A Phase 2, Randomized Double-Blind, Placebo-Controlled, Multi-Center Study to Assess the Efficacy, Safety and Tolerability of Oral LPCN 1144 in Subjects with Nonalcoholic Steatohepatitis (NASH)

Protocol Number: LPCN 1144-18-002

Phase: 2

Coordinating Investigator: [redacted]

IND Number: 140203

Sponsor: Lipocine Inc.

Version Number: 3.0

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STATEMENT OF COMPLIANCE

The trial will be carried out in accordance with International Conference on Harmonization Good Clinical Practice (ICH GCP)*, applicable state, local and federal regulatory requirements,* guidelines governing clinical study conduct and ethical principles that have their origin in the Declaration of Helsinki and the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812)

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the Institutional Review Board (IRB) for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. In addition, all changes to the consent form will be IRB-approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

Responsibilities of the clinical investigator conducting the trial are specified in **Appendix** A.

1 SUMMARY OF CHANGES IN PROTOCOL VERSION 3.0

Version 3.0 of the LPCN 1144-18-002 study protocol was developed to make the following changes to the study:

Affected Section(s)	Summary of Revisions Made	Rationale
3.1 4.1 9.3.6.1 10.1	Inclusion Criterion #2: Biopsy eligibility criterion was changed.	To include stage 1 fibrotic subjects with NAS ≥ 4 and advanced fibrosis subjects regardless of NAS ballooning score in the study.
3.1 3.3 4.1 9.1.2.2	Inclusion Criterion #1, testosterone screening assessment: Subjects without previously documented hypogonadal status will be eligible for the study if subject has a single AM testosterone level < 400 ng/dL	Expand the criteria of subjects eligible for the trial to better reflect the NASH population.
3.1, 4.2	Cholecystectomy was removed from EC #18	Expand the criteria of subjects eligible for the trial to better reflect the NASH population.
3.1 3.3 4.1 9.1.2.3 9.3.2	MRI-PDFF, DXA imaging timing and data analysis was updated	To allow a subject unable to undergo MRI-PDFF or DXA imaging due health condition (e.g. claustrophobia, difficulty holding breath during the procedure etc.) to enter the study.
3.1 3.3 4.1	Lab value targets and procedure for approval to proceed to biopsy have been updated; Fibroscan target removed.	Predictive value of Fibroscan is low in this obese population
8.2	Update procedures related to Participant Discontinuation/Withdrawal from the Study	Clarify the procedures for subject who discontinue dosing and/or choose to discontinue the study
8.3	Close monitoring and stopping criteria have been updated	To reflect the Endocrine Society Clinical Practice Guidelines; clarification
3.1 3.3 4.2 9.1.2.1-2	Labs thought to be spurious can be repeated	Clarification
9.1.3	Randomization visit section is being updated to collect testosterone and hormones prior to dosing	To collect true t=0 (baseline) T levels
9.1.4.2 9.1.4.3	Week 12 and Week 16 visits (of the specified sections) have been clarified and updated	To clarify which lab should be drawn with the fasting labs
9.3.3	Prior to Fibroscan, subjects must not eat or drink for at least 3 hours prior to the procedure	Fibroscan accuracy is decreased if subject has recently eaten/drank.
9.3.10	Table 1: Listing of the Clinical Laboratory Tests for all Subject is being updated to include more tests in hematology panel. This change will not increase the amount of blood drawn from the subject.	To collect and analyze Complete Blood Count (CBC), PT and INR along with hemoglobin and hematocrit
Not applicable	Minor editorial changes for consistency.	

2 SUMMARY OF CHANGES IN PROTOCOL VERSION 2.0

Affected Section	Summary of Revisions Made	Rationale
2.1; 9.1	Interim data analysis changed to primary endpoint, and primary endpoint analysis changed to secondary endpoint	To properly power this study, calculations are based on previous experience regarding the effects of LPCN 1144 on MRI-PDFF hepatic fat fraction
2.1; 5.1; 8.1.3	Subjects will be randomized in a 1:1:1 ratio	For equal weightage between active and placebo groups
2.3; 8.1	Schedule of activities updated, including changes for DRE, serology, hormone markers, and cortisol.	Clarification, consistency, patient safety monitoring, and reducing the testing frequency
2.1; 3.1	Allowable timeframe for TZD/glitazones stable dose was decreased from 6 to 3 months.	To evaluate the effect
3.2	Clarified the exclusion criteria for serum AST and ALT are 200 IU/L. Further, both AST or ALT values should not exceed 200 IU/L and the second reading should not be >1.5x from the first screening value.	Per FDA's recommendation
3.2	Clarified both total bilirubin screening values should not exceed the upper limit of normal, and the second screening value should not be >1.5x from the first screening value.	Per FDA's recommendation
2.1; 3.2; 8.1; 8.3.7	Insulin, allergy shots, and vaccines are allowable injectable drugs; clarification on sliding scale insulin was added.	Clarification
7.3	Dose reduction, and stopping parameters for creatinine, blood pressure, and testosterone were added and clarified.	Per FDA's recommendation
8.1.4	Changes in baseline dose of blood pressure medications or introduction of new blood pressure medications will be captured at each visit.	Per FDA's recommendation
8.2	The role of the Data Safety Monitoring Board was more broadly defined.	Allow the external charter to describe its role more specifically
9.4.5	Subgroup analyses of the blood pressure data for subjects with/without diabetes or diagnosis of hypertension were added.	Per FDA's recommendation
11	Various appendices and questionnaires added	Clarification, data collection
Not applicable	Minor editorial changes for consistency.	

3 PROTOCOL SYNOPSIS

3.1 Synopsis

Title:	A Phase 2, Randomized Double-Blind, Placebo-Controlled, Multi-Center Study to Assess the Efficacy, Safety and Tolerability of Oral LPCN 1144 in Subjects with Nonalcoholic Steatohepatitis (NASH)
Study Description:	The study is a Phase 2, multicenter, double-blinded, placebo-controlled study.
Phase:	2
Sites	The study site will be multi-center study. Approximately 10 – 30 sites.
Objectives:	Primary Objective: To evaluate the change in hepatic fat fraction from Baseline to Week 12 based on magnetic resonance imaging-proton density fat fraction (MRI-PDFF) measurements in LPCN 1144 treated subjects. Additional Analysis: To evaluate whether 36 weeks of treatment with LPCN 1144 (Oral Testosterone (T)) lowers nonalcoholic steatohepatitis (NASH) activity as determined from hepatic histology in adult men with NASH. Secondary Objectives: To evaluate the change in hepatic fat fraction from baseline to Week 36 based on MRI-PDFF measurements in LPCN 1144 treated subjects. To assess tolerability of oral LPCN 1144 in the study population.
Eligibility	Inclusion Criteria: 1. Male between 18 and 80 years of age, inclusive 2. Subjects with histologic evidence of NASH upon central read of a liver biopsy, defined by a. Stage 1 fibrosis (according to the NASH CRN staging system) with a NAFLD activity score (NAS) greater than or equal to 4 with at least 1 point each in inflammation and ballooning, or b. Advanced fibrosis (Stage 2 or 3 according to the NASH CRN staging system) with at least 1 point for inflammation in the NAS i. A historical biopsy no more than 4 months before Screening may be considered for use with medical monitor approval if the following criteria are met: 1. Stable weights between the time of the biopsy and Screening. Stable weight is defined as no more than a 5% change. 2. Is either not taking or is on stable doses of TZDs/glitazones for 3 months before Day 1. ii. Subjects without a historical biopsy may undergo liver biopsy during Screening if at least one screening AST value is ≥ 22 U/L and at least one screening ALT value is ≥ 30 U/L. Approval to proceed with biopsy when values of AST and/or ALT are below these levels will require review and approval by the medical monitor. 3. Background therapy for other ongoing chronic conditions, and weight should be stable for at least 3 months before trial enrollment. Stable weight is defined as no more than a 5% change. 4. Subjects must satisfy one of the following to meet these criteria: a. A previous historical diagnosis of hypogonadism i. If a subject is on androgen replacement therapy, then the subject must proceed with an appropriate washout (12 weeks following long acting intramuscular androgen injections; 4 weeks following topical or buccal androgens; 3 weeks following oral androgens)

prior to collection of baseline serum T sample.
ii. If naïve to androgen replacement, there is no need for washout.
b. If a subject does not have a previous hypogonadism diagnosis, a single screening of testosterone level < 400 ng/dL will be used as an eligibility criterion, and subject will be allowed to proceed to the next step of screening process.

5. Naïve to vitamin E or has discontinued current treatment of vitamin E > 100 IU/Day and completed adequate washout (at least four weeks) of prior vitamin E therapy (Including vitamin E contained in multivitamins).
6. Judged to be in good general health as determined by the investigator at screening.

Exclusion Criteria:

1. Significant alcohol consumption more than 30 g/day on average, either currently (as determined by the AUDIT and Skinner alcohol questionnaire) or for a period of more than 3 consecutive months in the 5 years prior to screening.
2. Inability to reliably quantify alcohol intake.
3. Biochemical, clinical or histologic evidence of cirrhosis on liver biopsy (stage 4 fibrosis).
4. Evidence of other causes of chronic liver disease determined by medical history, including alcoholic liver disease, viral hepatitis, primary biliary cirrhosis, primary sclerosing cholangitis, autoimmune hepatitis, Wilson's disease, hemochromatosis, alpha-1 antitrypsin deficiency, human immunodeficiency virus, etc.
5. Suspected or proven liver cancer.
6. Clinically significant abnormal laboratory value, in serum chemistry, hematology, or urinalysis including but not limited to:
   - Hematocrit > ULN
   - Hemoglobin > ULN
   - PSA > 4 ng/mL
   - Serum AST or ALT > 200 IU/L
   - Serum ALP > 2 x ULN
   - Serum creatinine of 2.0 mg/dL or greater
   - Total Bilirubin > ULN
   - International normalized ratio (INR) ≥ 1.3.
   - Prolactin > ULN

   Also:
   - Clinically significant abnormal prostate digital rectal examination (DRE) in the opinion of the PI
   - International Prostate Symptom Score > 19 points
   - History of stroke or myocardial infarction within the past 5 years
   - Screening systolic BP or diastolic BP above 140 mmHg or 90 mmHg, respectively

   If screening value is considered spurious by the investigator, the test may be repeated.
7. Subjects with evidence of worsening liver function (ALP and GGT second Screening assessment value greater than the ULN and 1.5x greater than the first Screening assessment value. Both AST or ALT screening values must not exceed 200 IU/L and the second screening value must not be > 1.5x from the first screening value. Both TB screening values must not exceed ULN and the second screening value must not be > 1.5x from the first screening value. A second assessment will be performed no less than 14 days after the first assessment) based on the two initial laboratory values used to establish the screening / baseline values. If baseline value is suspected to be considered spurious, the test may be.
8. Model for End-Stage Liver Disease (MELD) score greater than 12.
9. Subjects with a documented history of Gilbert's syndrome.

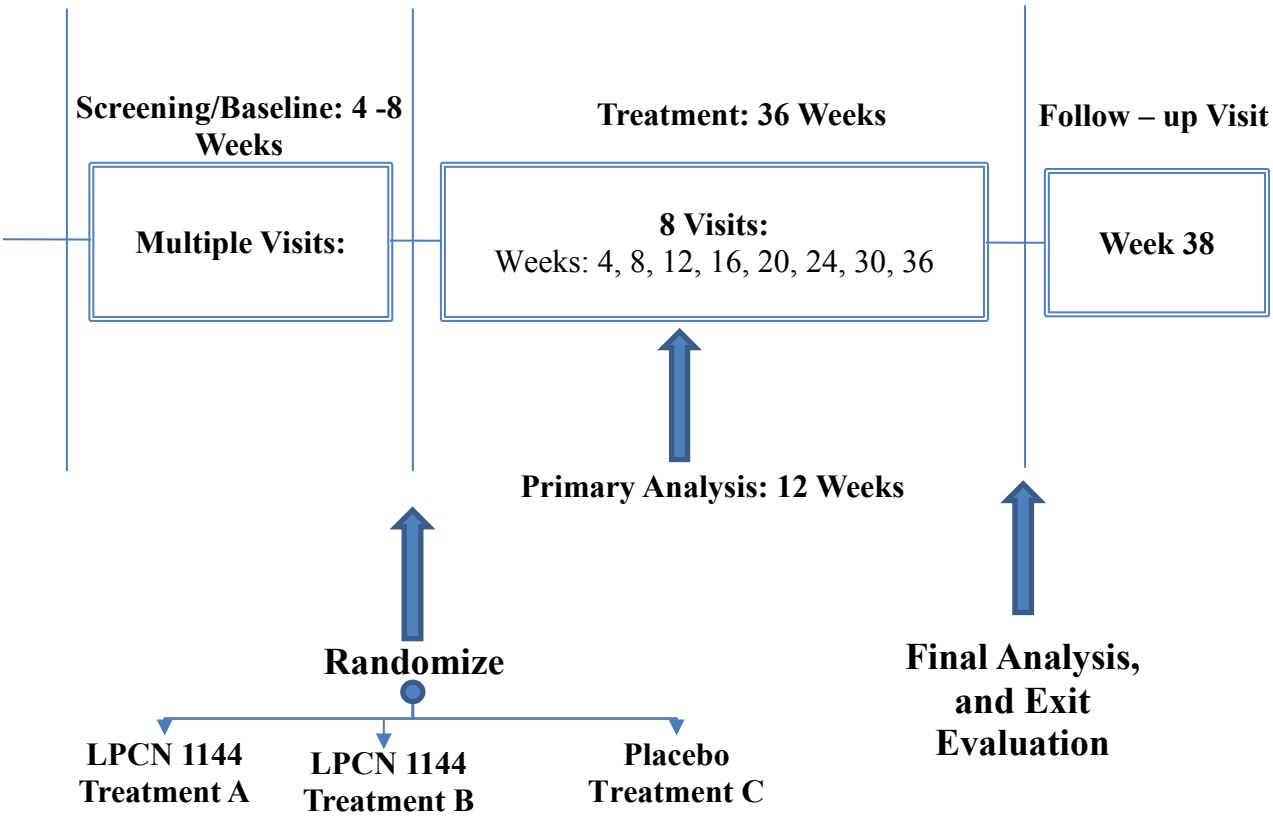
	10. Evidence of portal hypertension (e.g., lower than normal platelet counts, esophageal varices, ascites, history of hepatic encephalopathy, splenomegaly). 11. Use of drugs historically associated with NAFLD (amiodarone, methotrexate, systemic glucocorticoids, tetracyclines, tamoxifen, estrogens, anabolic steroids, valproic acid, other known hepatotoxins) for more than 2 weeks in the 2 years prior to randomization. 12. Subjects who are on a non – stable dose of lipid-lowering drugs, diabetic and / or hypertensive medication in the 3 months prior to biopsy or the 3 months prior to randomization and through the end of the study. 13. Any over-the-counter medication or herbal remedy that is being taken with an intent to improve hyperlipidemia must be stable for at least 3 months prior to randomization and through the end of the study. 14. Vitamin E supplementation of greater than 100 IU/day, unless completed adequate washout for at least 4 weeks prior to Day 1 or biopsy if one is required. 15. Inability to safely obtain a liver biopsy. 16. History of total parenteral nutrition in the year prior to screening. 17. History of bariatric surgery or currently undergoing evaluation for bariatric surgery. 18. History of gastric surgery, , vagotomy, bowel resection or any surgical procedure that might interfere with gastrointestinal motility, pH or absorption. 19. History of biliary diversion. 20. Known positivity for antibody to Human Immunodeficiency Virus (HIV). 21. Known heart failure of New York Heart Association class 3, or 4. 22. Active, serious medical disease with likely life-expectancy less than 5 years. 23. History of current or suspected prostate or breast cancer. 24. History of diagnosed, severe, untreated, obstructive sleep apnea. 25. Active substance abuse, such as alcohol or inhaled or injection drugs, in the year prior to screening. Insulin, allergy shots, and vaccines are allowed. 26. History of significant sensitivity or allergy to any androgens, including testosterone, or product excipients. 27. History of seizures or convulsions, including alcohol or drug withdrawal seizures. Childhood febrile seizures are not exclusionary. 28. Use of known strong 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. 29. Subjects who are currently receiving any androgens (testosterone or other androgens or androgen supplements). 30. Use of any investigational drug within 5 half-lives of the last dose or in the past 6 months prior to Study Day –2 without medical monitor and/or Sponsor approval 31. Receipt of any drug by injection within 30 days or 10 half-lives (whichever is longer) prior to study drug administration without Medical Monitor and/or Sponsor approval. Insulin, allergy shots, and vaccines are allowed. 32. Subject who is not willing to use adequate contraception for the duration of the study. 33. Any other condition, which in the opinion of the investigator would impede compliance or hinder completion of the study. 34. Failure to give informed consent.
Endpoints:	**Primary Outcome Measure:** Change in hepatic fat fraction based on MRI-PDFF measurements in LPCN 1144 treated subjects after 12 weeks of treatment. **Key Secondary Outcome Measures:** • Change in NASH activity evaluated via a standardized scoring of liver biopsies at baseline and after 36 weeks of treatment in LPCN 1144 treated subjects.

	• Change in fibrosis evaluated via NASH CRN fibrosis score of liver biopsies at baseline and after 36 weeks of treatment in LPCN 1144 treated subjects. **Other Secondary Outcome Measures:** • Relative change in hepatic fat fraction based on MRI-PDFF measurements in LPCN 1144 treated subjects after 12 weeks of treatment. • Change in hepatic fat fraction based on MRI-PDFF measurements in LPCN 1144 treated subjects after 36 weeks of treatment. • Relative change in hepatic fat fraction based on MRI-PDFF measurements in LPCN 1144 treated subjects after 36 weeks of treatment. • NAFLD resolution of subjects who at baseline is at least 5% with a decrease to less than 5% at end of study. • Resolution of NASH on overall histopathological reading. Resolution of NASH is defined as NAS score of 0–1 for inflammation, 0 for ballooning, and any value for steatosis. • Change in individual NAS component scores (inflammation, ballooning, steatosis) in LPCN 1144 treated subjects after 36 weeks of treatment. • Resolution of NASH on overall histopathological reading and no worsening of liver fibrosis on NASH CRN fibrosis score. • Improvement in liver fibrosis greater than or equal to one stage (NASH CRN fibrosis score). • Change in anthropometric measurements (weight, body mass index (BMI), waist to hip ratio, waist circumference, triceps skin fold thickness, upper arm circumference,) in LPCN 1144 treated subjects. • Change in insulin resistance (assessed by Homeostasis Model Assessment (HOMA)) in LPCN 1144 treated subjects. • Changes in liver enzymes aspartate transaminase (AST), (alanine transaminase (ALT), alkaline phosphatase (ALP), gamma-glutamyltransferase (GGT), Total Bilirubin (TB) and Creatine Kinase (CK) in LPCN 1144 treated subjects compare to placebo. • Changes in non-invasive markers of fibrosis and steatosis including cytokines, leptin, fibrosis markers, and lipid profile in LPCN 1144 treated subjects compare to placebo. • Changes in lipid parameters (triglycerides, very low-density lipoprotein cholesterol (VLDL-C), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and free fatty acids) in LPCN 1144 treated subjects compare to placebo. • Changes in Functional Activity (**Appendix E**), Health-Related Quality of Life (HR-QOL) as measured by Short Form-36 (**Appendix G**), Patient Global Impression of Severity (PGI-S; **Appendix H**), Patient Global Impression of Change Scale (PGI-C; **Appendix I**) Chronic Liver Disease Questionnaire (CLDQ) (**Appendix J**), and Sexual desire and distress (**Appendix K**) questionnaire, in LPCN 1144 treated subjects. • Changes in safety laboratory parameters (clinical chemistry, hematology and urinalysis) in LPCN 1144 treated subjects compare to placebo.
Scoring of Liver Biopsies for Enrollment and Data Analysis	The tissue will be examined by light microscopy and scored based upon the NASH Clinical Research Network (CRN) Nonalcoholic Fatty Liver Disease (NAFLD)/NASH scoring system. Baseline and follow-up liver biopsies will be scored by central review of the slides. The scores obtained centrally will be used for study eligibility and data analysis.
Sample Size	Approximately 75 subjects, 1:1:1 active to placebo.
Description of 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 daily dose of 450 mg TU. Two different formulations of LPCN 1144 will be evaluated, along with placebo.
Treatment Arms	Subjects will be randomized in a 1:1:1 ratio to the following study treatments: • Treatment A: Oral LPCN 1144 total daily dose of 450 mg TU administered as BID.

	• Treatment B: Oral LPCN 1144 d-alpha tocopherol formulation, total daily dose of 450 mg TU administered as BID. • Treatment C: Oral placebo administered as BID.
Study Duration:	36 weeks of study treatment plus two weeks for follow up visit.
Study Description	Each participant will be in the study for a duration of 36 weeks, not including screening and follow up period. Screening Visits: Subjects will undergo a washout prior to screening period, if necessary. Screening periods to complete the pre-study examinations to evaluate study eligibility (See Schedule of Activities (SOA)). During Screening Visit, hepatic fat fraction will be measured by MRI-PDFF, and NASH will be confirmed by liver biopsy. At the Randomization Visit, subjects will be assigned to a treatment arm, and they will complete any outstanding study procedures. Visits at Weeks 4, 8, 12, 16, 20, 24, 30, 36 and 38 will be performed to evaluate safety clinical laboratory tests, adverse events, and overall subject health. Primary Analysis will be performed after the Week 12 visit to evaluate treatment effect. The change in hepatic fat fraction from Baseline (Screening Visit) to Week 12 will be measured by MRI-PDFF. At Week 36, End of Treatment (EOT) and exit procedures will be performed including the NASH activity, defined from change in standardized scoring of liver biopsies at baseline and after 36 weeks of treatment will be assessed. At Week 38, Follow-up procedure will include review of adverse events, PGI-S (**Appendix H**), PGI-C (**Appendix I**) questionnaires, Urinalysis and blood samples for clinical laboratory tests including testosterone assay, hormones and related markers (see SOA).
Monitoring for Prostate, Cardiovascular, and Renal Stopping Criteria	Subjects will be monitored for hematocrit, hemoglobin, 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 section 8.3.
Reduced Dose	Subjects will be monitored for liver enzymes, hemoglobin, hematocrit, blood pressure, 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 (study drug one capsule once daily). If subjects continue to exceed target, subject will proceed to exit procedures.

3.2 Scheme

Trial Design



3.3 Schedule of Activities (SOA)

Assessment / Procedure	Optional Washout	Screening Visits Day -56 to -1 / Baseline		On Treatment								Follow-up Visit
	Testosterone/ Androgen / Vitamin E > 100 IU/day Washout -12 to -3 weeks prior to Screening	Screening assessments are completed over multiple visits	Day 1	Week 4 (Day 28±7)	Week 8 (Day 56±7)	Week 12 (Day 84±7)	Week 16 (Day 112±7)	Week 20 (Day 140±7)	Week 24 (Day 168±7)	Week 30 (Day 210±7)	Week 36 (Day 252±7) EOT	Week 38 (Day 266±7)
Informed consent	X [1]	X										
Medical history	X	X	X									
Review of concomitant medication	X	X	X	X	X	X	X	X	X	X	X	
Anthropomorphic measurements [2]		X				X					X	
Review of adverse events		X	X	X	X	X	X	X	X	X	X	X
Physical examination (D: detailed / A: abbreviated) [3]		D	A	A	A	D*	A	A	A	A	D	
Imaging – Fibroscan [4]		X				X			X		X	
Review of historical biopsy [5]		X										
Imaging – MRI-PDFF [6]		X				X					X	
Biopsy[7]		X									X	
Imaging – DXA [8]		X						X			X	
Enrollment / Randomization			X									
Drug dispensing [17]			X	X		X		X		X		
Drug accountability / adherence check				X	X	X	X	X	X	X	X	
Questionnaires												
Alcohol questionnaire AUDIT and Skinner		X										
Alcohol questionnaire AUDIT-C						X						
Functional Activity		X									X	
I-PSS		X				X					X	
HR-QOL (SF-36)		X									X	

Assessment / Procedure	Optional Washout	Screening Visits Day -56 to -1 / Baseline		On Treatment								Follow-up Visit
	Testosterone/ Androgen / Vitamin E > 100 IU/day Washout -12 to -3 weeks prior to Screening	Screening assessments are completed over multiple visits	Day 1	Week 4 (Day 28±7)	Week 8 (Day 56±7)	Week 12 (Day 84±7)	Week 16 (Day 112±7)	Week 20 (Day 140±7)	Week 24 (Day 168±7)	Week 30 (Day 210±7)	Week 36 (Day 252±7) EOT	Week 38 (Day 266±7)
PGI-S		X		X	X	X	X	X	X	X	X	
PGI-C						X					X	X
CLDQ		X									X	
Sexual Desire and Distress		X		X	X	X	X	X	X	X	X	
Clinical Laboratory Tests [15]												
Urinalysis [18]		X	X	X	X	X	X	X	X	X	X	X
Serology		X										
C-Reactive Protein, Fasting glucose and insulin			X			X					X	
Lipid profile [9]			X	X	X	X	X	X	X	X	X	X
Hematology panel [10]		X	X	X	X	X	X	X	X	X	X	X
HbA1c		X				X					X	
Metabolic and renal function panel [11]		X	X	X	X	X	X	X	X	X	X	X
Hepatic panel [12]		X	X	X	X	X	X	X	X	X	X	X
Biomarkers [13]			X								X	
Testosterone assay (Total and calculated free T, SHBG)		X [14]	X	X	X	X	X	X	X	X	X	X
Hormones and related markers (DHT, LH, FSH, TSH, SHBG)			X	X	X	X	X	X	X	X	X	X
PSA, prolactin		X		X	X	X	X	X	X	X	X	X
Cortisol and cortisol binding globulin (CBG)[19]		X		X	X	X	X	X	X	X	X	
Drug and alcohol screen		X		X		X			X			

Assessment / Procedure	Optional Washout	Screening Visits Day -56 to -1 / Baseline		On Treatment								Follow-up Visit
	Testosterone/ Androgen / Vitamin E > 100 IU/day Washout -12 to -3 weeks prior to Screening	Screening assessments are completed over multiple visits	Day 1	Week 4 (Day 28±7)	Week 8 (Day 56±7)	Week 12 (Day 84±7)	Week 16 (Day 112±7)	Week 20 (Day 140±7)	Week 24 (Day 168±7)	Week 30 (Day 210±7)	Week 36 (Day 252±7) EOT	Week 38 (Day 266±7)
Serum and plasma for banking			X			X					X	
Gait Speed and Hand Grip [16]		X									X	
Study exit evaluation											X	

DHT = dihydrotestosterone; LH = Luteinizing Hormone; FSH = Follicle Stimulating Hormone; PSA = Prostate Specific Antigen; TSH = Thyroid Stimulating Hormone; SHBG = Sex Hormone Binding Globulin

1. For subjects requiring washout
2. Anthropomorphic measurements: include weight, body mass index (BMI), waist to hip ratio, waist circumference, triceps skin fold thickness, upper arm circumference.
3. Detailed (D) physical defined in section 9.3.8. Abbreviated (A) physical defined section 9.3.8 *Week 12 will have a detailed physical examination without a DRE.
4. Fibroscan will be done on all subjects but only required for eligibility on subject without a historical biopsy within 4 months from Screening.
5. Review of Historical Biopsy: Historical biopsy must be done within 4 months of Screening and reviewed by a central reader.
6. MRI-PDFF should be performed prior to randomization but not need to be performed prior to biopsy.
7. Biopsy: Subjects without a biopsy within 4 months of Screening may have a biopsy during Screening if at least one screening AST value is ≥ 22 U/L and at least one screening ALT value is ≥ 30 U/L. Approval to proceed with biopsy when values of AST and/or ALT are below these levels will require review and approval by the medical monitor.
    a. Subject must meet all other eligibility criteria including qualifying testosterone and retest of hepatic panel prior to performing biopsy.
8. Subject should meet all inclusion criteria including eligible biopsy as assessed by the central reader and qualifying testosterone levels prior to performing DXA scan.
9. Lipid profile: total cholesterol, triglyceride, fatty acids, VLDL-C, LDL-C, HDL-C.
10. Hematology Panel: complete blood count (CBC) including hemoglobin and hematocrit, prothrombin time (PT), international normalized ratio (INR).

11. Metabolic and renal function panel: sodium, potassium, chloride, bicarbonate, calcium, phosphate, BUN, creatinine, uric acid, albumin, total protein, estimated glomerular filtration rate (GFR).
12. Hepatic panel: total bilirubin (TB), direct bilirubin, ALT, AST, ALP, GGT, Bile acid and creatine kinase (CK).
    a. The Hepatic panel is assessed at two separate Screening assessments to determine if a subject's liver enzymes are stable. Last Screening assessment value will be used as baseline value.
    b. A second Screening assessment of ALT, AST, TB, and ALP will be performed no less than 14 days after the first Screening assessment. Values must meet criteria defined in Exclusion criteria 6.
13. Biomarkers: Heat-Shock Protein 47 fibroblast marker (HSP47 fibroblast marker), Alpha-Smooth Muscle Actin (Alpha SMA), 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-Beta (TGF-Beta), Tissue Necrosis Factor-alpha (TNF-alpha).
14. Testosterone Screening Assessments: Only for subjects not previously diagnosed with hypogonadism
    a. Individuals without a diagnosis of hypogonadism are eligible for inclusion in the study with a single screening testosterone level < 400 ng/dL.
    b. Subject should have prior diagnosis of hypogonadism or confirmed inclusionary testosterone levels prior to completing MRI-PDFF, liver biopsy, and DXA.
15. If baseline value is considered spurious, the test may be repeated.
16. Gait speed and hand grip may be assessed for some subjects at select sites.
17. Drug dispensing as necessary.
18. Urinalysis consists of general routine tests – Color, appearance, specific gravity, pH, protein, blood, ketones, urobilinogen, glucose, bilirubin, leukocyte esterase, nitrite.
19. Morning levels (7-9 AM) of Cortisol and CBG will only be performed at Screening, Week 12 and Week 36. There is no time restriction for all other cortisol and CBG labs.

4 STUDY POPULATION

4.1 Inclusion Criteria

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

1. Male between 18 and 80 years of age, inclusive
2. Subjects with histologic evidence of NASH upon central read of a liver biopsy, defined by
    a. Stage 1 fibrosis (according to the NASH CRN staging system) with a NAFLD activity score (NAS) greater than or equal to 4 with at least 1 point each in inflammation and ballooning, or
    b. Advanced fibrosis (Stage 2 or 3 according to the NASH CRN staging system) with at least 1 point for inflammation in the NAS.
        i. A historical biopsy no more than 4 months before Screening may be considered for use with medical monitor approval if the following criteria are met:
            1. Stable weights between the time of the biopsy and Screening. Stable weight is defined as no more than a 5% change.
            2. Is either not taking or is on stable doses of TZDs/glitazones for 3 months before Day 1.
        ii. Subjects without a historical biopsy may undergo liver biopsy during Screening if at least one screening AST value is ≥ 22 U/L and at least one screening ALT value is ≥ 30 U/L. Approval to proceed with biopsy when values of AST and/or ALT are below these levels will require review and approval by the medical monitor.
3. Background therapy for other ongoing chronic conditions, and weight should be stable for at least 3 months before trial enrollment. Stable weight is defined as no more than a 5% change.
4. Subjects must satisfy one of the following criteria:
    a. A previous historical diagnosis of hypogonadism
        i. If androgen replacement therapy, the subject must proceed with an appropriate washout (12 weeks following long acting intramuscular androgen injections; 4 weeks following topical or buccal androgens; 3 weeks following oral androgens) prior to collection of baseline serum T sample.
        ii. If naïve to androgen replacement, there is no need for washout.
    b. If a subject does not have a previous hypogonadism diagnosis, a single screening of testosterone level < 400 ng/dL will be used as an eligibility criterion and subject will be allowed to proceed to the next step of screening process.
5. Naïve to vitamin E or has discontinued current treatment of vitamin E > 100 IU/Day and completed adequate washout (at least four weeks) of prior vitamin E therapy
6. Judged to be in good general health as determined by the investigator at screening.

4.2 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 (PI) and the Sponsor:

1. Significant alcohol consumption more than 30 g/day on average, either currently (as determined by the AUDIT and Skinner alcohol questionnaire) or for a period of more than 3 consecutive months in the 5 years prior to screening
2. Inability to reliably quantify alcohol intake.
3. Biochemical, clinical or histologic evidence of cirrhosis on liver biopsy (stage 4 fibrosis).

4. Evidence of other causes of chronic liver disease determined by medical history, including alcoholic liver disease, viral hepatitis, primary biliary cirrhosis, primary sclerosing cholangitis, autoimmune hepatitis, Wilson's disease, hemochromatosis, alpha-1 antitrypsin deficiency, human immunodeficiency virus, etc.
5. Suspected or proven liver cancer.
6. Clinically significant abnormal laboratory value, in serum chemistry, hematology, or urinalysis including but not limited to:
    - Hematocrit > ULN
    - Hemoglobin > ULN
    - PSA > 4 ng/mL
    - Serum AST or ALT > 200 IU/L
    - Serum ALP > 2 x ULN
    - Serum creatinine of 2.0 mg/dL or greater
    - Total Bilirubin > ULN
    - International normalized ratio (INR) ≥ 1.3.
    - Prolactin > ULN

Also

- Clinically significant abnormal prostate digital rectal examination (DRE) in the opinion of the PI
- International Prostate Symptom Score > 19 points
- History of stroke or myocardial infarction within the past 5 years
- Screening systolic BP or diastolic BP above 140 mmHg or 90 mmHg, respectively

If screening value is considered spurious, the test may be repeated.

7. Subjects with evidence of worsening liver function (ALP and GGT second Screening assessment value greater than the ULN and 1.5x greater than the first Screening assessment value. The first and second screening values for AST or ALT must not exceed 200 IU/L. The first and second screening for TB must not exceed the ULN. The second screening for AST, ALT and TB must not be > 1.5x the first screening value. A second assessment will be performed no less than 14 days after the first assessment) based on the two initial laboratory values used to establish the screening / baseline values. If baseline value is suspected to be considered spurious, the test may be repeated.
8. Model for End-Stage Liver Disease (MELD) score greater 12.
9. Subjects with a documented history of Gilbert's syndrome.
10. Evidence of portal hypertension (e.g., lower than normal platelet counts, esophageal varices, ascites, history of hepatic encephalopathy, splenomegaly).
11. 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 randomization.
12. Subjects who are on a non – stable dose of lipid-lowering drugs, diabetic and / or hypertensive medication in the 3 months prior to biopsy or the 3 months prior to randomization and through the end of the study.
13. Any over-the-counter medication or herbal remedy that is being taken with an intent to improve hyperlipidemia must be stable for at least 3 months prior to randomization and through the end of the study.
14. Vitamin E supplementation of greater than 100 IU/day, unless completed adequate washout for at least 4 weeks prior to Day 1 or biopsy if one is required.
15. Inability to safely obtain a liver biopsy.
16. History of total parenteral nutrition in the year prior to screening.

17. History of bariatric surgery or currently undergoing evaluation for bariatric surgery.
18. History of gastric surgery, , vagotomy, bowel resection or any surgical procedure that might interfere with gastrointestinal motility, pH or absorption.
19. History of biliary diversion.
20. Known positivity for antibody to Human Immunodeficiency Virus (HIV).
21. Known heart failure of New York Heart Association class 3, or 4.
22. Active, serious medical disease with likely life-expectancy less than 5 years.
23. History of current or suspected prostate or breast cancer.
24. History of diagnosed, severe, untreated, obstructive sleep apnea.
25. Active substance abuse, such as alcohol or inhaled or injection drugs, in the year prior to screening. Insulin, allergy shots, and vaccines are allowed.
26. History of significant sensitivity or allergy to any androgens, including testosterone, or product excipients.
27. History of seizures or convulsions, including alcohol or drug withdrawal seizures.
28. Use of known strong 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.
29. Subjects who are currently receiving any androgens (testosterone or other androgens or androgen supplements).
30. Use of any investigational drug within 5 half-lives of the last dose or in the past 6 months prior to Study Day –2 without medical monitor and/or Sponsor approval
31. Receipt of any drug by injection within 30 days or 10 half-lives (whichever is longer) prior to study drug administration without MM and/or Sponsor approval. Insulin, allergy shots, and vaccines are allowed.
32. Subject who is not willing to use adequate contraception for the duration of the study.
33. Any other condition, which in the opinion of the investigator would impede compliance or hinder completion of the study.
34. Failure to give informed consent.

4.3 Lifestyle Considerations

Some NASH subjects are treated with vitamin E or glitazone. Because enrollment of such subjects in clinical trials may confound treatment effects, subjects must either discontinue glitazone or be on stable doses for 3 months before enrollment. As one of the treatment arms is vitamin E formulation, subjects treated with vitamin E must washout prior to randomization (at least four weeks).

Subjects should maintain their normal level of physical activity, diet, and lifestyle throughout the entire study (i.e., will not begin a new exercise program or participate in any unusually strenuous physical exertion).

Subjects will be allowed to continue on prescription antihyperlipidemic agents. Subjects will be interviewed in a detailed fashion at screening, randomization, and at every clinic visit to document the absence or stable doses of such use. If using a statin or fibrate medication, the subject must have been on a stable dose in the 3 months prior to liver biopsy and must have been on a stable dose in the 3 months prior to randomization.

4.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently randomly assigned to the study intervention or entered in the study. A minimal set of

screen failure information will be collected to ensure transparent reporting of screen failure participants and to respond to queries from regulatory authorities. Minimal information includes data for any procedure conducted until the point of screen failure (excluding questionnaires unless the questionnaire data leads to the screen failure), including but not limited to demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

Individuals who do not meet the criteria for participation in this trial (screen failure) because of some of the clinical lab values may be allowed to re-screen, subject to Medical Monitor/Sponsor approval. Rescreened participants will be assigned a new participant number.

5 INTRODUCTION

5.1 Study Rationale

5.1.1 Nonalcoholic Fatty Liver Disease (NAFLD) and Nonalcoholic Steatohepatitis (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.[i,ii] Recent studies estimate that between 30 and 40% of the population in the US, 80-100 million Americans, is affected by NAFLD.[iii,iv,v] 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).[vi,vii] There are no FDA approved drugs for NASH.

5.1.2 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.[i] 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.[viii] NAFL and NASH have traditionally been considered two separate clinical entities, rather than two points on a disease continuum.[ix] Recent studies evaluating sequential liver biopsies are challenging this notion.[x,xi,xii] 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.[xiii] 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. [xiii] 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%, $p = 0.65$).[xi] 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.[xiv]

In the western world, NAFLD is most commonly associated with obesity, metabolic syndrome and diabetes.[xv] 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. [xv] Metabolic syndrome, diabetes and advanced age have all been shown to increase the risk of liver disease progression in NAFLD patients.[xvi,xvii]

It is estimated that NASH occurs in 20% of patients with NAFLD (3–12% of the US population).[xviii,xix] Approximately 30–40% of patients with NASH will develop fibrosis.[xx,xxi,xxii,xiii] Although fibrosis regresses in some patients,[xxiii,viii,xxiv] others progress to advanced fibrosis or cirrhosis. [viii,xxv] In fact, NASH is the third leading cause of cirrhosis in the US, and the third most common indication for liver transplant.[xxvi,xxvii] In addition to cirrhosis, and the complications that accompany it, NASH places patients at risk for hepatocellular carcinoma (HCC).[xxviii]

5.1.3 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.

5.1.4 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 as a preliminary proof of concept study evaluating efficacy and tolerability of oral LPCN 1144 in the NASH subject population.

Scientific Rationale for Study Design

Currently, there is no proven pharmacotherapy available for the treatment of NASH. In the current study, the Sponsor intends to test if T benefits subjects with NASH. The efficacy of LPCN 1144 will be compared to placebo. As there is no proven pharmacologic therapy for NASH, using a placebo for comparative purposes is justified.

Given the study is a Phase 2 proof of concept study, the outcome measures will be evaluated for comparison purpose and where applicable a superiority test will be conducted.

LPCN 1144, also referred to as “Oral T”, is an oral capsule product containing an ester prodrug of T, TU. Testosterone undecanoate 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.[1] 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.

5.1.5 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.[2]

[1] Shackleford DM, Faassen WA, Houwing N, Lass H, Edwards GA, Porter CJ, Charman WN. Contribution of lymphatically transported testosterone undecanoate to the systemic exposure of testosterone after oral administration of two andriol formulations in conscious lymph duct-cannulated dogs. J Pharmacol Exp Ther. 2003 Sep;306(3):925-33. Epub 2003 Jun 13.
[2] Shen M, Shi H. Sex Hormones and Their Receptors Regulate Liver Energy Homeostasis. International Journal of Endocrinology, vol. 2015, Article ID 294278, 12 pages, 2015.

- Androgens are known to provide benefits in terms of:
    - Anti-inflammatory properties.
    - Immune-modulating properties.[3]
- Androgens aid in liver regeneration.[4]
- Glucose homeostasis: increase insulin receptor, reduce insulin resistance/increase insulin sensitivity;[5] 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:

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
    - 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.
- 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. Additionally, liver weight was significantly higher in the testosterone enanthate treated group, as early as 24 hours post-hepatectomy.

Proof of Concept Liver Fat Evaluation using MRI-PDFF

Study LPCN 1021-18-001, included an assessment of liver fat via Magnetic Resonance Imaging-Proton Density Fat Fraction (MRI-PDFF) on a cohort of Oral T treated hypogonadal male subjects at baseline (MRI-1), at interim (MRI-2: 2 months), and at end of study (MRI-3: 4 months). The cohort included 36 hypogonadal males, with 34 evaluable subjects who had at least one post-baseline MRI-PDFF visit. Of these subjects, 62% had non-alcoholic fatty liver disease (NAFLD), defined as baseline liver fat of at least 5%. The study showed a 5% and 20% decrease in mean percent liver fat from baseline to MRI-2 and to MRI-3 respectively in all subjects, 14% and 33% decrease in mean percent liver fat in subjects with MRI-PDFF measurement of >5% at baseline, and 38% and 40% decrease in mean percent liver fat in subjects with MRI-PDFF measurements of >10% at baseline.

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).

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3 Malkin CJ, Pugh PJ, Jones RD, Kapoor D, Channer KS, Jones H, The Effect of Testosterone Replacement on Endogenous Inflammatory Cytokines and Lipid Profiles in Hypogonadal Men. JCEM, Vol. 89 (7), July, 2004, p 3313 – 3318.
[4] Vic P, Saint-Aubert, Astre C, Bories P, Bonardet A, Descomps B, Humeau C, Joyeux H. Complete Liver Regeneration in One-Stage 90% Hepatectomized Rats Treated with Testosterone. Hepatology; 1982; Vol. 2, No. 2, p. 247.
[5] Tsai EC, Matsumoto AM, Fujimoto WY, Boyko EJ: Association of bioavailable, free, and total testosterone with insulin resistance: influence of sex hormone-binding globulin and body fat. Diabetes Care 2004, 27:861–868.

- 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.
- 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.

5.2 Justification for Dose and Safety for Use in Proposed Population

LPCN 1144 is an easy to administer oral capsule product containing TU with a proprietary formulation comprised of lipids. The product is designed to enable absorption of TU via intestinal lymphatic pathway. Testosterone undecanoate, is a straight chain fatty acid ester of T, which is not alkylated at the 17-alpha position. Testosterone undecanoate is converted to T by non-specific esterases that are abundantly present in the body.

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 administered can be considered as a safe starting dose in NASH subjects.

5.2.1 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.

5.2.2 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.

5.2.3 Clinical Safety

5.2.3.1 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.

5.2.3.2 Prior Experience with LPCN 1144: US Clinical Studies

Sponsor conducted numerous clinical studies with LPCN 1144 (Oral T), a total of 597 individuals were dosed with LPCN 1144 including 525 hypogonadal men across eight clinical studies, 6 healthy adult men in one clinical study, and 66 postmenopausal women across four clinical studies, at doses ranging 75 mg TU to 300 mg TU, with up to 52 weeks exposure.

LPCN 1144 was generally well tolerated, and the safety findings were consistent with those observed with other TRT products. Gastrointestinal adverse events were of low frequency. Most adverse events that occurred were mild or moderate in severity. No severe cardiac or hepatic disorders occurred during any clinical studies and no deaths were reported.

In the 52-week clinical study, 210 subjects received LPCN 1144 treatment at a dose with 300 mg to 600 mg TU daily, and 105 received T gel. In the LPCN 1144 arm, a total of 16 treatment-emergent serious adverse events (SAEs) were reported for 12 LPCN 1144-treated subjects (5.7%) in the clinical study. The SAEs were varied in nature and none were considered by the investigator to be related to study drug.

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.

There were no excess in hypertension-associated adverse events with LPCN 1144 (1.6% and 0.8%, respectively) as compared to the T gel active control (4.8% and 1.9%, respectively).

In summary, the overall safety results demonstrate that LPCN 1144 has an acceptable safety profile.

5.2.3.3 Prior Experience with Testosterone in Men with NASH and Liver Cirrhosis

There is a large body of evidence supporting the role of T in NAFLD / NASH / liver cirrhosis. Prior clinical studies as discussed have evaluated role of administering T in both hypogonadal and eugonadal men with liver cirrhosis, and / or liver injury, as discussed in section 4.2.

5.3 Inclusion of D-alpha-Tocopherol Acetate in LPCN 1144 Formulation

Vitamin E (d-alpha tocopherol acetate) is included in one of the LPCN 1144 formulations. In previous nonalcoholic steatohepatitis (NASH) trials, d-alpha tocopherol has been evaluated as a potential treatment. Sanyal et al. showed that d-alpha tocopherol therapy (800 mg IU per day), as compared with placebo, was associated with a significantly higher rate of improvement in NASH (43% vs. 19%, p=0.001).[xxix] Therefore, d-alpha-tocopherol acetate (at a dose of 800 mg IU day) was included in one of the LPCN 1144 formulations in proof of concept LPCN 1144-18-002 Study to evaluate if a higher rate of improvement in NASH is observed when LPCN 1144 (Oral T) is used in combination with d-alpha tocopherol. The amount of d-alpha tocopherol included in the LPCN 1144 formulation is the same amount evaluated by Sanyal et al. At 800 IU daily dose, d-alpha tocopherol has shown no significant toxicity in adults.[xxx,xxxi]

6 STUDY DESIGN

6.1 Overall Design

This is a proof of concept, Phase 2, randomized, double-blind, placebo controlled, three arm study in adult men with biopsy confirmed NASH. The study will be conducted across multiple centers in the United States.

Approximately 75 subjects will be randomized in 1:1:1 ratio to receive one of the following treatments:

- Treatment A: Oral LPCN 1144 total daily dose of 450 mg TU administered as BID
- Treatment B: Oral LPCN 1144 d-alpha tocopherol formulation, total daily dose of 450 mg TU administered as BID
- Treatment C: Oral matching placebo administered as BID

Subjects will undergo a screening period to determine study eligibility. As a part of screening, liver biopsies will be performed for subjects who have not had a liver biopsy within 4 months of Screening Visit 1. Adult male subjects with histologic evidence of NASH will be enrolled into the study. Baseline fat fraction will be measured by MRI-PDFF in all eligible subjects.

Eligible subjects will be randomized to one of the three treatment arms. The treatment phase will be for a duration of 36-weeks (without including screening and follow up periods) with assessments of liver biopsies, hepatic fat fraction, liver enzymes, lipid levels and other safety parameters. Safety and tolerability will be assessed throughout the study. A follow-up visit will be performed to assess adverse events, complete patient reported questionnaires including PGI-C (Appendix I), a urinalysis and to obtain blood samples for clinical laboratory tests including, lipid panel, hematology panel, metabolic and renal function panel, hepatic panel, Testosterone, and hormones and related markers.

7 STUDY INTERVENTION

7.1 Study Intervention(s) Administration

7.1.1 Study Intervention Description

The following study treatments will be administered:

- Treatment A: Oral LPCN 1144 capsule, total daily dose of 450 mg TU administered as BID
- Treatment B: Oral LPCN 1144 capsule, d-alpha tocopherol formulation, total daily dose of 450 mg TU administered as BID
- Treatment C: Oral placebo capsule administered as BID

Subjects may be switched to a reduced dose (LPCN 1144 or placebo) of once daily administration (one capsule, once daily) based on criteria described in section 8.3.

7.1.2 Dosing and Administration

All subjects will be instructed to take Treatment A (225 mg TU per dose), B (225 mg TU per dose), or C (placebo) twice daily, approximately 12 hours apart, approximately 30 minutes after morning and evening meals, with water. If a dose is missed, the subjects should take it as soon as they remember (within 4 hours of missed dose). If 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 meal, with water.

7.2 Preparation/Handling/Storage/Accountability

7.2.1 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 eCRF.

> Treatment compliance is calculated as follows:
> % compliance = [(number of capsules dispensed – number of capsules returned)/ number of capsules expected to be used] * 100

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

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

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

7.2.2 Formulation, Appearance, Packaging, and Labeling

Both LPCN 1144 active treatment arms will be provided as gelatin capsule products that contain 225 mg TU per capsule. The placebo capsules will be matching gelatin capsules.

Each bottle will be labeled appropriately and at minimum will contain, quantity, manufactured by, retest date and a caution that the product is an investigational drug. The containers will not contain the treatment name as the study is blinded. Instead a unique individual bottle identification number will be provided.

7.2.3 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 drugs in the United States and must be handled according to applicable federal and local regulations. The study drugs are for investigational use only and are to be used only within the context of this study. The study drug supplied for this study must be maintained under adequate security and stored under the conditions specified on the label until dispensed for subject use or returned to the Sponsor.

7.3 Measures to Minimize Bias: Randomization and Blinding

7.3.1 Description of Enrollment

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

7.3.2 Randomization and Blinding Procedures

Subjects meeting the enrollment criteria will be randomly assigned to one of the three treatment arms. The randomization will be carried out by central assignment. The study is a blinded study; therefore, all the randomization codes will be centrally maintained and no data from the randomization will be available to Sponsor, contract research organization (CRO) operations team, medical monitors, monitors or any site staff. The treatment assigned to the study subject will not be available to anyone except pre-identified study personnel.

7.3.3 Maintenance of Trial Randomization Codes and Blinding

All randomization codes will be centrally assigned and stored. Each subject will receive a unique treatment ID that does not directly associate with the treatment assigned.

7.3.4 Procedures for Unblinding Treatment Assignment

The study is a double blinded study and treatments will remain masked throughout the study until all data collection has been completed.

Every effort will be made to maintain the blinding throughout the study except in emergency situations. The assignment code for the treatment will not be broken without the knowledge of the PI.

The following conditions describe when unblinding may be allowed:

- Severe allergic reaction: Study medication is stopped indefinitely. The subject, primary care provider (PCP), and the investigator will be unblinded.
- Pregnancy in partner during the study: Study medication will be stopped indefinitely, and the coded medication will be unblinded. The subject, PCP, and investigator will be notified of the assigned treatment and the associated risks in the partner.

In unforeseen situations where the clinical center PI considers unblinding is in the best interest of the participant's health and well-being, unblinding may be done after notifying the Sponsor and/or medical monitor. The DSMB will review all instances of unblinding that occur.

8 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

8.1 Discontinuation of Study Intervention

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:

- Biomarker 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 experience any of the following serious adverse events associated with T use during the trial, then study drug should be discontinued:
    a. Venous thromboembolism
    b. Myocardial infarction
    c. Stroke
    d. Edema with or without congestive heart failure, as a complication in subjects with cardiac, renal and hepatic disease
    e. New onset of any malignancy. Exceptions may be approved by PI, such as basal cell carcinoma of the skin.
    f. 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 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). Subjects who sign the informed consent form and are randomized but do not receive the study intervention may be replaced. Subjects who sign the informed consent form, and are randomized and receive the study intervention, and subsequently withdraw, or are withdrawn or discontinued from the study, will not be replaced.

8.3 Monitoring and Stopping Criteria

Baseline for Safety assessments is the Day 1 pre-dose values or last screening value.

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.

Close Monitoring

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.

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. Creatinine Stopping Criteria

8.3.2 Creatinine Stopping Criteria

Subjects will be monitored for Creatinine throughout the study. Stopping criteria for Creatinine are provided below:

Stopping Criteria

For Creatinine, an increase in Creatinine > 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. PSA Monitoring and Stopping Criteria

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:

Close Monitoring

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, then subject will be switched to a reduced dose (LPCN 1144 or placebo) of once daily administration (one capsule, once daily).

Stopping Criteria

For PSA, an increase in PSA > 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 and Hemoglobin Monitoring and Stopping Criteria

Plasma Volume Depletion

Subjects who develop elevated hematocrit of 52% 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, then schedule weekly hematocrit and hemoglobin tests, with a reassessment of subject symptoms until levels return to target.

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

Close Monitoring and Stopping: Hematocrit

The ULN for hematocrit is 52% according to our reference laboratory. Subjects with hematocrit > 52% (ULN) during the study will trigger the following close monitoring procedures.

- Hematocrit > 52% (ULN): Confirm that subject is hydrated and retest the hematocrit as soon as possible, ideally within 48 hours.
- Hematocrit > 52% (ULN) on two consecutive assays: dose reduction (once daily dosing) will be initiated
    - Weekly 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 > 48% (ULN -4%) and symptoms of polycythemia: study drug discontinued and subject followed until the end of study.

Close Monitoring and Stopping: Hemoglobin

The ULN for hemoglobin is 18 g/dL according to our reference laboratory. Subjects with hemoglobin > 18.0 g/dL (ULN) during the study will trigger the following close monitoring procedures.

- Hemoglobin > 18 g/dL (ULN): confirm that subject is hydrated and retest as soon as possible, ideally within 48 hours
- Hemoglobin > 18 g/dL (ULN) on two consecutive assays: dose reduction (once daily dosing) will be initiated
  - Weekly monitoring of hemoglobin for subjects on once-daily dosing
  - Phlebotomy may be initiated at investigator discretion
- Hemoglobin continues to increase while on once daily dosing: study drug discontinued
- Hemoglobin does not return to normal range within 4-8 weeks of once daily dosing: study drug discontinued
- Hemoglobin returns to normal range within 4-8 weeks of initiation of once-daily dosing: remain on once daily dosing

8.3.5 Monitoring for Hepatotoxicity and Stopping Criteria for Hepatoxicity

Each subject's baseline values of ALT, AST, ALP, and TB (by at least two samples obtained at least 2 weeks apart) will be established during screening. 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 Monitoring and Stopping Criteria

Testosterone will be measured periodically during the study to ensure subjects do not experience elevated T levels. An independent safety physician, not a part of the study team, will be assigned to monitor testosterone levels and implement appropriate protocol directed procedures throughout the study.

Close monitoring and stopping criteria for T are provided below:

Stopping Criteria for T

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.[xxxii] If T concentrations in excess of 1500 ng/dL are repeated in the subject, the subject will be placed on a reduced dose (LPCN 1144 or placebo) of 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 DSMB will assess the causality of these adverse events; if adverse events are deemed to be unrelated, determined by the DSMB, 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 A**, discontinue the study drug.
b. The DSMB will perform a causality assessment. The study drug may be restarted if the DSMB 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 A**, study drug must be discontinued permanently.

8.4 Lost to Follow-Up

A participant will be considered lost to follow-up if he or she 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 or she 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 Overview

There are four phases of study:

- Screening Phase for Subject requiring testosterone/androgen washout up to 12 weeks (12 weeks following intramuscular androgen injections; 4 weeks following topical or buccal androgens; 3 weeks following oral androgens).
- Screening Phase for eligibility assessments (maximum 8 weeks prior to randomization)
- Randomization Phase (one visit)
- Treatment Phase (eight visits)
- Follow-up (one visit)

The visits are described in the following sections. Note that given that all the procedures noted for a visit may not be available at a given clinic, visit procedures may take place over several days, at different sites.

9.1.1 Screening Phase for Subject requiring testosterone/androgen washout

Subjects who are on medications that require washout for eligibility prior to screening will complete the following procedures:

- Obtain informed consent.
- Baseline medical history and chart review to determine basic eligibility based on history.
- Review current and past medication history to determine eligibility or require discontinuation.

9.1.2 Screening Visits and Baseline Data Collection

Investigators will review subject charts for their eligibility and complete standard of care tests and procedures for NASH and invite to undergo screening. All screening related activities will be conducted after subject reads and signs study specific informed consent.

Screening and baseline data collection procedures will include questionnaires, physical examination, determination of the subject's hypogonadal status based on T levels below the normal range, measurement of serum glucose, routine liver tests, and urine analysis. Prior therapy for NASH, lipid lowering, diabetes, hypertension medication will be reviewed, and subjects will be asked to stop any specific or contraindicated / prohibited treatments, if medically acceptable. Subjects taking diabetic, lipid lowering, hypertensive medication will be reviewed and only enrolled if they are on stable medication for at least 3 months prior to screening and encouraged to maintain stable medication after randomization. Sliding scale insulin is allowable, so long as the parameters of the scale do not change.

Subjects who are currently taking an androgen (wash out period described earlier) or vitamin E > 100 IU/day (at least 4 weeks washout period prior to randomization during screening) will be washed out.

Subject charts will be reviewed for historical information.

All subjects screening outcomes will be captured in the source documents; further all subjects should either be screen pass to continue, or a screen fail.

9.1.2.1 Screening period will consist of multiple visits with confirmation of subject eligibility through progression.

Subjects who appear to qualify based on physician chart review and invited to participate will complete the following procedures as provided in Schedule of Activities (SOA):

Initial assessments:

- Obtain Informed Consent (unless main Informed Consent was given at Washout).
- Baseline medical history and chart review to determine basic eligibility based on history.
- Obtain demographic information, anthropomorphic measurements.
- Review current and past medication history to determine eligibility or require discontinuation.
- 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 detailed physical examination.

- Assess if any Fibroscan data collected within 30 days of screening

If subject appears to qualify based on initial assessments:

- Perform Urinalysis
- Perform drug and alcohol screen.
- Fibroscan if needed for subjects but only evaluated for eligibility on subjects without a qualifying historical biopsy within 4 months of Screening.
- Obtain data on historical liver biopsy if available within 4 months from Screening and submit to the central reader for review.
- Collect blood samples for clinical laboratory tests including Serology, Hematology panel including HbA1c, Metabolic panel and renal function, Hepatic panel, Testosterone Assay for subjects without history of previous diagnosis of hypogonadism, Hormones and related markers, cortisol and CBG (see SOA).

9.1.2.2 Second Screening Assessment

- Collect blood samples for repeat of clinical laboratory tests (see SOA) to establish baseline ALT, AST, ALP, TB in second Screening. Second assessment must occur not less than 14 days after first Screening assessment. If baseline value is suspected to be spurious, the test may be repeated.

9.1.2.3 Screening Visit if no prior liver biopsy within the last 4 months

- MRI-PDFF scans should be completed for eligible subjects prior to randomization.
- If a subject is unable to undergo MRI-PDFF or DXA imaging due to health condition (e.g. claustrophobia, difficulty holding breath during the procedure, etc.), the missing MRI-PDFF will be treated as missing data, and the subject will be allowed to proceed to randomization or continue therapy upon investigator and medical monitor approval.
- 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.
- Subject reported questionnaires will be completed and includes Alcohol (**Appendix D**), Functional Activity (**Appendix E**), I-PSS (**Appendix F**), HR-QOL (**Appendix G**), PGI-S (**Appendix H**), Chronic Liver Disease Questionnaire (CLDQ)(**Appendix J**) and Sexual Desire and Distress (**Appendix K**) questionnaires. Details are provided in section 7.3.1.
- Liver biopsy.
- Continued eligibility with respect to medications taken or new medical history developed or reported.

9.1.2.4 Imaging Screening Visit

- Imaging study: dual-energy absorptiometry (DXA) scan for whole body lean mass, appendicular lean mass, fat mass, and bone mineral density (femoral and lumbar).
- If not completed in an earlier visit, complete subject reported questionnaires (see SOA) (See **Appendix D**-**K**). Details are provided in section 7.3.1.
- Continued eligibility with respect to medications taken or new medical history developed or reported
- Perform gait speed and hand grip assessments, as applicable

9.1.3 Randomization Visit (RZ; Day1)

- Subjects who meet all the inclusion criteria and do not meet any exclusion criteria will be allowed to participate in the study.
- Screening medical history and chart review to determine basic eligibility based on history.
- Review current and past medication history to determine eligibility or require discontinuation.
- 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.
- The Randomization Visit marks the Day 1 of treatment and subsequent time duration of treatment will be based on the randomization day.
- Subject's eligibility will be randomly assigned to receive Treatment A (LPCN 1144 formulation) B (LPCN 1144 formulation with Vitamin E) or C (placebo) at 1:1:1 randomization.
- The random treatment assignment will consist of assigning medication bottle numbers; these numbers will be unique and will be specific to the particular subject and visit it was generated for. Once the assignment has been generated, the subject will be issued the assigned study drugs (in person) and instructed about starting the drugs and monitoring for adverse effects.
- Conduct an abbreviated physical examination.
- If not completed at Screening visit, complete subject reported questionnaires (see SOA). Details are provided in section 7.3.1.
- Collect blood samples prior to meal and study drug administration for all clinical laboratory tests including testosterone, hormones, C-reactive protein, fasting glucose and insulin, lipid panel, hematology panel, hepatic panel, biomarkers, and related markers (see SOA) for baseline assessment prior to meal and study drug administration.
- Perform baseline urinalysis.
- An additional blood sample will be collected for serum and plasma banking. Remind subjects to call or return to the clinic before next visit if they develop any of the signs/symptoms listed in the hepatoxicity assessment/stopping criteria section 8.3.

9.1.4 On Treatment and Follow – up Visits

The following visit durations are referenced from the day of randomization. Subjects will return to the clinic for On Treatment visits at Week 4, Week 8, Week 12, Week 16, Week 20, Week 24, Week 30, Week 36 and Week 38.

9.1.4.1 Week 4, Week 8, Week 12, Week 16, Week 20, Week 24, Week 30, Week 36 Visits

- Review current and past medication history to determine eligibility or require discontinuation.
- 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 investigation product (IP) bottle and perform accountability / adherence checks.
- Dispense IP at Week 4, Week 12, Week 20, and Week 30
    - Re-dispense all returned IP.
- Conduct physical examination (see SOA).

- Complete subject reported questionnaires (see SOA). Details are provided in section 7.3.1.
- Perform Urinalysis
- Obtain blood sample for clinical laboratory tests (see SOA). Hematology panel, HbA1c will not be collected at every visit.
- To ensure target T levels are achieved, subjects will have their T, hormones and related markers measured 3 to 5 hours post-dose; instruction for the evaluation of T levels is provided in section 8.3.6.
- Drug and alcohol screen (during Week 4, Week 12, and Week 24).
- An additional blood sample will be collected for serum and plasma banking drawn at Week 12 and Week 36.
- Remind subjects to call or return to the clinic before next visit if they develop any of the signs/symptoms listed in the hepatoxicity assessment/stopping criteria section 8.3.

9.1.4.2 Week 12 Visit (Additional Analysis)

- Perform anthropomorphic measurements, including weight, body mass index (BMI), waist to hip ratio, waist circumference, triceps skin fold thickness, upper arm circumference,
- Conduct a Detailed physical examination, except for DRE.
- Fibroscan imaging.
- MRI-PDFF imaging.
- Alcohol questionnaire AUDIT-C (**Appendix D**), I-PSS (**Appendix F**), and PGI-C (**Appendix I**).
- Blood draws for all required labs except testosterone and hormones will be taken prior to meal and study drug administration. Include HbA1c in Hematology panel.
- Subject eats breakfast.
- 30 minutes post meal the subject will dose.
- 3-5 hours after dosing, testosterone and hormone samples are drawn.

PRIMARY ANALYSIS

The DSMB reviews the planned primary analysis of the MRI-PDFF outcome measure and will be communicated to Sponsor unblinded at the treatment group level but, without unblinding up to the individual patient level. This review will occur when 100% of the MRI-PDFF measurements are complete.

The DSMB also reviews the overall progress of the trial in terms of recruitment and data quality and makes a formal recommendation to Sponsor at the end of each scheduled meeting as to whether the trial should continue unmodified, continue with protocol modifications, or be stopped.

9.1.4.3 Week 36 Visit End of treatment (Additional Analysis)

- Perform anthropomorphic measurements.
- Collect dispensed IP bottle and perform accountability / adherence checks.
- Blood draws for all required labs except testosterone and hormones will be taken prior to meal and study drug administration.
- Include HbA1c in Hematology panel
- An additional blood sample will be collected for serum and plasma banking.
- Subject eats breakfast

- 30 minutes post meal the subject will dose.
- 3-5 hours after dosing, testosterone and hormone samples are drawn
- Conduct a detailed physical examination.
- Patient reported questionnaires will be completed including Functional Activity (**Appendix E**), I-PSS (**Appendix F**), HR-QOL (**Appendix G**), PGI-S (**Appendix H**), PGI-C (**Appendix I**), Chronic Liver Disease Questionnaire (CLDQ)(**Appendix J**) and Sexual Desire and Distress questionnaires (**Appendix K**).
- Perform Gait Speed and Hand Grip assessments.
- Imaging study: DXA scan.
- Fibroscan imaging
- Perform Biopsy.
- Study exit evaluation.

9.1.4.4 Follow up visit

- 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.
- Patient reported questionnaire will be completed including PGI-C (**Appendix I**).
- Perform Urinalysis
- Collect blood samples for clinical laboratory tests including, lipid profile, hematology panel, metabolic and renal function panel, hepatic panel, Testosterone assay, and hormones and related markers (see SOA).

9.2 Data and Safety Monitoring Board (DSMB)

An independent Data and Safety Monitoring Board (DSMB), appointed by Sponsor, is responsible for monitoring the accumulated interim data as the trial progresses to ensure subject safety and to review efficacy. The DSMB is a multidisciplinary group with a written charge provided by Sponsor. The DSMB will include three or more members, at least one of whom is a hepatologist. After the trial commences, the DSMB will establish a charter and meet to review data, evaluate emerging safety information, or other issues.

Interim data on safety measures requested by the DSMB are reviewed at each of the scheduled meetings. Serious adverse events will be reviewed by the DSMB as they occur with the option of a teleconference discussion if any DSMB member so requests.

9.3 Procedure Overview

9.3.1 Subject Questionnaires

Standardized questionnaires will be administered to subjects participating in the trial at baseline (prior to randomization) and during follow-up at specified intervals. The purpose of the questionnaires is to obtain important information regarding alcohol intake to assess eligibility, functional activity, health-related quality of life, and Chronic Liver Disease Questionnaire (CLDQ)

Alcohol questionnaires: Subjects enrolled in the treatment protocol will complete AUDIT (**Appendix D**) and Skinner (**Appendix D**) (lifetime drinking history) questionnaires during screening, and AUDIT-C (**Appendix D**) questionnaire at interim follow-up visits. The purpose of these questionnaires is to ascertain that there is no significant alcohol consumption at enrollment.

Functional Activity: The NHANES III Activity Questionnaire will be administered during screening and after 36 weeks of treatment. The scores can be converted to METS; then the activity of NASH subjects can be compared to U.S. population, and the activity of NASH subjects can be compared to other liver disease subjects. (**Appendix E**)

I-PSS: A questionnaire used for men who are having problems that are likely to be related to an enlarged prostate. (**Appendix F**)

Health-Related Quality of Life (HR-QOL): The SF-36 questionnaire will be administered during screening and after 36 weeks of treatment. (**Appendix G**)

Patient Global Impression of Severity (PGI-S) Scale: The Patient Global Impression of Severity (PGI-S) is a global index that may be used to rate the severity of a specific condition (a single-state scale). It is a simple, direct, easy to use scale that is intuitively understandable to clinicians. (**Appendix H**)

Patient Global Impression of Change (PGI-C) Scale: This scale evaluates all aspects of subjects' health and assesses if there has been an improvement or decline in clinical status. (**Appendix I**)

Chronic Liver Disease Questionnaire (CLDQ): A questionnaire on liver symptoms developed by the NASH CRN will be administered at screening and after 36 weeks of treatment. (**Appendix J**)

Sexual Desire and Distress Questionnaire: A questionnaire used to assess level of a subject's distress due to low sexual desire. (**Appendix K**)

Alcohol questionnaires (AUDIT and Skinner; **Appendix D**) and I-PSS questionnaire (**Appendix F**) are primarily used for eligibility assessment, therefore they need to be completed during the Screening visits (prior to biopsy).

9.3.2 Liver MRI-PDFF

Sites will schedule subjects to have their hepatic fat fraction measured via MRI-PDFF at a local MRI facility. A local MRI facility capable of performing the MRI-PDFF test will be pre-identified by Sponsor/CRO within the geographic location of the site. Alternatively, if the site has a preferred MRI facility, the site can use their preferred facility following confirmation by the Sponsor/CRO. The MRI-PDFF details are as follows:

- MRI-PDFF scan will be conducted at baseline, Week 12, and Week 36. All subjects capable of undergoing MRI will be scheduled to undergo an MRI scan of the liver. In case if a subject is unable to undergo MRI-PDFF imaging due to health condition (e.g. claustrophobia, difficulty holding breath during the procedure, etc.), the missing MRI-PDFF will be treated as missing data, and the subject will be allowed to proceed to randomization or continue the therapy upon investigator and medical monitor approval.
- Individual subjects should have MRI-PDFF scans performed on the same MRI machine throughout screening and the study.
- A central reader will assess the MRI-PDFF scans to determine the liver fat fraction.
- All imaging sites will be provided with the LPCN 1144-18-002 Manual to help with the imaging.
- Further, all imaging sites are qualified to ensure the scan obtained is centrally readable and meets the criteria for a valid imaging.

- MRI-PDFF should be performed prior to randomization but not need to be performed prior to biopsy, if one is required.

9.3.3 Fibroscan (transient elastography)

For all screening and on-treatment Fibroscans, subjects must not eat food and must avoid drinking large volumes of water (> 400 mL, 13.5 oz) for at least 3 hours prior to the procedure. [xxxvi, xxxvii]

Sites will measure subject liver fibrosis and (if available) Controlled Attenuation Parameter (CAP) using Fibroscan devices. The Fibroscan device works by measuring shear wave velocity. A 50-MHz wave is passed into the liver from a small transducer on the end of an ultrasound probe. The probe also has a transducer that can measure the velocity of the shear wave (in meters per second) as this wave passes through the liver. The shear wave velocity can then be converted into liver stiffness, which is expressed in kilopascals.

9.3.4 Gait Speed

Gait speed may be assessed for some subjects at select sites. Standing start, usual pace, over ground gait speed was assessed. Time to complete the 10-meter walk will be measured using a stopwatch, and the tester will start the time when the participant step over the starting line and will stop when the participant completely crosses the end line.

9.3.5 Hand Grip Strength Test

Hand Grip Strength test may be assessed for some subjects at select sites.

Supplies

- Hydraulic Hand Dynamometer

Definition and Purpose

Handgrip strength is a simple and commonly used test of a person's general strength level.

Measurement

1. Have subject sit comfortably with the shoulder adducted and neutrally rotated, with the elbow towards/against the body and flexed at 90 degrees, and the forearm and wrist in a neutral position.
2. Place the hand dynamometer in the participant's hand, and gently support the base to prevent accidental dropping and damage to the instrument.
3. Let the participant arrange the instrument so that it fits comfortably in the hand. Adjust the handle, if necessary, for a comfortable grip. Make sure that the handle clip is located at the lower (furthest) post from the gauge. If the handle is not in the correct position, results will be inaccurate.
4. Reset the indication needle by rotating it to zero.
5. Request that the subject squeeze with maximum strength. The needle will automatically record the highest force exerted. Grip force should be applied smoothly, without rapid wrenching or jerking motion. Minimal wrist extension (30 degrees or less) is permissible as maximum grip is achieved. Wrist extension greater than 30 degrees shall be noted with results.
6. Test each hand twice and record the handgrip strength measurement (in pounds) for each measurement. Reset the indicator needle before each and every effort.

9.3.6 Liver Biopsy

9 . 3 . 6 . 1 Baseline liver biopsy:

Subjects who have not had a liver biopsy within 4 months of Screening or whose previous liver biopsy is not available for review or whose previous liver biopsy is of inadequate quality must have a liver biopsy prior to randomization. The biopsy should be done once the subject has been found to be eligible with respect to all other criteria. Biopsy slides should be of adequate size, preferably 1.5 cm or more and of adequate quality for interpretation. The subject must have not been using anti-NASH drugs in the 3 months prior to baseline biopsy, and the subject must have histologic evidence of definite or possible NASH and F1-F3 fibrosis as described in section 3.1 of this protocol.

In the case of a biopsy done previously as standard of care, the NASH CRN study physician should check if tissue blocks and/or additional slides can be obtained from the original biopsy. If the liver biopsy is completed as part of screening for this trial, the liver tissue will be prepared for light microscopy and stains will include hematoxylin and eosin, Masson's trichrome and iron stain; additionally, a piece of liver tissue will be snap frozen and stored at -70 degrees C and set aside for banking.

In the event that a subject has two liver biopsies with 4 months of Screening, and both are of sufficient quality, the higher biopsy scoring will be used for baseline.

9.3.6.2 Follow-up Liver Biopsy:

A follow-up liver biopsy will be obtained at the Week 36 Visit. Guidelines for obtaining the biopsy specimen are provided in the LPCN 1144-18-002 Liver Biopsy Procedure and NAFLD/NASH Histology Scoring System Manual; a 16-gauge needle is preferred, and the specimen should be at least 1.5 cm in length. The slides should be of adequate size (preferably 1.5 cm or more) and adequate quality for interpretation. The follow-up liver biopsy should be taken from the same lobe of the liver as the baseline/historical biopsy. The liver tissue will be prepared for light microscopy and stains will include hematoxylin and eosin, Masson's trichrome and iron stain; additionally, a piece of liver tissue will be snap frozen and stored at -70 degrees C and set aside for banking.

9.3.6.3 Overview of Scoring of Liver Biopsies

The tissue will be examined by light microscopy and scored based upon the NAS and NASH CRN fibrosis score. The scoring system is detailed in the LPCN 1144-18-002 Liver Biopsy Procedure Manual.

The component scores will be used to determine eligibility as well as primary histologic outcome measure defined elsewhere in this protocol. Baseline and follow-up liver biopsies will be scored by central review of the slides. The scores obtained centrally will be used for inclusion criteria, and data analysis.

9.3.7 Medical and Medication History

The subject's medical history (key events) during the past 5 years will be obtained and recorded on the Medical History Electronic Case Report Form (eCRF). Any new information / changes 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 on the Medical History

eCRF.

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

Subjects participating in the trial must be naive to androgen replacement and vitamin E or has discontinued current therapy and completed an adequate washout. Recommended adequate washout is up to 12 weeks following long acting intramuscular androgen injections; 4 weeks following topical or buccal androgens; 3 weeks following oral androgens; 4 weeks following oral vitamin E > 100 IU/day, or, in the judgement of the Medical Monitor, the subject has had an adequate washout window to be eligible.

Subjects with a chronic condition requiring medication must:

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

9.3.8 Physical Examination

Physical examinations will be performed at visits throughout the study noted in the SOA. A detailed physical includes measurement of height, weight, waist, and hips; vital signs (temperature (single measurement), respiratory rate (single measurement), a prostate digital rectal examination (DRE), and clinic BP (triplicate measurement) and pulse rate (triplicate measurement); triceps skin fold thickness, mid upper arm circumference; examination for scleral icterus and pedal edema and auscultation of the heart and lungs; general physical findings (hepatosplenomegaly, peripheral manifestations of liver disease, ascites, wasting, fetor). An abbreviated physical 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.

9.3.9 Clinic BP and Pulse Rate (PR) Measurement Methodology:

Clinic BP and PR will be measured at visits 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.

9.3.10 Clinical Laboratory Tests

For all subjects, blood and urine samples will be taken as directed in the SOA. Sites will collect samples for serum chemistry tests in the morning prior to meals. Specific stopping criteria for hematocrit, hemoglobin, 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 for all Subjects

Hematology/Coagulation	**Clinical Chemistry**	**Hormones**
Hematocrit Hemoglobin Hemoglobin A1c (HBA1C) Complete Blood Count (CBC) Prothrombin time (PT) International normalized ratio (INR)	Albumin Alkaline phosphatase (ALP) Bile acid Bilirubin Blood urea nitrogen (BUN) Cortisol and Cortisol Binding Globulin C-reactive protein Creatinine kinase Gamma-glutamyltransferase (GGT) Glucose Prolactin Prostate Specific Antigen (PSA) Serum glutamic-pyruvic transaminase (SGPT/ALT) Serum glutamic-oxaloacetic transaminase (SGOT/AST)	DHT FSH Insulin LH Prolactin Prostate specific antigen SHBG Testosterone TSH
Lipids		
Free fatty acid HDL cholesterol LDL cholesterol Total cholesterol Triglycerides VLDL cholesterol		

Clinical laboratory testing must be performed by appropriately credentialed laboratories. Certified central laboratories will process and provide results for the tests conducted at screening and throughout the study. The certified study laboratories for sample shipment and contact information will be provided in lab manual.

9.3.11 Screens for Drugs of Abuse and Alcohol

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

9.3.12 Prostate-Specific Antigen (PSA) and Digital Rectal Exam

Sites will collect samples for PSA at screening. A digital rectal exam (DRE) is also part of screening procedures. The PSA samples must be collected prior to the DRE.

9.3.13 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 < 18 mcg/dL 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.

9.4 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.

9.4.1 Safety Concerns Related to the Therapeutic Agents

The following paragraphs discuss the important potential adverse effects and the proposed safeguards to minimize the risks involved.

9.4.1.1 Safety Issues Related to LPCN 1144

LPCN 1144 was extensively studied in non-clinical and clinical studies. In clinical studies a twice daily dose 225 mg of TU (450 mg total daily dose) was exposed 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.

9.4.1.2 Safety Issues Related to Placebo

The ingredients in the placebo capsules are commonly used compendial excipients. Subjects with known hypersensitivity to any of the ingredients shall not be included in the trial. Participants will be seen frequently during the study period for assessment of symptoms, clinical laboratory tests, and reporting of adverse events.

9.4.1.3 Safety Issues Related to Vitamin E (d-alpha tocopherol)

Vitamin E at 800 IU daily dose has no significant toxicity in adults.[xxxiii,xxxiv] Although use of antioxidants may improve insulin resistance and thereby may reduce the incidence of new-onset diabetes, it is safe to assume that the magnitude of risk of new-onset diabetes mellitus in subjects randomized to vitamin E is the same as placebo.

9.4.1.4 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, in keeping with the "intention-to-treat" paradigm.

9.4.2 Safety Issues Related to Liver Biopsy

Subjects will have up to two liver biopsies for research purposes during their participation in this protocol. 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 in the NASH CRN 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.

9.4.3 Safety Issues 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.

9.5 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.

9.5.1 Definition of Adverse Events (AE)

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.

9.5.2 Definition of Serious Adverse Events (SAE)

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

Event	Description of Event
Death of Subject	An event that results in the death of a subject.
Life-Threatening	An event that, in the opinion of the investigator, would have resulted in immediate fatality if medical intervention had not been taken. This does not include an event that would have been fatal if it had occurred in a more severe form.
Hospitalization or Prolongation of Hospitalization	An event that results in an admission to the hospital for any length of time or prolongs the subject's hospital stay. This does not include an emergency room visit or admission to an outpatient facility.
Congenital Anomaly	An anomaly detected at or after birth, or any anomaly that results in fetal loss in the female partner of a study subject.
Persistent or Significant Disability/Incapacity	An event that results in a condition that substantially interferes with the activities of daily living of a study subject. Disability is not intended to include experiences of relatively minor medical significance such as headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle).
Important Medical Event Requiring Medical or Surgical Intervention to Prevent Serious Outcome	An important medical event that may not be immediately life-threatening or result in death or hospitalization, but based on medical judgment may jeopardize the subject and may require medical or surgical intervention to prevent any of the outcomes listed above (i.e., death of subject, life-threatening, hospitalization, prolongation of hospitalization, congenital anomaly, or persistent or significant

disability/incapacity). Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

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

9.5.3 Classification of an Adverse Event

9.5.3.1 Severity of 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".]

9.5.3.2 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.

9.5.3.3 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.

9.5.4 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.

9.5.5 Adverse Event Reporting

To report an SAE, complete the SAE eCRF in the EDC system for the study. When the form is completed, Medpace Clinical Safety personnel will be notified electronically and will retrieve the form. If the event meets serious criteria and it is not possible to access the EDC system, send an email to Medpace Clinical Safety at medpace-safetynotification@medpace.com or call the Medpace SAE hotline (phone number listed below), and fax/email the completed paper back-up SAE form to Medpace (contact information listed below) within 24 hours of awareness. When the EDC system becomes available, the SAE information must be entered within 24 hours of the system becoming available. Incoming reports are reviewed during normal business hours.

Safety Contact Information:

Medpace Clinical Safety Medpace SAE hotline – USA: Telephone: +1-800-730-5779, dial 3 or +1-513-579-9911, dial 3 Facsimile: +1-866-336-5320 or +1-513-579-0444 e-mail: medpace-safetynotification@medpace.com

9.5.6 Monitoring for Adverse Events

Summary data on adverse events will be monitored by the DSMB as needed. These summaries will include analyses comparing rates of adverse events by treatment group, by clinic, or in other subgroups requested by the DSMB. 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.

After each meeting, the DSMB will issue a written summary of its review of the study data, including adverse events, for transmission to the IRBs at each of the study centers. 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.

9.5.7 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.

The study site staff will fill a Pregnancy in Partner form and the Sponsor will be notified within 24 hours.

10 STATISTICAL CONSIDERATIONS

A formal Statistical Analysis Plan (SAP) will be completed and incorporated prior to database lock and unblinding of the study data. The SAP will govern the statistical analysis for the study. The following sections only outlines key statistical points.

10.1 Outcomes

Primary Outcome Measure:
Change in hepatic fat fraction based on MRI-PDFF measurements in LPCN 1144 treated subjects after 12 weeks of treatment.

Key Secondary Outcome Measures:
Change in NASH activity or change in fibrosis. Changes in NASH activity will be evaluated via a standardized scoring of liver biopsies at baseline and after 36 weeks of treatment in LPCN 1144 treated subjects, while changes in fibrosis will be evaluated via NASH CRN fibrosis score of liver biopsies at baseline and after 36 weeks of treatment.

Change in NASH activity is derived from changes from baseline to the end of treatment in NAS. The NAS ranges from 0 to 8 (highest activity) and is calculated as the sum of three components of the standardized histologic feature scoring system for liver biopsies:

NAS = Steatosis score (0-3) +
Lobular inflammation score (0-3) +
Hepatocyte ballooning score (0-2)

The analysis of the Key Secondary Outcome Measure will include both improvement in NAS and fibrosis, and numerical change in NAS and fibrosis. The analysis for improvement of NAS will only include subjects with a baseline hepatocyte ballooning score of 1 or 2. The definition of improvement of NAS after treatment as the key secondary outcome measure requires the following three conditions:

- No worsening of the NASH CRN scoring system.
- Improvement by at least 1 point in the hepatocyte ballooning feature score.

- Either:
  1. Improvement in NAS by 2 or more points spread across at least two of the NAS components, OR
  2. Post-treatment NAS is 3 points or less.

Similarly, improvement in fibrosis will be defined as improvement in liver fibrosis greater than or equal to one stage using the NASH CRN fibrosis score with no worsening of ballooning, inflammation, or steatosis.

Other Secondary Outcome Measures:

- Relative change in hepatic fat fraction based on MRI-PDFF measurements in LPCN 1144 treated subjects after 12 weeks of treatment.
- Change in hepatic fat fraction based on MRI-PDFF measurements in LPCN 1144 treated subjects after 36 weeks of treatment.
- Relative change in hepatic fat fraction based on MRI-PDFF measurements in LPCN 1144 treated subjects after 36 weeks of treatment.
- NAFDL resolution of subjects who at baseline is at least 5% of hepatic fat fraction with a decrease to less than 5% at end of study.
- Resolution of NASH on overall histopathological reading. Resolution of NASH is defined as NAS score of 0–1 for inflammation, 0 for ballooning, and any value for steatosis.
- Change in individual NAS component scores (inflammation, ballooning, steatosis) in LPCN 1144 treated subjects after 36 weeks of treatment.
- Resolution of NASH on overall histopathological reading and no worsening of liver fibrosis on NASH CRN fibrosis score.
- Improvement in liver fibrosis greater than or equal to one stage (NASH CRN fibrosis score).
- Change in anthropometric measurements (weight, body mass index (BMI), waist to hip ratio, waist circumference, triceps skin fold thickness, upper arm circumference,) in LPCN 1144 treated subjects.
- Change in insulin resistance (assessed by HOMA) in LPCN 1144 treated subjects.
- Changes in liver enzymes (AST, ALT, ALP, GGT, TB and CK) in LPCN 1144 treated subjects.
- Changes in non-invasive markers of fibrosis and steatosis including cytokines, leptin, fibrosis markers, and lipid profile in LPCN 1144 treated subjects.
- Changes in lipid parameters (triglycerides, VLDL-C, HDL-C, LDL-C, and free fatty acids) in LPCN 1144 treated subjects.
- Changes in Functional Activity (**Appendix E**), HR-QOL as measured by Short Form-36 (**Appendix G**), PGI-S (**Appendix H),** PGI-C (**Appendix I**), and Chronic Liver Disease Questionnaire (CLDQ) (**Appendix J**) and Sexual desire and distress (**Appendix K**) questionnaires in LPCN 1144 treated subjects.
- Changes in laboratory parameters (clinical chemistry, hematology and urinalysis) in LPCN 1144 treated subjects.

10.2 Sample Size Determination

This is a proof of concept Phase 2 study aimed at evaluating the LPCN 1144 as potential therapeutic agent in the treatment and / or management of NASH. The sample size for the study was not based on any statistical considerations but based on similar Phase 2 studies in this therapeutic area.

10.3 Populations for Analyses

The study populations that will be used in various analysis are defined as:

- Intention-to-Treat (ITT) Analysis Dataset (i.e., all randomized participants)
- Modified Intention-to-Treat (mITT) Analysis Dataset (e.g., participants who took at least one dose of study intervention and/or have some particular amount of on-treatment data)
- Safety Analysis Dataset: defines the subset of participants for whom safety analyses will be conducted (e.g., participants who took at least one dose of study intervention)
- Per-Protocol (PP) Analysis Dataset: defines a subset of the participants in the full analysis (ITT) set who complied with the protocol sufficiently to ensure that these data would be likely to represent the effects of study intervention according to the underlying scientific model (e.g., participants who took at least 80% of study intervention for 80% of the days within the maintenance period).

10.4 Statistical Analyses

10.4.1 General Approach

A p-value of 0.05 will be considered significant. No adjustments for the additional analysis or multiple comparisons will be applied; however, any significant findings must be interpreted taking into account the strength of the finding and its biologic plausibility.

Continuous data will be summarized using count, mean, median, standard deviation (SD), minimum, and maximum. For continuous data specified to be analyzed using parametric procedures, non-parametric procedures will be used if the parametric procedure is felt to be inappropriate.

Potential treatment-by-site interactions in terms of the baseline data and the primary efficacy and safety endpoints will be investigated by visual inspection of the data by site. Visual evidence of extreme imbalance by site will be handled in subsequent models by including site as a term in the model.

Summary tables, listings, and figures, and statistical analyses will be done using SAS version 9.1 or higher or R, version 2.0 or higher.

Unless otherwise noted, efficacy analyses will be conducted for the ITT. Safety analyses will be conducted for the Safety population only.

When an analysis calls for statistical modeling of the outcome variable using potential confounders as well as the treatment effect, the analysis will begin with the full model. If a potential confounder is not statistically significant in the full model, it will be dropped, and the analysis repeated using a reduced model.

10.4.2 Procedures for Missing Data

Missing data will be reported as such. Raw data will be subjected to a statistical screen for outliers using commonly accepted procedures.

10.4.3 Efficacy Analyses

10.4.3.1 Primary Efficacy Analyses

The primary outcome measure will be analyzed using an analysis of covariance (ANCOVA) model with treatment group as a factor and baseline hepatic fat fraction (%) based on MRI-PDFF measurements as a covariate. The LPCN 1144 dose groups will be compared to each other and compared to placebo independently using linear contrasts.

The analysis of the primary outcome measure will be performed using the ITT population. The mITT and PP populations will be used as sensitivity analyses.

10.4.3.2 Key Secondary Efficacy Analyses

Change from baseline in key secondary outcome measures will be analyzed both as a binary outcome (improved vs. not improved) and also in terms of the numerical change in the outcomes. For the key secondary outcomes, improvement will be assessed based on the criteria provided in section 10.1.

Comparative analyses for the key secondary outcome measure will be analyzed both as a binary outcome (improved vs. not improved) and also in terms of the numerical change in the outcome. Binary outcomes will be compared using Fisher's exact test. Numerical changes will be analyzed by descriptively comparing the between-treatment group differences in mean and median changes; P-values will be derived from Wilcoxon rank sum tests for comparison of the distribution of changes in each group. If concerns about confounding arise, logistic regression models for improvement outcomes and linear regression models for numerical change outcomes will be used to correct for the confounding. Analyses for outcome measures will generally involve three separate analyses, one for each treatment group comparison.

10.4.3.3 Other Secondary Efficacy Analyses

Other secondary efficacy outcome measures will be conducted in the similar methods of the primary and secondary efficacy analyses. The details of other secondary efficacy analyses will be provided in the SAP.

10.4.3.4 Subgroup Analyses

The analyses of the primary outcome measure will be performed for the following subgroups:

1. Subjects with baseline liver fat ≥ 5%
2. Subjects with baseline liver fat ≥ 8%
3. Subjects with baseline liver fat ≥ 10%

The details of the subgroup analyses will be provided in the SAP.

10.4.4 Safety Analyses

An AE that starts during a unique treatment or that already exists before the start of that unique treatment but worsens during the treatment will be considered as treatment emergent for that unique treatment.

AEs will be reported on a per-subject basis, i.e., counting subjects rather than events. This means that if a subject suffers the same AE repeatedly during the applicable study period, the event will be counted only once for that period. Repeated events per subject will be summarized according to the following rule; if a subject suffered the same AE more than once, the event will be assigned the worst severity, the closest relationship to the study drug, and the earliest onset date. Only treatment-emergent events will be reported. For each unique treatment, treatment-emergent AEs will be summarized per primary System Organ Class (SOC) and per Preferred Term (PT) using the MedDRA classification system. All AEs, serious AEs and deaths, Serious AEs that are considered treatment-related, and AEs leading to premature discontinuation from the study will also be provided in data listings.

10.4.5 Cardiovascular Risk Evaluation

Each subject will be evaluated for cardiovascular risk using the following algorithms.

- Framingham Coronary Heart Disease Risk Score.
- Framingham Risk Score for cardiovascular disease
- Reynolds Risk Score.

A subgroup analysis will be performed showing the central tendency towards increased blood pressure in subjects who have a diagnosis of diabetes mellitus at baseline, in subjects who do not have a diagnosis with hypertension and are normotensive at baseline, and in subjects who have a diagnosis of hypertension at baseline and are controlled with medical management.

10.4.6 Other Assessments or Analysis

Demographics and other baseline characteristics will be summarized by analysis set. Medical history will be summarized. Major protocol deviations will be listed. Abnormal physical examination assessments will be summarized for the Safety population. Medication use will be summarized for the Safety population. Prior (prior to the start of treatment) medication use and concomitant (after the start of treatment) medication use will be summarized separately. If the end date of a prior medication occurs after treatment starts, then the medication will be reported in both the prior and concomitant listings. Concomitant medication use will be summarized per treatment group. These listings will present the number and percentage of subjects for each medication.

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

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/CRO.

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 [redacted]

11.1.6 Safety Oversight

Safety oversight will be under the direction of the Sponsor and CRO 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

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

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

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

All imaging evaluations will be conducted by certified central reader. The source documents / site documents shall capture the information of the personnel and facilities including qualifications.

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

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 eCRFs as required. Data collected during this study must be recorded on the appropriate source document.

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

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 CRF data for this study will be collected with an electronic data capture (eEDC) system (e.g., Rave, Medidata). The EDC system and the study-specific eCRFs will comply with Title 21 CFR Part 11. The documentation related to the validation of the EDC system is available through the system vendor, while the validation of the study-specific eCRFs will be conducted by the clinical research organization (CRO) and will be maintained in the Trial Master File at the CRO.

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

personnel in the EDC system. All data entered into the eCRF will be supported by source documentation.

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

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

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	**Alternate Contact**
[redacted]	[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 eligibility and/or 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
ANCOVA	Analysis of Covariance
ALP	Alkaline Phosphatase
ALT	Alanine Transaminase
AST	Aspartate Transaminase
CFR	Code of Federal Regulations
CK	Creatine Kinase
CMP	Clinical Monitoring Plan
COC	Certificate of Confidentiality
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
DHHS	Department of Health and Human Services
DILI	Drug-Induced Liver Injury
DRE	Digital Rectal Examination
DSMB	Data and Safety Monitoring Board
EC	Ethics Committee
eCRF	Electronic Case Report Forms
EOT	End of Treatment
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
GCP	Good Clinical Practice
GGT	Gamma-Glutamyltransferase
GLP	Good Laboratory Practices
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
IB	Investigator's Brochure
ICH	International Conference on Harmonization
IND	Investigational New Drug Application
IRB	Institutional Review Board
ITT	Intention-To-Treat
MedDRA	Medical Dictionary for Regulatory Activities
MELD	Model for End-Stage Liver Disease
mITT	Modified-Intent-To-Treat
MOP	Manual of Procedures
MSDS	Material Safety Data Sheet
NAFL	Non-Alcoholic Fatty Liver
NAFLD	Non-Alcoholic Fatty Liver Disease
NAS	NAFLD Activity Score
NASH	Non-Alcoholic Steatohepatitis
NCT	National Clinical Trial
NIH	National Institutes of Health
NIH IC	NIH Institute or Center
OHRP	Office for Human Research Protections
PI	Principal Investigator
PP	Per-Protocol

QA	Quality Assurance
QC	Quality Control
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SMC	Safety Monitoring Committee
SOA	Schedule of Activities
SOC	System Organ Class
SOP	Standard Operating Procedure
TB	Total Bilirubin
ULN	Upper Limit of Normal
UP	Unanticipated Problem
US	United States

12 APPENDICES

APPENDIX A: Investigator's Agreement

APPENDIX B: DILI monitoring algorithm

APPENDIX C: Close Observation for Potential Drug Induced Liver Injury

APPENDIX D: Alcohol Questionnaire (AUDIT, AUDIT-C and Skinner)

APPENDIX E: Functional Activity Questionnaire

APPENDIX F: I-PSS Questionnaire

APPENDIX G: HR-QOL (SF-36) Questionnaire

APPENDIX H: PGI-S Questionnaire

APPENDIX I: PGI-C Questionnaire

APPENDIX J: Chronic Liver Disease Questionnaire (CLDQ)

APPENDIX K: Sexual Desire and Distress Questionnaire

APPENDIX L: Sponsor Signatures

APPENDIX A: INVESTIGATOR'S AGREEMENT

Study Title: A Phase 2, Randomized Double-Blind, Placebo-Controlled, Multi-Center Study to Assess the Efficacy, Safety and Tolerability of Oral LPCN 1144 in Subjects with Nonalcoholic Steatohepatitis (NASH)

Study Number: LPCN 1144-18-002

Final Date: 7 January 2020

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

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

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

1. I have received and reviewed the Investigator's Brochure for LPCN 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

Treatment-Emergent ALT	Treatment-Emergent TB	Liver Symptoms	Action
Normal baseline: ALT > 5x ULN Elevated 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 or placebo) to once daily administration (one capsule, once daily). Follow-up for symptoms.
Normal baseline: ALT > 8x ULN Elevated 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 or placebo) once daily administration (one capsule, once daily).
Normal baseline: ALT > 5x ULN Elevated 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 or placebo) once daily administration (one capsule, once daily).
Normal baseline: ALT > 5x ULN Elevated 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 or placebo) once daily administration (one capsule, once daily).

Source: Adapted from Chalasani, Naga and Regev, Arie et al. Drug-Induced Liver Injury in Subjects with Preexisting Chronic Liver Disease in Drug Development: How to Identify and Manage? Gastroenterology, Volume 151, Issue 6, 1046 – 1051
**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 liver 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: ALCOHOL QUESTIONNAIRE (AUDIT)

The Alcohol Use Disorders Identification Testl:nterview Version

Read questions as written. Record answers carefull.yBegin the AUDIT by saying " Now I am going to ask you some questions about your use of alcoholic beverages during this past year." Explain what is meant by " alcoholic beverages" by using local examples of beer, wine, vodka, etc. Code answers in terms of " standard drinks" . Place the correct answer number in the box at the right.

1. How often do you have a drink containing alcohol?

   (0) Never [Skip to Qs 9-10]
   (1) Monthly or less
   (2) 2 to 4 times a month
   (3) 2 to 3 times a week
   (4) 4 or more times a week

2. How many drinks containing alcohol do you have on a typical day when you are drinking?

   (0) 1 or 2
   (1) 3 or 4
   (2) 5 or 6
   (3) 7, 8, or 9
   (4) 10 or more

3. How often do you have six or more drinks on one occasion?

   (0) Never
   (1) Less than monthly
   (2) Monthly
   (3) Weekly
   (4) Daily or almost daily

   Skip to Questions 9 and 10 if Total Score for Questions 2 and 3 = 0

4. How often during the last year have you found that you were not able to stop drinking once you had started?

   (0) Never
   (1) Less than monthly
   (2) Monthly
   (3) Weekly
   (4) Daily or almost daily

5. How often during the last year have you failed to do what was normally expected from you because of drinking?

   (0) Never
   (1) Less than monthly
   (2) Monthly
   (3) Weekly
   (4) Daily or almost daily

6. How often during the last year have you needed a first drink in the morning to get yourself going after a heavy drinking session?

   (0) Never
   (1) Less than monthly
   (2) Monthly
   (3) Weekly
   (4) Daily or almost daily

7. How often during the last year have you had a feeling of guilt or remorse after drinking?

   (0) Never
   (1) Less than monthly
   (2) Monthly
   (3) Weekly
   (4) Daily or almost daily

8. How often during the last year have you been unable to remember what happened the night before because you had been drinking?

   (0) Never
   (1) Less than monthly
   (2) Monthly
   (3) Weekly
   (4) Daily or almost daily

9. Have you or someone else been injured as a result of your drinking?

   (0) No
   (2) Yes, but not in the last year
   (4) Yes, during the last year

10. Has a relative or friend or a doctor or another health worker been concerned about your drinking or suggested you cut down?

    (0) No
    (2) Yes, but not in the last year
    (4) Yes, during the last year

Record total of specific items here

If total is greater than recommended cut-off, consult User's Manual.

APPENDIX D: Alcohol Questionnaire (AUDIT)

STANDARD DRINK EQUIVALENTS	APPROXIMATE NUMBER OF STANDARD DRINKS IN:
BEER or COOLER	
12 oz.  **~5% alcohol**	12 oz. = 1 16 oz. = 1.3 22 oz. = 2 40 oz. = 3.3
MALT LIQUOR	
8-9 oz.  **~7% alcohol**	12 oz. = 1.5 16 oz. = 2 22 oz. = 2.5 40 oz. = 4.5
TABLE WINE	
5 oz.  **~12% alcohol**	a 750 mL (25 oz.) bottle = 5
80-proof SPIRITS (hard liquor)	
1.5 oz.  **~40% alcohol**	a mixed drink = 1 or more* a pint (16 oz.) = 11 a fifth (25 oz.) = 17 1.75 L (59 oz.) = 39 *Note: Depending on factors such as the type of spirits and the recipe, one mixed drink can contain from one to three or more standard drinks.

http://pubs.niaaa.nih.gov/publications/Practitioner/pocketguide/pocket_guide2.htm

APPENDIX D: Alcohol Questionnaire – AUDIT-C

AUDIT-C Questionnaire

Patient Name Date of Visit___

1. **How often do you have a drink containing alcohol?**
   a. Never
   b. Monthly or less
   c. 2-4 times a month
   d. 2-3 times a week
   e. 4 or more times a week

2. **How many standard drinks containing alcohol do you have on a typical day?**
   a. 1 or 2
   b. 3 or 4
   c. 5 or 6
   d. 7 to 9
   e. 10 or more

3. **How often do you have six or more drinks on one occasion?**
   a. Never
   b. Less than monthly
   c. Monthly
   d. Weekly
   e. Daily or almost daily

APPENDIX D: Alcohol Questionnaire - Skinner

LIFETIME DRINKING HISTORY

IDENTIFIER ___/___/___/___/___/___ NAME: ______________________________

DATE: ____/_____ _____/______ _____/______ # OF PHASES ____/____ WEIGHT: ___ ___ ___ KG HEIGHT: ___ ___ ___ CM

AGE RANGE YOUNGER TO OLDER	FREQUENCY DAYS/MONTH	QUANTITY DRINKS/DAY	TYPE (%)	STYLE (CIRCLE ONE)	LIFE EVENTS OR CHANGES POSITIVE (+) OR NEGATIVE (-)	CONTEXT %	TIME %
From ___________ To ______________	_____________	Average ______ Maximum ____	Beer ____ Liquor ___ Wine ____	1 Occasional 2 Weekend 3 Binge 4 Frequent	______ 1 Family ______ 7 Financial ______ 2 Work ______ 8 Peer Group ______ 3 School ______ 9 Drug Use ______ 4 Medical ______ 10 Treatment ______ 5 Residence ______ 11 Death ______ 6 Legal - Jail ______ 12 Emotional	Alone _______ With Others _______	Morning ______ Afternoon ______ Evening ______
From ___________ To ______________	_____________	Average ______ Maximum ____	Beer ____ Liquor ___ Wine ____	1 Occasional 2 Weekend 3 Binge 4 Frequent	______ 1 Family ______ 7 Financial ______ 2 Work ______ 8 Peer Group ______ 3 School ______ 9 Drug Use ______ 4 Medical ______ 10 Treatment ______ 5 Residence ______ 11 Death ______ 6 Legal - Jail ______ 12 Emotional	Alone _______ With Others _______	Morning ______ Afternoon ______ Evening ______
From ___________ To ______________	_____________	Average ______ Maximum ____	Beer ____ Liquor ___ Wine ____	1 Occasional 2 Weekend 3 Binge 4 Frequent	______ 1 Family ______ 7 Financial ______ 2 Work ______ 8 Peer Group ______ 3 School ______ 9 Drug Use ______ 4 Medical ______ 10 Treatment ______ 5 Residence ______ 11 Death ______ 6 Legal - Jail ______ 12 Emotional	Alone _______ With Others _______	Morning ______ Afternoon ______ Evening ______
From ___________ To ______________	_____________	Average ______ Maximum ____	Beer ____ Liquor ___ Wine ____	1 Occasional 2 Weekend 3 Binge 4 Frequent	______ 1 Family ______ 7 Financial ______ 2 Work ______ 8 Peer Group ______ 3 School ______ 9 Drug Use ______ 4 Medical ______ 10 Treatment ______ 5 Residence ______ 11 Death ______ 6 Legal - Jail ______ 12 Emotional	Alone _______ With Others _______	Morning ______ Afternoon ______ Evening ______

1mo = .1 2mo = .2 3mo = .3 4mo = .3 5mo = .4 6mo = .5 7mo = .6 8mo = .7 9mo = .8 10mo = .8 11mo = .9 12mo = 1.0

1 Drink (approx.) = 12 oz. Beer; 1 1/2 oz. Liquor; 5 oz. Wine; 3 oz. Fortified wine; 13.6 g. Absolute alcohol;

Liquor: 1 mickey (12 oz) = 8 drinks; 1 bottle (25 oz) = 17 drinks Wine: 1 bottle (25 oz) = 5 drinks; 1 bottle fortified = 8 drinks

APPENDIX E: FUNCTIONAL ACTIVITY QUESTIONNAIRE (NHANES)

NHANES 2017

PAQ.605 Next I am going to ask you about the time {you spend/SP spends} doing different types of physical activity in a typical week.

Think first about the time {you spend/he spends/she spends} doing work. Think of work as the things that {you have/he has/she has} to do such as paid or unpaid work, household chores, and yard work.

Does {your/SP's} work involve **vigorous**-intensity activity that causes **large increases** in breathing or heart rate like carrying or lifting heavy loads, digging or construction work for **at least 10 minutes continuously**?

YES	1	
NO	2	(PAQ.620)
REFUSED	7	(PAQ.620)
DON'T KNOW	9	(PAQ.620)

PAQ.610 In a typical week, on how many days {do you/does SP} do **vigorous**-intensity activities as part of {your/his/her} work?

PROBE IF NEEDED: Vigorous-intensity activity causes large increases in breathing or heart rate and is done for at **least 10 minutes continuously**.

INTERVIEWER: REMEMBER, WE ARE ONLY ASKING ABOUT WORK AND CHORES IN THIS QUESTION.
HARD EDIT: 1-7.
ERROR MESSAGE: THE NUMBER OF DAYS SHOULD BE BETWEEN 1 AND 7.

|___|___|
ENTER NUMBER OF DAYS

REFUSED	77	(PAQ.620)
DON'T KNOW	99	(PAQ.620)

PAQ.615 How much time {do you/does SP} spend doing **vigorous**-intensity activities at work on a typical day? Q/U

PROBE IF NEEDED: Think about a typical day when {you do/he does/she does} vigorous-intensity activities during {your/his/her} work.

PROBE IF NEEDED: Vigorous-intensity activity causes large increases in breathing or heart rate and is done for at **least 10 minutes continuously**.

INTERVIEWER: REMEMBER, WE ARE ONLY ASKING ABOUT WORK AND CHORES.

SOFT EDIT: >4 HOURS.
ERROR MESSAGE: INTERVIEWER, YOU HAVE RECORDED THAT THE SP SPENDS MORE THAN 4 HOURS DOING VIGOROUS-INTENSITY ACTIVITIES AT WORK ON A TYPICAL DAY. PLEASE CONFIRM WITH SP THAT OVER 4 HOURS IS CORRECT.

HARD EDIT: ≥24 HOURS.
HARD EDIT: <10 MINUTES.
ERROR MESSAGE: THE TIME SHOULD BE 10 MINUTES OR MORE, BUT LESS THAN 24 HOURS.

|___|___|___|
ENTER NUMBER OF MINUTES OR HOURS

REFUSED 7777 (PAQ.620)

APPENDIX E: con't.

DON'T KNOW 9999 (PAQ.620)

ENTER UNIT

MINUTES 1
HOURS 2

PAQ.620 Does {your/SP's} work involve **moderate**-intensity activity that causes **small increases** in breathing or heart rate such as brisk walking or carrying light loads for **at least 10 minutes continuously**?

YES	1	
NO	2	(PAQ.635)
REFUSED	7	(PAQ.635)
DON'T KNOW	9	(PAQ.635)

PAQ.625 In a typical week, on how many days {do you/does SP} do **moderate**-intensity activities as part of {your/his/her} work?

PROBE IF NEEDED: Moderate-intensity activity causes small increases in breathing or heart rate and is done for at **least 10 minutes continuously**.

INTERVIEWER: REMEMBER, WE ARE ONLY ASKING ABOUT WORK AND CHORES.

HARD EDIT: 1-7.
ERROR MESSAGE: THE NUMBER OF DAYS SHOULD BE BETWEEN 1 AND 7.

|___|___|
ENTER NUMBER OF DAYS

REFUSED 77 (PAQ.635)
DON'T KNOW 99 (PAQ.635)

PAQ.630 How much time {do you/does SP} spend doing **moderate**-intensity activities at work on a typical day? Q/U

PROBE IF NEEDED: Think about a typical day when {you do/he does/she does} moderate-intensity activities during {your/his/her} work.

PROBE IF NEEDED: Moderate-intensity activity causes small increases in breathing or heart rate and is done for at **least 10 minutes continuously**.

INTERVIEWER: REMEMBER, WE ARE ONLY ASKING ABOUT WORK AND CHORES.

SOFT EDIT: >4 HOURS.
ERROR MESSAGE: INTERVIEWER, YOU HAVE RECORDED THAT THE SP SPENDS MORE THAN 4 HOURS DOING MODERATE-INTENSITY ACTIVITIES AT WORK ON A TYPICAL DAY. PLEASE CONFIRM WITH SP THAT OVER 4 HOURS IS CORRECT.

HARD EDIT: ≥24 HOURS.
HARD EDIT: <10 MINUTES.
ERROR MESSAGE: THE TIME SHOULD BE 10 MINUTES OR MORE, BUT LESS THAN 24 HOURS.

APPENDIX E: con't.

|___|___|___|
ENTER NUMBER OF MINUTES OR HOURS

REFUSED 7777 (PAQ.635)
DON'T KNOW 9999 (PAQ.635)

|___|
ENTER UNIT

MINUTES 1
HOURS 2

PAQ.635 The next questions exclude the physical activities at work that you have already mentioned. Now I would like to ask you about the usual way {you travel/SP travels} to and from places. For example to work, for shopping, to school.

In a typical week {do you/does SP} walk or use a bicycle for **at least 10 minutes continuously** to get to and from places?

YES 1
NO 2 (PAQ.650)
REFUSED 7 (PAQ.650)
DON'T KNOW 9 (PAQ.650)

PAQ.640 In a typical week, on how many days {do you/does SP} walk or bicycle for **at least 10 minutes continuously** to get to and from places?

HARD EDIT: 1-7.
ERROR MESSAGE: THE NUMBER OF DAYS SHOULD BE BETWEEN 1 AND 7.

|___|___|
ENTER NUMBER OF DAYS

REFUSED ..... 77(PAQ.650)
DON'T KNOW ..... 99(PAQ.650)

PAQ.645 How much time {do you/does SP} spend walking or bicycling for travel on a typical day?
Q/U

PROBE IF NEEDED: Think about a typical day when {you walk or bicycle/SP walks or bicycles} for travel.

SOFT EDIT: >4 HOURS.
ERROR MESSAGE: INTERVIEWER, YOU HAVE RECORDED THAT THE SP SPENDS MORE THAN 4 HOURS WALKING OR BICYCLING TO GET TO AND FROM PLACES ON A TYPICAL DAY. PLEASE CONFIRM WITH SP THAT OVER 4 HOURS IS CORRECT.

HARD EDIT: ≥24 HOURS.
HARD EDIT: <10 MINUTES.
ERROR MESSAGE: THE TIME SHOULD BE 10 MINUTES OR MORE, BUT LESS THAN 24 HOURS.

|___|___|___|
ENTER NUMBER OF MINUTES OR HOURS

APPENDIX E: con't.

REFUSED 7777 (PAQ.650)
DON'T KNOW 9999 (PAQ.650)

|___|
ENTER UNIT

MINUTES 1
HOURS 2

PAQ.650 The next questions exclude the work and transportation activities that you have already mentioned. Now I would like to ask you about sports, fitness and recreational activities.

In a typical week {do you/does SP} do any **vigorous**-intensity sports, fitness, or recreational activities that cause **large increases** in breathing or heart rate like running or basketball for **at least 10 minutes continuously**?

YES 1
NO 2 (PAQ.665)
REFUSED 7 (PAQ.665)
DON'T KNOW 9 (PAQ.665)

PAQ.655 In a typical week, on how many days {do you/does SP} do **vigorous**-intensity sports, fitness or recreational activities?

PROBE IF NEEDED: Vigorous-intensity activity causes large increases in breathing or heart rate and is done for at **least 10 minutes continuously**.

HARD EDIT: 1-7.
ERROR MESSAGE: THE NUMBER OF DAYS SHOULD BE BETWEEN 1 AND 7.

|___|___|
ENTER NUMBER OF DAYS

REFUSED 77 (PAQ.665)
DON'T KNOW 99 (PAQ.665)

PAQ.660 How much time {do you/does SP} spend doing **vigorous**–intensity sports, fitness or recreational activities on a typical day?

PROBE IF NEEDED: Think about a typical day when {you do/SP does} vigorous-intensity sports, fitness or recreational activities.

SOFT EDIT: >4 HOURS.
ERROR MESSAGE: INTERVIEWER, YOU HAVE RECORDED THAT THE SP SPENDS MORE THAN 4 HOURS DOING VIGOROUS-INTENSITY RECREATIONAL ACTIVITIES ON A TYPICAL DAY. PLEASE CONFIRM WITH SP THAT OVER 4 HOURS IS CORRECT.

Q/U

APPENDIX E: con't.

HARD EDIT: ≥24 HOURS.
HARD EDIT: <10 MINUTES.
ERROR MESSAGE: THE TIME SHOULD BE 10 MINUTES OR MORE, BUT LESS THAN 24 HOURS.

|_|_|_|
ENTER NUMBER OF MINUTES OR HOURS

REFUSED 7777 (PAQ.665)
DON'T KNOW 9999 (PAQ.665)

|_|
ENTER UNIT

MINUTES 1
HOURS 2

PAQ.665 In a typical week {do you/does SP} do any **moderate**-intensity sports, fitness, or recreational activities that cause a **small increase** in breathing or heart rate such as brisk walking, bicycling, swimming, or golf for **at least 10 minutes continuously**?

YES	1	
NO	2	(PAQ.680)
REFUSED	7	(PAQ.680)
DON'T KNOW	9	(PAQ.680)

PAQ.670 In a typical week, on how many days {do you/does SP} do **moderate**-intensity sports, fitness or recreational activities?

PROBE IF NEEDED: Moderate-intensity sports, fitness or recreational activities cause small increases in breathing or heart rate and is done for at **least 10 minutes continuously**.

HARD EDIT: 1-7.
ERROR MESSAGE: THE NUMBER OF DAYS SHOULD BE BETWEEN 1 AND 7.

|_|_|
ENTER NUMBER OF DAYS

REFUSED	77	(PAQ.680)
DON'T KNOW	99	(PAQ.680)

PAQ.675
Q/U

How much time {do you/does SP} spend doing **moderate**-intensity sports, fitness or recreational activities on a typical day?

PROBE IF NEEDED: Think about a typical day when {you do/SP does} moderate-intensity sports, fitness or recreational activities.

APPENDIX E: con't.

PROBE IF NEEDED: Moderate-intensity sports, fitness or recreational activities cause small increases in breathing or heart rate and is done for at **least 10 minutes continuously**.

SOFT EDIT: >4 HOURS.
ERROR MESSAGE: INTERVIEWER, YOU HAVE RECORDED THAT THE SP SPENDS MORE THAN 4 HOURS DOING MODERATE-INTENSITY RECREATIONAL ACTIVITIES ON A TYPICAL DAY. PLEASE CONFIRM WITH SP THAT OVER 4 HOURS IS CORRECT.

HARD EDIT: >24 HOURS.
HARD EDIT: <10 MINUTES.
ERROR MESSAGE: THE TIME SHOULD BE 10 MINUTES OR MORE, BUT LESS THAN 24 HOURS.

|___|
ENTER NUMBER OF MINUTES OR HOURS

REFUSED 7777 (PAQ.680)
DON'T KNOW 9999 (PAQ.680)

|_|
ENTER UNIT

MINUTES 1
HOURS 2

PAQ.680
Q/U

The following question is about sitting at work, at home, getting to and from places, or with friends, including time spent sitting at a desk, traveling in a car or bus, reading, playing cards, watching television, or using a computer. Do not include time spent sleeping.

How much time {do you/does SP} usually spend sitting on a typical day?

|___|
ENTER NUMBER OF MINUTES OR HOURS

REFUSED ..... 7777 (BOX 2)
DON'T KNOW ..... 9999 (BOX 2)

|_|
ENTER UNIT

MINUTES 1
HOURS 2

SOFT EDIT: 18 HOURS OR MORE.
ERROR MESSAGE: PLEASE VERIFY TIMES OF 18 HOURS OR MORE.

HARD EDIT: 24 HOURS OR MORE.
ERROR MESSAGE: THE TIME SHOULD BE LESS THAN 24 HOURS.

APPENDIX E: con't.

BOX 2
CHECK ITEM PAQ.720:
IF SP AGE 18+, GO TO NEXT SECTION.

PAQ.706 Now I'd like to ask you some questions about {your/SP's} activities.

During the **past 7 days**, on how many days {were you/was SP} physically active for a total of **at least 60 minutes per day**? Add up all the time {you/he/she} spent in any kind of physical activity that increased {your/his/her} heart rate and made {you/him/her} breathe hard some of the time.

0 days..... 0
1 day..... 1
2 days..... 2
3 days..... 3
4 days..... 4
5 days..... 5
6 days..... 6
7 days..... 7
REFUSED 77
DON'T KNOW 99

PAQ.710 Now I will ask you first about TV watching and then about computer use.

Over the past 30 days, on average how many **hours per day** did {you/SP} sit and watch TV or videos? Would you say . . .

less than 1 hour, ... 0
1 hour, ... 1
2 hours, ... 2
3 hours, ... 3
4 hours, ... 4
5 hours or more, or 5
{You do/SP does} not watch TV or videos..... 8
REFUSED 77
DON'T KNOW 99

PAQ.715 Over the past 30 days, on average how many **hours per day** did {you/SP} use a computer or play computer games outside of school? Include time spent on things such as Xbox, PlayStation, an iPod, an iPad or other

APPENDIX E: con't.

tablet, a smart phone, YouTube, Facebook or other social networking tools, and the internet. Would you say

. . .

less than 1 hour, ... 0
1 hour, ... 1
2 hours, ... 2
3 hours, ... 3
4 hours, ... 4
5 hours or more, or 5
{You do/SP does} not use a computer outside of work or school 8
REFUSED 77
DON'T KNOW 99

HELP SCREEN:

If the SP watches T.V. or video at the same time as working on the computer, count this time as watching T.V.
or video.

APPENDIX F: INTERNATIONAL-PROSTATE SYMPTOM SCORE (I-PSS) QUESTIONNAIRE

INTERNATIONAL-PROSTATE SYMPTOM SCORE (I-PSS)

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

Total I-PSS Score S =

APPENDIX F. International-Prostate Symptom Score (I-PSS) (CONTINUED)

QUALITY OF LIFE DUE TO URINARY SYMPTOMS

		Delighted	Pleased	Mostly Satisfied	Mixed About Equally Satisfied and Dissatisfied	Mostly Dissatisfied	Unhappy	Terrible
1	If you were to spend the rest of your life with your urinary condition just the way it is now, how would you feel about that?	0	1	2	3	4	5	6

Quality of life assessment index L =

APPENDIX G: HR-QOL (SF-36) QUESTIONNAIRE

SF-36 QUESTIONNAIRE

Name:_____ Ref. Dr:_____ Date: _____

ID#: _____ Age: _____ Gender: M / F

Please answer the 36 questions of the **Health Survey** completely, honestly, and without interruptions.

GENERAL HEALTH:
In general, would you say your health is:
○ Excellent ○ Very Good ○ Good ○ Fair ○ Poor

Compared to one year ago, how would you rate your health in general now?
○ Much better now than one year ago
○ Somewhat better now than one year ago
○ About the same
○ Somewhat worse now than one year ago
○ Much worse than one year ago

LIMITATIONS OF ACTIVITIES:
The following items are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports.
○ Yes, Limited a lot ○ Yes, Limited a Little ○ No, Not Limited at all

Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf
○ Yes, Limited a Lot ○ Yes, Limited a Little ○ No, Not Limited at all

Lifting or carrying groceries
○ Yes, Limited a Lot ○ Yes, Limited a Little ○ No, Not Limited at all

Climbing several flights of stairs
○ Yes, Limited a Lot ○ Yes, Limited a Little ○ No, Not Limited at all

Climbing one flight of stairs
○ Yes, Limited a Lot ○ Yes, Limited a Little ○ No, Not Limited at all

Bending, kneeling, or stooping
○ Yes, Limited a Lot ○ Yes, Limited a Little ○ No, Not Limited at all

Walking more than a mile
○ Yes, Limited a Lot ○ Yes, Limited a Little ○ No, Not Limited at all

Walking several blocks
○ Yes, Limited a Lot ○ Yes, Limited a Little ○ No, Not Limited at all

Walking one block
○ Yes, Limited a Lot ○ Yes, Limited a Little ○ No, Not Limited at all

APPENDIX G: con't.

Bathing or dressing yourself
○Yes, Limited a Lot ○Yes, Limited a Little ○No, Not Limited at all

PHYSICAL HEALTH PROBLEMS:
During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

Cut down the amount of time you spent on work or other activities
○Yes ○No

Accomplished less than you would like
○Yes ○No

Were limited in the kind of work or other activities
○Yes ○No

Had difficulty performing the work or other activities (for example, it took extra effort)
○Yes ○No

EMOTIONAL HEALTH PROBLEMS:
During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

Cut down the amount of time you spent on work or other activities
○Yes ○No

Accomplished less than you would like
○Yes ○No

Didn't do work or other activities as carefully as usual
○Yes ○No

SOCIAL ACTIVITIES:
Emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?

○Not at all ○Slightly ○Moderately ○Severe ○Very Severe

PAIN:
How much bodily pain have you had during the past 4 weeks?

○None ○Very Mild ○Mild ○Moderate ○Severe ○Very Severe

During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?

○Not at all ○A little bit ○Moderately ○Quite a bit ○Extremely

APPENDIX G: con't.

ENERGY AND EMOTIONS:
These questions are about how you feel and how things have been with you during the last 4 weeks. For each question, please give the answer that comes closest to the way you have been feeling.

Did you feel full of pep?
- All of the time
- Most of the time
- A good Bit of the Time
- Some of the time
- A little bit of the time
- None of the Time

Have you been a very nervous person?
- All of the time
- Most of the time
- A good Bit of the Time
- Some of the time
- A little bit of the time
- None of the Time

Have you felt so down in the dumps that nothing could cheer you up?
- All of the time
- Most of the time
- A good Bit of the Time
- Some of the time
- A little bit of the time
- None of the Time

Have you felt calm and peaceful?
- All of the time
- Most of the time
- A good Bit of the Time
- Some of the time
- A little bit of the time
- None of the Time

Did you have a lot of energy?
- All of the time
- Most of the time
- A good Bit of the Time
- Some of the time
- A little bit of the time
- None of the Time

APPENDIX G: con't.

Have you felt downhearted and blue?
- All of the time
- Most of the time
- A good Bit of the Time
- Some of the time
- A little bit of the time
- None of the Time

Did you feel worn out?
- All of the time
- Most of the time
- A good Bit of the Time
- Some of the time
- A little bit of the time
- None of the Time

Have you been a happy person?
- All of the time
- Most of the time
- A good Bit of the Time
- Some of the time
- A little bit of the time
- None of the Time

Did you feel tired?
- All of the time
- Most of the time
- A good Bit of the Time
- Some of the time
- A little bit of the time
- None of the Time

SOCIAL ACTIVITIES:
During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)?

- All of the time
- Most of the time
- Some of the time
- A little bit of the time
- None of the Time

APPENDIX G: con't.

GENERAL HEALTH:
How true or false is each of the following statements for you?

I seem to get sick a little easier than other people
○Definitely true ○Mostly true ○Don't know ○Mostly false ○Definitely false

I am as healthy as anybody I know
○Definitely true ○Mostly true ○Don't know ○Mostly false ○Definitely false

I expect my health to get worse
○Definitely true ○Mostly true ○Don't know ○Mostly false ○Definitely false

My health is excellent
○Definitely true ○Mostly true ○Don't know ○Mostly false ○Definitely false

APPENDIX H: PGI-S QUESTIONNAIRE

PGI Scales PGI-S (Severity) Scale

Please choose the response below that best describes the severity of your symptoms over the past 4 weeks.

1. None.
2. Mild.
3. Moderate.
4. Severe.
5. Very severe.

APPENDIX I: PGI-C QUESTIONNAIRE

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 J: CHRONIC LIVER DISEASE QUESTIONNAIRE (CLDQ)

THE CHRONIC LIVER DISEASE QUESTIONNAIRE

(CLDQ)—QUALITY OF LIFE INDEX FOR PATIENTS WITH CHRONIC LIVER DISEASE

This questionnaire is designed to find out how you have been feeling during the last two weeks. You will be asked about your symptoms related to your liver disease, how you have been affected in doing activities, and how your mood has been. Please complete all of the questions and select only one response for each question.

RESPONSE OPTIONS

1 All of the time

2 Most of the time

3 A good bit of the time

4 Some of the time

5 A little of the time

6 Hardly any of the time

7 None of the time

QUESTIONS

1. How much of the time during the last two weeks have you been troubled by a feeling of abdominal bloating?

2. How much of the time have you been tired or fatigued during the last two weeks?

3. How much of the time during the last two weeks have you experienced bodily pain?

4. How often during the last two weeks have you felt sleepy during the day?

5. How much of the time during the last two weeks have you experienced abdominal pain?

6. How much of the time during the last two weeks has shortness of breath been a problem for you in your daily activities?

7. How much of the time during the last two weeks have you not been able to eat as much as you would like?

8. How much of the time in the last two weeks have you been bothered by having decreased strength?

9. How often during the last two weeks have you had trouble lifting or carrying heavy objects?

10. How often during the last two weeks have you felt anxious?

11. How often during the last two weeks have you felt a decreased level of energy?

12. How much of the time during the last two weeks have you felt unhappy?

13. How often during the last two weeks have you felt drowsy?

14. How much of the time during the last two weeks have you been bothered by a limitation of your diet?

15. How often during the last two weeks have you been irritable?

16. How much of the time during the last two weeks have you had difficulty sleeping at night?

17. How much of the time during the last two weeks have you been troubled by a feeling of abdominal discomfort?

18. How much of the time during the last two weeks have you been worried about the impact your liver disease has on your family?

19. How much of the time during the last two weeks have you had mood swings?

20. How much of the time during the last two weeks have you been unable to fall asleep at night?

21. How often during the last two weeks have you had muscle cramps?

22. How much of the time during the last two weeks have you been worried that your symptoms will develop into major problems?

23. How much of the time during the last two weeks have you had a dry mouth?

24. How much of the time during the last two weeks have you felt depressed?

25. How much of the time during the last two weeks have you been worried about your condition getting worse?

26. How much of the time during the last two weeks have you had problems concentrating?

27. How much of the time have you been troubled by itching during the last two weeks?

28. How much of the time during the last two weeks have you been worried about never feeling any better?

29. How much of the time during the last two weeks have you been concerned about the availability of a liver if you need a liver transplant?

APPENDIX K: SEXUAL DESIRE AND DISTRESS QUESTIONNAIRE

PROVIDE A 7-PAGE PRINTOUT OF THE FOLLOWING QUESTION FOR SUBJECTS TO COMPLETE DURING SCREENING, AND PRIOR TO WEEKS 4, 8, 12, 16, 20, 24, 30, AND 36.

Sexual Desire Question: Daily Rating

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

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

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

PROVIDE A SINGLE PAGE PRINTOUT OF THE FOLLOWING QUESTION FOR SUBJECTS TO COMPLETE DURING SCREENING, AND PRIOR TO WEEKS 4, 8, 12, 16, 20, 24, 30, AND 36.

Sexual Distress Question: Weekly Rating

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

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

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

APPENDIX L: SPONSOR SIGNATURES

Study Title: **A Phase 2, Randomized Double-Blind, Placebo-Controlled, Multi-Center Study to Assess the Efficacy, Safety and Tolerability of Oral LPCN 1144 in Subjects with Nonalcoholic Steatohepatitis (NASH)**

Study Number: LPCN 1144-18-002

Final Date: 7 January 2020

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

Signed [redacted]

Date: 01/07/2020

Vice President, Product Development
Lipocine Inc.

13 REFERENCES

i Chalasani N, Younossi Z, Lavine JE, et al. The diagnosis and management of non-alcoholic fatty liver disease: practice Guideline by the American Association for the Study of Liver Diseases, American College of Gastroenterology, and the American Gastroenterological Association. Hepatology. 2012;55:2005–2023.
ii Loomba R, Sanyal AJ. The global NAFLD epidemic. Nat Rev Gastroenterol Hepatol. 2013;10:686–690.
iii Vernon G, Baranova A, Younossi ZM. Systematic review: the epidemiology and natural history of non-alcoholic fatty liver disease and non-alcoholic steatohepatitis in adults. Aliment Pharmacol Ther. 2011;34:274–285.
iv Fraser A, Longnecker MP, Lawlor DA. Prevalence of elevated alanine aminotransferase among US adolescents and associated factors: NHANES 1999–2004. Gastroenterology. 2007;133:1814–1820.
v Williams CD, Stengel J, Asike MI, et al. Prevalence of nonalcoholic fatty liver disease and nonalcoholic steatohepatitis among a largely middle-aged population utilizing ultrasound and liver biopsy: a prospective study. Gastroenterology. 2011;140:124–131.
vi Adams LA, Lymp JF, St Sauver J, et al. The natural history of nonalcoholic fatty liver disease: a population-based cohort study. Gastroenterology. 2005;129:113–121.
vii Bhala N, Angulo P, van der Poorten D, et al. The natural history of nonalcoholic fatty liver disease with advanced fibrosis or cirrhosis: an international collaborative study. Hepatology.
viii Singh S, Allen AM, Wang Z, Prokop LJ, Murad MH, Loomba R. Fibrosis Progression in Nonalcoholic Fatty Liver vs Nonalcoholic Steatohepatitis: A Systematic Review and Meta-analysis of Paired-Biopsy Studies. Clin Gastroenterol Hepatol. 2014
ix Teli MR, James OF, Burt AD, Bennett MK, Day CP. The natural history of nonalcoholic fatty liver: a follow-up study. Hepatology. 1995;22:1714–1719.
x Adams LA, Sanderson S, Lindor KD, Angulo P. The histological course of nonalcoholic fatty liver disease: a longitudinal study of 103 patients with sequential liver biopsies. J Hepatol. 2005;42:132–138.
xi Matteoni CA, Younossi ZM, Gramlich T, Boparai N, Liu YC, McCullough AJ. Nonalcoholic fatty liver disease: a spectrum of clinical and pathological severity. Gastroenterology. 1999;116:1413–1419.
xii McPherson S, Hardy T, Henderson E, Burt AD, Day CP, Anstee QM. Evidence of NAFLD progression from steatosis to fibrosing-steatohepatitis using paired biopsies: Implications for prognosis and clinical management. J Hepatol. 2015;62:1148–1155.
xiii Singh S, Allen AM, Wang Z, Prokop LJ, Murad MH, Loomba R. Fibrosis Progression in Nonalcoholic Fatty Liver vs Nonalcoholic Steatohepatitis: A Systematic Review and Meta-analysis of Paired-Biopsy Studies. Clin Gastroenterol Hepatol. 2014
xiv Pais R, Charlotte F, Fedchuk L, et al. A systematic review of follow-up biopsies reveals disease progression in patients with non-alcoholic fatty liver. J Hepatol. 2013;59:550–556.
xv Loomba R, Abraham M, Unalp A, et al. Association between diabetes, family history of diabetes, and risk of nonalcoholic steatohepatitis and fibrosis. Hepatology. 2012;56:943–951.
xvi Grundy SM, Cleeman JI, Daniels SR, et al. Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement. Circulation. 2005;112:2735–2752.
xvii Noureddin M, Yates KP, Vaughn IA, et al. Clinical and histological determinants of nonalcoholic steatohepatitis and advanced fibrosis in elderly patients. Hepatology. 2013;58:1644–1654.
xviii Williams CD, Stengel J, Asike MI, et al. Prevalence of nonalcoholic fatty liver disease and nonalcoholic steatohepatitis among a largely middle-aged population utilizing ultrasound and liver biopsy: a prospective study. Gastroenterology. 2011;140:124–131.
xix Wong VW, Wong GL, Choi PC, et al. Disease progression of non-alcoholic fatty liver disease: a prospective study with paired liver biopsies at 3 years. Gut. 2010;59:969–974.
xx Vernon G, Baranova A, Younossi ZM. Systematic review: the epidemiology and natural history of non-alcoholic fatty liver disease and non-alcoholic steatohepatitis in adults. Aliment Pharmacol Ther. 2011;34:274–285.
xxi Fassio E, Alvarez E, Dominguez N, Landeira G, Longo C. Natural history of nonalcoholic steatohepatitis: a longitudinal study of repeat liver biopsies. Hepatology. 2004;40:820–826.
xxii Argo CK, Northup PG, Al-Osaimi AM, Caldwell SH. Systematic review of risk factors for fibrosis progression in non-alcoholic steatohepatitis. J Hepatol. 2009;51:371–379.

xxiii Wong VW, Wong GL, Choi PC, et al. Disease progression of non-alcoholic fatty liver disease: a prospective study with paired liver biopsies at 3 years. Gut. 2010;59:969–974.
xxiv Hamaguchi E, Takamura T, Sakurai M, et al. Histological course of nonalcoholic fatty liver disease in Japanese patients: tight glycemic control, rather than weight reduction, ameliorates liver fibrosis. Diabetes Care. 2010;33:284–286.
xxv Neuschwander-Tetri BA, Caldwell SH. Nonalcoholic steatohepatitis: summary of an AASLD Single Topic Conference. Hepatology. 2003;37:1202–1219.
xxvi Wong RJ, Cheung R, Ahmed A. Nonalcoholic steatohepatitis is the most rapidly growing indication for liver transplantation in patients with hepatocellular carcinoma in the U.S. Hepatology. 2014;59:2188–2195.
xxvii Wong RJ, Aguilar M, Cheung R, et al. Nonalcoholic Steatohepatitis Is the Second Leading Etiology of Liver Disease Among Adults Awaiting Liver Transplantation in the United States. Gastroenterology. 2014
xxviii Hashimoto E, Yatsuji S, Tobari M, et al. Hepatocellular carcinoma in patients with nonalcoholic steatohepatitis. J Gastroenterol. 2009;44(Suppl 19):89–95.
xxix Sanyal A.J, Calsani N., Kowdley K.V. et al. Pioglitazone, Vitamin E, or Placebo for Nonalcoholic Steatohepatitis. N Engl J Med 2010;362:1675-1685
xxx Bendich A, Machlin LJ. Safety of oral intake of vitamin E. Am J Clin Nutr 1988; 48(3):612-619.
xxxi Machlin LJ. Use and safety of elevated dosages of vitamin E in adults. Int J Vitam Nutr Res Suppl 1989; 30:56-68.
xxxii Testosterone stopping criteria based on guidance from the FDA received 7-15-19 and 8-15-19.
xxxiii Bendich A, Machlin LJ. Safety of oral intake of vitamin E. Am J Clin Nutr 1988; 48(3):612-619.
xxxiv Machlin LJ. Use and safety of elevated dosages of vitamin E in adults. Int J Vitam Nutr Res Suppl 1989; 30:56-68.
xxxv Bhasin S, Brito JP, Cunningham GR, et al. Testosterone therapy in men with androgen deficiency syndromes: An endocrine society clinical practice guideline. J Clin Endcocrinol Metab. 2018. Doi: 10.1210/jc.2018-00229
xxxvi Mederacke I, Wursthorn K, Kirschner J, Rifai K, Manns MP, Wedemeyer H, Bahr MJ, Food intake increase liver stiffness in patients with chronic or resolved hepatitis C virus infection. Liver International 2009; 29:1500-1506
xxxvii Arena U, Lupsor Platon M, Stasi C, Moscarella S, Assarat A, Bedogni G, Piazzolla V, et el. Liver stiffness is influenced by a standardized meal in patient with chronic hepatitis C virus at different stages of fibrotic evolution. Hepatology 2013;58:65:-75