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Oral LPCN 1148 improves sarcopenia and hepatic encephalopathy in male patients with cirrhosis: A randomized, placebo-controlled phase 2 trial

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Abstract

Background and Aims: Sarcopenia is highly prevalent in patients with liver cirrhosis and is associated with adverse clinical outcomes, including HE. Androgen receptor agonists, androgen receptor agonists, can address these conditions through multimodal mechanisms of action; however, their safety and efficacy in patients with cirrhosis have not been well established.

Approach and Results: In this multicenter, double-blind, phase 2 trial, men with sarcopenia and cirrhosis awaiting liver transplant were randomized 1:1 to receive either oral Androgen Receptor Agonist LPCN 1148 or placebo for 24 weeks (NCT04874350). The primary end point was the change from baseline to 24 weeks in skeletal muscle index measured by a CT scan of the

Abbreviations: ARA, androgen receptor agonist; HU, Hounsfield Unit; IMAT, intramuscular adipose tissue; L3-SMI, Skeletal Muscle Index of the third lumbar region; LFI, Liver Frailty Index; SMI, Skeletal Muscle Index.

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L3 region, analyzed with a prespecified modified intent-to-treat population. The secondary end point was the number of overt HE events. Twenty-nine participants (mean age = 59 y, MELD = 17) received at least 1 dose of LPCN 1148 (n = 15) or placebo (n = 14). Baseline characteristics were similar between groups. Primary end point analysis demonstrated an increase in L3-skeletal muscle index measured by a CT scan of the L3 region in the LPCN 1148 group (n = 15) compared to placebo (n = 10), with a mean group difference of 4.4 cm^2/m^2 (95% CI: 1.3–7.4 cm^2/m^2, $p = 0.007$). Participants in LPCN 1148 experienced fewer episodes of overt HE (Common Terminology Criteria for Adverse Events grade ≥ 2; $p = 0.02$) than placebo. The number and severity of treatment-emergent adverse events were similar between arms.

Conclusions: LPCN 1148 treatment improved sarcopenia and reduced the number of overt HE episodes in men with cirrhosis and sarcopenia awaiting liver transplant. These findings support additional research on the efficacy of LPCN 1148 in treating sarcopenia and preventing HE recurrence.

Keywords: androgen, CT, intramuscular adipose tissue, liver disease, muscle loss

INTRODUCTION

Sarcopenia is an important determinant of clinically meaningful outcomes in patients with cirrhosis.[1] While sarcopenia is commonly present in those with metabolic dysfunction–associated steatohepatitis and alcohol-associated liver disease,[2,3] 2 common causes of cirrhosis, it is typically worse in those with clinically decompensated cirrhosis, especially those with ascites and encephalopathy.[4] Sarcopenia in patients with cirrhosis is associated with higher overall mortality, more severe HE, worse pretransplant, peritransplant, and post-transplant outcomes, and reduced quality of life and ability to conduct activities of daily living.[5–7] While targeting sarcopenia to improve these outcomes is an important objective of care for these patients, this paradigm remains to be experimentally verified.

The pathogenesis of sarcopenia in patients with cirrhosis is multifactorial, including reduced physical activity, nutritional deficiencies, endocrine abnormalities, hyperammonemia, and inflammation. These changes alter, in part, myostatin activation and Akt-mediated mammalian target of rapamycin signaling pathways, which result in an impaired balance between muscle synthesis and degradation. Androgens are key modulators of several pathways linked to the pathogenesis of sarcopenia and decrease muscle turnover while supporting muscle growth.[8]

LPCN 1148 comprises an orally available androgen receptor agonist (ARA), testosterone dodecanoate. Studies using an oral ARA have reported improvements in steatotic liver disease[9] and muscle mass[10] independent of gonadal status. Through its androgenic properties, it was hypothesized that LPCN 1148 would enhance muscle mass and hematopoiesis in those with advanced cirrhosis. Additionally, these improvements were expected to ameliorate HE[11] and anemia. Therefore, a phase 2 multicenter, randomized, placebo-controlled, double-blind trial was conducted to test the hypothesis that LPCN1148 can safely improve sarcopenia and other clinical outcomes in male patients with cirrhosis and sarcopenia. The results after 24 weeks of drug or placebo exposure, the principal time point for primary end point analysis, are presented below.

METHODS

Study design and participants

LPCN 1148-21-001 (NCT#04874350) is a two-stage phase 2 clinical trial, including a 24-week randomized, double-blind, placebo-controlled stage 1 (participants randomized 1:1, to receive either oral ARA LPCN 1148 or placebo) followed by a 28-week single-arm open-label extension stage 2. Analyses from stage 1 are reported here, with week 24 being the primary end point for the analysis of the study. Stage 2, an exploratory open-label extension, final data analyses are ongoing at

the time of this writing. Participants reported to 1 of 8 study centers within the United States. For six sites, the protocol and all amendments were approved by a central IRB (Advarra; Columbia, MD, USA). Local IRBs approved the protocol and all amendments for Drs. Danford (IRB #1051767) and Carey (IRB #21-010747).. Site investigators were required to submit, maintain, and archive study essential documents according to the International Conference on Harmonization. The study was conducted according to the International Conference on Harmonization Good Clinical Practice guidelines and the Declarations of Helsinki and Istanbul. Written informed consent was obtained by the participant or their legal representative.

Patients assessed for eligibility were referred by clinicians and included adult males on, or being evaluated for, the liver transplant list due to liver cirrhosis. Assessment of basal testosterone level was not required for study eligibility, and there were no restrictions or modifications to diet, exercise, or background therapies (including rifaximin or lactulose; see Supplemental Materials for breakdown, http://links.lww.com/HEP/J241), with the exception of substance abuse. Additional eligibility requirements included (1) male adults 18 years of age or above, and (2) evidence of sarcopenia, defined by height-adjusted skeletal muscle area, termed skeletal muscle index (SMI) on abdominal CT scan capturing the L3 region. L3-SMI cutoffs for sarcopenia were determined mainly in populations of elderly, or in those with liver cirrhosis secondary to alcohol or viral hepatitis. When the etiology of cirrhosis is not associated with alcohol or viral hepatitis, patients are characterized by high rates of obesity. Thus, cutoff thresholds for determining evidence of sarcopenia were adapted from previous studies by linear extrapolation for BMI >30,[12,13] as reported in Supplemental Materials, http://links.lww.com/HEP/J241.

Key exclusion criteria included (1) suspected or proven HCC, (2) history of uncontrolled or recurrent portal hypertensive bleeding, complications of ascites (eg, spontaneous bacterial peritonitis) in the past 6 months, or having a TIPS procedure in the past 6 months, (3) MELD score >25, (4) acute liver failure as an indication for addition to the liver transplant list, and (5) participants currently receiving androgens. Active substance abuse, including alcohol, was also an exclusion criterion and was tested by urine and breath tests at the beginning of each study visit. Additional details on inclusion and exclusion criteria are provided in the Supplemental Materials, http://links.lww.com/HEP/J241.

Randomization and masking

Participants meeting the enrollment criteria were randomly assigned (1:1) to receive LPCN 1148 or placebo study intervention kits upon entering the clinic on the first study day. Stratified balanced block randomization was carried out by central assignment in site-specific blocks of 2. An independent Data Monitoring Committee, consisting of preidentified personnel, reviewed unblinded safety and efficacy data on a regular basis throughout the study. Dose reductions and discontinuations were triggered by a safety monitor and were required if participants met criteria for elevated blood pressure, prostate-specific antigen, hematocrit, or testosterone (see Supplemental Materials, http://links.lww.com/HEP/J241); however, all other study personnel remained blinded.

Procedures

Demographic data were collected, and all participants underwent unenhanced CT scans of the skeletal muscle area at the third lumbar region unless a historical CT scan of the L3 region was available within 30 days from screening, for confirmation of sarcopenia status prior to any intervention. The skeletal muscle area was normalized for the participant's height at screening, providing the SMI of this region (L3-SMI), a well-established marker of sarcopenia in a cirrhotic population.[14,15] Randomized participants were allocated to either oral LPCN 1148 or matching oral placebo on day 1. LPCN 1148 treatment consisted of testosterone dodecanoate capsules at a dose of 300 mg twice daily. Testosterone levels were measured in the morning of each visit, ~4 hours following dose administration. If a dose reduction was triggered by the safety monitor, the dose was reduced by 50% (150 mg twice daily). If the abnormality persisted, dosing was then discontinued. If treatment was discontinued, the participants were encouraged to remain in the study and complete procedures per protocol, in which case their data were still included in safety analyses. Participants who underwent liver transplants discontinued treatment but were invited to remain in the study; however, no post-liver transplant data were included in the analyses.

Following the first study visit, participants reported to the clinic every 4 weeks, up to week 24, for drug accountability checks and study procedures. CT scans were obtained at baseline (ie, screening visit) and weeks 12 and 24 for the evaluation of L3-SMI and muscle composition. Muscles were identified using previously validated Hounsfield Unit (HU) threshold values of −29 to +150 HU.[16] Intramuscular adipose tissue (IMAT) area was identified using HU threshold values of −190 to −30 HU, poor-quality muscle area was defined by the range of −29 to +29 HU, and high-quality muscle area was defined by the range of +30 to +150 HU.[17,18] Dedicated central radiologists interpreted all CT scans blinded to treatment. HE was assessed using the five-point West Haven Criteria scale (range 0–4) and a validated electronic Stroop test (EncephalApp[19])

at screening, week 12 and week 24. Physical function was assessed by the 6-minute walk test and the Liver Frailty Index (LFI) at screening and weeks 12 and 24. LFI was also assessed at weeks 4, 8, 16, and 20. Clinical status was assessed by the patient global impressions of change scale (7-point scale, range 1–7) on day 1 and weeks 4, 8, 12, 16, 20, and 24. Clinical biomarkers were collected at screening, day 1, and weeks 4, 8, 12, 16, 20, and 24. At these same time points, the international normalized ratio and MELD were calculated. Participants were assessed for adverse events at each study visit.

Outcomes

The study's primary end point analysis time point was week 24. End points were based on the comparisons between and within LPCN 1148 and placebo-treated groups. The primary end point was the change from baseline in L3-SMI week 24. Prespecified key end points included events of breakthrough overt HE, with a prespecified definition of an increase in the West Haven Criteria scale from 0 or 1 to ≥ 2. However, the frequency in which West Haven Criteria scores were captured was insufficient to provide meaningful resolution on HE events. Thus, in post hoc analyses, breakthrough overt HE was defined as HE adverse events greater than Common Terminology Criteria for Adverse Events v 5.0 grade 1. Additionally, recurrence of overt HE was defined as an overt HE event during the study in participants with a medical history of HE. Other secondary end points included the change from baseline in L3-SMI at week 12; the change from baseline in IMAT, poor quality muscle area, and high-quality muscle area at week 24; the change in functional assessments at week 24, including the 6-minute walk test, LFI, and electronic Stroop test; the change from baseline in clinical biomarkers at week 24; the score of the patient global impressions of change scale at week 24; and the number of safety events at week 24, comprised of total decompensation events, liver transplants, and all-cause mortality.

Statistical analysis

All hypotheses were tested against two-sided alternatives, using procedures at the nominal level α of 0.05. As a proof-of-concept study, no formal power and sample size calculations were performed.

Two prespecified study populations were used for data analysis. All data were analyzed according to the safety population (ie, all randomized participants who received at least one dose of the study drug) with the exception of CT measures. For parameters obtained via CT, including the primary end point, a modified intent-to-treat (mITT) population was evaluated. This prespecified population included all participants who received at least one dose of study treatment and had at least 1 evaluable postbaseline CT at week 12 or 24. Postbaseline CTs were considered nonevaluable if they were not captured or if they met the criteria for low compliance. Low compliance was conservatively defined as missing a total of $\geq 33\%$ of capsules between day 1 and week 12 or between 12 and 24 for the 12- and 24-week assessments, respectively. The number of capsules missed was conservatively calculated with the default assumption that the participant was 100% compliant up to the maximum number of capsules the participant had in their possession.

The prespecified primary outcome measure is presented as the least squares mean estimate and 95% CI (Figure 2) in addition to the group least squares mean difference and 95% CI. An ANCOVA model for treatment differences with baseline as a covariate was employed for both the primary outcome and L3-SMI at week 12. Participant characteristics, demographics, and secondary outcome measures are reported as mean (SD) for continuous data and frequencies and proportions for categorical data. Unpaired *t* tests were used for comparisons of the change from baseline for continuous data, while categorical data were assessed by binomial statistics. For the purpose of hypothesis generation, statistical assumptions were not assessed, and the effect of multiplicity was not controlled for, in secondary end points. Therefore, any significant findings of secondary end points must be interpreted considering the size of this proof-of-concept study. Missing and nonevaluable data were imputed by the last observation carried forward. Analyses were done with SAS version 9.4.

Role of the funding source

The funder, Lipocine Inc., had a role in study design, data collection, data analysis, data interpretation, and writing of the manuscript.

RESULTS

Demographics and baseline characteristics

Forty-eight potential participants were assessed for eligibility between November 30, 2021, and December 16, 2022. A total of 32 participants were randomly assigned to treatment groups, 17 to LPCN 1148 and 15 to placebo (Figure 1). Three participants were removed from the trial prior to receiving any study medication; 2 of whom had been randomized to LPCN 1148 (withdrawal of consent), and one had been randomized to placebo (failed L3-SMI inclusion criteria and was

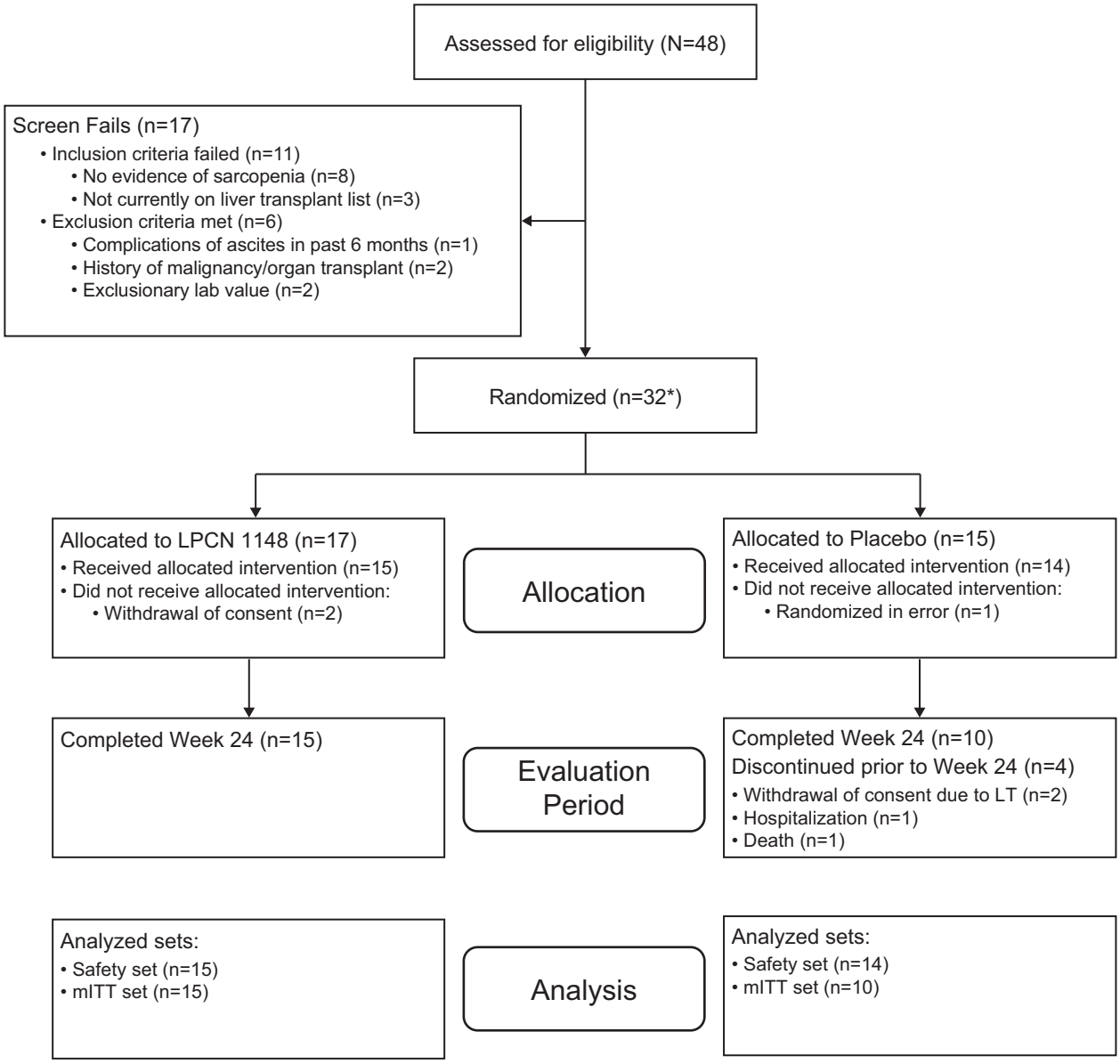

FIGURE 1 Consort diagram for stage 1 of LPCN 1148-21-001 investigating LPCN 1148 in men with cirrhosis of the liver and sarcopenia (NCT# 04874350). The safety set included all randomized participants who received at least 1 dose of study drug. The mITT set was based on prespecified conditions including having a pos-baseline CT scan and compliance criteria. Analyses based on CT parameters (eg, skeletal muscle index of the third lumbar) used the mITT set, whereas all other analyses used the Safety set. Black arrows represent the flow of study events. *Note one screen failed participant was randomized in error and was removed from the study prior to receiving any intervention. Abbreviations: LT, liver transplant; mITT, modified intent-to-treat.

randomized in error). As a result, safety analyses included a total of 29 participants; 15 in the LPCN 1148 group and 14 in the placebo group. The study population was characterized by an average MELD of 17, with 25 (86%) participants having 2 or more decompensation events prior to study enrollment. Of the 22 (76%) participants with a medical history of HE, 21 (96%) were on medical therapy including lactulose, rifaximin, or both. The primary etiology of cirrhosis was alcohol-associated liver disease (n = 16, 55%), and further details on demographics and baseline characteristics can be found in Table 1.

Primary end point—L3-SMI

Four participants from the placebo group were excluded due to missing postbaseline CTs or interrupted dosing prior to week 24, resulting in noncompliance (Figure 1). As a result, 25 participants were included in the primary efficacy analysis set (modified intent-to-treat population, mITT), resulting in 15 and 10 participants in the LPCN 1148 and placebo group, respectively. Note that one participant in the placebo withdrew due to liver transplantation just prior to the week 4 visit, and thus only baseline data are available for this participant.

TABLE 1 Baseline characteristics and demographics of participants in the safety population

	LPCN 1148 (N = 15)	Placebo (N = 14)	Total N = 29)
Characteristics			
Age (y)	58.3 (7.5)	58.8 (9.5)	58.5 (8.4)
Race [n (%)]			
White	13 (87)	11 (79)	24 (83)
Black or African American	0	2 (14.3)	2 (7)
American Indian or Alaskan Native	2 (13)	0	2 (7)
Asian	0	1 (7.1)	1 (3)
Ethnicity [n (%)]			
Hispanic or Latino	2 (13)	1 (7)	3 (10.3)
Not Hispanic or Latino	13 (87)	13 (93)	26 (90)
Height (cm)	176.6 (7.3)	179.1 (8.8)	177.8 (8.0)
Weight (kg)	91.5 (20.8)	93.7 (32.2)	92.6 (26.4)
BMI (kg/m^2)	29.2 (5.5)	29.0 (8.6)	29.1 (7.0)
MELD score	15.9 (3.7)	18.1 (4.6)	16.9 (4.2)
Hemoglobin (g/dL)	11.4 (3.3)	13.2 (2.3)	12.2 (2.9)
Testosterone (ng/dL)	467 (368)	403 (353)	436 (359)
Free testosterone (ng/dL)	4.8 (3.2)	3.8 (3.1)	4.3 (3.2)
Etiology [n (%)]			
Alcohol-associated liver disease	9 (60)	7 (50)	15 (52)
Hepatitis C	2 (13)	4 (29)	6 (21)
Metabolic dysfunction–associated steatohepatitis	4 (27)	2 (14)	6 (21)
Primary sclerosing cholangitis	1 (7)	1 (7)	2 (7)
Alcohol-related liver disease + hepatitis C	1 (7)	0	1 (3)
Medical history [n (%)]			
≥ One decompensation event	14 (93)	14 (100)	28 (97)
≥ Two decompensation events	13 (87)	12 (86)	25 (86)
Esophageal varices	8 (53)	8 (57)	16 (55)
Ascites	11 (73)	10 (71)	21 (72)
Portal hypertension	11 (73)	12 (86)	23 (79)
HE	11 (73)	11 (79)	22 (76)
Medical therapy for HE	11 (100)[a]	10 (91)[a]	21 (96)[a]
Imaging [n (%)]			
L3-SMI (cm^2/m^2)	47.8 (7)	44.8 (9)	46.3 (8)
IMAT area (cm^2)	5.0 (3)	4.3 (4)	4.7 (3)
Poor muscle quality area (cm^2)	47.2 (24)	40.4 (15)	43.9 (20)
High muscle quality area (cm^2)	97.3 (23)	98.5 (23)	97.9 (22)

Note: Data are mean (SD) unless otherwise noted. Frequency data are n/N*100. Safety population consists of all participants who received at least one dose of the study drug. Imaging parameters were obtained via CT of L3 region. Decompensation events included HE, esophageal varices (bleeding and nonbleeding), ascites, portal hypertension, and spontaneous bacterial peritonitis.

[a]Medical therapy for HE is reported for those with a medical history of HE and includes therapies of Lactulose, Rifaximin, or both.

Abbreviations: BMI, body mass index; IMAT, intramuscular adipose tissue; L3-SMI, skeletal muscle index of the third lumbar region.

Efficacy analyses of the mITT cohort on the primary end point revealed a significant treatment effect of LPCN 1148 compared to placebo (Figure 2). By week 24, the least squares mean the difference between LPCN 1148 and placebo was significant at 4.4 cm^2/m^2 (95% CI: 1.3–7.4 cm^2/m^2; $p = 0.007$). For the secondary end point of change in L3-SMI at week 12, 14 participants in LPCN 1148 and 9 in placebo had evaluable CT scans. In these participants, L3-SMI significantly increased from baseline by week 12 with LPCN 1148 ($p = 0.008$), whereas the placebo group remained unchanged at this same time point (Figure 2).

Muscle composition

LPCN 1148 treatment diminished L3 IMAT area (Δ −1.5 ± 2.2 cm^2, $p = 0.037$) and augmented high-quality

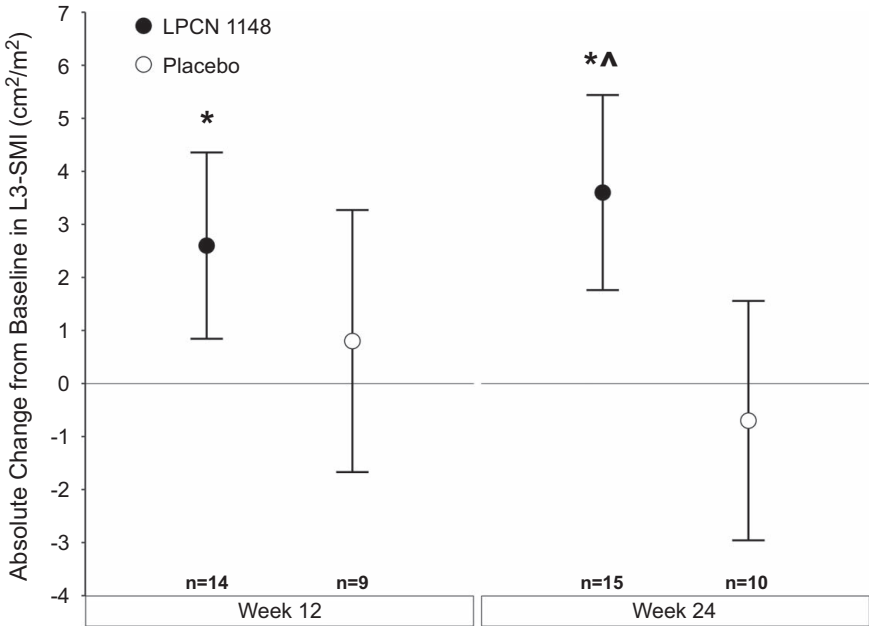

FIGURE 2 Change in L3-SMI following LPCN 1148 treatment. Data are LS mean (95% CI), and last observation carried forward for the change in L3-SMI at weeks 12 (left) and 24 (right). Filled and open symbols represent the LPCN 1148 and Placebo groups, respectively. Baseline mean L3-SMI was not different between LPCN 1148 and placebo groups at week 12 (49.0 ± 1.7 vs. 45.6 ± 2.2 cm^2/m^2) or 24 (47.8 ± 1.8 vs. 45.8 ± 2.3 cm^2/m^2) analyses, respectively. *$p < 0.05$ for change from baseline; ^$p = 0.007$ versus Placebo. Abbreviation: L3-SMI, skeletal muscle index of the third lumbar region.

muscle area (Δ 13.2 ± 14.4, $p = 0.013$) at week 24 compared to baseline. Meaningful changes were not observed for IMAT (Δ -0.3 ± 1.7 cm^2) nor high-quality muscle (Δ -0.3 ± 9.0 cm^2) with placebo treatment ($p > 0.34$). Area designated as poor-quality muscle remained unchanged from baseline in both LPCN 1148 (Δ 0.9 ± 9.9 cm^2) and placebo (Δ -1.3 ± 10.3 cm^2) groups ($p > 0.53$).

Hepatic encephalopathy

LPCN 1148 reduced the number of overt HE events (2 vs. 6; $p = 0.02$), and recurrence of overt HE events (1 vs. 6; $p < 0.05$) compared to placebo. Exploratory analyses examining the time to first recurrence of overt HE found a time of 115 days for the single participant in LPCN 1148 compared to 35.8 ± 34.8 days in placebo (n = 4, 29%) for the 4 participants with recurrent overt HE in placebo. Furthermore, mean hospitalization time associated with overt HE events was lower for LPCN 1148 (n = 1, 1 hospitalization, 3 d) compared to placebo [n = 2, 4 hospitalizations, 8.3 (6.8) days. The total time to complete the EncephalApp Stroop Test run (5 on and 5 off) was similar between LPCN 1148 (216.7 ± 71.2 s) and placebo (172.7 ± 25.3 s) at baseline, and the change at week 24 was not significantly different between LPCN 1148 (Δ -4.8 ± 59.0 s) and placebo (Δ 13.8 ± 37.3 s).

Additional secondary end points

As measured by patient global impressions of change scale, participants treated with LPCN 1148 reported greater improvement in symptoms (3.0 ± 1.0 vs. 3.8 ± 0.9; $p = 0.03$) at week 24 compared to placebo, respectively. Additionally, treatment with LPCN 1148 resulted in a greater increase in hemoglobin compared to placebo (Δ$+1.3 \pm 1.6$ vs. -0.2 ± 0.8 g/dL; $p = 0.005$), respectively. Other clinical biomarkers are reported in Table 2.

Treatment effects on physical functioning were examined by the change from baseline in LFI and the 6-minute walk test at week 24. At baseline, participants were well-matched for both LFI (4.04 ± 0.89 vs. 3.88 ± 1.18; $p > 0.05$) and 6-minute walk test (948 ± 611 vs. 1110 ± 667 ft; $p > 0.05$) in LPCN 1148 and placebo groups, respectively. Following 24 weeks of treatment, the change in both LFI (Δ -0.05 ± 0.68 vs. -0.17 ± 0.58; $p > 0.05$) and the 6-minute walk test (Δ $+270 \pm 494$ vs. -16 ± 966; $p > 0.05$) were not statistically different between LPCN 1148 and placebo groups.

Safety

No participants presented with elevated blood pressure, defined as systolic > 140 mm Hg or diastolic > 90 mm Hg, at baseline. During the 24-week study, 3 (20%)

participants in LPCN 1148 and 2 (14%) participants in placebo met the criteria for elevated blood pressure responses; however, none had a blood pressure >160 mm Hg systolic or >100 mm Hg diastolic.

Discontinuation of study drug occurred in 6 participants in both LPCN 1148 and placebo. Reasons for discontinuation in LPCN 1148 included physician decision to stop treatment following a dose interruption and elevated testosterone (defined as >1500 ng/dL). In the placebo group, treatment was discontinued in 2 participants due to disease progression and four due to liver transplants (mean time in a trial prior to transplant for these participants was 11.2 [5.5] weeks, with transplant occurring just prior to week 4 visit [28 d] in one participant. Of note, there was not an apparent site or region bias for participants with liver transplants. Taken with a mean change from baseline in MELD of 0.3 for these 4 participants, factors external to the study likely contributed to the decision for liver transplantation.

Although liver transplantation led to discontinuation of study drug, participants had the option to remain in the study and complete study procedures per protocol to generate exploratory data. Two participants decided to withdraw consent prior to week 24 (Figure 1), and 2 remained in the study with post-liver transplant data censored from analyses. Three of the 4 participants had data prior to the liver transplant, which met the criteria for inclusion in the mITT analysis.

Adverse events are summarized by event frequency in the safety population ($n=29$; Table 3). At least 1 adverse event was reported in 8 (53%) participants taking LPCN 1148 and 10 (71%) taking placebo. Overall, the most common adverse events were HE (9 events), COVID-19 (4 events), and anemia (4 events). One adverse event related to kidney injury occurred in each group: increased blood creatine phosphokinase (LPCN 1148) and acute kidney injury (placebo). Major decompensation events of ascites, varices and spontaneous bacterial peritonitis were comparable between LPCN 1148 and placebo, respectively (Table 3).

Adverse events categorized as serious occurred in 5 participants in each arm. All serious adverse events were reported as unrelated to the study drug. Severe adverse events, defined as a Common Terminology Criteria for Adverse Events grade ≥ 3, occurred in 4 participants in each arm. The tumor marker, alpha-fetoprotein, remained unchanged for LPCN 1148 and with 24 weeks of treatment (Table 2), and there were no cases of HCC or DILI. Adverse events led to hospitalizations in 5 participants from each study arm, resulting in a total of 54 and 117 days stayed in hospital for LPCN 1148 and placebo participants, respectively. The median length of stay for those hospitalized was 3 days (IQR: 1.8) for LPCN 1148 and 5 days (IQR: 6.3) for placebo. There were no deaths in the LPCN 1148 group reported during the 24-week study, while one participant died in the placebo group.

TABLE 2 Clinical laboratory measurements

		LPCN 1148, n (%)	Placebo, n (%)
	n	15	13
	Baseline	3.6 (0.6)	3.5 (0.7)
Albumin (g/dL)	Week 24	3.7 (0.8)	3.5 (0.7)
	Δ	0.1 (0.5)	−0.1 (0.2)
	n	15	13
	Baseline	5.9 (6.8)	3.7 (1.3)
Alpha-fetoprotein (ng/mL)	Week 24	4.4 (2.5)	3.5 (0.9)
	Δ	−1.5 (6.2)	−0.3 (1.1)
	n	15	13
	Baseline	0.3 (0.2)	0.6 (0.6)
Prostate-specific Ag (ng/mL)	Week 24	0.5 (0.4)	0.8 (0.8)
	Δ	0.3 (0.4)	0.2 (0.6)
	n	15	13
	Baseline	1.1 (0.4)	1.1 (0.3)
Creatinine (mg/dL)	Week 24	1.6 (1.7)	1.1 (0.2)
	Δ	0.5 (1.7)	0.0 (0.2)
	n	15	13
	Baseline	1.8 (1.1)	2.4 (1.3)
Bilirubin (mg/dL)	Week 24	2.0 (1.3)	2.3 (1.3)
	Δ	0.3 (0.7)	0.0 (0.6)
	n	15	13
	Baseline	1.7 (0.3)	1.7 (0.3)
INR	Week 24	1.7 (0.3)	1.6 (0.3)
	Δ	0 (0.3)	−0.1 (0.3)
	n	15	13
	Baseline	15.9 (3.7)	18.2 (4.8)
MELD	Week 24	18.3 (6.7)	17.7 (4.7)
	Δ	2.5 (5.8)	−0.5 (3)
	n	15	13
	Baseline	86.6 (36.2)	95.7 (24)
Sex hormone-binding globulin (nmol/L)	Week 24	76.2 (35.9)	98.7 (33)
	Δ	−10.4 (17.4)	3.0 (25.2)

Note: Data are mean (SD) and last observation carried forward. No significant group differences were observed.
Abbreviation: INR, prothrombin time international normalized ratio.

DISCUSSION

In this double-blinded, multicenter, randomized trial of men with cirrhosis and sarcopenia awaiting liver transplantation, LPCN 1148 therapy resulted in significant improvement in sarcopenia at 24 weeks when

TABLE 3 Adverse events and clinical end points

Safety overview	LPCN 1148 (N = 15)		Placebo (N = 14)	
	n (%)	No. events	n (%)	No. events
Treatment-emergent adverse events (TEAEs)	8 (53)	33	10 (71)	36
Severe TEAEs	4 (27)	6	4 (29)	10
Serious TEAEs	5 (33)	15	5 (36)	16
Adverse events leading to treatment discontinuation	1 (7)	1	3 (21)	6
Most frequent adverse events				
COVID-19	2 (13)	2	2 (14)	2
Epistaxis	2 (13)	2	0	0
Esophageal varices	0	0	3 (21)	3
HE	3 (20)	3	4 (29)	6
HE > grade 1	2 (13)	2	4 (29)	6*
Recurrent HE > grade 1	1 (7)	1	4 (49)	6*
Urinary tract infection	0	0	2 (14)	2
Clinical end points				
Liver transplant	0	—	4 (29)	—
Death	0	—	1 (7)	—

Note: Percentages are calculated as n/N*100. Severe TEAEs, TEAES ≥common terminology criteria for adverse events grade ≥3. Most Frequent Adverse Event were events with >1 participant in a given study arm. AEs Coded using Medical Dictionary for Regulatory Activities v 22·0. Event grade was determined by the Common Terminology Criteria for Adverse Events v 5.0. *$p = 0.02$ compared to LPCN 1148.
Abbreviation: TEAE, treatment-emergent adverse event.

compared with placebo. Furthermore, despite most participants already on background therapies for HE, participants receiving LPCN 1148 also experienced significantly fewer episodes of overt HE compared to those on placebo. Collectively, to our knowledge, LPCN 1148 therapy is the first pharmacologic intervention to demonstrate improvements in both sarcopenia and overt HE outcomes in patients with advanced cirrhosis. These data provide support for further investigation of LPCN 1148 for the treatment of sarcopenia and the prevention of overt HE recurrence in patients with advanced cirrhosis.

Administration of LPCN 1148 for 24 weeks, without any prescribed modifications to diet or exercise, resulted in a placebo-adjusted increase in L3-SMI of 9.3%, with an improvement from baseline occurring as early as week 12 (Figure 2). The androgenic nature of LPCN 1148 may address many of the underlying processes leading to sarcopenia in patients with cirrhosis. ARAs act on multiple pathways regulating protein homeostasis, including Atk, myostatin, and IGF1, which would have a positive impact on sarcopenia and muscle wasting in this population. LPCN 1148 treatment also improved muscle composition as the area of muscle infiltrated by adipose tissue (ie, IMAT) was reduced, and high-quality muscle area increased, compared to baseline values. To our knowledge, this is the first evidence of a pharmacologic intervention attenuating IMAT in this population.

In addition to enhancing muscle, LPCN 1148 treatment resulted in improved clinical outcomes for the recurrence of overt HE compared to placebo. The current standard of care for HE has focused on reducing ammonia levels, with treatments such as rifaximin and lactulose acting to reduce ammonia production in the gut. In the current study, 86% of participants were taking some combination of rifaximin and/or lactulose. Compared to previous work,[20] the rate of breakthrough HE for those on placebo with standard care treatment was slightly higher in the current study. This difference in breakthrough HE events is not unexpected, however, as the presence of sarcopenia increases the risk of HE[21] and increases episodes of HE recurrence. Furthermore standard of care treatments have been shown to be less effective in preventing HE in patients with increased MELD scores.[20] Considering that all participants with overt HE in the current study were taking rifaximin and lactulose, our findings demonstrate that LPCN 1148 offers added benefit compared to standard treatments. While a limited number of HE events and corresponding CT measures in the current study preclude a direct analysis, it has been suggested that augmenting muscle mass and quality may reduce overt HE events through increased metabolism of ammonia.[21]

Liver transplantation remains the only curative treatment option for liver cirrhosis; however, muscle mass has been shown to decline in the period prior to and post-liver transplantation, and is associated with negative post-transplant outcomes.[22] Additionally, liver transplant does not normalize body composition or muscle function to pretransplant values when monitored

over a 12-month period.[22] Consequently, interrupting muscle atrophy and reducing adiposity with LPCN 1148 treatment represents promising therapeutic value for patients pretransplantation, peritransplantation, and post-transplantation.

Improvements in patient-reported symptoms were observed with LPCN 1148 treatment compared to placebo at week 24, with analyses demonstrating differences as early as week 4. Although many secondary indices were trending in a positive direction, LPCN 1148 treatment did not translate into functional improvements compared to placebo. This potentially stems from several factors, including a delay in neuromuscular adaptations compared to muscle growth, along with a large variability within groups in functional assessments due to the end-stage nature of the studied population. Given the improvements in patient symptoms, along with increases in Hb and muscle mass/quality, a longer study period or larger sample size is potentially needed to resolve the benefits of LPCN 1148 on physical functioning in this population.

The current study population of men with advanced liver disease awaiting liver transplantation was characterized by multiple decompensation events and low-normal testosterone values at baseline (Table 1). LPCN 1148 administration was well tolerated during the study period, eliciting adverse events of similar frequency and severity as placebo (Table 3). Specifically, in this small population, adverse events typically associated with androgenic administration, such as cardiovascular-related events and HCC, were not different between the LPCN 1148 and placebo arms. The safety of LPCN 1148 administration is further supported by the comparable clinical biomarkers associated with disease progression observed between LPCN 1148 and placebo groups (Table 2). Although the change in MELD was numerically larger in LPCN 1148, the MELD score is influenced by muscle mass secondary to changes in creatinine.[23] Consequently, neither creatinine nor MELD scores may be appropriate markers of disease progression when considering interventions that alter muscle mass. Acknowledging the small sample size, mortality was similar between LPCN 1148 and placebo groups, with one death occurring in the placebo arm.

Existing literature investigating the safety and efficacy of ARAs in cirrhosis is limited, with most studies from a single center and employing vastly different designs, treatment groups, and outcomes evaluated (for review see the study by Deng et al[24]). Pertinent to the findings of the present study, only 2 randomized clinical trials have evaluated the impact of ARAs on muscle mass in men with cirrhosis, with one being published only in abstract form.[25,26] Sinclair et al,[25] reported ARA administration led to changes in appendicular lean mass without improvements in HE outcomes. However, as sarcopenia was not required for study eligibility,[25] the potential inclusion of participants without sarcopenia may have underestimated the impact of ARAs on changes in muscle mass and clinical outcomes, a barrier addressed in the current study. Additionally, participants in the current study had higher average MELD score, with larger proportion of patients with a medical history of HE, indicating more advanced disease, compared to that of Sinclair et al.[25] Finally, the present study used CT analysis of L3-SMI, considered the "gold standard" for assessing sarcopenia,[27] which offers benefits compared to DEXA as it is not impacted by fluid retention and allows for the simultaneous evaluation of muscle area and quality.[28] As both sarcopenia and myosteatosis are independently associated with overt HE in patients with cirrhosis,[21] characterizations of muscle and intramuscular adipose changes may be critical for the clinical improvement of HE.

Although statistical significance was achieved for prespecified primary and key secondary end points, the results of the present study should be interpreted within the context of the study design. First, this was a proof-of-concept phase 2 study and, while meeting the primary end point, was not powered for secondary analyses. In view of the small sample size, secondary end points in this study should be viewed in the lens of hypothesis generation rather than definitive evidence of the benefit of LPCN 1148 in end-stage liver disease. Second, the results presented herein are following 24 weeks of treatment with LPCN 1148. A longer period of intervention may provide more insight into mortality and functional changes impacting daily living. Third, although the impact of LPCN 1148 on HE events was a prespecified outcome, the spontaneous nature of HE events resulted in limited data collection at event onset. Thus, overt HE analyses presented herein are based on post hoc analyses of adverse event frequency. Fourth, as women were not included in the study population, the generalizability of the present findings is currently constrained to a male population. However, female patients with cirrhosis and lower natural testosterone levels have been shown to exhibit greater signs of muscle wasting and encephalopathy compared to those with higher testosterone levels.[29] This observation suggests that administering an androgen receptor agonist, such as LPCN 1148, even at sex-specific dosages, may offer potential benefits for the female population, highlighting the need for future work in this area. Finally, while trends are expected to be similar for patients at earlier stages of cirrhotic liver disease, these results were observed in an end-stage population characterized by multiple clinical decompensation events at baseline.

In conclusion, LPCN 1148 treatment was efficacious in treating sarcopenia and diminishing the rate of overt HE in men with advanced cirrhosis. Furthermore, 24 weeks of LPCN 1148 treatment was well tolerated with similar safety signals to that observed in placebo. These

findings support the case for conducting further research trials on the efficacy of LPCN 1148 in treating sarcopenia and for preventing HE recurrence.

DATA AVAILABILITY STATEMENT

Data sharing requests will be considered by the trial management group on written request to BJB@lipocine.com. Deidentified participant data or other prespecified data will be available following a review of a written proposal and approval of a data-sharing agreement.

AUTHOR CONTRIBUTIONS

Benjamin J. Bruno, Nachiappan Chidambaram, Elizabeth J. Carey, Anthony DelConte, Mahesh V. Patel, Jennifer C. Lai, and Arun J. Sanyal were involved in the study concept and design. Elizabeth J. Carey, Christopher J. Danford, Zarchary P. Fricker, Joseph S. Galati, William M. Lee, Parvez S. Mantry, Kirti Shetty, and Jennifer C. Lai were study investigators in the trial and were responsible for the provision of study materials, recruiting patients, and data collection. All authors had access to the data and contributed to the critical revision and approval of the manuscript for submission. All authors accept responsibility for the decision to submit the manuscript for publication. Benjamin J. Bruno, Joshua C. Weavil, Jonathan Ogle, and Anthony DelConte had access to the raw data and verified the underlying data.

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CONFLICTS OF INTEREST

Benjamin J. Bruno owns stock in and is employed by Lipocine. Joshua C. Weavil is employed by Lipocine. Jonathan Ogle is employed by Lipocine. Nachiappan Chidambaram is employed by Lipocine. Zachary P. Fricker consults for Pick Research. He received grants from Lipocine, Mallinckrodt, Bausch, and River2Renal. William M. Lee consults for Seattle Genetics, GSK, Veristant, and Genentech. He received grants from Gilead, Intercept, Lipocine, Camaurus, and Madrigal. Kirti Shetty received grants from Ocera Therapeutics, Glycotest, and Lipocine. Anthony DelConte consults for Lipocine. Mahesh V. Patel owns stock in and is employed by Lipocine. Jennifer C. Lai consults for and advises Novo Nordisk. She consults for Genfit. She advises Boehringer Ingelheim. She received grants from Nestle Nutrition Institute and Lipocine. Arun J. Sanyal consults for and owns stock in Genfit and Northsea. He consults for Eli Lilly, Echosens, Abbott, Promed, Satellite Bio, Corcept, Arrowhead, Boston Pharmaceuticals, Variant, Cascade, 89 Bio, AstraZeneca, Alnylam, Regeneron, Boehringer Ingelheim, Bristol Myers Squibb, Genetech, Gilead, Histoindex, Janssen, Lipocine, Madrigal, Merck, Glaxo Smith Kline, Novartis, Akero, Novo Nordisk, Path AI, Histoindex, Pfizer, Poxel, Salix, Myovant, Median Technologies, Sequana, Surrozen, Takenda, Terns, and Zydus. His institution received grants from AstraZeneca, Bristol Myers Squibb, Gilead, Intercept, Mallinckrodt, Merck, Ocelot, Novartis, Tobira, Shire, and Salix. He received royalties from Elsevier and UptoDate. He owns stock in Akarna, Durect, Tizsiana, Hemoshear, Northsea, Diapin, Liponexus, Galmed, and Inversago. The remaining authors have no conflicts to report.

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