 6:30 AM on ABPM Day 1, the 24-hour interval will be 6:30 AM on ABPM Day 1 to 6:29 AM on ABPM Day 2.

7.5.3. Weighted Average of Blood Pressure

For the computation of average blood pressure values, time weighted area under the curve (AUC) of the measured BP values (AUC of BP values divided by time duration) will be assessed and a time weighted average will be calculated. AUC of BP can be calculated based on the trapezoidal rule, then the weighted average of BP will be AUC/(time duration).

For the purpose of computing average values, all the data for different timepoints will be used.

Average values for daytime will start at 7:00 AM in the morning and end at 11:00 PM in the night [7:00 AM, 11:00 PM). Average values for night time will start at 11:00 PM and end at 7:00 AM [11:00 PM, 7:00AM).

Average 24-hour ABPM will start as close as possible to 7:00 AM in the morning until the same time the following day.

7.5.4. Hourly Average of Blood Pressure

The hourly SBP will be calculated for each hour over 24 hours by taking the average of the readings taken in the corresponding hour (i.e, 7:00 AM to 7:59 AM). The Visit 3 and Visit 5 hourly daytime SBP is the average of the hourly SBP [7:00 AM, 11:00 PM) reviewed at Visit 3 and Visit 5, respectively. If there are missing measurements within the 24-hours, the hours without any measurements will be ignored when calculating the average.

For the purpose of presenting graphical information on the blood pressure and pulse rate values, average of measure pulse and mean arterial pressure over each hour will also be computed. An average of SBP from 7 to 8 AM will be based on the collected data at 7:00, 7:15, 7:30 and 7:45 AM. The data will be presented at 7 AM.

7.5.5. Mean Average of Blood Pressure

The mean average of blood pressure will be calculated as the mean of hourly average of blood pressure. For example, the mean average of the daytime SBP will be calculated by taking the average of daytime hourly average SBP.

7.5.6. Blood Pressure Dip

Optimal blood pressure fluctuates over a 24-hour sleep-wake cycle, with values rising in the daytime and falling after midnight. The fall in pressure, called the "dip", is defined as the difference between daytime mean systolic pressure and nighttime mean systolic pressure expressed as a percentage of the day value.

$$Dip = \left(1 - \frac{SBP_{nighttime}}{SBP_{daytime}}\right) \times 100\%$$

10% to 20% is considered normal. Dips less than 10%, referred to as blunted or absent, have been considered as predicting an adverse cardiovascular event.

7.6. Pharmacokinetic Analyses

There is no pharmacokinetic analysis in the study. However, concentrations of TU measured at Visit 5 will be summarized and listings presented.

7.7. Safety Endpoints

Key safety endpoints are AEs, physical examination, clinical laboratory tests and vital signs (oral temperature, Clinic BP and PR). Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA, version 17.1). An AE is considered treatment emergent if the event begins or worsens in severity after initiation of study drug.

8. GENERAL ASPECTS FOR STATISTICAL ANALYSIS

8.1. General Methods

All relevant data will be presented in patient data listings ordered by Subject ID. All categorical data will be summarized using frequency counts and percentages of subjects. Percentage will be calculated using the study population as the denominator. The continuous variables will be summarized using number of observations (n), mean, standard deviation (SD), median, first quartile, third quartile, minimum, and maximum unless otherwise specified. All the analyses of safety and efficacy data for this study will be performed using SAS® statistical software package, version 9.3, higher or equivalent.

8.2. Missing Data

For the measurement of endpoints there will no imputation of missing data.

If an AE has a completely missing onset date, then the AE will be considered a treatment emergent adverse event (TEAE).

The following section applies to medication prior to the start of the study. A medication with a completely missing start date is considered a prior medication. A medication with a completely missing stop date is considered a concomitant medication. If an adverse event or a medication has a partial missing start or stop date, the following rules will be used to impute the date; then the imputed date will be used to determine whether it is a prior or concomitant medication.

Partial Missing Start or Stop Date	**Imputed Start Date**	**Imputed Stop Date**
Missing month and day, and the year is present	January 1 of that year or first dose date if the year is the same as the year of first dose date	December 31 of that year
Missing day, but year and month are present	First day of that month or first dose date if the year and month are the same as the year and month of first dose date	Last day of that month
Missing month, but year and day are present	Missing month imputed as January or the month of the first dose date	Missing month imputed as December

8.3. Visit Windows

For visit 5, the protocol allowed visit window is Day 100 to Day 114 day.

9. DEMOGRAPHIC, OTHER BASELINE CHARACTERISTICS AND MEDICATION

9.1. Subject Disposition and Withdrawals

The number and percentage of subjects enrolled, treated, completed, and discontinued will be presented. Reasons for discontinuation will be detailed, and the number and percentage of subjects who discontinued for each reason will be presented.

9.2. Demographic and Other Baseline Characteristics

Subject age, race, weight and body mass index (BMI) will be summarized overall. Age and race will be characterized by number and percentage of subjects who give each response (per Electronic Case Report Form (eCRF)). Weight and BMI will be summarized using descriptive statistics for continuous measures (mean, standard deviation, median, minimum, first quartile, third quartile, maximum).

9.3. Medical History and Concomitant Diseases

The subject's medical history (lifetime significance including key events) during the past 5 years will be updated during each clinic visit and recorded on the Medical History eCRF.

Medical history terms will be coded and summarized. Summary of medical history will be presented. Subjects with a medical history of hypertension, diabetes will be presented separately. A subject data listing for reported medical history will be provided. The listing will be sorted by study center and subject identifier.

9.3.1. Prior and Concomitant Medication

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 on the Concomitant Medication eCRF.

If a subject reports taking any over-the-counter or prescription medications, vitamins and/or herbal supplement or if administration becomes necessary from 3 months prior to study drug administration through the end of the study, the name of the medication, dosage information including dose and frequency, date(s) of administration including start and end dates, and reason for use will be recorded. For any medications taken after study drug administration and through the end of the study, the subject may continue to participate in the study only after the investigator agrees the subject may continue.

A prior medication is any medication taken and stopped before the first dose of study medication. A concomitant medication is defined as any medication taken on or after the first dose day of study medication.

Medications with missing stop dates and medications with a missing start date will be counted as concomitant. Concomitant medications will be listed and summarized for the SS by WHO Drug Dictionary preferred drug name. The number and percentage of subjects who used each medication will be reported.

Medications for hypertension and diabetes will be summarized separately by class of medication. Changes in medication history from the start of the study through Visit 6 will be presented for hypertension medications.

9.4. Protocol Deviations

All deviations from the Protocol will be documented. At the end of the study, subjects who meet the criteria of "Major Protocol Deviations" will be identified. The basic rules for classification as major protocol deviations are:

- Subjects who are enrolled but who did not meet all inclusion criteria or met any exclusion criteria.
- Subjects who are significantly noncompliant with study drug administration (took more than 120% of anticipated dose units or less than 80% of anticipated dose units).
- Subjects who significantly deviated from follow protocol recommended dose or dosing regimen. The significant deviation is defined as when a subject did not take 225 mg two times a day for at least 20 days preceding Visit 5. However, this does not include subjects who had minor deviations of a missed dose.

10. ANALYSIS OF EFFICACY

10.1. Analysis of Primary Efficacy Endpoint

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

A linear regression model will be used with baseline SBP as a covariate to analyze the primary efficacy endpoint. The change in SBP from baseline to Visit 5 will be predicted at the median baseline level, and the predicted value, standard error and 95% confidence interval will be listed. The upper limit of 95% CI will be compared with 4.9 mmHg, and p-value will be calculated. Example SAS® code for performing this analysis is provided below:

```
************************************************************
** chg     = change of 24-hour SBP from Visit 3 to Visit 5    **
** base    = hourly SBP at Visit 3                            **
** median  = median weighted average of SBP at baseline       **
************************************************************
proc glm;
     model chg = base / clparm;
     estimate 'Mean Change for Median Baseline Level'
            intercept 1 base median;
run;
```

Change of 24-hour SBP from baseline will be calculated using the time weighted average of area under the curve (AUC divided by time duration) of SBP obtained over 24-hours. That is, the time weighted average of AUC of 24-hour SBP obtained at baseline (Visit 3) will be subtracted from corresponding time weighted average of AUC of SBP at the end of the study (Visit 5).

Median weighted average of SBP at baseline is the sample median of the weighted average of AUC of SBP at baseline.

10.2. Analysis of Secondary Efficacy Endpoints

10.2.1. Hourly Average of Blood Pressure

The change of hourly average SBP from baseline will be calculated by taking the difference between the corresponding hourly SBP at Visit 5 and Visit 3 for a given post-dosing hour.

The change from baseline in daytime hourly SBP (hour 7, 8, 9, …, 23) will be modeled by an ANCOVA model for repeated measures. The factors in the ANCOVA model will include: post-dosing daytime hour (hour 7, 8, 9, …, 23) and the baseline value as a covariate. The upper limit of 95% CI by hour will be compared with 4.9 mmHg.

```
************************************************************
** chg     = change in hourly SBP from Visit 3 to Visit 5     **
** base    = hourly SBP at Visit 3                            **
** usubjid = subject id                                       **
** hour    = post-dosing hour                                 **
** median  = median weighted average of SBP at baseline       **
************************************************************
proc mixed data=data;
     class hour;
     model chg = base hour /s;
     repeated hour / type=un sub=usubjid;
Estimate "Hour=7" Intercept 1 base median age 1 /cl;
Estimate "Hour=8" Intercept 1 base median age 0 1 /cl;
......
run;
```

As in Section , median weighted average of SBP at baseline is the sample median of the weighted average of AUC of SBP at baseline.

Other change in hourly average BP endpoints will be analyzed using the same model above.

10.2.2. Analysis of Other Secondary Efficacy Endpoints

Other secondary efficacy endpoints listed below will be analyzed using the model described in Section :

- Change in weighted average daytime and nighttime SBP, weighted average daytime DBP, weighted average nighttime DBP, and weighted average 24-hour DBP assessed by ABPM from Visit 3 to Visit 5.
- Change in mean average daytime and nighttime SBP, mean average 24-hour SBP, mean average daytime DBP, mean average nighttime DBP, and mean average 24-hour DBP assessed by ABPM from Visit 3 to Visit 5.
- Change in dip from Visit 3 to Visit 5.
- Change in weighted average daytime, nighttime, and24-hour 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.

10.3. Analysis by Subgroup

The primary efficacy endpoint analysis will be repeated using the following subgroups:

1) Excluding subjects with either SBP >140 mmHg or DBP > 90 mmHg at screening;

2) Excluding subjects with SBP >140 mmHg and DBP > 90 mmHg at screening.

3) Subjects with three risk levels of cardiovascular events based on the Framingham Heart Study:[1]

- Low risk: age 25, total cholesterol of 161, high-density lipoprotein (HDL) of 55, untreated SBP of 125, nonsmoker, nondiabetic.
- Moderate risk: age 40, total cholesterol of 205, HDL of 45, untreated SBP of 135, nonsmoker, diabetic.
- High risk: age 70, total cholesterol of 225, HDL of 39, treated SBP of 150, nonsmoker, diabetic.

10.4. Handling of Missing Data

If a subject's data is missing at the start or the end, the values will be considered missing for the computation of averages, the actual times for analyzing the average will be taken based on the

data available.

If a subject's data is missing in the middle of the data collection window, it will be considered as missing for the given timepoints and the average will be computed based on the area under the curve for the remaining timepoints.

For a subject if there is data missing at baseline and / or at the end of the study for a complete hour, for the purpose of computing the average values, the corresponding times from both the baseline and end of study will be considered missing. For example, at baseline if a subject's data is missing from 2 to 3 PM in the afternoon, however corresponding exit values are available, for assessing change from baseline, the average calculation will not consider the 2 to 3 PM data even at the end of the study.

This approach is true only if an entire hour data is missing. If there is partial data within an hour missing, the all the available data will be used in computation of averages.

10.5. Presentation of Data and Additional Analysis

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, 11:00 PM), nighttime [11:00 PM, 7:00AM), and 24-hour ABPM parameters (pulse 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 include SBP exceeding 160 mmHg or a change in SBP > 20 mmHg, or a DBP exceeding 100 mmHg or a change in DBP > 15 mmHg.
- Graphical display of hourly ABPM averages that include standard deviation bars for both SBP and DBP at baseline and at endpoint (mid-trial data optional).
- Cumulative distribution curves of 24-hour average SBP and DBP 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 SBP and DBP.

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.

11. ANALYSIS OF SERUM CONCENTRATION DATA

11.1. Data Sets Analyzed

The PK set as defined earlier will be used for the summarizing serum concentration data. Data from subjects with missing concentration values (missed blood draws, lost samples, samples unable to be quantified) will be considered as missing and will not be a part of PK set. Otherwise relevant data from these subjects will be excluded from the final analysis.

11.2. Sample Collection

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.

11.2.1. Handling of Missing Data and Values Below the Quantification Limit

Missing concentration values for subjects who were administered the scheduled study drug will be considered as non-informative missing. No concentration estimates will be provided for missing sample values.

11.2.2. Serum Concentration Summarization

Serum TU concentrations below the LLOQ in the samples will be set to zero. Descriptive statistics for serum concentrations including: number of observations (n), mean, standard deviation (SD), coefficient of variation (CV), minimum, median, and maximum will be calculated and presented.

11.3. PK Parameters

No PK parameters will be calculated in the study.

12. PATIENT REPORTED QUESTIONNAIRE

12.1. Data Collection

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, responses to a sexual desire question will be answered each day for 7 days preceding to Visit 3.

For the sexual distress question, subjects will answer a sexual distress question at Visit 3.

Responses to these questions will be repeated at the end of the study.

12.2. Questionnaire Data Analysis and Reporting

(A) Sexual desire: responses to the questionnaire will be given for seven continuous days at the start and end of the study. An average of all the responses received at baseline and end of the study will be computed. Change from baseline to end of the study in average responses for each subject will be computed. Descriptive statistics of all subject's data along with subject level listing will be presented.

(B) Sexual distress: this is a single question questionnaire that is answered by subjects once at Visit 3 and end of study. Change from baseline to end of the study in the response for each subject will be computed. Descriptive statistics of all subject's data along with subject level listing will be presented.

Summary data and change from baseline will be presented for all subjects. Descriptive statistics and individual subject listing will be presented.

13. LIVER FAT ASSESSMENTS

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 measurement will be performed for all subjects who complete MRI-1.

MRI data will be evaluated centrally by a central reader and % liver fat will be assessed. Changes and percent Changes in the % liver fat from baseline to end of study will be computed for all subjects.

Summary data will be presented for all subjects with MRI data in the MRI-FAS dataset. Further, subgroup analysis will be conducted for those subjects who had baseline liver fat based on MRI-PDFF of > 5% and also for subjects who had baseline liver fat based on MRI-PDFF of > 10%.

Descriptive statistics and individual subject listing will be presented.

14. SAFETY

The population used for safety analyses will be the SS. Safety will be assessed on the basis of adverse event (AE) reports, clinical laboratory data, physical examinations, and vital signs.

14.1. Extent of Exposure

Treatment exposure will be measured as number of days since first dosing day of last dosing day.

14.2. Treatment Compliance

Compliance will be based on the overall medication used by each subject during the study and will be computed as follows:

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

Further, treatment compliance will also include assessment of TU levels post 3 hours dosing. Based on the pharmacokinetic data of LPCN 1021 from prior trials, measurable levels of TU should be presented in these subjects.

14.3. Adverse Events

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 (including an abnormal laboratory finding), 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 considered to be AEs only if they result in discontinuation from the study, necessitate therapeutic medical intervention, and/or if the investigator considers them to be AEs.

An elective surgery/procedure scheduled to occur during a study will not be considered an AE if the surgery/procedure is being performed for a preexisting condition and the surgery/procedure has been preplanned prior to study entry. However, if the preexisting condition deteriorates unexpectedly during the study (e.g., surgery performed earlier than planned), then the deterioration of the condition for which the elective surgery/procedure is being done will be

considered an AE.

Adverse events will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA) terminology and the severity of the toxicities will be graded according to the NCI CTCAE, v4.03, where applicable.

Treatment emergent AEs (TEAEs) are AEs that begin or worsen in severity after initiation of randomized study drug and do not necessarily have a causal relationship to the use of the study medication.

A Serious Adverse Event (SAE) is an AE which falls into one or more of the following categories:

- Results in death;
- Is life-threatening;
- Requires inpatient hospitalization or prolongation of existing hospitalization;
- Is a congenital anomaly/birth defect;
- Results in persistent or significant disability or incapacity;
- Is any other important medical event requiring medical or surgical intervention to prevent a serious outcome;

The following adverse event summary tables will be generated:

- Overall Summary of Treatment-Emergent Adverse Events(TEAE)
- Summary of Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
- Summary of Serious Treatment-Emergent Adverse Events
- Summary of Treatment-Emergent Adverse Events Leading to Study Drug Discontinuation
- Summary of Treatment-Emergent Adverse Events Resulting in Death

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; a summaries based on event count will also be presented. 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, and treatment-emergent AEs resulting in discontinuation will be summarized.

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

14.4. Laboratory Evaluations

Baseline, end of study and change from baseline for the laboratory data will be presented for each subject. Descriptive summary statistics of all laboratory data along with individual subject listing will be presented.

Laboratory tests results will include lipids, and liver enzymes.

14.5. 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 will 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).

For the blood pressure and pulse rate, the average value of the three measurements will be computed and change from baseline to end of study will be calculated. Descriptive summary statistics of Clinic BP and PR along with individual subject listings will be presented. Further an exploratory comparison of cuff-based measurements and ABPM measurement will be carried out and presented.

14.6. Abbreviated Physical Examination

Abbreviated physical examination results will be summarized.

15. CHANGES FROM THE PROTOCOL

None.

16. PROGRAMMING CONSIDERATIONS

All tables, data listings, and figures (TLFs), and statistical analyses will be generated using SAS version 9.3, higher or equivalent. Computer-generated table output will adhere to the following specifications.

16.1. General Considerations

One SAS program can create several outputs.

Each output will be stored in a separate file.

Output files will be delivered in Word format.

Numbering of TFLs will follow ICH (International Council for Harmonisation) E3 guidance.

16.2. Table, Listing, and Figure Format

16.2.1. General

All TLFs will be produced in landscape format, unless otherwise specified.

All TLFs will be produced using the Courier New font, size 8

The data displays for all TLFs will have a 1-inch binding margin on top of a landscape oriented page and a minimum 1-inch margin on the other 3 sides.

Headers and footers for figures will be in Courier New font, size 8.

Legends will be used for all figures with more than 1 variable, group, or item displayed.

TLFs will be in black and white (no color), unless otherwise specified

Specialized text styles, such as bolding, italics, borders, shading, and superscripted and subscripted text, will not be used in the TLFs, unless otherwise specified. On some occasions, superscripts 1, 2, or 3 may be used (see below).

Only standard keyboard characters will be used in the TLFs. Special characters, such as non-printable control characters, printer-specific, or font-specific characters, will not be used. Hexadecimal-derived characters will be used, where possible, if they are appropriate to help display math symbols (e.g., μ). Certain subscripts and superscripts (e.g., C_{max}, cm^2) will be employed on a case-by-case basis.

Mixed case will be used for all titles, footnotes, column headers, and programmer-supplied formats, as appropriate.

16.2.2. Headers

All outputs should have the following header at the top left of each page:

```
Lipocine, Inc.                                                    Page X of Y
LPCN 1021-18-001                                                  Draft/Final Run
```

The date (date output was generated) should appear along with program name and location as the last footer on each page.

16.2.3. Display Titles

Each TLF should be identified by the designation and a numeral (i.e., Table 14.1.1). The title will be centered and the analysis set should be identified on the line immediately following the title. The title and table designation are single spaced. A solid line spanning the margins will separate the display titles from the column headers. There will be 1 blank line between the last title and the solid line.

<Table/Listing/Figure x.y.z>

<First Line of Title>

<Second Line of Title if Needed>

<Analysis Set>

16.2.4. Column Headers

Column headings should be displayed immediately below the solid line described above in initial upper-case characters.

In the case of efficacy tables, the variable (or characteristic) column will be on the far left followed by the treatment group columns and total column (if applicable). P-values may be presented under the total column or in separate p-value column (if applicable). Within-treatment comparisons may have p-values presented in a row beneath the summary statistics for that treatment.

For numeric variables, include "unit" in column or row heading when appropriate.

Analysis set sizes will be presented for each treatment group in the column heading as (N=xx) (or in the row headings if applicable). This is distinct from the 'n' used for the descriptive statistics representing the number of subjects in the analysis set.

16.2.5. Body of the Data Display

16.2.5.1. General Conventions

Data in columns of a table or listing should be formatted as follows:

alphanumeric values are left-justified;

whole numbers (e.g., counts) are right-justified; and

numbers containing fractional portions are decimal aligned.

16.2.5.2. Table Conventions

- Units will be included where available

- If the categories of a parameter are ordered, then all categories between the maximum and minimum category should be presented in the table, even if n=0 for all treatment groups in a given category that is between the minimum and maximum level for that parameter. For example, the frequency distribution for symptom severity would appear as:

Severity / Rating	N
severe	0
moderate	8
mild	3

Where percentages are presented in these tables, zero percentages will not be presented and so any counts of 0 will be presented as 0 and not as 0 (0%).

If the categories are not ordered (e.g., Medical History, Reasons for Discontinuation from the Study, etc.), then only those categories for which there is at least 1 subject represented in 1 or more groups should be included.

An Unknown or Missing category should be added to any parameter for which information is not available for 1 or more subjects.

Unless otherwise specified, the estimated mean, median, first-, and third-quartile for a set of values should be printed out to 1 more significant digit than the original values, and standard deviations should be printed out to 2 more significant digits than the original values. The minimum and maximum should report the same significant digits as the original values. For example, for systolic blood pressure:

N	XX
Mean (SD)	XXX.X (X.XX)
Median	XXX.X
Q1, Q3	XXX.X, XXX.X
Minimum	XXX
Maximum	XXX

P-values should be output in the format: “0.xxx”, where xxx is the value rounded to 3 decimal places. Any p-value less than 0.001 will be presented as <0.001. Any p-value greater than 0.999 will be presented as >0.999

Percentage values should be printed to one decimal place, in parentheses with no spaces, one space after the count (e.g., 7 (12.8%), 13 (5.4%)). Values that round down to 0.0% or up to 100.0% will be presented as such. Unless otherwise noted, for all percentages, the number of subjects in the analysis set for the treatment group who have an observation will be the denominator. Percentages after zero counts will not be displayed.

Tabular display of data for medical history, prior / concomitant medications, and all tabular displays of adverse event data should be presented by the body system, treatment class, or SOC with the highest occurrence in the active treatment group in decreasing order, assuming all terms are coded. Within the body system, drug class and SOC, medical history (by preferred term), drugs (by ATC1 code), and adverse events (by preferred term) should be displayed in decreasing order. If incidence for more than 1 term is identical, they should then be sorted alphabetically. Missing descriptive statistics or p-values which cannot be estimated should be reported as “N/A”.

For categorical summaries (number and percentage of subjects) where a subject can be included in more than one category, a footnote (and possibly programming note) will be included to detail whether the subject should be included in the summary statistics for all relevant categories or just one (1) category and if so the criteria for selecting the criteria will be given as well.

Where a category with a subheading (such as system organ class) has to be split over more than one page, output the subheading followed by "(cont)" at the top of each subsequent page. The overall summary statistics for the subheading should only be output on the first relevant page.

16.2.5.3. Listing Conventions

Listings will be sorted for presentation in order of treatment groups as above, subject number, visit/collection day, and visit/collection time.

Missing data will be represented on subject listings as "N/A", with the footnote "N/A = not applicable".

Dates will be printed in SAS® DATE9.format ("ddMMMyyyy": 01JUL2000). Missing portions of dates will be represented on subject listings as dashes (--JUL2000). Dates that are missing because they are not applicable for the subject are output as "N/A", unless otherwise specified.

All observed time values will be presented using a 24-hour clock HH:MM or HH:MM:SS format (e.g., 11:26:45, or 11:26). Time will only be reported if it was measured as part of the study.

Units will be included where available.

16.2.5.4. Figure Conventions

Unless otherwise specified, for all figures, study visits will be displayed on the X-axis and endpoint (e.g., treatment change from Baseline) values will be displayed on Y-axis.

16.2.6. Footnotes

- A solid line spanning the margins will separate the body of the data display from the footnotes.
- All footnotes will be left justified with single-line spacing immediately below the solid line underneath the data display.
- Footnotes should always begin with "Note:" if an informational footnote, or a, b, c, etc. if a reference footnote. Each new footnote should start on a new line where possible.
- Footnotes will be present on the page where they are first referenced and thereafter on each page of the table, unless the footnote is specific only to certain pages. Subject specific footnotes should be avoided.
- Footnotes will be used sparingly and will add value to the table, figure, or data listing. If more than six lines of footnotes are planned, then a cover page may be used to display footnotes, and only those essential to comprehension of the data will be repeated on each

page.

- The last line of the footnote section will be a standard source line that indicates the name of the program used to produce the data display and the date the program was run (e.g., 'Program: myprogram.sas Date: 10OCT2013').

17. QUALITY CONTROL

SAS programs are developed to produce clinical trial output such as analysis data sets, summary tables, data listings, figures or statistical analyses. {CRO SOP Number} provide an overview of the development of such SAS programs.

CRO SOP will be used for the quality control procedures that are performed for all SAS programs and output. Quality control is defined here as the operational techniques and activities undertaken to verify that the SAS programs produce the proper clinical trial output by checking for their logic, efficiency and commenting and by review of the produced output. Details will be provided in a project-specific Quality Control Plan (QCP).

18. INDEX OF TABLES, LISTINGS AND FIGURES

{Will be updated later}

[i] D'Agostino RB et al., 2008, General Cardiovascular Risk Profile for Use in Primary Care: The Framingham Heart Study, Circulation, 117(6):743–753.