An Open Label Extension Study of the Safety and Tolerability of LPCN 1144 for the Treatment of Subjects with Nonalcoholic Steatohepatitis (NASH) who have Completed the LPCN 1144-18-002 Trial

Protocol Phase: 2
Protocol Number: LPCN 1144-20-002
Coordinating Investigator: [redacted]
IND Number: 140203
Sponsor: Lipocine Inc.

Version Number: 2.0
February, 2021

1. SUMMARY OF CHANGES IN PROTOCOL VERSION 2.0

Version 2.0 of the LPCN 1144-20-002 study protocol was developed to make the following changes to the study:

Affected Section(s)	Summary of Revisions Made	Rationale
2.3 9.1.1 9.1.2 9.2.4 Appendix D	PGI-S questionnaire was replaced with the PGI-C questionnaire	To evaluate the effect of treatment on the subject's overall impression of his health
7.3.1 9.1.2	Allow the re-dispensing of returned study drug to the subject	After an accountability check, the study drug may be returned to the subject, to limit wasting of the investigational product
7.3.1	Study drug may be destroyed on-site at completion or premature discontinuation of the study, at Sponsor's discretion	To give sites/Sponsor flexibility in managing IP returns and/or on-site destruction
8.3.7	'DSMB' was replaced by a Safety Team	To accurately reflect the safety oversight of this protocol
9.2.6	Criteria that triggers testing for adrenal insufficiency has been updated	To reflect the changes made in a previous administrative letter; the proper cortisol level which requires sites to perform a stimulation test: < LLN
Not applicable	Minor editorial changes for consistency and clarity	

2. PROTOCOL SYNOPSIS

2.1. Synopsis

Sponsor: Lipocine Inc.

Protocol Number: LPCN 1144-20-002

Study Drug Name: Testosterone Undecanoate Capsule

Phase of Development: Phase 2

Active Ingredient: Testosterone Undecanoate

Date of Protocol: February 2021

Protocol Title: An Open Label Extension Study of the Safety and Tolerability of LPCN 1144 for the Treatment of Subjects with Nonalcoholic Steatohepatitis (NASH) who have Completed the LPCN 1144-18-002 Trial

Objectives: The objective of this protocol is to monitor the safety and tolerability of extended therapy with LPCN 1144 in male subjects with NASH who have completed the LPCN 1144-18-002 protocol.

Design: This is a multicenter, open-label extension protocol to provide LPCN 1144, an investigational drug, to subjects with NASH who have completed the LPCN 1144-18-002 protocol. Enrolled subjects will be given LPCN 1144 for up to 36 weeks. Subjects will be seen at Weeks 6, 12, 24, and 36 to evaluate safety clinical laboratory tests, tolerability of LPCN 1144, adverse events, and overall subject health. Subjects will be given the option of having a liver biopsy performed at Week 36.

Study Intervention: LPCN 1144 is an oral capsule formulation of testosterone undecanoate (TU) administered as 225 mg TU two times a day for a total dose of 450 mg TU.

Study Population: Subjects who have completed the LPCN 1144-18-002 protocol

Inclusion Criteria:

1. Subjects who have completed the 38 week study LPCN 1144-18-002 as planned and wish to be treated with LPCN 1144
2. Subject must sign the Informed Consent Form to participate in the study

Exclusion Criteria:

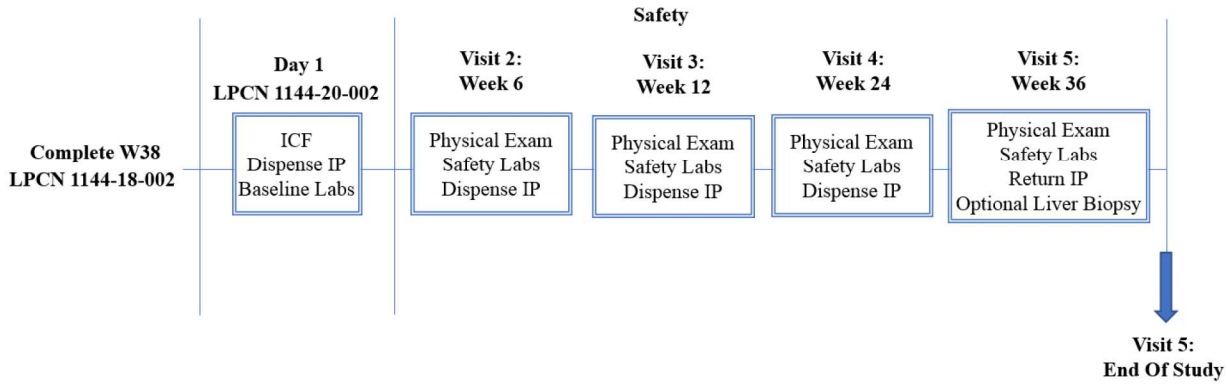
1. Has participated or is participating in any other clinical (investigational) study after completion of LPCN 1144-18-002 study
2. Subjects who are currently receiving any androgens or estrogens
3. Use of drugs historically associated with NAFLD (amiodarone, methotrexate, systemic glucocorticoids, tetracyclines, tamoxifen, estrogens, anabolic steroids, valproic acid, other known hepatotoxins) for more than 2 weeks in the 2 years prior to enrollment
4. Subjcts who are not willing to use adequate contraception for the duration of the study
5. Any other condition, which in the opinion of the investigator would impede compliance or hinder completion of the study

Monitoring for Prostate, Cardiovascular, and Renal Stopping Criteria: Subjects will be monitored for hematocrit, creatinine, prostate specific antigen (PSA), and blood pressure, with added close monitoring and discontinuation criteria noted in Section 8.3.

Monitoring for Hepatotoxicity and Stopping Criteria: To minimize the risk of hepatotoxicity, aminotransferase levels will be monitored, with added close monitoring and discontinuation criteria noted in Section 8.3.

Reduced Dose: Subjects will be monitored for liver enzymes, hematocrit, PSA, and testosterone with close monitoring and discontinuation triggers; if levels exceed target criteria during close monitoring, subjects will be placed on a reduced dose (LPCN 1144 one capsule once daily). If a subject continues to exceed the target, the subject will proceed to exit procedures. If a subject required a dose reduction in the LPCN 1144-18-002 trial due to androgenic adverse effects (see Section 7.1), the subject will be initiated on the dose he was on at Week 36 of LPCN 1144-18-002.

2.2. Scheme



2.3. Schedule of Activities

Assessment / Procedure	On Treatment				
	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5
	Day 1	Week 6 (Day 42±7)	Week 12 (Day 84±7)	Week 24 (Day 168 ±7)	Week 36 (Day 252±7)
Informed consent	X				
Review of concomitant medication	X	X	X	X	X
Review of adverse events	X	X	X	X	X
Physical examination [1]	X	X	X	X	X
Enrollment	X				
Drug dispensing	X	X	X	X	
Drug accountability/adherence check		X	X	X	X
PGI-C questionnaire			X	X	X
Clinical Laboratory Tests [2]					
Urinalysis [3]	X [9]	X	X	X	X
Lipid profile [4]	X [9]	X	X	X	X
Hematology panel [5]	X [9]	X	X	X	X
HbA1c	X [9]		X		X
Metabolic and renal function panel [6]	X [9]	X	X	X	X
Hepatic panel [7]	X [9]	X	X	X	X
Biomarkers [8]	X [9]		X		X
Testosterone assay (Total and calculated free T, SHBG)	X [9]	X	X	X	X
Hormones and related markers (DHT, LH, FSH, TSH)	X [9]	X	X	X	X
PSA, prolactin	X [9]	X	X	X	X
Cortisol and cortisol binding globulin (CBG)	X [9]	X	X	X	X
Serum and plasma for banking	X [9]		X		X
Liver Biopsy (optional) [10]					X
Study Exit					X

PGI-C: Patient Global Impression of Change Scale; T: Testosterone; SHBG: Sex Hormone Binding Globulin; DHT: Dihydrotestosterone; LH: Luteinizing Hormone; FSH: Follicle Stimulating Hormone; TSH: Thyroid Stimulating Hormone; PSA: Prostate Specific Antigen

1. A physical examination includes measurement of height, weight, waist, and hips; vital signs (temperature (single measurement), respiratory rate (single measurement), and clinic BP (triplicate measurement) and pulse rate (triplicate measurement); examination for scleral icterus and pedal edema and auscultation of heart and lungs. Any changes during the study will be documented. Subject's height and weight will be used to calculate BMI.
2. Labs should be drawn 3-5 hours after the morning dose of LPCN 1144.
    a. If performed, Day 1 labs should be drawn prior to LPCN 1144 dosing
    b. There are no blood draws that require fasting in this study
3. Urinalysis consists of general routine tests – Color, appearance, specific gravity, pH, protein, blood, ketones, urobilinogen, glucose, bilirubin, leukocyte esterase, nitrite.
4. Lipid profile: total cholesterol, triglyceride, fatty acids, VLDL-C, LDL-C, HDL-C.
5. Hematology Panel: complete blood count (CBC) including hemoglobin and hematocrit, prothrombin time (PT), international normalized ratio (INR).
6. Metabolic and renal function panel: sodium, potassium, chloride, bicarbonate, calcium, phosphate, BUN, creatinine, uric acid, albumin, total protein, estimated glomerular filtration rate (GFR).
7. Hepatic panel: total bilirubin (TB), direct bilirubin, ALT, AST, ALP, GGT, Bile acid and creatine kinase (CK).
8. Biomarkers: Enhanced Liver Fibrosis (ELF), Hyaluronic Acid (HA), N-terminal propeptide of type III collagen (PIIINP), Tissue inhibitor of metalloproteinase 1 (TIMP-1), Transforming Growth Factor-β (TGF-β), Tissue Necrosis Factor-α (TNF-α).
9. To be performed if there is ≥ 2 weeks between Week 38 of LPCN 1144-18-002 and Day 1 of LPCN 1144-20-002. If performed, Day 1 labs should be drawn prior to LPCN 1144 dosing.
10. The optional liver biopsy should be completed within the two weeks prior to Visit 5 (Weeks 34-36)

3. TABLE OF CONTENTS

4. INTRODUCTION

4.1. Study Rationale

4.1.1. Nonalcoholic Fatty Liver Disease (NAFLD) and NASH

Nonalcoholic fatty liver disease (NAFLD) is the most common cause of chronic liver disease in the United States (US) and its prevalence and clinical importance is increasing worldwide.[1, 2] Recent studies estimate that between 30 and 40% of the population in the US, 80 100 million Americans, is affected by NAFLD.[3-5] The number of people at risk for NAFLD is even greater given the increasing prevalence of obesity, diabetes, and metabolic syndrome. Nonalcoholic steatohepatitis (NASH) is a frequently progressive subset of NAFLD that can be complicated by cardiovascular disease, cirrhosis and hepatocellular carcinoma (HCC).[6, 7] There are no FDA approved drugs for NASH.

4.1.2. Histology, Epidemiology, and Disease Course

Non-alcoholic fatty liver disease is characterized by hepatic steatosis, without a history of excessive alcohol use, in the absence of other known liver disease.[1] NAFLD can be broadly classified into two subtypes; nonalcoholic fatty liver (NAFL), which is generally considered to be benign with negligible risk of progression to advanced fibrosis and liver-related mortality, and NASH, which is generally considered to be progressive with substantial risk of progression to advanced fibrosis, and liver-related mortality.[8] NAFL and NASH have traditionally been considered two separate clinical entities, rather than two points on a disease continuum.[9] Recent studies evaluating sequential liver biopsies are challenging this notion.[10-12] Based upon evidence derived from systematic review and meta-analysis of paired liver biopsy studies, both patients with NAFL and NASH may develop progressive liver fibrosis. The annual fibrosis progression rate (FPR) in patients with NAFL versus NASH, with baseline stage 0 fibrosis, was 0.07 stages versus 0.14 stages, respectively, corresponding to an average progression by 1 stage over 14.3 versus 7.1 years, respectively.[13] Patients with NAFL and mild lobular inflammation, without ballooning or fibrosis (and thus not qualifying as NASH), had increased risk of disease progression compared to those without inflammation.[8] Another retrospective study evaluated serial liver biopsies in 108 patients and found no significant difference in the proportion of fibrosis progression between patients with NAFL and NASH at index biopsy (37% vs. 43%, $p = 0.65$).[11] Similarly, a recent study analyzing paired liver biopsies over time showed that even patients with bland steatosis can progress to NASH, especially in the setting of metabolic risk factors.[14]

In the western world, NAFLD is most commonly associated with obesity, metabolic syndrome, and diabetes.[15] As with other metabolic conditions, NAFLD appears to have a strong genetic component. Both family history of diabetes and Hispanic ethnicity have been identified as risk factors.[15] Metabolic syndrome, diabetes, and advanced age have all been shown to increase the risk of liver disease progression in NAFLD patients.[16, 17]

It is estimated that NASH occurs in 20% of patients with NAFLD (3–12% of the US population).[5, 18] Approximately 30–40% of patients with NASH will develop fibrosis.[3, 18-20] Although fibrosis regresses in some patients,[8, 18, 21] others progress to advanced fibrosis or cirrhosis.[8, 22] In fact,

NASH is the third leading cause of cirrhosis in the US, and the third most common indication for liver transplant.[23, 24] In addition to cirrhosis, and the complications that accompany it, NASH places patients at risk for hepatocellular carcinoma (HCC).[25]

4.1.3. Current Treatment Options

There are no approved treatment options for NAFLD or NASH. Numerous clinical trials are underway with multiple products in development for the treatment of NAFLD, NASH, NASH fibrosis and NASH cirrhosis.

4.1.4. Clinical Trial Rationale

Numerous literature reports support a role for T therapy in management and / or treatment of NASH and liver cirrhosis. The current study is planned to study the long-term safety of LPCN 1144 in subjects who completed the Phase 2 trial LPCN 1144-18-002.

LPCN 1144, also referred to as "Oral T," is an oral capsule product containing an ester prodrug of T, Testosterone Undecanoate (TU). TU is an esterified T derivative that is orally bioavailable, unlike T which undergoes extensive first pass metabolism. After oral administration, TU is absorbed into systemic circulation primarily via the lymphatic system following incorporation into chylomicrons.[26] Once within systemic circulation TU is de-esterified by plasma esterases to T and becomes available to systemic target tissues. Additionally, dihydrotestosterone undecanoate (DHTU), formed from TU and transported into systemic circulation via lymphatic absorption, also becomes de-esterified in plasma to dihydrotestosterone (DHT). Based on a receptor binding study, TU and DHTU had negligible binding and therefore, TU and DHTU can be thought of as "inactive transport forms" that provide systemically active T and DHT.

4.1.4.1. Rationale for Testosterone Treatment for NASH

LPCN 1144 has a number of potential mechanisms of action that could prove to be beneficial to subjects with NASH and NASH cirrhosis:

- Androgens aid in the maintenance of liver homeostasis.[27]
- Androgens are known to provide benefits in terms of:
    - Anti-inflammatory properties.
    - Immune-modulating properties.[28]
- Androgens aid in liver regeneration.[29]
- Glucose homeostasis: increase insulin receptor, reduce insulin resistance/increase insulin sensitivity;[30] favorable impact on glucose metabolism.

A growing body of evidence from nonclinical and clinical studies reported in the literature support that T should be evaluated a potential treatment for NASH and NASH cirrhosis.

4.1.4.1.1. Nonclinical Studies Reported in the Literature

- Two nonclinical studies have investigated the effects of T on the pathogenesis of hepatic steatosis in intact and castrated rats fed a high-fat diet.
    - A study by Nikolaeno et al. showed that T deficiency may contribute to the severity of hepatic steatosis, and that T may play a protective role in hepatic steatosis and nonalcoholic fatty liver disease development without insulin resistance.[31]
    - A study by Jia et al. showed that T suppressed endoplasmic reticulum (ER) stress, inhibited the formation of macrovesicular lipid droplets, promoted lipid export, and ameliorated steatohepatitis induced by high fat diet and castration in male rats.[32]
- A survival study by Vic et al. found that rats treated with testosterone enanthate prior to a 90% hepatectomy had a striking difference in post-procedure survival compared to an untreated control, with 100% of the untreated control dying before Hour 40, while 80 % of the testosterone enanthate treated rats survived beyond Hour 40, and of the 80% alive at Hour 40, 50% survived for a normal life span.[29] Additionally, liver weight was significantly higher in the testosterone enanthate treated group, as early as 24 hours post-hepatectomy

4.1.4.1.2. Proof of Concept Liver Fat evaluation using MRI-PDFF

[redacted]

4.1.4.1.3. Clinical Studies in the Literature

- A retrospective observational cross-sectional study by Kim et al. found that patients with serum T levels in the lowest quintile had an odds ratio (OR) (95% confidence interval (CI)) of 5.12 (2.43–10.77) for NAFLD (P value, 0.0004).[33]
- A study by Yurci et al. evaluating the efficacy and safety of T replacement on muscle strength, bone mineral density (BMD), body composition and gynecomastia in hypogonadal men with liver cirrhosis found that T replacement improves muscle strength, ameliorates gynecomastia, alters body fat distribution and causes upper body adiposity in hypogonadal men with cirrhosis.[34]
- A 12-month, double-blinded, placebo-controlled trial by Sinclair et al. evaluating of intramuscular TU in 101 men with established cirrhosis and low serum T showed that T therapy in men with cirrhosis and low serum T safely increases muscle mass, bone mass and hemoglobin, and reduces fat mass and HbA1c.[35]

4.2. Justification for Dose and Safety for Use in the Proposed Population

[redacted]

In summary, LPCN 1144 in as inactive agent that converts to active testosterone. Based on a 90 day toxicology study in dogs, the non-androgenic no observed adverse effect level (NOAEL) was identified as 240 mg/kg/day, translating to a dose of about 7,776 mg in an average adult male. This level is approximately 17 times proposed daily human dose in the current study and therefore provides adequate support for a proof of concept study being proposed.

The comorbid conditions that are normally seen in the NAFLD/NASH population are consistent with the comorbid conditions of hypogonadism. Clinical evidence summarized in the Investigator Brochure suggest beneficial trends in liver-related biomarkers at a daily dose of 450 mg TU as evaluated by the Sponsor. This is further supported by beneficial roles of T administration in liver cirrhotic and transplant patients as discussed in literature.

Based on the summary above and discussion provided below, the proposed daily dose of 450 mg LPCN 1144 administered in two equal divided doses of 225 mg can be considered as a safe starting dose in NASH subjects. This was the dose used in the Phase 2 trial LPCN 1144-18-002, and will be offered under this open-label extension protocol. To date, 50 subjects have been randomized, 43 of whom are still on therapy. 4 subjects have completed the trial. The study DSMB recently (June 2020) reviewed the accumulated data from the 37 subjects randomized under this protocol, stating there were no alarming SAEs, no specific concerns regarding patient safety were raised, and recommended the study continue as planned.

4.2.1. Receptor Pharmacology

Testosterone undecanoate is a bio-reversible ester prodrug of testosterone. An androgen receptor binding study was conducted to investigate the pharmacological activity of TU relative to T in the in vitro human androgen receptor (AR) binding assay. This study showed that binding of TU is negligible compared to T (TU inhibitory concentration 50% (IC50) binding affinity was in the order of 1.0E-04 lower compared to testosterone) and can be considered to be inactive transport entities for delivery of testosterone.

4.2.2. Non-Clinical Toxicology

Numerous non-clinical studies were conducted in rats and dogs. Repeat dose toxicity and toxicology studies were conducted at various doses with the longest studies being 26 weeks in rats and the previously reference 90-day toxicology study in dogs, with results described below in greater detail.

In dogs, doses of up to 1000 mg/kg were evaluated (equivalent human dose of 35,100 mg, approximately 78X human daily dose). The NOAEL for non-reproductive effects was 240

mg/kg/day corresponding to 7,776 mg human dose (approximately 17 times proposed human dose). Hepatocellular effects were minimal with focal hepatocellular degeneration/necrosis and one of dog had minimal periportal acute/subacute inflammation and minimal bile duct hyperplasia with correlating elevations in ALT, AST and ALP at the 1000 mg/kg dose, corresponding to 78X the proposed human daily dose. Bile duct hyperplasia was also seen in 1 animal at 240 mg/kg/day but was not considered to be adverse since the severity was minimal.

Based on the 90 days dog toxicology study, doses of 450 mg TU/day in human for a duration of 36 weeks is well justified as a starting dose.

4.2.3. Clinical Safety

4.2.3.1. Prior Human Experience- Ex-US

In the UK, TU is approved as an intramuscular injection (Nebido: 1000 mg TU every 10 to 14 weeks) and oral (Restandol: 40 mg TU capsule 3 to 4 times daily) dosage forms. A post marketing cohort study was conducted using the UK-based General Practice Research Database (GPRD) to explore the risk of idiopathic liver disease in association with use of T products. The study provides data on ~8400 patients accounting for ~ 15600 patient years of T use over 19 years, of which oral T use accounted for ~ 1800 patients over 19 years (~1945 person years). Based on the findings of liver disease or liver adenoma (or liver adenocarcinoma) occurrence in T users, the upper 95 % CI for event rate in users of TU was 0.0537 per 10,000 person-days (0 cases in 686,791 person-days). Based on the findings of rates of various adverse outcomes among users of oral T was comparable or lower to other routes that are commercially used in the US.

4.2.3.2. Prior Experience with LPCN 1144: US Clinical Studies

[redacted]

Overall, key laboratory parameters and other biomarkers were mostly within reference ranges and/or were consistent with levels observed for other approved T replacement products. Increased hematocrit is a known androgenic effect of T administration and mean increases observed were minor.

Liver and renal function tests did not reveal any safety concerns with respect to LPCN 1144, and an evaluation of ALT and bilirubin showed no Hy's law cases in the LPCN 1144 clinical database. Therefore, drug induced liver injury is not expected with LPCN 1144.

[redacted]

Sponsor is conducting LPCN 1144-18-002 to investigate the safety and efficacy of LPCN 1144 for the treatment of men with NASH. To date, 50 subjects have been randomized, 43 of whom are still on therapy. 4 subjects have completed the trial. The study DSMB recently (June 2020) reviewed the accumulated data from the 37 subjects randomized under this protocol, stating there were no alarming SAEs, no specific concerns regarding patient safety were raised, and recommended the study continue as planned.

5. STUDY DESIGN

5.1. Overall Design

This open-label extension protocol is designed to investigate the safety of LPCN 1144 for subjects who complete the Phase 2 LPCN 1144-18-002 clinical trial. The study will be conducted across multiple centers in the United States.

Subjects who complete LPCN 1144-18-002 will be asked if they would like to participate in this study, which will allow access to the study drug LPCN 1144, used in the LPCN 1144-18-002 trial. If the subject would like to participate, he will be dispensed capsules containing 225 mg LPCN 1144. The dose of the study drug is one capsule twice daily, 30 minutes after a meal (total daily dose of 450 mg TU). If a subject was on a reduced dose of study drug at Week 36 of the LPCN 1144-18-002 study due to androgenic effects (see Section 7.1), the subject will continue on that reduced dose under this protocol.

The treatment phase will be for a duration of 36 weeks with assessment of liver enzymes, lipid levels, and other safety parameters at Weeks 6, 12, 24, and 36. Subjects may have an optional liver biopsy, timeframe Week 34 to Week 36. Subjects will be exited from the study at Visit 5, Week 36.

6. STUDY POPULATION

6.1. Inclusion Criteria

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

1. Subjects who have completed the 38 week study LPCN 1144-18-002 and wish to be treated with LPCN 1144
2. Subject must sign the Informed Consent Form to participate in the study

6.2. Exclusion Criteria

An individual who meets any of the following criteria will be excluded from participation in this study unless agreed upon by the Principal Investigator and the Sponsor:

1. Has participated or is participating in any other clinicial (investigational) study after completion of LPCN 1144-18-002 study
2. Subjects who are currently receiving any androgens or estrogens
3. Subjects who are not willing to use adequate contraception for the duration of the study
4. Use of drugs historically associated with NAFLD (amiodarone, methotrexate, systemic glucocorticoids, tetracyclines, tamoxifen, estrogens, anabolic steroids, valproic acid, other known hepatotoxins) for more than 2 weeks in the 2 years prior to enrollment
5. Any other condition, which in the opinion of the investigator would impede compliance or hinder completion of the study

7. STUDY INTERVENTION

7.1. Study Intervention Description

The following study treatment will be administered:

- Oral LPCN 1144 capsule, total daily dose of 450 mg TU administered as 225 mg BID
    - If a subject was on a reduced dose of study drug at Week 36 of the LPCN 1144-18-002 study because he met the dose reduction criteria related to the androgenic effects of the study drug (see Section 7.1), the subject will remain on the reduced dose during this study. These androgenic effects of LPCN 1144 include:
        - Increased hematocrit
        - Increased hemoglobin
        - Increased PSA
        - Testosterone levels that meet the dose reduction criteria

7.2. Dosing and Administration

All subjects will be instructed to take LPCN 1144 (225 mg TU per dose) twice daily, approximately 12 hours apart, approximately 30 minutes after morning and evening meals, with water. If a dose is missed, the subject should take it as soon as they remember (within 4 hours of missed dose). If the second dose is not taken within 16 hours of the first dose of the day, the subject should skip that dose and resume dosing at 24 hours past the last dose. If a subject is switched to a reduced dose, the subject should take the dose in the morning approximately 30 minutes after the morning meals, with water.

7.3. Preparation/Handling/Storage/Accountability

7.3.1. Acquisition and Accountability

LPCN 1144 will be provided in high-density polyethylene (HDPE) bottles. Adequate supplies of study drug will be provided to the study center.

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. 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 Case Report Form (CRF). The study drug may be re-dispensed to the subject after it is accounted for in the IP log and CRF.

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 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 destroyed on-site or returned to the Sponsor (or a designee), according to instructions from the Sponsor and according to local regulations. Labels must remain attached to the containers.

7.3.2. Formulation, Appearance, Packaging, and Labeling

LPCN 1144 will be provided as a gelatin capsule product that contains 225 mg TU per capsule. Each bottle will be labeled appropriately and at a minimum will contain the quantity, manufactured by, retest date, and a caution that the product is an investigational drug. The container will contain the treatment name, as this study is not blinded.

7.3.3. Product Storage and Stability

The study drug must be stored at room temperature 15°C to 25°C (59°F to 77°F). LPCN 1144 capsules are listed as Drug Enforcement Administration (DEA) Schedule CIII drug in the United States and must be handled according to applicable federal and local regulations. The study drug is for investigational use only and is to be used only within the context of this study. The study drug supplied for this study must be maintained under adequate security and stored under the conditions specified on the label until dispensed for subject use or returned to the Sponsor.

7.4. Description of Enrollment

All subjects meeting the inclusion criteria and not meeting any of the exclusion criteria will be enrolled into this study.

8. STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

8.1. Discontinuation of Study Drug

Discontinuation from LPCN 1144 does not mean discontinuation from the study, and remaining study procedures should be completed as indicated by the study protocol. If a clinically significant finding is identified (including, but not limited to changes from baseline) after enrollment, the investigator or qualified designee will determine if any change in participant management is needed (see Section 8.3 for stopping criteria). Any new clinically relevant finding will be reported as an adverse event (AE).

The data to be collected at the time of study intervention discontinuation will include the following:

- Biomarkers and clinical safety markers samples
- Adverse Events
- Investigational product return

8.2. Participant Discontinuation/Withdrawal from the Study

All 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 (specific events are discussed in Section 8.3). Additionally, if a subject experiences any of the following serious adverse events associated with T use during the trial, then study drug should be discontinued:
    - Venous thromboembolism
    - Myocardial infarction
    - Stroke
    - Grade 3-4 pitting edema
    - New onset of any malignancy. Exceptions may be approved by PI, such as basal cell carcinoma of the skin
    - If a subject develops new onset or worsening of sleep apnea
- Significant noncompliance with the protocol requirements
- Lost to follow-up

Any subject who requires permanent discontinuation of the study drug will be followed at the scheduled procedures according to the protocol until at least the end of the study. If a subject is discontinued from the study with an ongoing AE or an unresolved laboratory result that is in the opinion of the investigator is significantly outside of the reference range, the investigator will attempt to provide follow-up until a satisfactory clinical resolution of the AE or laboratory result is achieved.

If a subject chooses to discontinue from the study, Week 36 procedures should be completed if the subject is willing. The reason for participant discontinuation or withdrawal from the study will be recorded on the Case Report Form (CRF).

8.3. Monitoring and Stopping Criteria

Baseline for safety assessments is the Week 38 labs from Study LPCN 1144-18-002 if the subject enters study LPCN 1144-20-002 within 2 weeks of the Week 38 visit (Week 36 data will be used for labs and questionnaires not scheduled/completed at Week 38). If not, baseline labs will be drawn on the day the subject enters study LPCN 1144-20-002, and those labs will be used as the baseline for safety assessments.

8.3.1. Blood Pressure Monitoring and Stopping Criteria

Subjects will be monitored for Blood Pressure exceeding 140/90 mmHg throughout the study. Standard clinical care should be provided to treat blood pressure.

8.3.1.1. BP Close Monitoring Criteria

While under standard clinical care, if blood pressure cannot be adequately controlled, the subject must be discontinued from study medication until stabilization and a level of <140/90 mmHg is achieved prior to resumption of the study medication.

8.3.1.2. BP Stopping Criteria

While under standard clinical care, if blood pressure exceeds 160/100 mmHg, an immediate repeat assessment should be performed, to confirm elevation of blood pressure. If confirmed, the subject must stop study medication and should be urgently treated.

8.3.2. Creatinine Stopping Criteria

The subject's creatinine will be monitored throughout the study. An increase in creatinine to > 2 mg/dL will be used as stopping criteria. Creatinine > 2 mg/dL will initiate a discussion with the medical monitor and initiation of clinical workup.

8.3.3. PSA Monitoring and Stopping Criteria

Subjects will be monitored for PSA throughout the study. Close monitoring and stopping criteria for PSA are provided below.

8.3.3.1. PSA Close Monitoring Criteria

Subjects with a change from baseline > 1.4 ng/mL will trigger close monitoring procedures. The subject should have the PSA measured again within one week. If the PSA value is still > 1.4 ng/mL from baseline, the subject will be switched to a reduced dose (LPCN 1144) of once daily administration (one capsule, once daily).

8.3.3.2. PSA Stopping Criteria

For PSA, an increase in PSA to > 4 ng/mL will be used as stopping criteria. Subjects with PSA > 4 ng/mL should have the PSA measured again within one week. If the PSA > 4 ng/mL value is repeated, the subject will have study drug discontinued, and will proceed to exit procedures.

8.3.4. Hematocrit Monitoring and Stopping Criteria

Subjects will be monitored for hematocrit throughout the study. Close monitoring and stopping criteria for hematocrit are provided below.

8.3.4.1. Plasma Volume Depletion

Subjects who develop elevated hematocrit > ULN during the study must be evaluated to ascertain if the elevation is due to plasma volume depletion. If the subject has experienced recent symptoms of postural dizziness, fatigue, confusion, muscle cramps, chest pain, abdominal pain, postural hypotension, or tachycardia or has recently experienced hemorrhage, vomiting, diarrhea, or diuresis, study drug should be held, confirm the subject is hydrated, and retest hematocrit as soon as possible, ideally within 48 hours. Then schedule routine hematocrit tests, with a reassessment of subject symptoms until levels return to target. Study drug may be restarted when hematocrit is < ULN.

8.3.4.2. Hematocrit Close Monitoring and Stopping Criteria

Subjects with hematocrit > ULN during the study will trigger the following close monitoring procedures.

- Hematocrit > ULN: Confirm that subject is hydrated and retest the hematocrit as soon as possible, ideally within 48 hours.
- Hematocrit > ULN on two consecutive assays: dose reduction (once daily dosing) will be initiated
    - Routine monitoring of hematocrit for subjects on once-daily dosing
    - Phlebotomy may be initiated at investigator discretion
- Hematocrit continues to increase while on once daily dosing: study drug discontinued
- Hematocrit does not return to normal range within 4-8 weeks of once daily dosing: study drug discontinued
- Hematocrit returns to normal range within 4-8 weeks of initiation of once-daily dosing: remain on once daily dosing
- Hematocrit > ULN-4% with symptoms of polycythemia: study drug discontinued and subject followed until the end of study.

8.3.5. Close Monitoring and Stopping Criteria for Hepatotoxicity

Each subject's baseline values of ALT, AST, ALP, and TB will be established using either values from Week 38 of LPCN 1144-18-002 or with labs performed at the Day 1 visit of this study (LPCN 1144-20-002). After the baseline values are established during screening, the DILI algorithm

provided in Appendix B and Appendix C will be used for monitoring liver safety AEs and drug-induced liver injury (DILI).

8.3.6. Testosterone Close Monitoring and Stopping Criteria

Testosterone will be measured periodically during the study to ensure subjects do not experience elevated T levels. If a subject experiences a T measurement in excess of 1500 ng/dL while on treatment, a repeat of the T assay should be scheduled within 48 hours. If T concentrations in excess of 1500 ng/dL are repeated in the subject, the subject will be placed on a reduced dose of LPCN 1144 once daily administration (one capsule, once daily).

If T concentrations in excess of 1500 ng/dL are repeated in a subject at a once daily dose, study drug must be discontinued, but the subject should be followed in the clinical trial. If the T concentration remains above 1500 ng/dL at exit, proceed with weekly T assays until T concentrations have returned to below 1500 ng/dL.

8.3.7. Common Terminology Criteria for Adverse Event Stopping Criteria

The trial will be stopped based on the following stopping criteria:

a. If one subject experience a Grade V CTCAE (Common Terminology Criteria for Adverse Event) related to study drug,
b. or two subjects experience the same Grade IV CTCAE related to study drug,
c. or three subjects experienced the same Grade III CTCAE related to study drug.
d. If four subjects experience the same Grade II CTCAE, enrollment of new subjects into the trial will be paused. The Safety Team will assess the causality of these adverse events; if adverse events are deemed to be unrelated, determined by the Safety Team, then enrollment may resume.

The following CTCAE criteria will be used for evaluating and discontinuing subjects in the trial:

a. If a subject experience a Grade IV CTCAE or meets criteria listed in Appendix B: DILI Monitoring Algorithm, discontinue the study drug.
b. The Safety Team will perform a causality assessment. The study drug may be restarted if the Safety Team concludes that the AE or laboratory abnormalities were not related to study drug, the AE has resolved, laboratory abnormalities have returned to baseline, and the subject is amenable to close clinical follow-up.
c. If, after re-challenge, a subject has a second serious AE or recurrent elevations of total bilirubin, ALT, or AST as defined in Appendix B: DILI Monitoring Algorithm, study drug must be discontinued permanently.

8.4. Lost to Follow Up

A participant will be considered lost to follow-up if he fails to return for the scheduled visits and is unable to be contacted by the study site staff.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site will attempt to contact the participant and reschedule the missed visit and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record or study file.
- Should the participant continue to be unreachable, he will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

9. STUDY ASSESSMENTS AND PROCEDURES

9.1. Visit Schedule

There are 5 study visits in this study.

9.1.1. Day 1

Subjects who qualify based on the inclusion and exclusion criteria will be invited to participate in this study and will complete the following procedures as provided in Schedule of Activities (SOA):

- Obtain Informed Consent
- Review current and past medication history
- Collect adverse events information (solicited or spontaneously reported). Subjects should be specifically queried if they have experienced any untoward signs or symptoms that would reflect cardiovascular or hypertensive adverse events, such as changes to medication due to elevations in blood pressure.
- Conduct a physical examination.
- Dispense Study Drug.
- Remind the subject to call or return to the clinic before the next visit if he develops any of the signs/symptoms listed in the monitoring and stopping criteria, Section 8.3.
- If Day 1 of the study is more than two weeks after the Week 38 Visit of study LPCN 1144-18-002, the following procedures will be completed prior to dosing with LPCN 1144.
  - Lipid profile
  - Hematology panel
  - HbA1C
  - Metabolic and renal function panel
  - Hepatic panel
  - Biomarkers
  - Testosterone assay
  - Hormones and related markers
  - PSA, prolactin
  - Cortisol and CBG

- Serum and plasma for banking
- Urinalysis

9.1.2. On-Treatment and Follow-Up Visits

The following visit durations are referenced from the day of enrollment in study LPCN 1144-20-002. Subjects will return to the clinic for On-Treatment visits at Week 6, Week 12, Week 24, and Week 36. The following procedures will be performed at each visit from Week 6 to Week 36.

- Review current medication history
- Collect adverse events information (solicited or spontaneously reported). Subjects must be specifically queried if they have experienced any untoward signs or symptoms that would reflect cardiovascular or hypertensive adverse events, such as changes to medication due to elevations in blood pressure.
- Collect dispensed investigational product (IP, LPCN 1144) bottle and perform accountability/adherence checks
- Dispense IP at Week 6, Week 12, and Week 24
  - IP returned by the subject should be re-dispensed. If IP is re-dispensed, record this in the IP accountability log.
    - Inform subject to use the IP in the open bottle prior to opening the new bottle
- Conduct a physical exam
- Have the patient fill out the PGI-C questionnaire (Appendix D: PGI-C Questionnaire)
  - Weeks 12, 24, and 36
- Collect blood and urine samples for the following analyses 3-5 hours after the morning LPCN 1144 dose:
  - Lipid profile
  - Hematology panel
  - HbA1C
  - Metabolic and renal function panel
  - Hepatic panel
  - Testosterone assay
  - Hormones and related markers
  - PSA, prolactin
  - Cortisol and CBG
  - Urinalysis
- Additional blood samples will be drawn at Week 12 and Week 36 for the following analyses:
  - Biomarkers
  - An additional blood sample will be collected for serum and plasma samples for banking

At Week 36, subjects will be exited from the study.

9.1.3. Week 36 Liver Biopsy (optional)

Subjects will be given the option of having a liver biopsy performed (timeframe: Week 34 to Week 36). Besides evaluation of the histological effects of 9 months of LPCN 1144 therapy for those on placebo during the LPCN 1144-18-002 study, this will allow long-term histological and biochemical effects of LPCN 1144 for some subjects who will have been on LPCN 1144 for up to 18 months.

Subjects will have the option to opt-in or opt-out of this liver biopsy at the time of study enrollment. Further, the subject may withdraw consent for this procedure at any time during the study.

9.2. Procedure Overview

9.2.1. Medical and Medication History

The subject's medical history (key events) during the past 5 years will be obtained from the LPCN 1144-18-002 study. Any new information / changes shall 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 shall also be recorded.

All subjects must be instructed to use adequate contraception for the duration of the study, acceptable methods of birth control for subjects and their partners 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) will be obtained from the LPCN 1144-18-002 study Week 38 visit. If a subject reports taking any new over-the-counter or prescription medications, vitamins and/or herbal supplement since the Week 38 visit, 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.

9.2.2. Physical Examination

Physical examinations will be performed at each study visit. The physical examination includes measurement of height, weight, waist, and hips; vital signs (temperature (single measurement), respiratory rate (single measurement), and clinic BP (triplicate measurement) and pulse rate (PR, triplicate measurement)); examination for scleral icterus and pedal edema and auscultation of heart and lungs. Any changes during the study will be documented. Subject's height and weight will be used to calculate BMI.

9.2.3. Clinic BP and PR

Clinic BP and PR will be measured at each visit throughout the study as part of physical examination. An appropriately sized cuff for the size of the subject's arm circumference must be utilized to minimize inaccurate readings. No smoking or exercise for at least 30 minutes before a blood pressure measurement. Subjects must sit in a chair with a back support and the arm supported at heart level with feet flat on the floor. If necessary, 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.

9.2.4. Patient Global Impression of Change Scale (PGI-C)

The PGI-C evaluates all aspects of subjects' health and assesses if there has been an improvement or decline in clinical status (Appendix D: PGI-C Questionnaire)

9.2.5. Clinical Laboratory Tests

For all subjects, blood and urine samples will be taken as directed in the SOA. No labs require fasting in this study. Specific stopping criteria for hematocrit, prostate specific antigen, testosterone, and liver enzymes are provided in Section 8.3. In addition, subjects will be monitored for other clinical laboratory tests provided in the SOA; if a subject develops clinically significant laboratory abnormality/ies for any other laboratory test during the study, closely monitor the subject and perform the laboratory test(s) weekly, until the laboratory abnormality/ies are normalized.

Table 1: Listing of Clinical Laboratory Tests

Hematology panel	**Lipid profile**	**Metabolic and renal function panel**
Hematocrit	Free Fatty Acids	Sodium
Hemoglobin	HDL cholesterol	Potassium
Complete Blood Count	LDL cholesterol	Chloride
Prothrombin time	Total Cholesterol	Bicarbonate
International Normalized Ratio	Triglycerides	Calcium
Urinalysis	VLDL cholesterol	Phosphate
Color	**Hepatic panel**	BUN
Appearance	Total Bilirubin	Creatinine
Specific Gravity	Direct Bilirubin	Uric acid
pH	ALT	**Hormones and related markers**
Protein	AST	Total testosterone
Blood	ALP	Calculated free testosterone
Ketones	GGT	SHBG
Urobilinogen	Bile acid	DHT
Glucose	Creatinine kinase	LH
Bilirubin	**Miscellaneous**	FSH
Leukocyte Esterase	HbA1c	TSH
Nitrite	Prostate Specific Antigen	
	Prolactin	
	Cortisol	
	Cortisol Binding Globulin	

Clinical laboratory testing must be performed by appropriately credentialed laboratories. Certified laboratories will process and provide results for the tests conducted throughout the study.

9.2.6. Testing for Adrenal Insufficiency

If, at any time during the study, a subject experiences signs and symptoms of adrenal insufficiency (AI) (i.e. unexplained extreme fatigue, abdominal pain, nausea, vomiting, unexplained hypoglycemia, hyponatremia with hyperkalemia), or, if the cortisol is less than the lower limit of normal at baseline or end of study, the subject will have a cosyntropin stim test as follows:

The current standard for diagnosing adrenal insufficiency is cosyntropin stimulation testing using the standard high-dose of cosyntropin (250 mcg). An adequate response is defined by a peak cortisol level of at least 18 mcg/dL (497 nmol/L) after 30 or 60 minutes of cosyntropin administration.

Subjects must be educated about the signs or symptoms of adrenal insufficiency (such as -- fatigue, muscle weakness, low appetite, weight loss, and belly pain); and cortisol will be drawn at any time during the study if AI is suspected, followed by a cosyntropin stim test as needed. If a subject develops AI or has an abnormal stimulation testing at the end of the study, they will be followed until normalization of the results or return to baseline.

9.3. Safety Issues

Safety issues can be divided into (a) safety concerns relating to the therapeutic interventions, (b) safety concerns related to liver biopsy, and (c) issues related to the central specimen repository.

9.3.1. Safety Concerns Related to LPCN 1144

LPCN 1144 was extensively studied in non-clinical and clinical studies. In clinical studies participants were exposed to a twice daily dose 225 mg of TU (450 mg total daily dose) in multiple studies for up to one-year duration. In clinical studies, the most frequently occurring adverse events in LPCN 1144 treated subjects were headache (4.0% of subjects), upper respiratory tract infection (3.0% of subjects), weight increased (2.3% of subjects), and nasopharyngitis (1.7% of subjects).

LPCN 1144 must not be used in any of the following subjects:

- Men with carcinoma of the breast or known or suspected carcinoma of the prostate.
- Women who are, or who may become pregnant, or who are breastfeeding. LPCN 1144 may cause fetal harm when administered to a pregnant woman. LPCN 1144 may cause serious adverse reactions in nursing infants. If a pregnant woman is exposed to testosterone, she must be apprised of the potential hazard to the fetus.

LPCN 1144 capsules shall not be used in subjects with known hypersensitivity to any of its ingredients.

9.3.2. Management of Adverse Effects Attributed to Study Medication

During the trial, if a participant develops side effects thought to be due to the study medication and requires cessation of study medication, the medication will be stopped for 4 weeks. If the side effects disappear, an attempt will be made to reintroduce the study medication after 4 weeks. If the symptoms reappear, study medication will be once again stopped, and the subject will no longer receive the study medication, but will be followed in the study according to the protocol.

9.3.3. Safety Issues Related to Liver Biopsy

Subjects will have the option of undergoing up to one liver biopsy for research purposes during their participation in this protocol. This is an optional procedure – a subject's participation in the trial is not dependent on his participation in the liver biopsy. About 20% of people who have a liver biopsy have some degree of pain over the liver that may last a few minutes up to several hours. This occasionally requires pain medication and usually disappears completely within a day or two. A rare complication of liver biopsy is severe bleeding such that a blood transfusion or even radiological/surgical interventions are required to stop the bleeding (less than 1 in 1,000). Very rarely (less than 1 in 10,000 reported cases) death has occurred from bleeding after a biopsy. We intend to minimize the risks associated with liver biopsy (a) by requiring that each of the physicians who will obtain liver biopsies be very experienced in safely obtaining the liver biopsy specimens, (b) by not enrolling subjects with cirrhosis or subjects with coagulopathy, and assuring that subjects do no develop coagulopathy during the course of the trial, (c) by adhering to the good clinical practice in performing the liver biopsy, (d) by assuring that an attending hepatologist or radiologist directly supervises if a physician trainee is performing the procedure, and (e) by considering a trans jugular liver biopsy in morbidly obese subjects in whom a percutaneous, mid-axillary approach may not be feasible.

9.3.4. Safety Issue Related to Specimen Repository

It is anticipated that serum, plasma, DNA, and liver tissue from the participants will be stored for future studies related to NASH and possibly other liver/metabolic diseases. These samples will be stored in a central repository.

9.4. Adverse Events and Serious 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.

9.4.1. Definition of Adverse Event

Adverse event means any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related (21 CFR 312.32 (a)).

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 will 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.

9.4.2. Definition of Serious Adverse Event

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.

9.4.3. Classification of an Adverse Event

9.4.3.1. Severity of the Event

For adverse events (AEs) not included in the protocol defined grading CTCAE system, the following guidelines will be used to describe severity:

- Mild – Events require minimal or no treatment and do not interfere with the participant's daily activities.
- Moderate – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- Severe – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term "severe" does not necessarily equate to "serious".

9.4.3.2. Relationship to Study Intervention

All adverse events (AEs) must have their relationship to study intervention assessed by the clinician who examines and evaluates the participant based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below. In a clinical trial, the study product must always be suspect.

- Related – The AE is known to occur with the study intervention, there is a reasonable possibility that the study intervention caused the AE, or there is a temporal relationship between the study intervention and event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study intervention and the AE.
- Not Related – There is not a reasonable possibility that the administration of the study intervention caused the event, there is no temporal relationship between the study intervention and event onset, or an alternate etiology has been established.

9.4.3.3. Expectedness

The investigator will be responsible for determining whether an adverse event (AE) is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study intervention.

9.4.4. Time Period and Frequency for Event Assessment and Follow-Up

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.

The occurrence of an adverse event (AE) or serious adverse event (SAE) may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor.

All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate case report form (CRF). Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

Site staff will record all reportable events with start dates occurring any time after informed consent is obtained until the last follow up visit. If the site becomes aware of a related SAE at any time after completion of the study, it must be reported. Events will be followed for outcome information until resolution or stabilization.

9.4.5. Adverse Event Reporting

To report an SAE, complete the CRF and contact Lipocine by phone or e-mail within 24 hours of awareness.

Safety Contact Information:

[redacted]

9.4.6. Monitoring for Adverse Events

Summary data on adverse events will be monitored as needed. These summaries will include analyses comparing rates of adverse events by clinic or in other subgroups. Where applicable, signs and symptoms associated with the adverse event will be graded as to severity by the clinical site staff as mild, moderate, or severe using the Common Terminology Criteria for Adverse Events.

Analyses or listings of adverse events will not be provided to the IRBs; however, adverse events involving unanticipated problems involving risks to participants, or breaches of protocol which might entail risk to participants must be reported to local IRBs as soon as possible after they are discovered. Each participating center is responsible for ensuring that all local IRB requirements for reporting adverse events are met.

9.4.7. Reporting of Pregnancy

The study only enrolls male participants who will be required to use adequate contraception throughout the duration of the study. However, if the subject's partner becomes pregnant while the subject is in the study, it must be reported to the site as soon as possible.

10. STATISTICAL CONSIDERATIONS

The objective of this protocol is to monitor the safety and tolerability of extended therapy with LPCN 1144 in male subjects with NASH who have completed the LPCN 1144-18-002 protocol. Therefore, data regarding the safety and tolerability of LPCN 1144 will be collected and reported.

11. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

11.1. Regulatory, Ethical, and Study Oversight Considerations

11.1.1. Informed Consent Process

Prior to the initiation of any 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.

11.1.2. Study Discontinuation and Closure

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to the investigator, IRB and regulatory authorities. If the study is prematurely terminated or suspended, the PI will promptly inform study participants, the Institutional Review Board (IRB), and Sponsor and will provide the

reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met
- Determination of futility
- Administrative reasons by the Sponsor

Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the Sponsor, IRB and/or Food and Drug Administration (FDA).

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.

11.1.3. Confidentiality and Privacy

All information concerning LPCN 1144 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 1144. 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.

11.1.4. Future Use of Stored Specimens and Data

Data collected for this study will be analyzed and stored at the central facility as indicated in the administrative study structure page. After the study is completed, the de-identified, archived data will be transmitted to and stored at the central facility.

With the participant's approval and as approved by local Institutional Review Boards (IRBs), de-identified biological samples will be stored.

During the conduct of the study, an individual participant can choose to withdraw consent to have biological specimens stored for future research. However, withdrawal of consent with regard to bio sample storage may not be possible after the study is completed.

When the study is completed, access to study data and/or samples will not be available to investigators or subjects.

11.1.5. Key Roles and Study Governance

Lipocine is the Sponsor of this study. On the initial approval date of this protocol, the administrative structure and the external organizations supporting the study are as follows:

Sponsor: Lipocine Inc
675 Arapeen Drive, Suite 202
Salt Lake City, Utah 84108 USA
Telephone: (801) 994-7383

Study Director: [redacted]
Vice President Product Development
Lipocine Inc
Telephone: (801) 994-7383
[redacted]

11.1.6. Safety Oversight

Safety oversight will be under the direction of the Sponsor and medical monitor of the study.

11.1.7. Clinical Monitoring

A separate Clinical Monitoring Plan (CMP) will be developed and used to govern the monitoring and quality control / conduct of the study.

11.1.8. Quality Assurance and Quality Control

The Sponsor or its qualified designee will monitor the study site throughout the study. Source document verification will be performed. A quality assurance check may be performed to ensure that the investigator is complying with the protocol and regulations. In addition, after the CRFs are submitted, a review of the data will be conducted by the designated monitor.

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 monitor, the investigator and other appropriate personnel from the Sponsor.

11.1.9. Data Handling and Record Keeping

11.1.9.1. 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 CRFs 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.

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

The investigator or an authorized member of the investigator's staff will make any necessary corrections to the CRF. All change information, including the date and person performing the corrections, will be available via the audit trail. For any correction, a reason for the alteration will be provided. The CRFs will be reviewed periodically for completeness, legibility, and acceptability. The Sponsor or their representatives will also be allowed access to all source documents pertinent to the study in order to verify CRF entries. The investigator will review the CRFs for completeness and accuracy and provide his or her signature and date to CRFs as evidence thereof.

11.1.10. Protocol Deviations

The investigator shall not implement any deviation from the protocol without prior review and written 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

[redacted]

Alternate Contact

[redacted]

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 safety must be reviewed and/or approved by the IRB, as applicable, prior to implementation.

11.1.11. Publication and Data Sharing Policy

The data obtained is confidential property of the Sponsor, Lipocine Inc. The publication policy with sites will be covered under the respective clinical trial agreements. In general, no part of the trial or data can be published by sites, investigator or staff without explicit written approval of the Sponsor.

11.1.12. Conflict of Interest Policy

All participating investigators will be required to provide a financial disclosure and conflict of interest statement.

11.2. Abbreviations

AE	Adverse Event
AI	Adrenal Insufficiency
ALP	Alkaline Phosphatase
ALT	Alanine Transaminase
AR	Androgen Receptor
AST	Aspartate Transaminase
BMD	Bone Mineral Density
BID	Twice Daily
CBC	Complete Blood Count
CBG	Cortisol Binding Globulin
CFR	Code of Federal Regulations
CI	Confidence Interval
CK	Creatine Kinase
CMP	Clinical Monitoring Plan

CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
DEA	Drug Enforcement Administration
DHT	Dihydrotestosterone
DHTU	Dihydrotestosterone Undecanoate
DILI	Drug-Induced Liver Injury
DSMB	Data and Safety Monitoring Board
ELF	Enhanced Liver Fibrosis
ER	Endoplasmic Reticulum
FDA	Food and Drug Administration
FSH	Follicle Stimulating Hormone
GCP	Good Clinical Practice
GGT	Gamma-Glutamyltransferase
GPRD	General Practice Research Database
HA	Hyaluronic Acid
HCC	Hepatocellular Carcinoma
HDPE	High Density Polyethylene
IB	Investigator's Brochure
IC50	Inhibitory Concentration 50%
IND	Investigational New Drug Application
IP	Investigational Product
IRB	Institutional Review Board
LH	Luteinizing Hormone
MRI-PDFF	Magnetic Resonance Imaging-Proton Density Fat Fraction
NAFL	Non-Alcoholic Fatty Liver
NAFLD	Non-Alcoholic Fatty Liver Disease
NASH	Non-Alcoholic Steatohepatitis
NIH	National Institutes of Health
NOAEL	No Observed Adverse Effect Level
OR	Odds Ratio
PGI-C	Patient Global Impression of Change Scale
PI	Principal Investigator
PIIINP	N-terminal propeptide of type III collagen
PR	Pulse Rate
PSA	Prostate Specific Antigen
PT	Prothrombin Time
SAE	Serious Adverse Event
SHBG	Sex Hormone Binding Globulin
SOA	Schedule of Activities
TB	Total Bilirubin
TGF-β	Transforming Growth Factor Beta

TIMP-1	Tissue Inhibitor of Metalloprotease 1
TU	Testosterone Undecanoate
TSH	Thyroid Stimulating Hormone
ULN	Upper Limit of Normal
US	United States

12. APPENDICES

Appendix A: Investigator's Agreement

Study Title:	An Open Label Extension Study of the Safety and Tolerability of LPCN 1144 for the Treatment of Subjects with Nonalcoholic Steatohepatitis (NASH) who have Completed the LPCN 1144-18-002 Trial
Study Number:	LPCN 1144-20-002
Final Date:	February 2021

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 that the drug is 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 amendment(s).
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 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 1144.

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 B: DILI Monitoring Algorithm

Baseline ALT (in italics) **Treatment-Emergent ALT**	**Treatment-Emergent TB**	**Liver Symptoms**	**Action**
ALT ≤ ULN at baseline: **ALT > 5x ULN** *ALT > ULN at baseline:* **ALT > 3x baseline or > 300 U/L (whichever occurs first)**	Normal	None	Repeat ALT, AST, ALP, TBL, in 2–5 days Reduce dose (LPCN 1144) to once daily administration (one capsule, once daily). Follow-up for symptoms.
ALT ≤ ULN at baseline: **ALT > 8x ULN** *ALT > ULN at baseline:* **ALT > 5x baseline or > 400 U/L (whichever occurs first)**	Normal	None	Interrupt study drug. Initiate **close observation** (see Appendix C below and FDA guidance*) and workup for competing etiologies. Study drug can be restarted only if an alternative etiology is identified, and liver enzymes return to baseline. Restart at reduced dose (LPCN 1144) once daily administration (one capsule, once daily).
ALT ≤ ULN at baseline: **ALT > 5x ULN** *ALT > ULN at baseline:* **ALT > 3x baseline or > 300 U/L (whichever occurs first)**	TB > 2x ULN	None	Interrupt study drug. Initiate **close observation** and workup for competing etiologies. Study drug can be restarted only if an alternative etiology is identified, and liver enzymes return to baseline. Restart at reduced dose (LPCN 1144) once daily administration (one capsule, once daily).
ALT ≤ ULN at baseline: **ALT > 5x ULN** *ALT > ULN at baseline:* **ALT > 3x baseline or > 300 U/L (whichever occurs first)**	Normal or elevated	Symptoms of clinical hepatitis - severe fatigue, nausea, vomiting, right upper quadrant pain	Interrupt study drug. Initiate **close observation** and workup for competing etiologies. Study drug can be restarted only if an alternative etiology is identified and liver enzymes return to baseline. Restart at reduced dose (LPCN 1144) once daily administration (one capsule, once daily).

Source: Adapted from [36]

** https://www.fda.gov/downloads/Drugs/Guidance/UCM174090.pdf*

Appendix C: Close Observation for Potential Drug Induced Liver Injury

Within 72 hours, perform a complete history, physical, and liver biochemistries, including:

New or worsening signs and symptoms of clinical hepatitis such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, or eosinophilia.

Concomitant medications, including acetaminophen, dietary supplements, herbal remedies, over-the-counter medications, recreational drug use, and special diets:

- Alcohol consumption
- Exposure to environmental chemical agents
- Past medical history
- Complete review of systems
- Obtain liver biochemistries including ALT, AST, alkaline phosphatase, total bilirubin, and INR.

Evaluate subjects two or three times a week for signs and symptoms of clinical hepatitis and liver biochemistries until biochemistries stabilize.

If biochemistries stabilize and the subject is asymptomatic, monitor liver biochemistries once a week until they return to baseline.

Subjects who live far from study sites can be evaluated locally for history, physical exam, and laboratories, if the results are communicated promptly to the site investigator.

Appendix D: PGI-C Questionnaire

Answer this question with regard to changes since starting study treatment in the open-label extension study.

PGI-C (Change) Scale

Please choose the response below that best describes the overall change in your symptoms since you started using the study treatment. .

1.Very much better.

2. Moderately better.

3. A little better.

4. No change.

5. A little worse.

6. Moderately worse.

7. Very much worse.

Appendix E: Sponsor Signature

Study Title:	**An Open Label Extension Study of the Safety and Tolerability of LPCN 1144 for the Treatment of Subjects with Nonalcoholic Steatohepatitis (NASH) who have Completed the LPCN 1144-18-002 Trial**
Study Number:	LPCN 1144-20-002
Final Date:	February 2021

This clinical study protocol was reviewed and approved by the sponsor.

Signed [redacted]

Vice President, Product Development
Lipocine Inc.

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