Oral LPCN 1148 Improves Sarcopenia and Hepatic Encephalopathy In Patients with Cirrhosis

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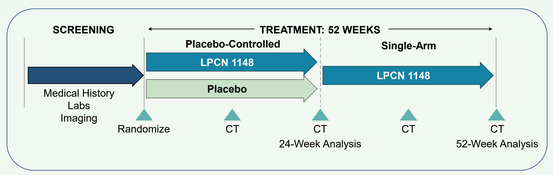
INTRODUCTION

- Sarcopenia (rates 30-70%)[1], myosteatosis (rates >50%)[3], and low testosterone (T, rates up to 90%) are highly prevalent in patients with liver cirrhosis resulting in frailty and poor physical functioning.
- Sarcopenia, myosteatosis, and low T are associated with negative clinical outcomes in cirrhotic patients, including, but not limited to, hepatic encephalopathy (HE) and increased mortality.
- LPCN 1148 is novel, multi-modal, orally available prodrug of androgen receptor agonist being developed for the treatment of sarcopenia and HE in men with liver cirrhosis
- **PURPOSE:** To report the 24-week efficacy and safety data for LPCN 1148 treatment in men with sarcopenia and cirrhosis (NCT 04874350).

METHODS

- Population: Men with cirrhosis and sarcopenia, confirmed via computerized tomography scan (CT), on the liver transplant waitlist.
- Design: Two-stage, randomized (1:1), blinded, placebo-controlled, Phase 2 clinical trial. The primary endpoint was the change in 3rd lumbar skeletal muscle index (L3-SMI) in LPCN 1148 vs Placebo at week 24.
  - Stage 1: Placebo-controlled (0-24 weeks, focus of present poster)
  - Stage 2: Single-arm open label extension (currently ongoing)

Figure 1: Schematic representation of LPCN 1148-21-001 study design



- There are two analysis populations:

1. Safety set (N=29): All participants who received at least 1 dose of study drug.
2. Modified intent-to-treat (mITT, n=25): Pre-specified subset of the Safety set based on having a qualifying post-baseline CT scan, defined as having a post-baseline CT and < 33% of capsules missed during a 12 week time window.

Table 1: Baseline Characteristics and History of Major Decompensation Events

Parameter	LPCN 1148 (n=15)	Placebo (n=14)
Age (years)	58.3 ± 7.5	58.8 ± 9.5
BMI (kg/m^2)	29.2 ± 5.3	29.0 ± 8.6
MELD	15.9 ± 3.7	18.1 ± 4.6
Etiology		
ALD	9 (60%)	7 (50%)
Hepatitis C	2 (13%)	4 (29%)
ALD and Hepatitis C	1 (7%)	0 (0%)
NASH	4 (27%)	2 (14%)
PSC	1 (7%)	1 (7%)
Medical History		
≥ 1 Decompensation Event	14 (93%)	14 (100%)
≥ 2 Decompensation Event	13 (87%)	12 (86%)
Esophageal Varices	8 (53%)	8 (57%)
Ascites	11 (73%)	10 (71%)
HE	11 (73%)	11 (79%)
Medical Therapy for HE*	11 (100%)	10 (91%)

BMI, body mass index; MELD, model for End-Stage Liver Disease; ALD, alcoholic liver disease; NASH, non-alcoholic steatohepatitis; PSC, primary sclerosing cholangitis; HE, hepatic encephalopathy. Decompensation events included HE, esophageal varices, ascites, portal hypertension, and spontaneous bacterial peritonitis. *Medical therapy for HE is reported for those with a medical history of HE and included therapies of Lactulose, Rifaximin, or both.

RESULTS

Improved Changes in Muscle Mass and Quality

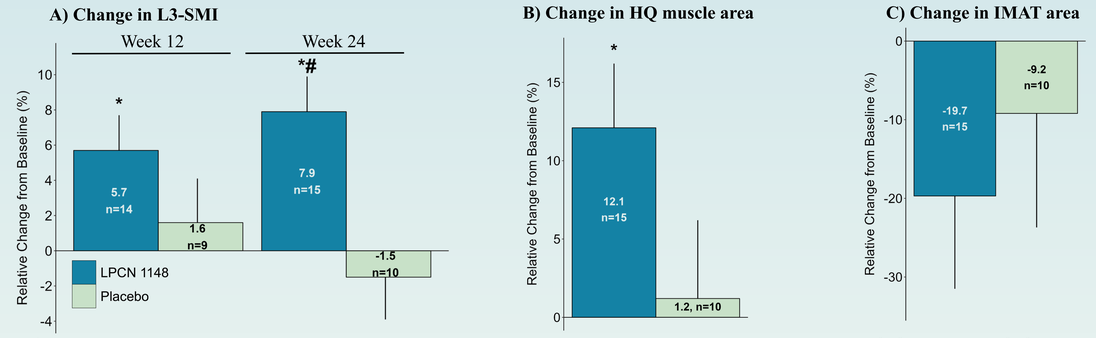


Figure 2: Data are LS mean (SE) and last observation carried forward (LOCF). **A)** Change in L3-SMI at weeks 12 and 24 (baselines: LPCN 1148 47.8 cm^2/m^2; Placebo 45.6 cm^2/m^2). **B)** Change in high quality (HQ) muscle area (Hounsfield unit range 30 to 150 HU) at week 24 (baselines: LPCN 1148 97.3 cm^2; Placebo 94.2 cm^2). **C)** Change in intramuscular adipose tissue (IMAT, Hounsfield unit range -190 to -30 HU) at week 24 (baselines: LPCN 1148 5.0 cm^2; Placebo 5.5 cm^2). * p <0.05 for change from baseline; # p=0.007 vs Placebo

Improved HE Events and Hematology

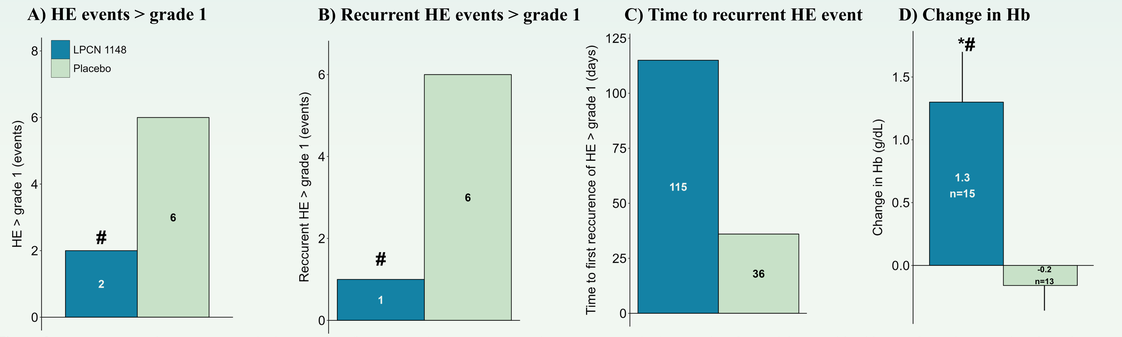


Figure 3: A) Data are number HE events > CTCAE grade 1 (i.e. overt HE) . **B)** Data are number HE events > CTCAE grade 1 for participants with a history of HE. **C)** Mean time from the start of study to the first recurrence of HE > CTCAE grade 1. Note data only 1 participant in LPCN 1148 demonstrated recurrent HE. **D)** Data are mean (SE) and LOCF. Change in hemoglobin (Hb) at week 24 (baselines: LPCN 1148 11.4 g/dL; Placebo 13.2 g/dL). * p <0.05 for change from baseline; # p <0.05 vs Placebo

Improved Patient Symptoms

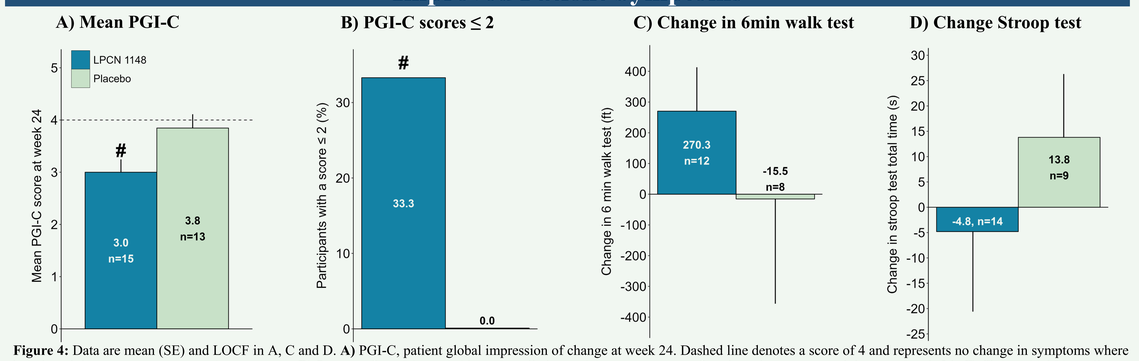


Figure 4: Data are mean (SE) and LOCF in A, C and D. **A)** PGI-C, patient global impression of change at week 24. Dashed line denotes a score of 4 and represents no change in symptoms where less than 4 demonstrates symptom improvement. **B)** Percent of participants with an overall change in symptom score of moderately to very much better at week 24. **C)** Change in 6min walk test (ft) at week 24 (baselines: LPCN 1148 893 ft; Placebo 889 ft). **D)** Change in EncephalApp Stroop test task total completion time (s) at week 24 (baselines: LPCN 1148 217 s; Placebo 183 s). * p <0.05 for change from baseline. # p< 0.05 vs Placebo

RESULTS

Summary of Safety and Clinical Events

Parameter	LPCN 1148 (n=15)		Placebo (n=14)	
	# Events	n, (%)	# Events	n, (%)
Total TEAEs	33	8 (53)	36	10 (71)
Serious AEs	15	5 (33)	16	5 (36)
Severe AEs	6	4 (27)	10	4 (29)
TEAEs leading to study drug discontinuation	1	1 (7)	6	3 (21)
Number of days hospitalized	54	5 (33)	117	5 (36)
Median length of hospitalization (days)	3		5	
Clinical events of anemia				
Resolution of anemia	4 (36%)		1 (14%)	
New onset of anemia	0		1 (17%)	
Clinical endpoints, n (%)				
Liver transplant	0		4 (29)	
Death	0		1 (7)	

Table 2: TEAE, treatment-emergent adverse event; Severe TEAEs, TEAES ≥ common terminology criteria for adverse events grade ≥ 3. TEAEs with visits starting at the same time, or included overlapping dates, were only counted once. Median length of hospital stay was determined as the median of all unique hospital visits for each group. Anemia resolution, participants that demonstrated anemia at baseline (hemoglobin <13 g/dL) who were not anemic at week 24. New onset of anemia were participants that were not anemic at baseline but were at week 24.

SUMMARY & CONCLUSIONS

- LPCN 1148 improved sarcopenia, reduced the number of overt HE episodes, reduced recurrent HE episodes, and improved anemia in men with cirrhosis awaiting liver transplant.
- LPCN 1148 improved patient reported symptoms with trends toward improvements in additional functional and clinical endpoints.
- LPCN 1148 was well tolerated with similar safety events as observed with placebo. There were no cases of drug-induced liver injury of hepatocellular carcinoma.
- These results provide support for further study of LPCN 1148 for the treatment of sarcopenia and HE.

DISCLOSURES & CONTACT

- EJC, CJD, ZPF, JSG, WML, PSM, KS, and JCL were study investigators
- AJS and AD are consultants of Lipocine Inc.

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REFERENCES

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2. Grossmann et al. *Clin Endocrinol* 2012; 77(2): 323-8
3. Montano-Loza et al. *J Cachexia Sarcopenia Muscle* 2016; 7(2): 126-135