Oral LPCN 2401 Reduces Fat Mass and Increases Lean Mass in Men with Obesity

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INTRODUCTION

- Approximately 74% of adults aged 20 and older are overweight or obese.[1]
- Incretin mimetic therapy results in clinically meaningful weight loss, but has significant limitations including lean mass loss,[2,3] increased fracture risk,[4] weight loss plateau[2], and reversal of effects upon treatment discontinuation.[5,6]
- LPCN 2401 is a novel oral treatment comprising prodrug of androgen receptor agonist (ARA). LPCN 2401 is being developed to address unmet needs of incretin mimetic therapy for obesity management.
- ARA may exert its effects by lipolysis induction and lipogenesis reduction,[7] stimulation of muscle activators and modulation of muscle growth suppressors,[8] effects on osteoblasts,[9] and may amplify incretin mimetic treatment effects through genomic and non-genomic actions. Additionally, long-term studies have demonstrated significant weight loss without an observed plateau with ARA administration over an 11 year period.[10]
- Addition of an antioxidant and metabolic modifier, vitamin E, could provide additional benefits on body composition and cardiometabolic health.
- **Purpose**: To evaluate safety and body composition changes with LPCN 2401 treatment in obese and overweight participants.

METHODS

- Participants: Men with metabolic dysfunction-associated steatohepatitis (MASH). Basal testosterone level was not a criteria for study eligibility. All participants had BMI ≥30 kg/m^2 or BMI ≥27 kg/m^2 with at least one weight-related comorbid condition. DEXA dataset includes subjects who completed baseline and at least one post-baseline whole body DEXA scan.
- Design: Blinded, 3-arm, randomized, placebo-controlled
  - Treatment phase (NCT04134091) was blinded; subjects were randomized (1:1:1) to one of three treatments:
    1. **LPCN 2401:** 284 mg Testosterone (T) equivalents daily
    2. **LPCN 2401+E (ARA + vitamin E ester):** 284 mg T equivalents + 800 IU vitamin E daily
    3. **Placebo**
  - Subjects who completed the treatment phase were invited to participate in an additional 36-week open label extension (NCT04685993) where they received LPCN 2401.

Figure 1. Study design

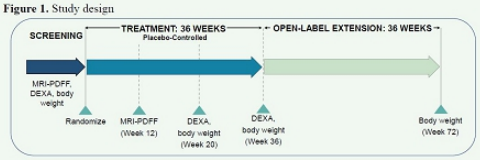


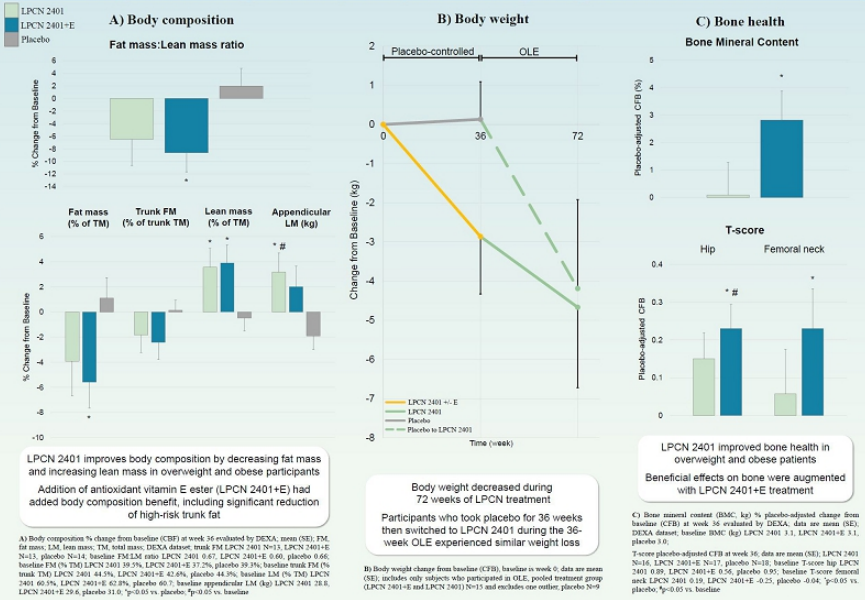
Table 1. Baseline characteristics

Parameter	LPCN 2401	LPCN 2401+E	Placebo
Mean age (years)[a]	53.2	53.8	51.1
Mean body weight (kg)[a]	111.3	107.8	118.6
Mean BMI (kg/m^2)[a]	35.9	34.7	37.2
Diabetes (% of patients)*	72.2	57.9	52.6
Hypertension (% of patients)*	66.7	57.9	68.4
Serum testosterone (ng/dL)*	358.9	301.7	316.6

BMI, body mass index; DEXA, dual energy x-ray absorptiometry; [a]DEXA dataset. LPCN 2401 N=13, LPCN 2401+E N=13, placebo N=14; *safety dataset: LPCN 2401 N=18, LPCN 2401+E N=19, placebo N=19

RESULTS

Improved Changes in Body Composition, Body Weight, and Bone Health



LPCN 2401 improves body composition by decreasing fat mass and increasing lean mass in overweight and obese participants

Addition of antioxidant vitamin E ester (LPCN 2401+E) had added body composition benefit, including significant reduction of high-risk trunk fat

Body weight decreased during 72 weeks of LPCN treatment

Participants who took placebo for 36 weeks then switched to LPCN 2401 during the 36-week OLE experienced similar weight loss

LPCN 2401 improved bone health in overweight and obese patients

Beneficial effects on bone were augmented with LPCN 2401+E treatment

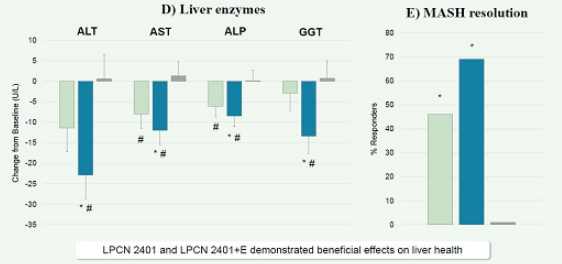
A) Body composition % change from baseline (CBF) at week 36 evaluated by DEXA; mean (SE); FM, fat mass; LM, lean mass; TM, total mass; DEXA dataset; trunk FM LPCN 2401 N=13, LPCN 2401+E N=13, placebo N=14; baseline FM:LM ratio LPCN 2401 0.67, LPCN 2401+E 0.60, placebo 0.66; baseline FM (% TM) LPCN 2401 39.5%, LPCN 2401+E 37.2%, placebo 39.3%; baseline trunk FM (% trunk TM) LPCN 2401 44.5%, LPCN 2401+E 42.6%, placebo 44.3%; baseline LM (% TM) LPCN 2401 60.5%, LPCN 2401+E 62.8%, placebo 60.7; baseline appendicular LM (kg) LPCN 2401 28.8, LPCN 2401+E 29.6, placebo 31.0; *p<0.05 vs. placebo; #p<0.05 vs. baseline

B) Body weight change from baseline (CFB), baseline is week 0; data are mean (SE); includes only subjects who participated in OLE; pooled treatment group (LPCN 2401+E and LPCN 2401) N=35 and excludes one outlier, placebo N=9

C) Bone mineral content (BMC, kg) % placebo-adjusted change from baseline (CFB) at week 36 evaluated by DEXA; data are mean (SE); DEXA dataset; baseline BMC (kg) LPCN 2401 3.1, LPCN 2401+E 3.1, placebo 3.0;

T-score placebo-adjusted CFB at week 36; data are mean (SE); LPCN 2401 N=16, LPCN 2401+E N=17, placebo N=18; baseline T-score hip LPCN 2401 0.89, LPCN 2401+E 0.56, placebo 0.95; baseline T-score femoral neck LPCN 2401 -0.19, LPCN 2401+E -0.25, placebo -0.04; *p<0.05 vs. placebo; #p<0.05 vs. baseline

Beneficial Liver Effects



LPCN 2401 and LPCN 2401+E demonstrated beneficial effects on liver health

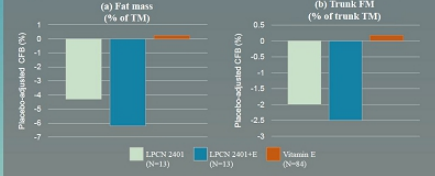
D) ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; GGT, gamma-glutamyl transferase; liver enzyme change from baseline (CFB) at week 36; LS mean (SE); safety dataset. LPCN 2401 N=18, LPCN 2401+E N=17, placebo N=17; baseline ALT (U/L) LPCN 2401 53.9, LPCN 2401+E 51.2, placebo 51.1; baseline AST (U/L) LPCN 2401 32.4, LPCN 2401+E 31.8, placebo 36.1; baseline ALP (U/L) LPCN 2401 67.5, LPCN 2401+E 72.5, placebo 64.2; baseline GGT (U/L) LPCN 2401 54.7, LPCN 2401+E 55.2, placebo 51.1; E) % of subjects with MASH at baseline with MASH resolution at week 36; MASH resolution defined per FDA guidance, LPCN 2401 N=13, ARA monotherapy N=13, placebo N=11; *p<0.05 vs. placebo, #p<0.05 vs. baseline;

Summary of Safety Events

- LPCN 2401 was well-tolerated with no concerning safety signals with up to 72 weeks of exposure
- Frequency and severity of treatment-emergent adverse events (TEAEs) and serious adverse events in LPCN treatment groups were comparable to placebo
- Androgenic (edema, BPH, PSA increase, hypertension), cardiovascular, and gastrointestinal (GI) adverse event rates and severities were similar in treatment groups compared to placebo
- There were no cases of muscle spasm or drug-induced liver injury

POTENTIAL ROLE OF VITAMIN E IN BODY COMPOSITION

In a clinical study conducted by Sanyal, et al.[11], overweight and obese male and female participants with MASH were treated with vitamin E 800 IU daily for 96 weeks. Body composition was evaluated by DEXA at week 96.



Vitamin E alone did not reduce whole body fat mass or trunk fat mass as observed with LPCN 2401+E treatment

Body composition changes observed with LPCN treatments are likely driven by ARA and may have a synergistic effect with vitamin E (LPCN 2401+E)

(a,b) Placebo-adjusted change from baseline (CFB) in body composition of LPCN 2401 and LPCN 2401+E assessed at week 36. Vitamin E monotherapy was not compared to 2401 as head-to-head studies and is taken from the data collected by Sanyal, et al.[11] (a) fat mass is whole body fat mass as a % of total mass, (b) trunk fat is % of truck region measured as fat, FM, fat mass; TM, total mass

CONCLUSIONS

- LPCN 2401 has the potential to improve lean mass and fat mass loss, including truck fat loss, with improved bone health.
- LPCN 2401 is safe and well-tolerated with up to 72 weeks of exposure with minimal GI effects, supporting safe chronic use.
- These results provide support to further study LPCN 2401 in body composition improvement when used as adjunct or as monotherapy post-cessation to incretin mimetic therapies, e.g. GLP-1RA agonists, for chronic weight management.
- Further studies may be needed to confirm positive effects of 2401+Vit E on observed improvements.

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DISCLOSURES & CONTACT

Authors JCW, JO, MG, BJB, NC, and MVP are employees of Lipocine Inc.
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