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Intervention with oral LPCN 1148 improves sarcopenia and hepatic encephalopathy (HE) in patients with cirrhosis: a 52-week phase 2 randomized clinical trial

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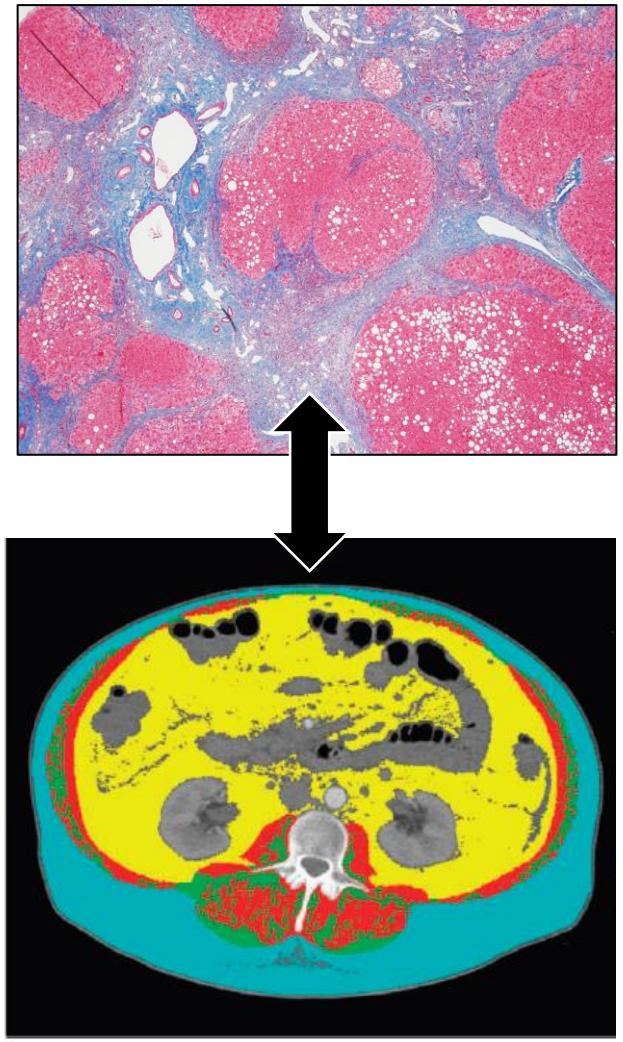
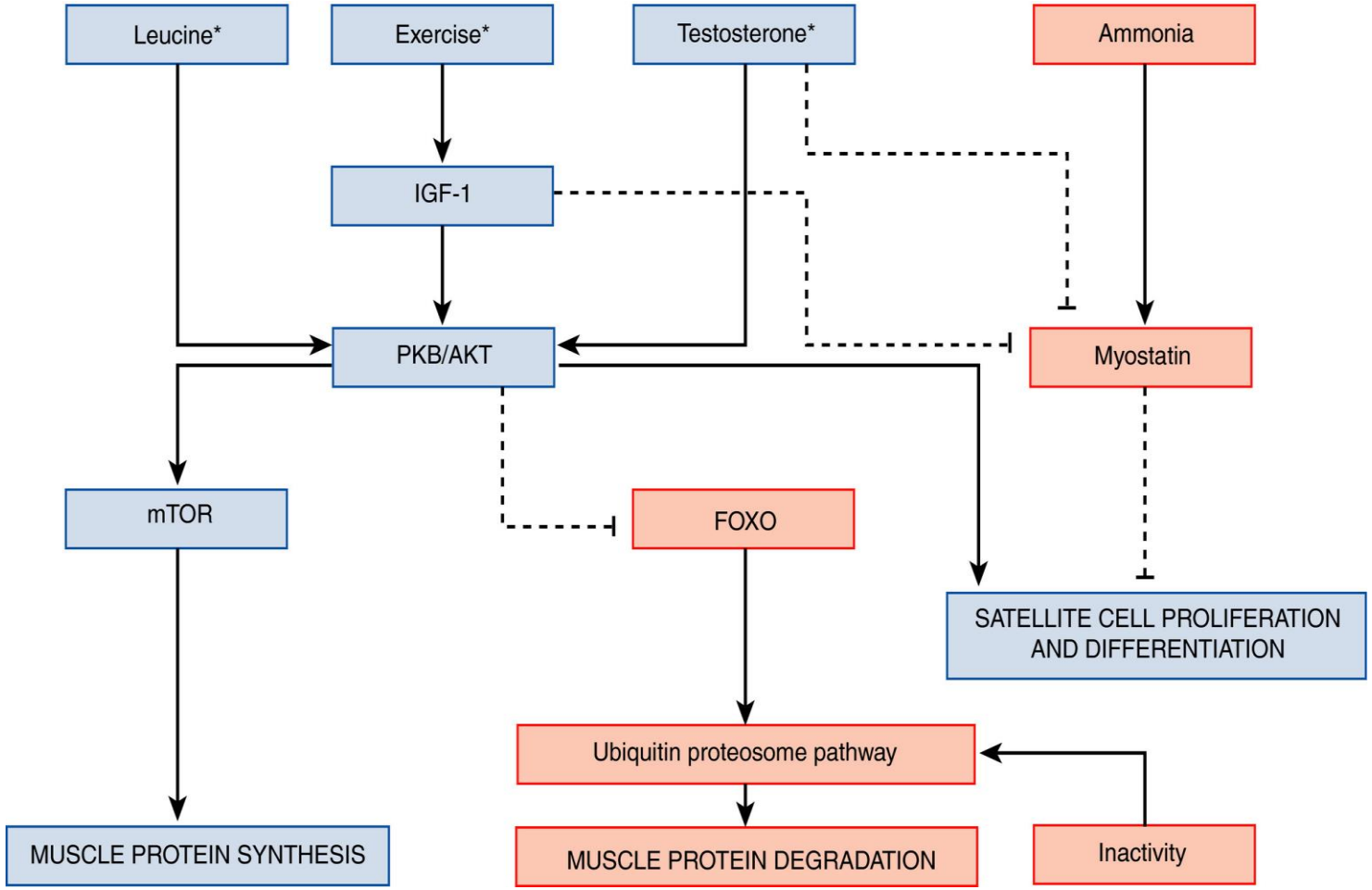
Sarcopenia is common in cirrhosis and impacts clinically meaningful outcomes



- How patients feel:
  - Health related quality of life
- How patients function:
  - Frailty
  - Activities of daily living
- How patients survive:
  - Hepatic encephalopathy
  - Mortality
  - Peri-transplant outcomes
- Health care resource utilization:
  - Hospitalization

1. Kim. PLoS One. 2017 2. Tandon. Clin Gastroenterol Hepatol. 2016 3. Tandon. J Hepatol. 2021
2. Jindal Clin Mol Hepatol 2019 5. Bhanji et al. Hepatology International 2018.

Multiple mechanisms contribute to sarcopenia in cirrhosis



Androgens:

- Linked to muscle mass
- Inhibits myostatin
- Modulates mTOR
- Increases protein synthesis
- Decreases turnover

- *90% of males with cirrhosis have low free testosterone*

1. Sinclair et al, Aliment Pharmacol Ther, Volume: 43, Issue: 7, Pages: 765-777, 2016,
2. Handelsman et al, *Clin Endocrinol* 1995; **43**: 331–7. Sinclair et al, *J Gastroenterol Hepatol* 2015

LPCN 1148: A novel MOA for management of cirrhosis

Product Candidate Attributes

Oral androgen receptor agonist

Dosage form comprising testosterone dodecanoate, a unique prodrug of the endogenous hormone

Targeted Mechanism of Action

Anabolic[1]

Increase muscle mass and strength[2]; Reduce fat mass[3]; Increase bone density[4]; Inhibit myostatin[5]; Improve appetite and nutritional status*

Ammonia Lowering

Via Improved liver function[6] and muscle disorders[7]; Antibacterial[8]

Androgenic

Induce hematopoiesis[9]; Improve endocrine/sexual dysfunction[10]

1. Gentile MA et al., J Mol Endocrine 2010
2. Sinclair et al., J Gastroenterol Hepatol 2016
3. Bhasin, Clin Infect Dis 2003
4. Snyder et al., JAMA Intern Med 2017
5. Dasarathy and Merli, J Hepatol 2016
6. Kenston et al., J Gastro Hep 2018
7. Di Cola et al., J Clin Med 2022
8. Jin et al., J Microbiol Biotechnol 2021
9. Basaria and Dobbs, Androgens and the Hematopoietic System. In: Bagatell, C.J.,Bremner, W.J. (eds) Androgens in Health and Disease, 2003
10. Rizk et al., Curr Opin Urol 2017

*individual's health condition as it is influenced by the intake and utilization of nutrients

Central Hypothesis:

LPCN 1148 will improve sarcopenia, sarcopenia related outcomes and clinically significant outcomes in patients with cirrhosis

Aims and objectives

Specific Aims

- To perform a phase 2 proof of concept study to establish the short term safety and efficacy of LPCN 1148 in male patients with advanced cirrhosis of any etiology with sarcopenia
- NCT # 04874350

Objectives

- To generate proof of concept of overall benefit of LPCN 1148 to support further development of this drug in the study population

Study population

Inclusion criteria

- Adult males
- Cirrhosis
- Sarcopenia – defined by BMI-adjusted SMI*
- Listed for liver transplantation

Exclusion criteria

- Failure to obtain consent
- Active severe encephalopathy
- Active infection
- Uncontrolled or recurrent GI bleed in past 6 months
- Prior HCC diagnosis or current HCC

SMI = L3 skeletal muscle index, *Adapted from Derstine et al., *Sci Rep* 2021; **11**, 279 and Martin et al., *J Clin Onc* 2013; **31** (12), 1539-47

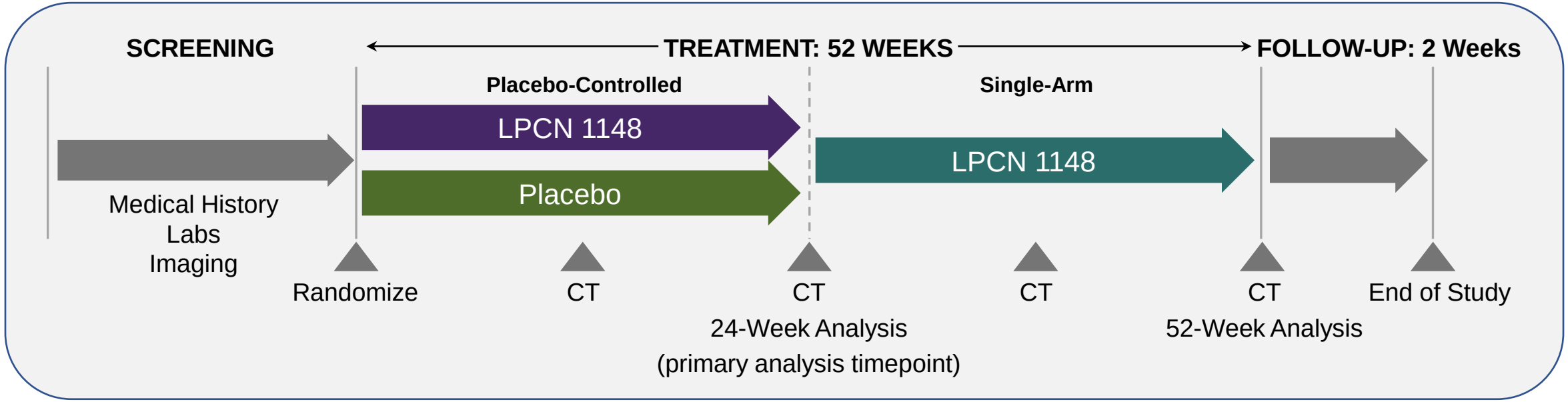
Study design

Two-arm, two stage (1:1 randomization, N=29)

- Oral LPCN 1148, T dodecanoate, vs. Placebo
- Standard of care treatments allowed, including HE therapies

Stages:

1. 24-week placebo-controlled
2. 28-week open-label extension (OLE)
   - All subjects receive LPCN 1148 during OLE



Endpoints

Primary endpoint

- Baseline-adjusted change in Skeletal Muscle Index (L3 region, L3-SMI) at Week 24 in LPCN 1148 treated participants compared to placebo

Secondary endpoints
(p values not adjusted for multiplicity)

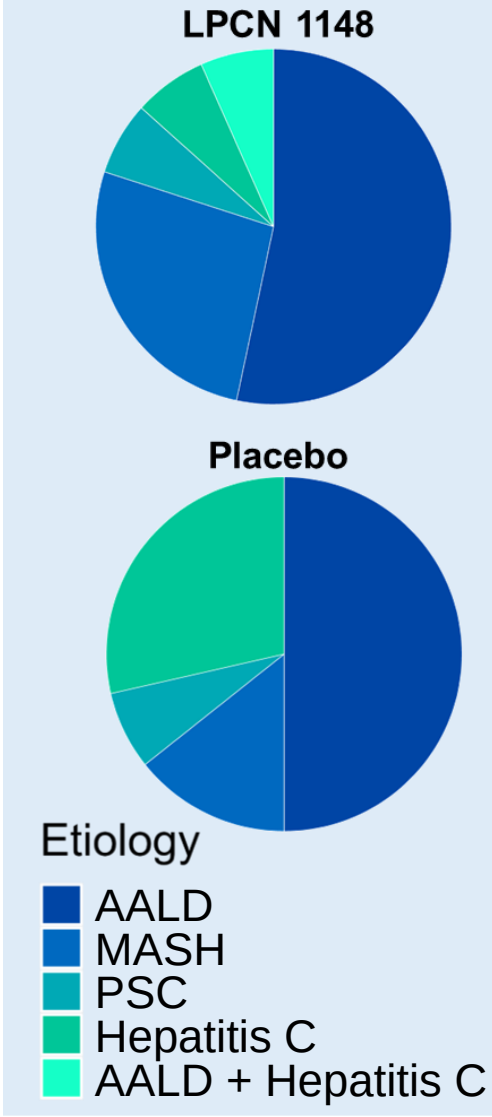
Week 24 and week 52:

- Feel and function:
  - patient reported outcomes (PGI-C)
- Survives:
  - acute worsening of encephalopathy
  - anemia
  - hospitalizations
  - mortality
- Biomarkers:
  - Liver Frailty Index™
  - myosteatosis

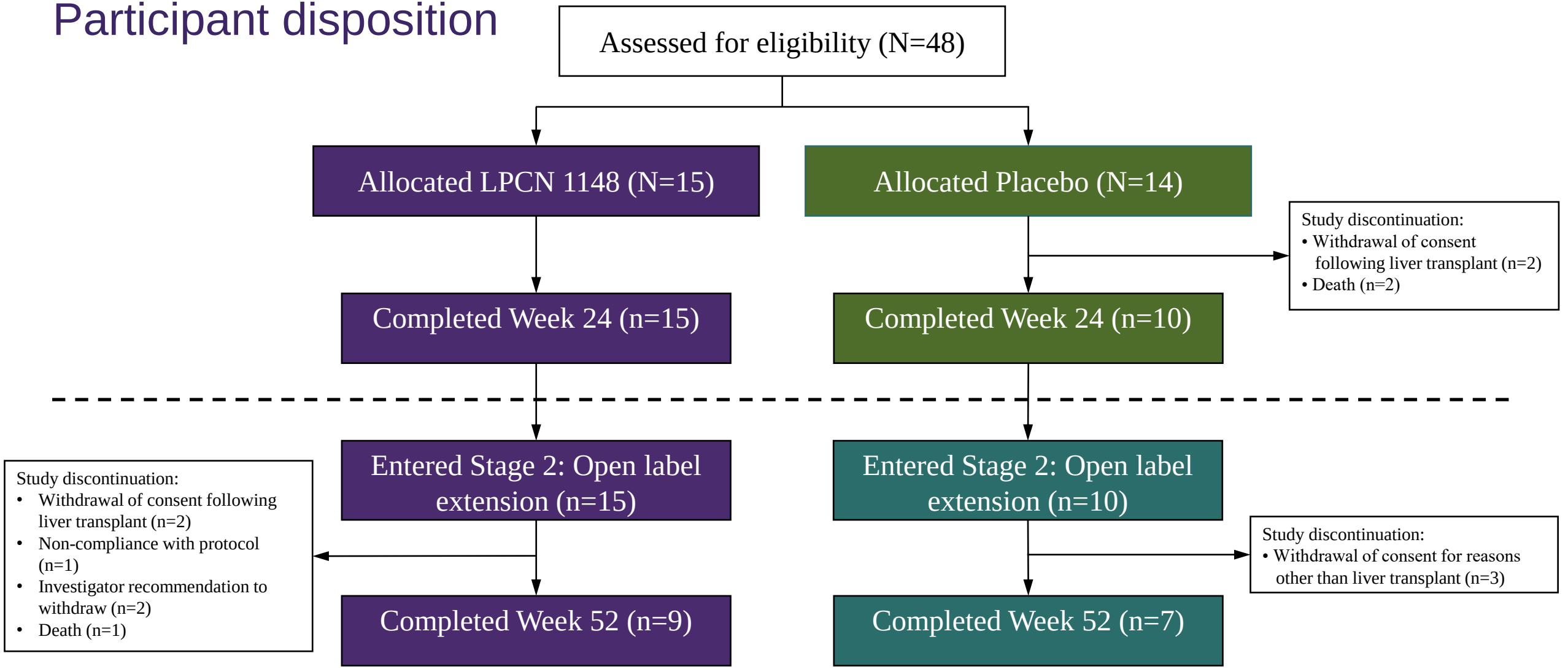
Baseline characteristics

	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
L3-SMI (cm^2/m^2)	47.8 ±7.0	44.8 ± 8.5
MELD Score	15.9 ± 3.7	18.1 ± 4.6
Medical History		
≥ 1 Decompensation Event#	14 (93%)	14 (100%)
≥ 2 Decompensation Event	13 (87%)	12 (86%)
Hepatic Encephalopathy (HE)	11 (73%)	11 (79%)
Medical Therapy for HE*	11 (100%)	10 (91%)
Ascites	11 (73%)	10 (71%)
Esophageal Varices	8 (53%)	8 (57%)

Safety dataset; characteristics are mean ± SD, medical history is reported as n (%)
Decompensation events include esophageal varices, ascites, hepatic encephalopathy, portal hypertension, and spontaneous bacterial peritonitis
*Medical therapy for HE includes lactulose and/or rifaximin; for those with a medical history of HE. MELD: Model for End-Stage Liver Disease



Participant disposition



Horizontal dashed line indicates break between Stage 1 (placebo-controlled) and Stage 1 (open-label extension)

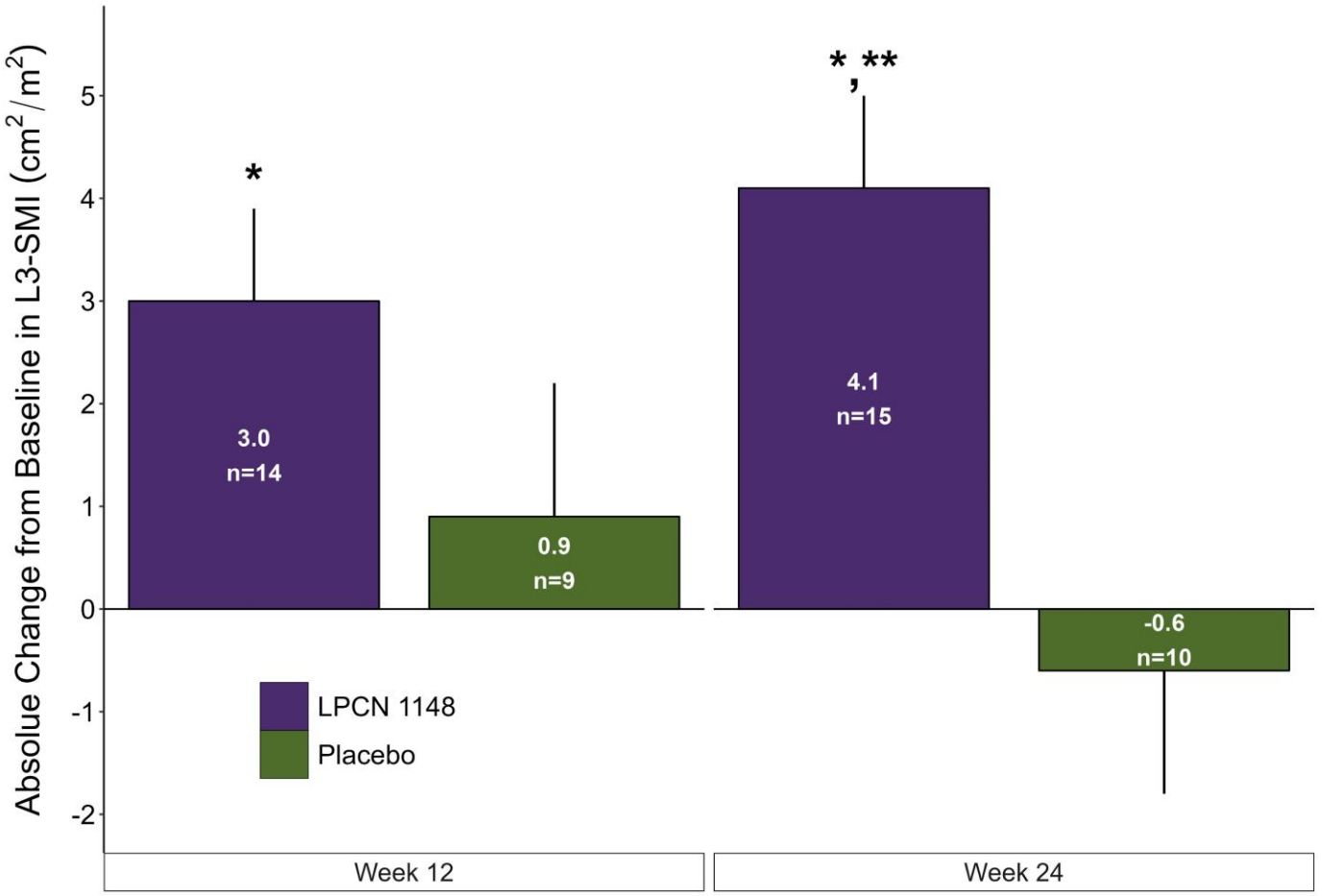
Analysis datasets

	LPCN 1148 **(N=15)**	Placebo **(N=14)**	LPCN 1148 switch from placebo **(N=10)**
Safety set*			
Stage 1	15	14	---
Stage 2	11	---	8
Modified intent-to-treat (mITT)#			
Stage 1	15	10	---
Stage 2	15	---	6

- For LPCN 1148 switch from placebo, change from baseline during Stage 2 is calculated using week 24 values
- Post liver transplant data not included in any analyses

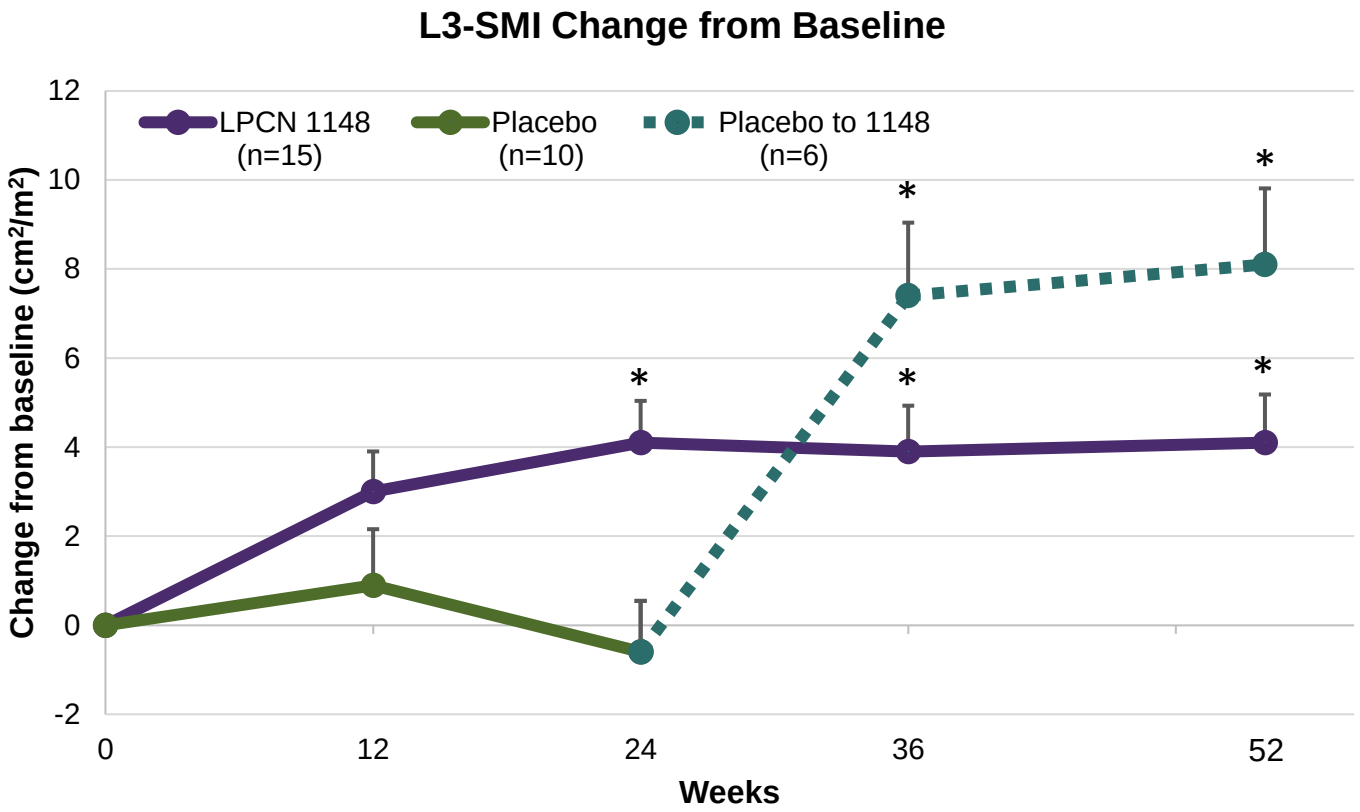
*Safety set data consists of all randomized participants that received study drug in a given stage. Used in adverse event (AE) and hepatic encephalopathy (HE) analyses
#Participants were eligible for mITT with at least one evaluable post-baseline CT using last observation carried forward (LOCF rules). Participants switching from placebo to LPCN 1148 were eligible for mITT in Stage 2 if they had a week 24 CT and at least one evaluable post-week 24 CT. One additional participant from placebo in stage 2 did not have a post-week 24 CT, however they are included in non-CT related outcomes as they met study drug compliance criteria

Primary endpoint met : LPCN 1148 improves in L3-SMI at week 24



Data are LS mean (SE). mITT set based on study drug compliance and having at least one post-baseline CT with LOCF.
* p < 0.05 for change from baseline; ** p =0.005 vs. placebo

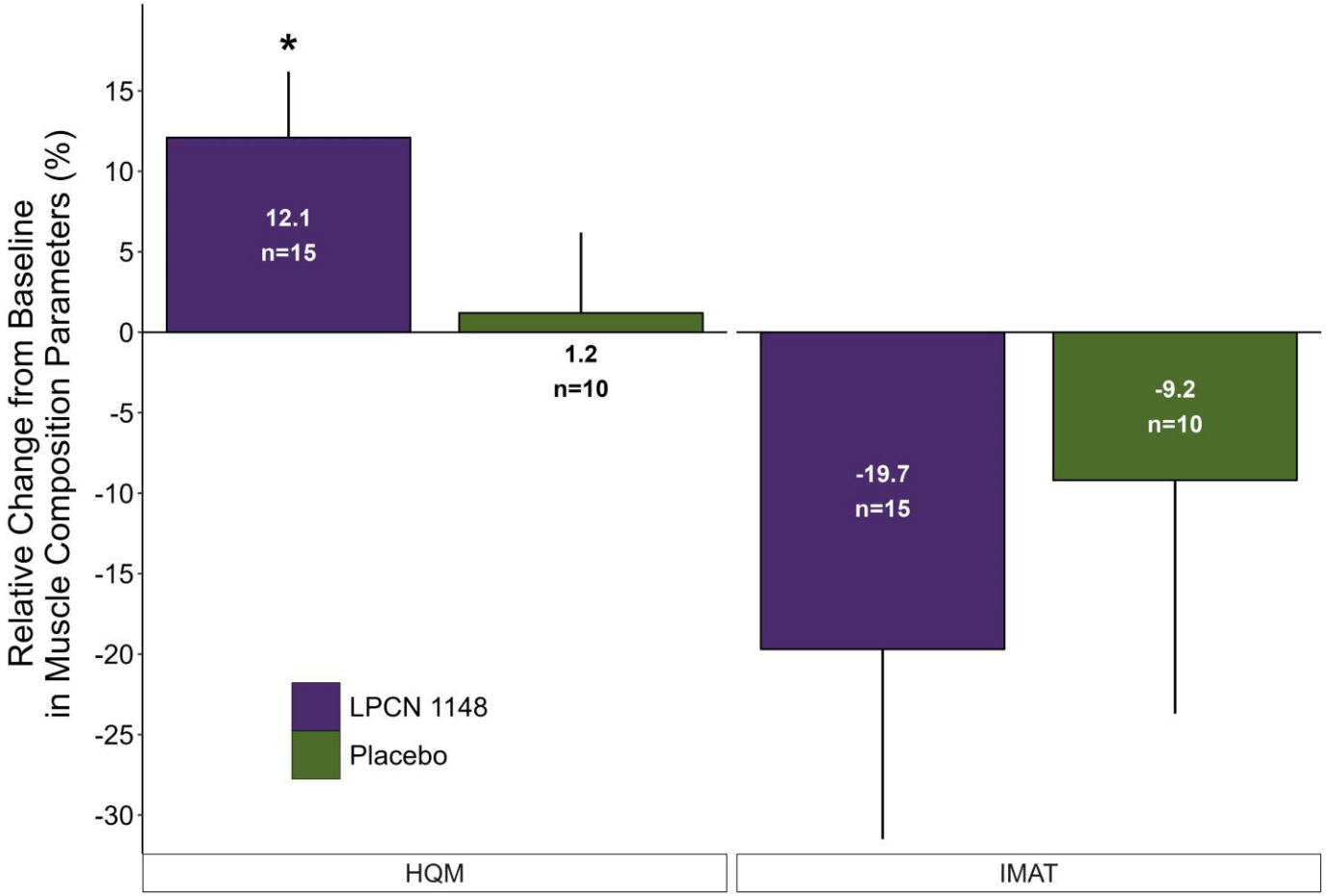
LPCN 1148 improvement in L3-SMI observed during OLE



- Increased muscle area was maintained through 52 weeks of treatment with LPCN 1148
- Placebo participants significantly increased muscle area when switched to LPCN 1148
  - Improvement as early as week 12 of LPCN 1148 intervention

Data are LS mean (SE). mITT set based on study drug compliance and having at least one post-baseline CT with LOCF.
* $p < 0.01$ compared to Week 24 placebo

LPCN 1148 improved myosteatosis and muscle quality at week 24



Data are LS mean (SE). mITT set based on study drug compliance and having at least one post-baseline CT with LOCF
* $p < 0.05$ for change from baseline

Substantial Changes in Muscle Quality seen with LPCN 1148 Therapy

- Significant increase in high quality muscle (HQM, +30 to +150 Hounsfield Units, HU)
- Decrease in intramuscular adipose tissue (IMAT, -190 to -30 HU)

Recurrence of Overt HE was decreased with LPCN 1148 while on HE standard medication(s)

Parameter	Placebo (Through Week 24) N=14	LPCN 1148 (Through Week 24) N=15	LPCN 1148 (Week 24 to EOS) N=11	LPCN 1148 switch from placebo (Week 24 to EOS) N=8
History of HE prior to randomization (n)	11 (79%)	11 (73%)	7 (64%)	6 (75%)
Overt HE (events)	6	2**	1	1
Recurrent Overt HE (events)	6	1**	1	1
Time to first recurrent event (days)	35†	114	294	140

All available data prior to liver transplant for participants that received study drug in a given stage. Overt HE is defined as an adverse event of HE with CTCAE severity > grade 1.
†Mean value.** $p < 0.05$ vs placebo in stage 1

- 76% of study participants had history of HE at baseline
- 95% participants with HE were on therapy at baseline and during the study (lactulose, rifaximin)

LPCN 1148 improved hemoglobin and anemia in cirrhosis

		Placebo (Through Week 24) N=14	LPCN 1148 (Through Week 24) N=15	LPCN 1148 switch from placebo (Week 24 to EOS) N=8
Hemoglobin (g/dL)	Baseline; mean (SE)	13.2 (0.6)	11.4 (0.8)	
	Week 24 CFB; mean (SE)	0.0 (0.3)	0.9 (0.3)*,**	--
	Week 52 CFB; mean (SE)	--	1.4 (0.5)*	1.7 (0.5) *

Data are mean (SE). mITT set. CFB: change from baseline
* $p < 0.05$ vs baseline; ** $p < 0.05$ vs placebo in stage 1

- 24 weeks of LPCN 1148 treatment increased hemoglobin compared to placebo
  - This increase was maintained throughout 52 weeks of treatment
- Participants who initiated LPCN 1148 in Stage 2 experienced significant increase in hemoglobin

LPCN 1148 improved patient reported symptoms severity

		Placebo (Through Week 24) N=14	LPCN 1148 (Through Week 52) N=15	LPCN 1148 switch from placebo (Week 24 to EOS) N=8
Patient Global Impression of Change (PGI-C)	Week 24 mean (SD)	3.8 (0.3)	3.1 (0.3)**	--
	Week 52 mean (SD)	--	2.9 (0.3)	3.9 (0.7)

Data are mean (SE). mITT set.
** $p < 0.05$ compared to placebo

- PGI-C – a score of 4 indicates no change in symptoms, with lower scores indicating improvement
- LPCN 1148 group reported significantly lower severity of symptoms at week 24 than placebo
  - Improvement maintained through 52 weeks of treatment
- Participants switching from placebo to LPCN 1148 did not report a difference in the severity of symptoms during the open-label extension stage 2

LFI changes were comparable between LPCN 1148 and placebo

		Placebo (Through Week 24) N=14	LPCN 1148 (Through Week 52) N=15	LPCN 1148 switch from placebo (Week 24 to EOS) N=8
Liver Frailty Index (LFI)	Baseline; mean (SE)	4.0 (0.3)	4.1 (0.2)	--
	Week 24 CFB; mean (SE)	-0.17 (0.18)	-0.17 (0.14)	--
	Week 52 CFB; mean (SE)	--	-0.21 (0.15)	-0.32 (0.15)

Data are mean (SE). mITT set. CFB: change from baseline.

- LFI – higher value represents increased frailty
- LPCN 1148 treatment resulted in a similar change in LFI compared to placebo at 24 weeks, with slight improvement observed with 52 weeks of treatment
- Participants switching from placebo to LPCN 1148 demonstrated a numerical decrease in LFI from their week 24 baseline

LPCN 1148: trends towards improvement in other secondary endpoints

	Placebo (Through Week 24) N=14	LPCN 1148 (Through Week 24) N=15	LPCN 1148 (Week 24 to EOS) N=11	LPCN 1148 switch from placebo (Week 24 to EOS) N=8
Deaths; n (%)	2 (14%)	0	1 (9%)	0
Hospitalizations; n (%)	5 (36%)	5 (33%)	5 (45%)	1 (13%)
Hospitalization time, days	114	54	51	4
EncelphalApp Stroop Test (total time, s)^	18.8 (13.0)	-15.3 (15.3)	-15.2 (15.3)	20.7 (20.5)

Clinical outcome endpoints (deaths, hospitalization characterizations) are based on Safety set.
^ Data are Mean (SE) . mITT set.

Overall, LPCN 1148 was well tolerated up to 52 weeks of treatment

	Placebo (Through Week 24) N=14	LPCN 1148 (Through Week 24) N=15	LPCN 1148 (Week 24 to EOS) N=11	LPCN 1148 switch from placebo (Week 24 to EOS) N=8
Total AEs; n (%)	9 (64%)	9 (60%)	7 (64%)	7 (88%)
Serious AEs; n (%)	5 (36%)	5 (33%)	5 (45%)	1 (13%)
Severe AEs; n (%)	4 (29%)	4 (27%)	3 (27%)	1 (13%)

Safety set. Post-transplant AEs excluded. Severe AEs: CTCAE severity ≥ Grade 3

- Administration of LPCN 1148 for up to 52 weeks was well tolerated in this end-stage population, with rates and severities of AEs similar to those within the placebo group
- No cases of drug-induced liver injury (DILI)
- 2 cases of HCC in LPCN 1148 group
  - One participant presented with a 2.2 cm hepatic lesion 250 days following start of treatment, considered resolved following ablation
  - A second participant had pre-existing nodules noted in imaging several months prior to study entry, later classified as LR-4 on explant

Summary and conclusions

- Oral androgen receptor agonist LPCN 1148 improved sarcopenia in adult male patients with cirrhosis
    - This improvement was maintained through 52 weeks of treatment
- LPCN 1148 was further associated with improvement in encephalopathy, anemia, total number of days hospitalized, and patient reported outcomes which are all clinically relevant
- Treatment was well tolerated without any DILI signals. Future studies will monitor cases of HCC as an event of special interest.
- Limitations: sample size
- Overall, these data demonstrate that LPCN 1148 improves multiple clinically relevant and surrogate outcomes while being well tolerated with up to 52 weeks of treatment in patients with advanced cirrhosis. These data support further development of LPCN 1148 for the treatment of sarcopenia and recurrent hepatic encephalopathy in this population.

Acknowledgements

- We acknowledge the contribution of all of the investigators and staff for this trial and express our gratitude to the patients who participated in this study