Lipocine Announces Positive Week 52 Results from LPCN 1148 Phase 2 Study in Patients with Cirrhosis

- Met primary and Hepatic Encephalopathy (HE) endpoints in Phase 2 study
    - Increase in Skeletal Muscle Index (SMI) observed at Week 24 was maintained through 52 weeks
    - Participants on placebo increased SMI when switched to LPCN 1148
    - Fewer Overt Hepatic Encephalopathy (OHE) events and time to first recurrent OHE event was longer while on LPCN 1148 therapy
- LPCN 1148 was well-tolerated, with AE rates and severities similar to placebo.
    - Participants on LPCN 1148 were hospitalized for fewer days

SALT LAKE CITY, March 28, 2024 /PRNewswire/ -- Lipocine Inc. (NASDAQ: LPCN), a biopharmaceutical company today announced positive topline results from a Phase 2 clinical study of LPCN 1148. LPCN 1148 is an oral candidate under development for the clinical management of cirrhosis, specifically prevention of OHE recurrence and treatment of sarcopenia. LPCN 1148 is targeted to be a "First in Class" product candidate with a novel mechanism of action (MOA). Lipocine plans to meet with the FDA to discuss a development path to NDA filing.

"We are encouraged with the positive results from our Phase 2 study. These results demonstrate that LPCN 1148 treatment benefits patients with cirrhosis who are sarcopenic and have experienced other serious decompensation events such as OHE," said Dr. Mahesh Patel, President and CEO of Lipocine Inc. "Cirrhosis management is a significant unmet medical need with a strong pharmaco-economic rationale. We believe LPCN 1148 both ameliorates sarcopenia and decreases the recurrence of OHE. If approved, this treatment is a compelling opportunity with the potential to be the standard of care as a mono or adjunct therapy in managing advanced cirrhosis."

This Phase 2 proof of concept study was a randomized placebo-controlled study in sarcopenic male patients with cirrhosis on the liver transplant waitlist. In Stage 1, 29 patients were randomized 1:1 to receive either LPCN 1148 or matching placebo for 24 weeks. At Week 24, the open-label extension Stage 2 of the study commenced. During Stage 2, 8 participants who were on placebo in Stage 1 converted to LPCN 1148, and 11 participants who started the study on LPCN 1148 continued treatment with LPCN 1148.

The study's primary endpoint was a change in L3-SMI at week 24. L3-SMI estimates whole body skeletal muscle mass. SMI was analyzed at baseline, and Weeks 12, 24, 36, and 52. Key secondary endpoints included rates of hepatic encephalopathy and the safety/tolerability of LPCN 1148.

Results

All LPCN 1148-treated participants completed Week 24 (n=15), and 10 of 14 placebo participants completed Week 24. During the initial 24 weeks, all LPCN 1148-treated participants had at least one evaluable post-baseline CT scan and are therefore part of the modified intent to treat (mITT) analysis; 10 placebo-treated participants had an evaluable post-baseline CT.
As prespecified, L3-SMI analysis was performed on the mITT population (n=25), with the last evaluable post-baseline observation carried forward (LOCF). Of those participants on placebo in Stage 1, 6 out of 8 who went on to receive LPCN 1148 starting at Week 24 had evaluable CT scans in Stage 2.

Primary endpoint

Participants who received LPCN 1148 during Stage 1 had a significant ($p<0.01$) increase in L3-SMI of 4.1 cm^2/m^2 (8.8%) at Week 24, the primary analysis timepoint, and this increase was maintained through the additional 28 weeks of the study (Week 52, 4.1 cm^2/m^2, 8.7%). Placebo participants who began receiving LPCN 1148 saw a marked increase in SMI as early as 12 weeks after therapy initiation (Week 36, 7.4 cm^2/m^2, 15.1%), and this increase was maintained through Week 52 (8.1 cm^2/m^2, 16.7%).

Table 1: Change in L3-SMI at Week 24 and Week 52

Timepoint	LPCN 1148 N=15	Placebo N=10	LPCN 1148 (Placebo converted) N=6
Baseline (cm^2/m^2)	47.8 (1.8)	45.8 (2.3)	50.1 (2.7)[#]

Week 24 CFB (cm^2/m^2)‡	4.1 (0.9) *†	- 0.6 (1.2)	
Week 52 CFB (cm^2/m^2)	4.1 (1.1) *	-	8.1 (1.7) *

Data are least squares mean (standard error), LOCF.
For Placebo participants converted to LPCN 1148, baseline is considered Week 24 data.
ANCOVA model with treatment and overall baseline L3-SMI as covariates.
* p<0.01 vs baseline.
† p<0.01 LPCN 1148 vs placebo at Week 24.
‡ Change from baseline in SMI at Week 24 was the study's primary endpoint.

Hepatic Encephalopathy

Recurrent OHE is defined as an event of OHE in a participant with a medical history of HE. Most (22/29, 76%) study participants had experienced HE prior to this study, and there were similar numbers of these participants in each study arm in both Stage 1 and Stage 2. Nearly all (21/22, 95%) participants with a history of HE were on therapy for HE at baseline and during the study (lactulose and/or rifaximin). During Stage 1, LPCN 1148 treatment resulted in significantly (p<0.05) fewer cases of recurrent OHE (1 vs 6), a potential FDA-approvable endpoint. During the open-label Stage 2, there were two cases of OHE, one in a participant who was receiving LPCN 1148 since Day 1, and one who began receiving LPCN 1148 at Week 24. The average time to first OHE recurrence was longer with LPCN 1148 treatment, at 183 days compared to 35 days for placebo.

Initial Randomization Group	**LPCN 1148**		**Placebo**	
	Stage 1 (Through Week 24) N=15	**Stage 2 (Week 24 to EOS) N=11**	**Stage 1 (Placebo) (Through Week 24) N=14**	**Stage 2 – LPCN 1148 (Placebo Converted) (Week 24 to EOS) N=8**
History of HE prior to randomization (n)	11	7	11	6
OHE (events)	2	1	6	1
Recurrent OHE (events)	1	1	6	1
Average time to first recurrent OHE event (days)	114	294	35	140

Safety set; includes all participants who received study drug in a given stage. Overt HE (OHE) is defined as an event of HE with CTCAE severity ≥ grade 2.

Safety

In this 52-week study, LPCN 1148 was well-tolerated with AE rates and severities similar to those observed in Stage 1 with placebo. Participants experienced fewer serious or severe adverse events when switched from placebo to LPCN 1148. Participants on LPCN 1148 were hospitalized for fewer total days with shorter hospital stays.

There were two deaths reported in placebo-treated participants and one in LPCN 1148-treated participants during the study.

The company plans to share additional results pertaining to other secondary endpoints at upcoming scientific conferences.

Dr. Arun J. Sanyal, MD, Director, Stravitz-Sanyal Institute for Liver Disease & Metabolic Health, Virginia Commonwealth University, commented, "I am delighted to see the durability of the results noted in this important trial to improve sarcopenia in a very sick population of patients with decompensated cirrhosis. The stability of improvement in sarcopenia and encephalopathy provide proof of concept that sarcopenia correction with LPCN 1148 may provide benefit to patients with decompensated cirrhosis and reduce the risk of breakthrough encephalopathy. These provide a strong rationale for further studies on the overall benefits and risks of LPCN 1148 in this population where there is a major unmet need to improve sarcopenia."

Dr. Jennifer Lai, MD, MBA, UCSF Professor of Medicine, transplant hepatologist, and study principal investigator, added, "The rapid and sustained increases in muscle mass seen in this study with LPCN 1148 are very exciting, especially as there are currently no FDA-approved pharmacotherapeutics for sarcopenia in cirrhosis. The observed trends towards improved clinical outcomes including hepatic encephalopathy support what we know about the importance of increasing and maintaining muscle mass in patients with cirrhosis."

About Cirrhosis

Cirrhosis is an end stage liver disease of varying etiologies such as alcoholic liver disease, chronic viral hepatitis, nonalcoholic fatty liver disease and primary cholangitis. Complications of cirrhosis include decompensation events such as hepatic encephalopathy due to systemic ammonia buildup, variceal bleeding, and ascites, which require frequent hospitalizations. In addition, many patients exhibit sarcopenia (low muscle mass).

Over 382,000 patients have been diagnosed with decompensated liver cirrhosis in the US, with few options for managing their disease other than liver transplant. Poor quality of life is common while waiting for a liver transplant. Although there is a limited supply of donor livers, transplant is the only cure for end-stage cirrhosis.

About HE

HE is a frequent complication and one of the most debilitating manifestations of liver disease, severely affecting the lives of patients and their caregivers. For patients with decompensated liver cirrhosis and sarcopenia, clinical outcomes tend to be worse - both sarcopenia and myosteatosis are associated with an increased risk of HE.

OHE is an episodic neurological disorder with a high recurrence rate. Up to 50% of patients with cirrhosis will experience an OHE episode in their lifetime. Patients can exhibit global neurological, psychiatric, and musculoskeletal deficits. HE has a complex pathophysiology that includes impairment of ammonia clearance and increased inflammatory cytokine and HE recurrence is common, despite use of standard-of-care therapies. Options for prevention/treatment are limited, resulting in significant enduring unmet medical need as the 1-year survival for patients with OHE is ~50%. Furthermore, cognitive impairment associated with cirrhosis results in utilization of more health care resources.

About LPCN 1148

LPCN 1148 comprises testosterone dodecanoate, a unique androgen receptor agonist. It is targeted as a differentiated intervention option with a novel multimodal MOA to elicit potential benefits in management of cirrhosis and associated comorbidities of cirrhosis.

About the Phase 2 study

This multi-center study enrolled and dosed a total of 29 patients across 8 centers in the United States. The primary objective was to evaluate the efficacy of 24 weeks of LPCN 1148 treatment in men with cirrhosis and sarcopenia. The secondary objective was to evaluate the safety and tolerability of LPCN 1148. Following Week 24, the open-label stage of the study began (Stage 2), wherein all participants received LPCN 1148 (no placebo in Stage 2).

Baseline characteristics, including age, disease etiology baseline L3-SMI, and other comorbidities were generally well-balanced between groups. Overall, the average baseline Model for End-Stage Liver Disease (MELD) score was 16.8, and 97% of patients had previously experienced at least one clinical decompensation event. Sarcopenia, or low muscle mass, was assessed by computed tomography (CT) scan; total skeletal muscle area at the third lumbar vertebra was measured by CT scan and normalized by participant height (L3-SMI, L3-skeletal muscle index). Patients had study visits every four weeks, with CTs performed at Weeks 12, 24, 36, and 52. Patients with a variety of cirrhosis etiologies were eligible. During the study there were no restrictions on standard of care medications, procedures, or other interventions. Further details on the study design, including inclusion and exclusion criteria, can be found on Clinicaltrials.gov (NCT04874350).

About Lipocine

Lipocine is a biopharmaceutical company leveraging its proprietary technology platform to augment therapeutics through effective oral delivery to develop products for CNS disorders. Lipocine has drug candidates in development as well as drug candidates for which we are exploring partnering. Our drug candidates represent enablement of differentiated, patient friendly oral delivery options for favorable benefit to risk profile which target large addressable markets with significant unmet medical needs.

Lipocine's clinical development candidates include: LPCN 1154, oral brexanolone, for the potential treatment of postpartum depression, LPCN 2101 for the potential treatment of epilepsy and LPCN 1148, an oral prodrug of bioidentical testosterone targeted for the management of symptoms associated with liver cirrhosis. Lipocine is exploring partnering opportunities for LPCN 1107, our candidate for prevention of preterm birth, LPCN 1148, for the management of decompensated cirrhosis, and LPCN 1144, our candidate for treatment of non-cirrhotic NASH. TLANDO, a novel oral prodrug of testosterone containing testosterone undecanoate developed by Lipocine, is approved by the FDA for conditions associated with a deficiency of endogenous testosterone, also known as hypogonadism, in adult males. For more information, please visit www.lipocine.com.

Forward-Looking Statements

This release contains "forward-looking statements" that are made pursuant to the safe harbor provisions of the Private Securities Litigation Reform Act of 1995 and include statements that are not historical facts regarding our product development

efforts, our product candidates and related clinical trials, our strategic plans for developing products to treat CNS disorders, our ability to monetize non-core product candidates, including through entering into partnering arrangements, the application of our proprietary platform in developing new treatments for CNS disorders, the timing and completion of regulatory reviews, outcomes of clinical trials of our product candidates, the potential uses and benefits of our product candidates, the potential uses and benefits of LPCN 1148, and the timing of and our ability to make any NDA filing relating to LPCN 1148. Investors are cautioned that all such forward-looking statements involve risks and uncertainties, including, without limitation, the risks that we may not be successful in developing product candidates to treat CNS disorders, we may not be able to enter into partnerships or other strategic relationships to monetize our non-core assets, the FDA will not approve any of our products, risks related to our products, expected product benefits not being realized, clinical and regulatory expectations and plans not being realized, new regulatory developments and requirements, risks related to the FDA approval process including the receipt of regulatory approvals and our ability to utilize a streamlined approval pathway for LPCN 1154, the results and timing of clinical trials, patient acceptance of Lipocine's products, the manufacturing and commercialization of Lipocine's products, and other risks detailed in Lipocine's filings with the SEC, including, without limitation, its Form 10-K and other reports on Forms 8-K and 10-Q, all of which can be obtained on the SEC website at www.sec.gov. Lipocine assumes no obligation to update or revise publicly any forward-looking statements contained in this release, except as required by law.

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