The Stravitz-Sanyal Institute

VCU Stravitz-Sanyal Institute for Liver Disease and Metabolic Health School of Medicine

ORAL LPCN 1148 IMPROVES SARCOPENIA AND CLINICAL OUTCOMES IN PATIENTS WITH DECOMPENSATED CIRRHOSIS

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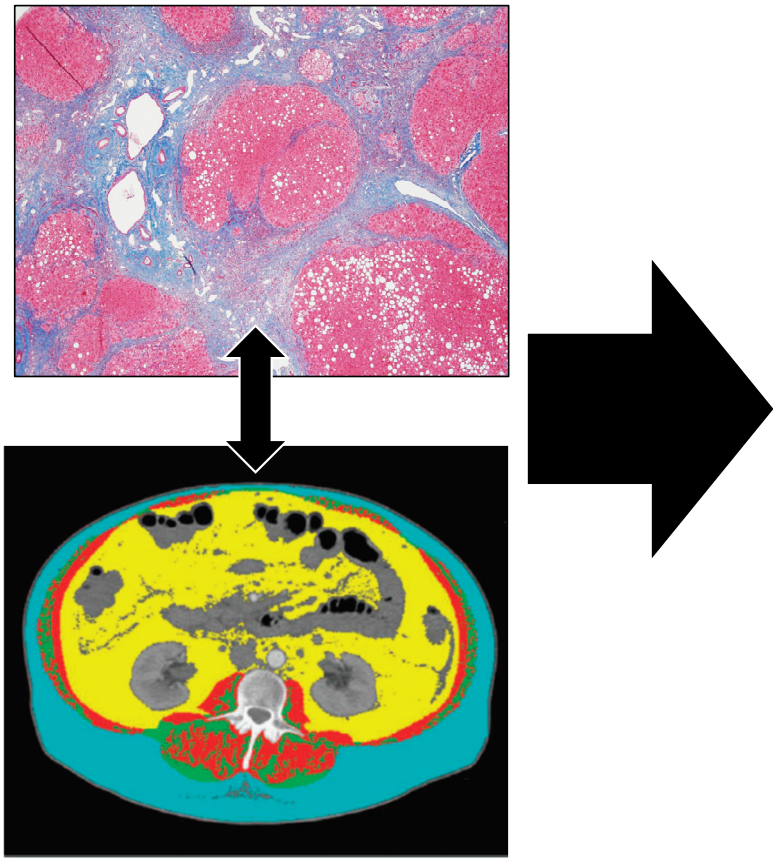
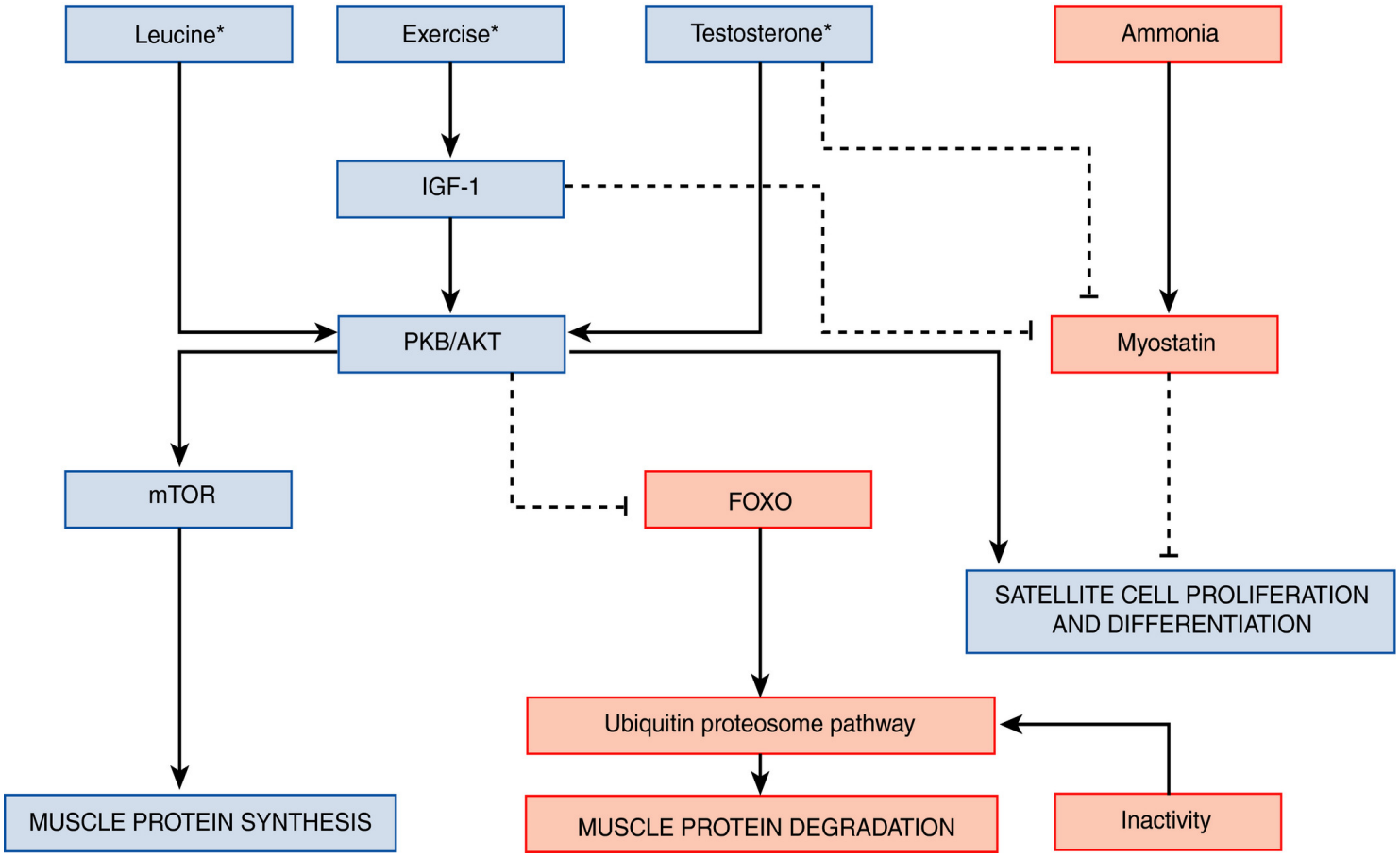
Sarcopenia is commonly present in those with decompensated cirrhosis and impacts clinically meaningful outcomes



- 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
4. 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 testosterone*

Sinclair et al, Aliment Pharmacol Ther, Volume: 43, Issue: 7, Pages: 765-777, 2016,
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

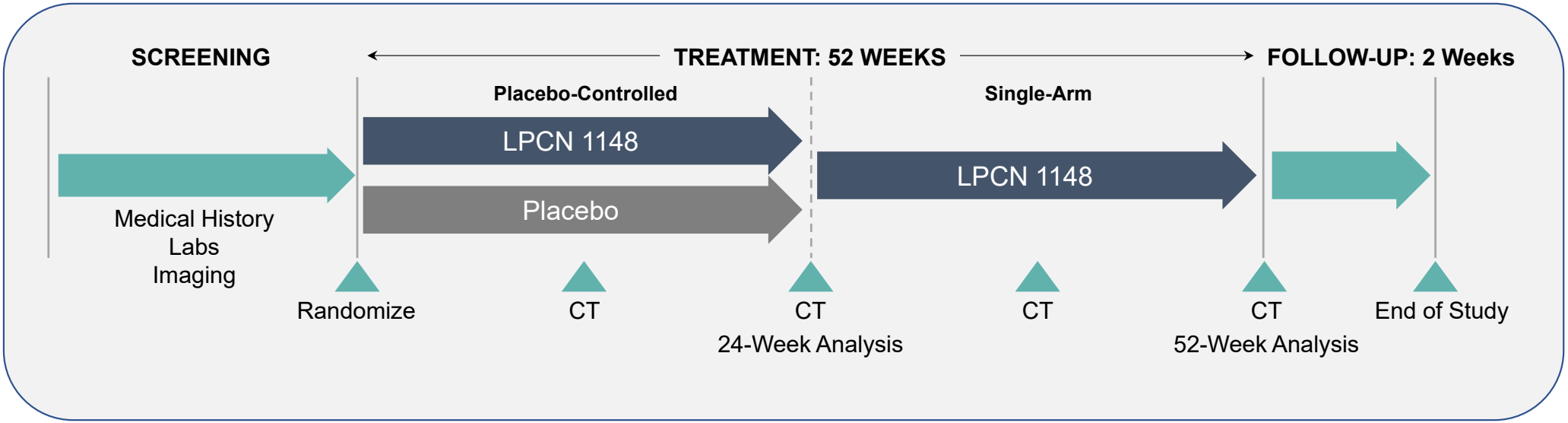
- Failure to obtain consent
- Active severe encephalopathy
- Active infection
- Uncontrolled or recurrent GI bleed in past 6 months
- Prior HCC diagnosis or current HCC

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

Study Design:

- Two-arm (1:1 randomization, N=29)
  - Oral LPCN 1148, T dodecanoate, vs. Placebo
  - Standard of care treatments/therapies allowed
- 24-week placebo-controlled
  - Followed by 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

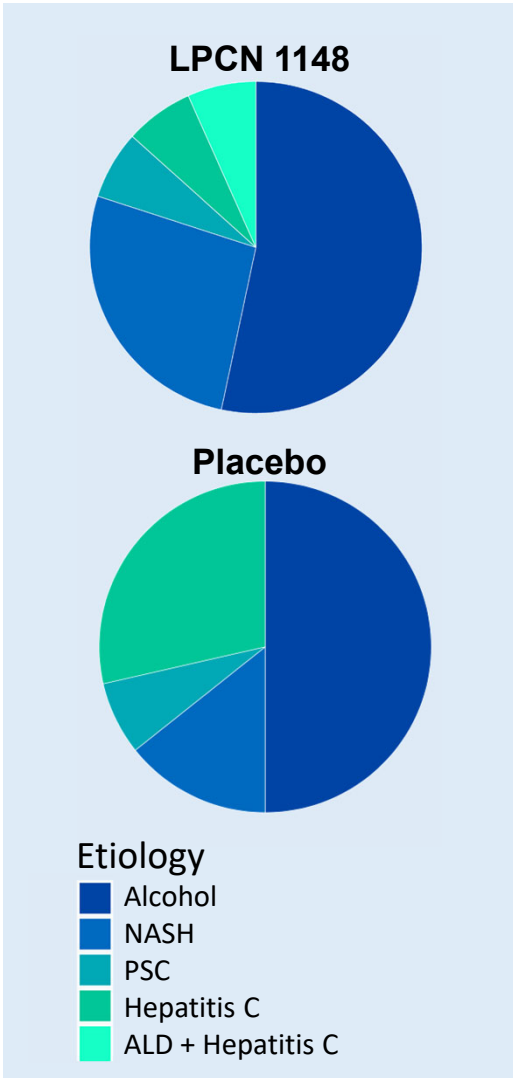
Secondary endpoints

(p value not adjusted for multiplicity)

- Feel and function:
  - 6 min walk test
  - 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 set
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

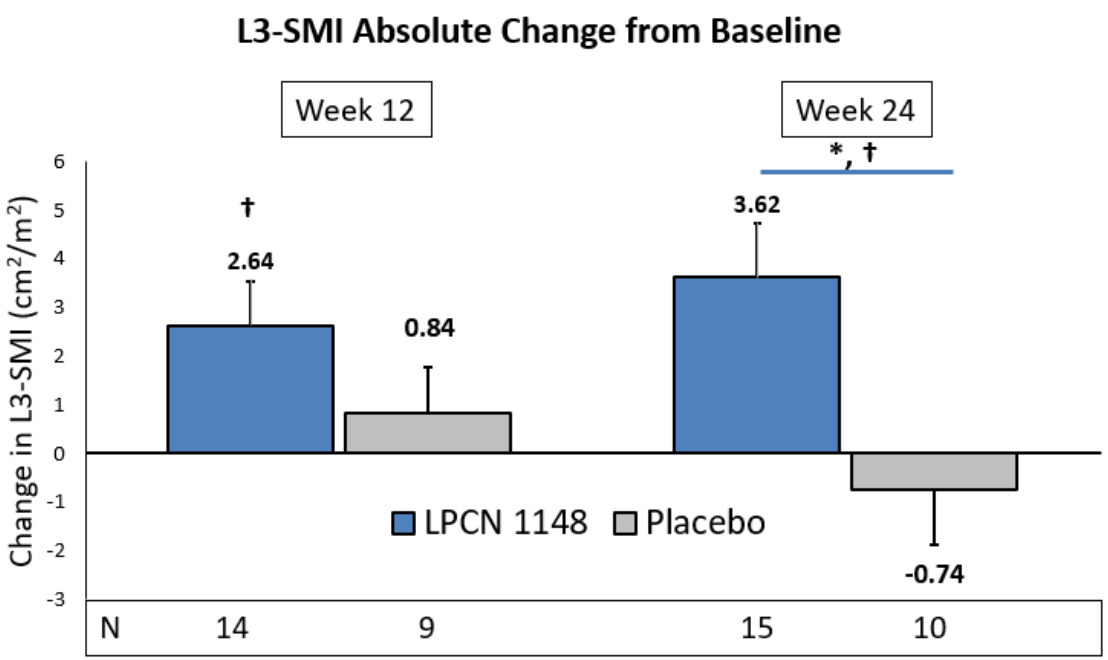
Subject disposition and analysis data-sets

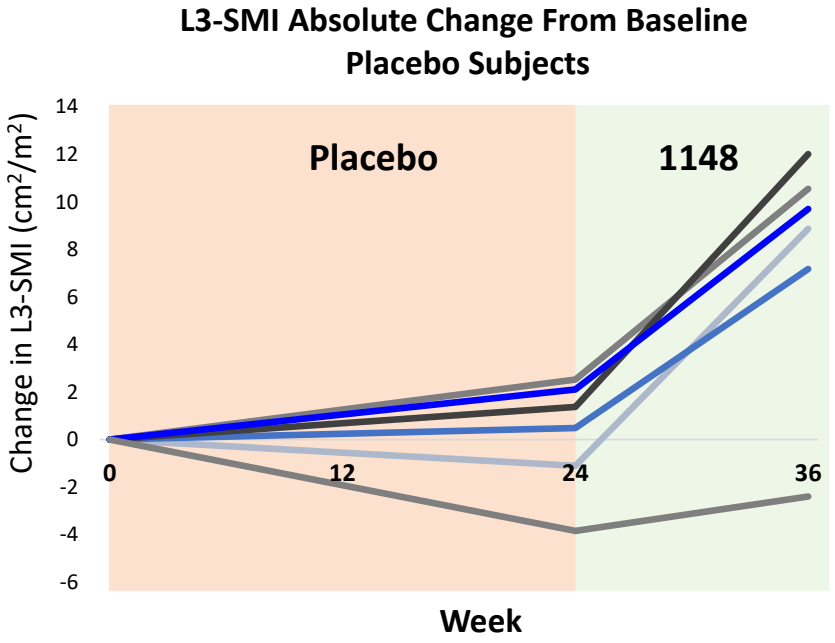
Subject Disposition	LPCN 1148 **(N=15)**	Placebo **(N=14)**
Completed Week 24	15	10
Withdrawal of informed consent post liver transplant	0	2
Death	0	1
Hospitalized	0	1

Analysis Datasets	LPCN 1148 **(N=15)**	Placebo **(N=14)**
Safety set*	15	14
Modified Intent to Treat (mITT)**	15	10
No post-baseline CT scan	0	3
Low compliance	0	1

*Randomized and received study drug
**Subjects were eligible for mITT with at least one evaluable post-baseline CT

Primary endpoint was met- improvement in skeletal muscle index





LS mean (SE), LOCF, †P<0.05 for change from baseline; * P=0.007 vs. placebo

Further recurrence of overt hepatic encephalopathy was decreased with increased time to recurrence with LPCN 1148

Parameter	LPCN 1148 (N=15)	Placebo (N=14)
Total decompensation events	7	10
Total decompensation events > Grade 1	6	10
Hepatic encephalopathy events	3	6
HE > Grade 1	2*	6
Recurrence of HE > Grade 1	1*	6
Time to first recurrence of HE > Grade 1 (days)	115	36**

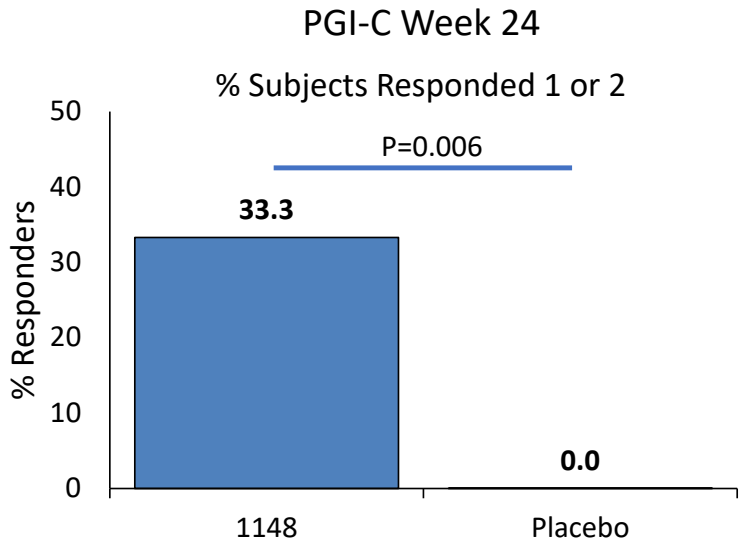
CTCAE grade; *P<0.05 vs. placebo. **Mean value

LPCN 1148 improved patient reported outcomes

Patient Global Impression of Change (PGI-C) 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



- Significantly more 1148-treated subjects reported feeling ‘very much’ or ‘moderately’ better
  - No 1148-treated subjects reported symptom worsening (>4) at Week 24
- Mean PGI-C score was significantly lower (improved) with 1148-treatment at Week 24
- Significant symptom improvement was noted as early as Week 4

Safety set, LOCF. n=15 for LPCN 1148, n=13 for placebo. PGI-C: Patient Global Impression of Change Scale

LPCN 1148 improved anemia in cirrhosis

Hemoglobin **Timepoint**	LPCN 1148 (N=15)	Placebo (N=13)	LPCN 1148 P-value	
			Change from Baseline	Vs. Placebo
Baseline (g/dL)	11.39 (0.84)	13.04 (0.66)	N/A	NS
Week 24 CFB (g/dL)	1.30 (0.40)	-0.16 (0.23)	0.003	0.005

Mean (SE)

Anemia Status	LPCN 1148 (N=15)	Placebo (N=14)
Anemic at baseline	11 (73%)	7 (50%)
Anemic at W24	7 (47%)	7 (54%)
Resolution	4 (36%)	1 (14%)
New onset	0 (0%)	1 (17%)

More subjects had resolution of anemia* at Week 24 with LPCN 1148

*Anemia defined as hemoglobin < 13g/dL. Safety set, LOCF. One placebo subject had no post-baseline data (liver transplant)

LPCN 1148 produced trends in improvement in other secondary end-points

Parameter	LPCN 1148	Placebo
Deaths (n)	0	1
Days in hospital (total)	54	117
Length of hospital stay (median, days)	3	5
6 min walk test (feet)*	270	-16
EncephalApp Stroop Test (total time, seconds)*	-4.8	13.8

*mean change from baseline (SE), LOCF

LFI: Observed change from baseline for LPCN 1148 is comparable to that of placebo at 24 week study duration

Timepoint	LPCN 1148 (N=15)	Placebo (N=12)	LPCN 1148 P-value	
			Change from Baseline	Vs. Placebo
Baseline	4.04 (0.23)	3.88 (0.34)	N/A	NS
Week 24 CFB	-0.05 (0.18)	-0.17 (0.17)	NS	NS

Mean (SE)

- Similar changes from baseline across the three LFI components with LPCN 1148 and Placebo

LPCN 1148 - AE profile

Parameter	LPCN 1148 (N=15)		Placebo (N=14)	
	#	n	#	n
Total AEs	33	8	36	10
Serious AEs	15	5	16	5
Severe AEs	6	4	10	4

- Administration of LPCN 1148 was well tolerated in this end-stage population, with rates and severities of adverse events (AEs) similar to those within the placebo group
- No cases of drug-induced liver injury
- No cases of HCC

Severe AE: CTCAE Grade ≥ 3

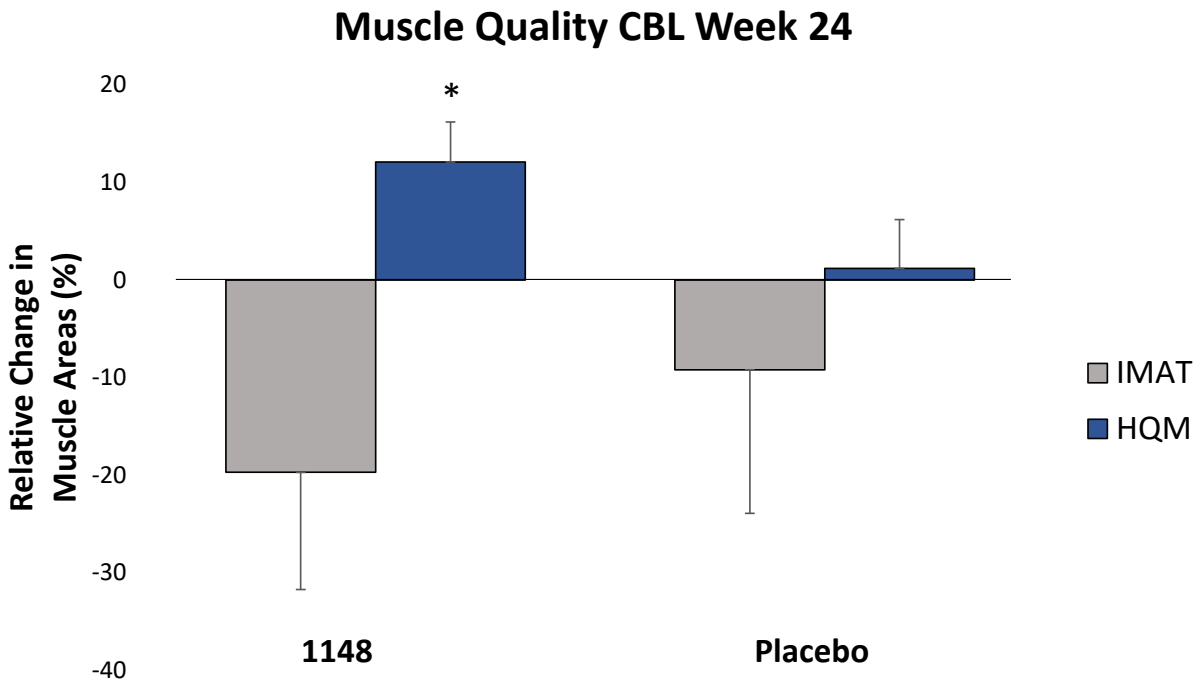
Summary and conclusions

- LPCN 1148, an oral androgen receptor agonist improved sarcopenia in adult male patients with cirrhosis.
- It was further associated with improvement in encephalopathy, anemia, total number of days hospitalized, and patient reported outcomes which are all clinically meaningful.
- It improved several other biomarkers associated with sarcopenia and end-stage liver disease.
- It was well tolerated and did not have any overt safety signals.
- Limitations: small sample size
- Overall, these data demonstrate that LPCN 1148 is well tolerated and improves multiple clinically significant and surrogate outcomes in patients with advanced cirrhosis with clinical decompensation and supports its further development in this population especially while patients await transplant or as a palliative measure.

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

LPCN 1148 improved myosteatosis



Substantial Changes in Muscle Quality seen with LPCN 1148 Therapy

- Decrease in intramuscular adipose tissue (IMAT)
- Significant increase in high quality muscle (HQM)