



CVI-LM001, a first-in-class novel small molecule PCSK9 modulator for hypercholesterolemia and NASH: preclinical and first-in-human studies

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PREMISE

- NAFLD/NASH and cardiovascular disease are associated with common metabolic risk factors such as hyperlipidemia.
- CVI-LM001, currently at Phase 2 Proof-of-Concept clinical development stage for the treatment of hypercholesterolemia, is a novel first-in-class oral small molecule PCSK9 modulator discovered and developed by CVI Pharmaceuticals.
- In preclinical studies, CVI-LM001 treatment of hamsters fed a high fat and high cholesterol diet (HFHCD) increased protein levels of LDL receptor and activated AMPK in liver tissues and decreased circulating PCSK9 levels concomitant with reductions of serum LDL-C, TC and TG levels.
- The studies aimed to demonstrate the effects of CVI-LM001 on hepatic steatosis and NASH in hamster models and conduct first-in-human Phase I clinical trials to demonstrate the safety and pharmacological activity of CVI-LM001 in Chinese healthy subjects and hyperlipidemic subjects.

METHODS

- The effects of CVI-LM001 on hepatic steatosis were evaluated in high fat and high cholesterol diet (HFHCD)-fed hamsters following 4 weeks of treatment by oral gavage at CVI-LM001 dose of 10 mg/kg, 20 mg/kg or 40 mg/kg, or 50 mg/kg fenofibrate, or vehicle once daily (QD).
- The effects of CVI-LM001 on hepatic inflammation, ballooning and fibrosis were evaluated in a diet-induced NASH hamster model following 5 weeks of treatment. Hamsters were fed a free choice diet (free choice between a chow diet with normal tap water or a high fat/cholesterol diet (Safe Diets) with 10% fructose enriched tap water) for up to 20 weeks (15 weeks diet and 5 weeks treatments of vehicle, CVI-LM001 at 100 mg/kg, or elafibranor 15 mg/kg orally QD).
- Double-blind, randomized single ascending-dose (100-800 mg per day) and multiple ascending-dose (MAD) studies were conducted to assess the tolerability, pharmacokinetics and pharmacodynamics of oral CVI-LM001 in healthy subjects. Subjects (Chinese males or females, 18-45 years) received 100, 200, or 300 mg once daily CVI-LM001 or placebo for 10 days. Blood for pharmacokinetics and/or pharmacodynamics were collected. Serum PCSK9 levels were measured.
- To explore the efficacies of CVI-LM001 in LDL-C lowering and serum PCSK9 reduction, a randomized, double-blind and placebo-controlled proof of mechanism (POM) study was further conducted in Chinese subjects with mild hypercholesterolemia (LDL-C ≥ 3.2 mM and ≤ 4.88 mM). Hyperlipidemic subjects (males or females, 18-65 years) received 200 mg (n=10), or 300 mg (n=11) once daily CVI-LM001 or placebo (n=11) for 28 days. Blood for pharmacokinetics and/or pharmacodynamics were collected. Serum PCSK9 and lipid levels including total cholesterol (TC), LDL-C, and ApoB were measured.

RESULTS SUMMARY

- CVI-LM001 demonstrated dose-dependent reductions in serum LDL-C, TC and TG of hyperlipidemic hamsters with an effective dose of 20 mg/kg that lowered LDL-C by 37%, TC by 39% and TG by 40% compared to vehicle and ameliorated the HFHCD-induced liver fat accumulation evidenced by a 67% ($p < 0.01$) reduction of Oil red-O staining intensity compared to vehicle.
- In the NASH model, CVI-LM001 treatment improved total NASH score (-2.1, $p < 0.01$) driven primarily by substantial reductions of hepatic ballooning (-73%, $p < 0.001$).
- CVI-LM001 was safe and well tolerated in healthy human volunteers at all doses evaluated. Circulating PCSK9 levels were reduced in healthy volunteers after 10 days of treatment.
- Moreover, in hyperlipidemic subjects, compared to placebo, LDL-C and PCSK9 levels were significantly reduced by CVI-LM001 at a daily dose of 300 mg after 28 days of treatment.

Preclinical Study Results

Figure 1. Significant reductions of serum TC, LDL-C, TG and liver fat accumulations by oral treatment of HFHCD-fed golden Syrian hamsters with 20 mg/kg and 40 mg/kg CVI-LM001 for 4 weeks (n=10 per group, fenofibrate (FENO) at 50 mg/kg was used as a positive control (A). In B, frozen liver sections were stained with Oil red-O and the intensity of each section was quantified (n=10 livers per group). In a parallel PK study of hamsters treated with CVI-LM001 at 40 mg/kg, CVI-LM001 showed similar plasma concentrations at day 1 and day 28, indicating no drug accumulation in this hamster model (C).

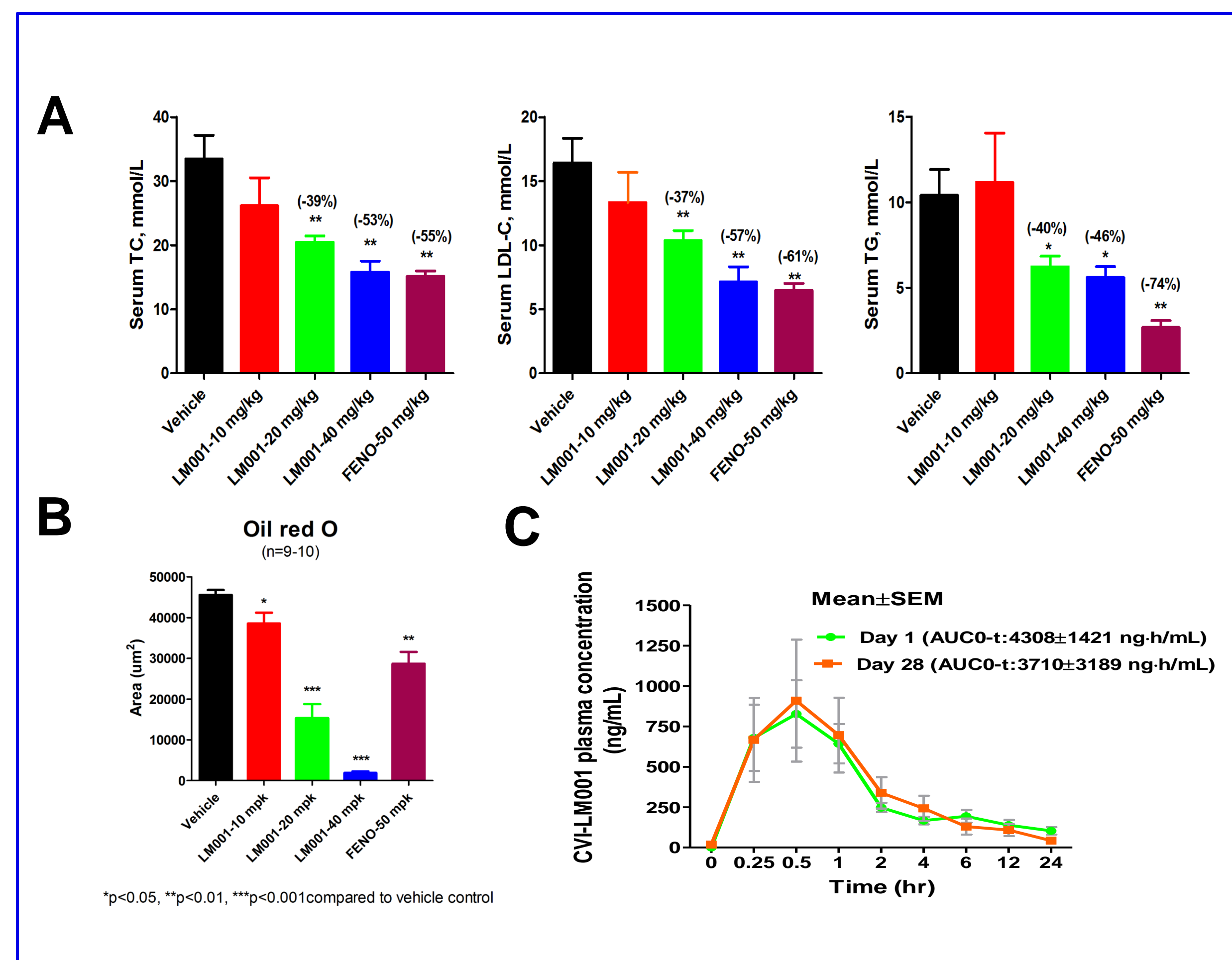
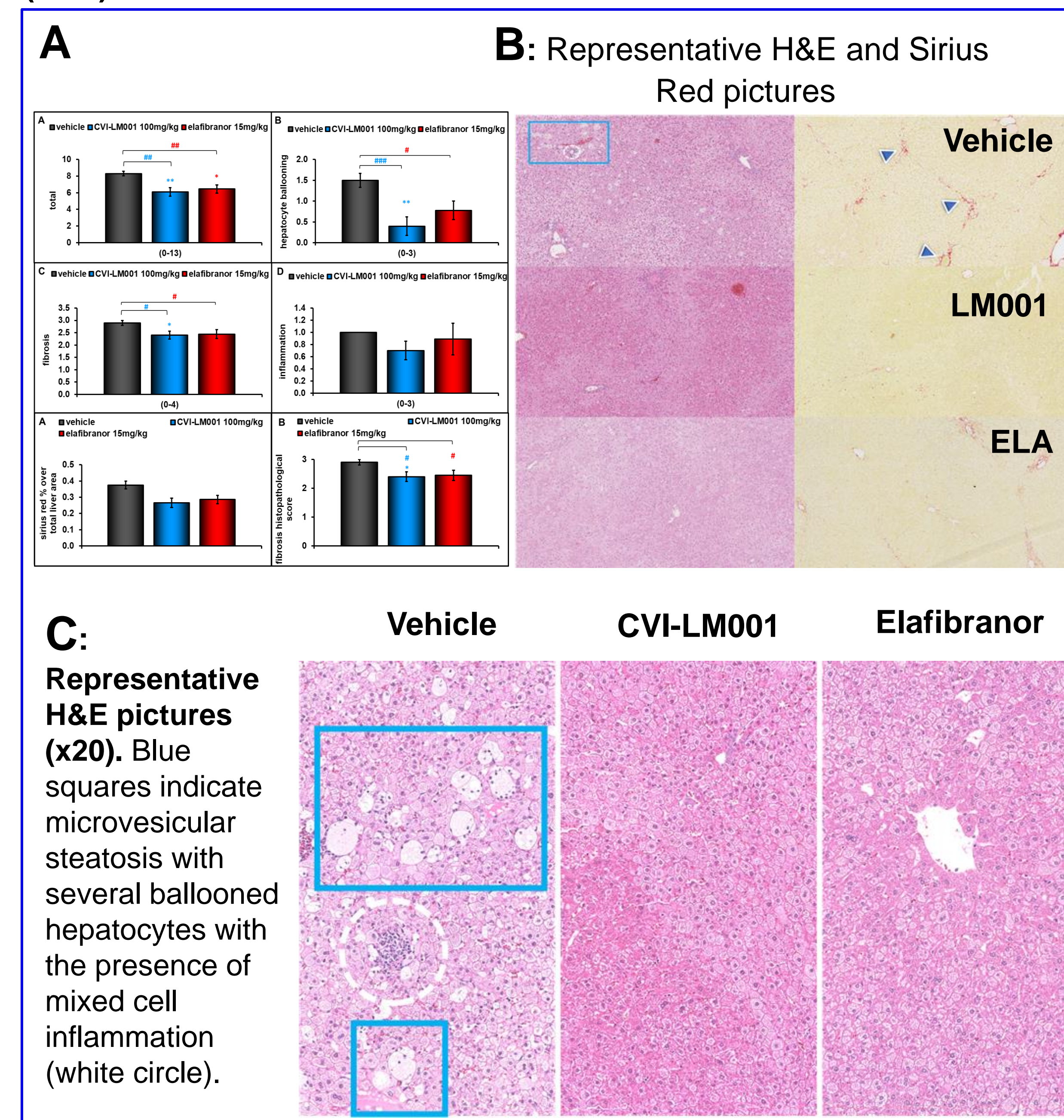


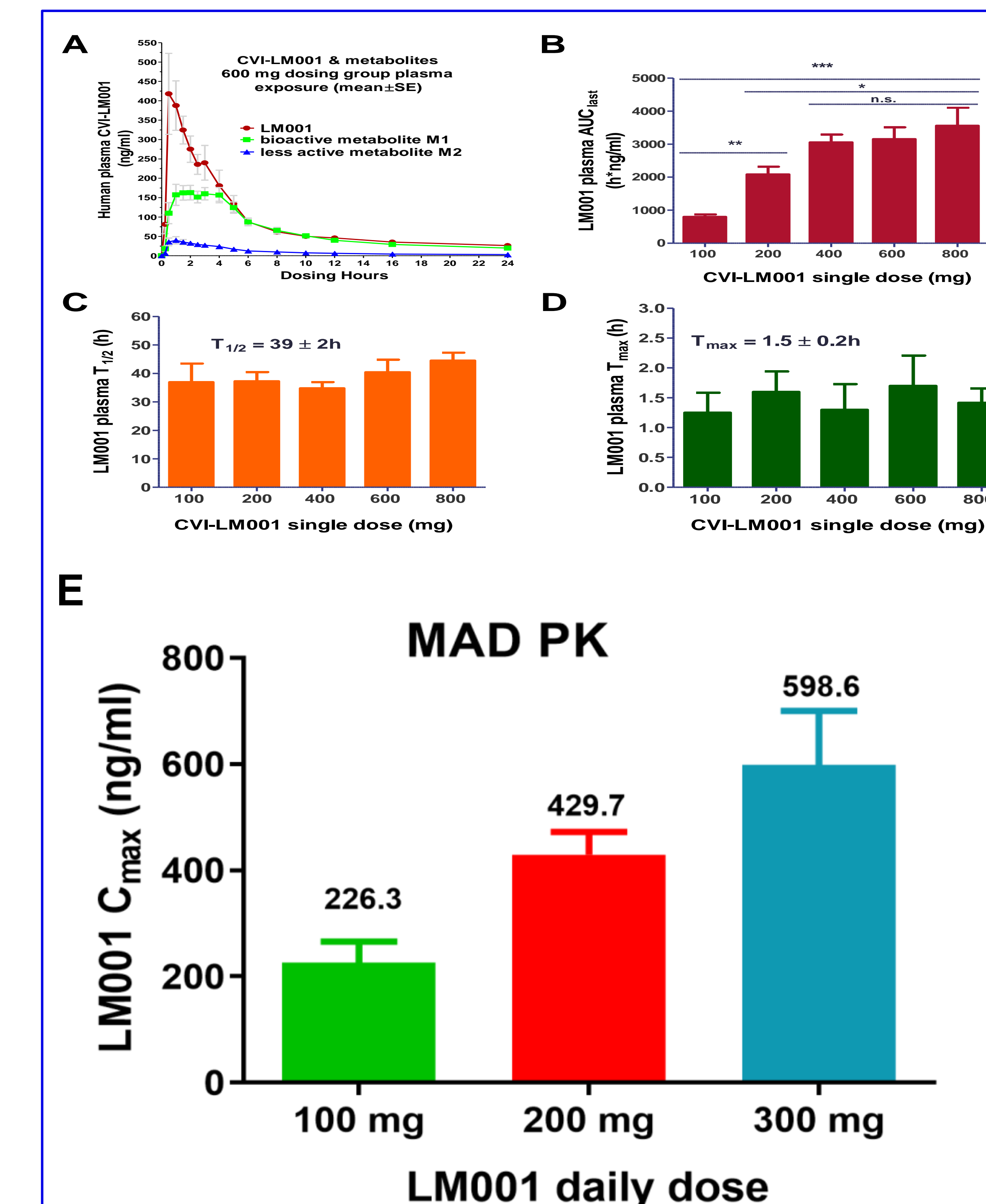
Figure 2. In the free-choice diet-induced NASH hamster model, CVI-LM001 showed benefits on NASH, with significantly lower fibrosis and hepatocyte ballooning and a trend towards lower steatosis and inflammation score, resulting in a significant reduction in NAS score, an effect also observed with the reference drug elafibranor (ELA).



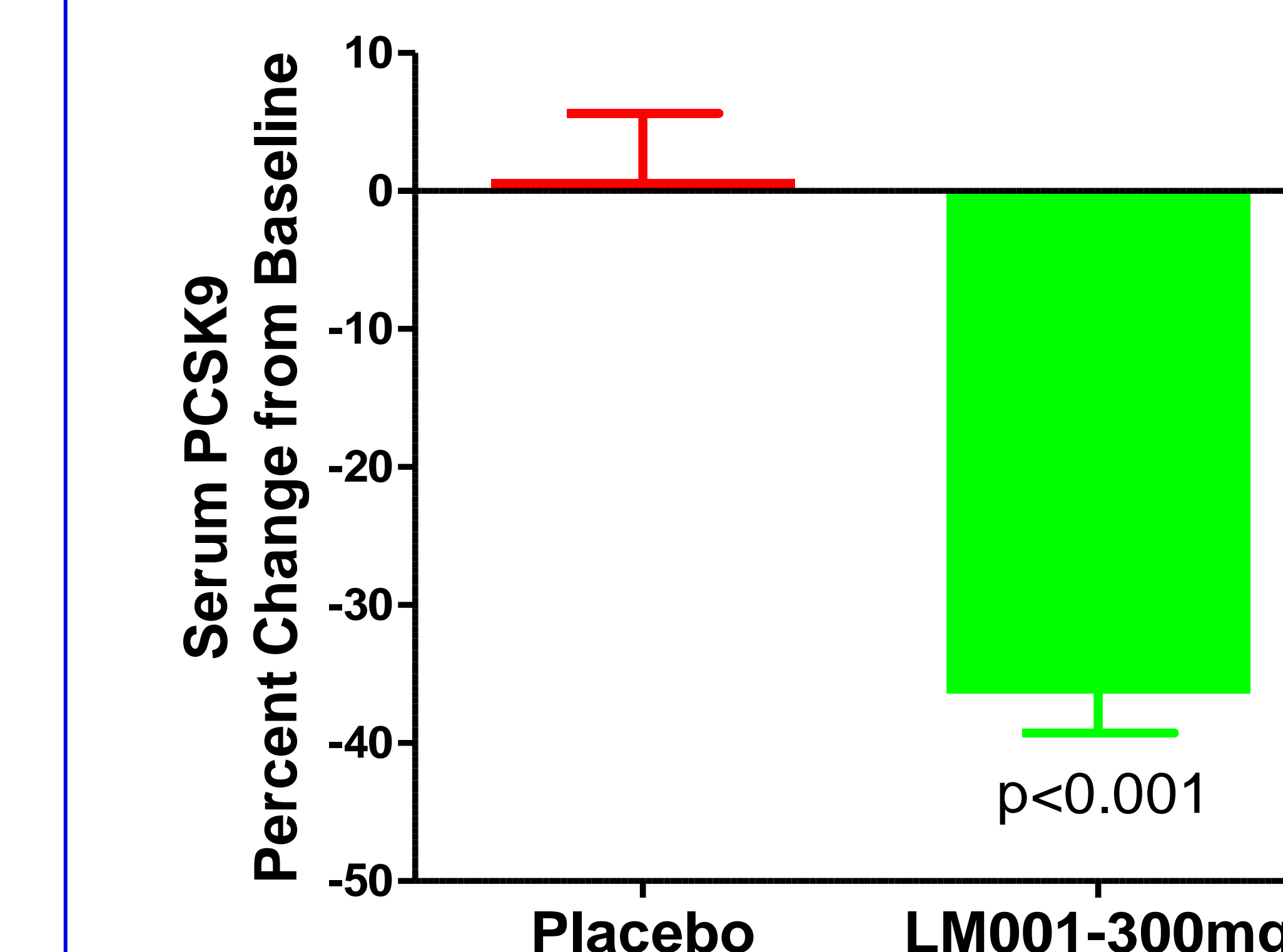
Phase 1a Healthy subjects MAD Results

Figure 3. CVI-LM001 Phase 1a Clinical Highlights:

- Excellent safety profile of SAD (100-800 mg QD) and MAD (100-300 mg QD) studies and good plasma exposure (SAD: A-D; E: MAD) were observed;
- Ten day treatment with CVI-LM001 led to substantial reduction of blood PCSK9 levels (F), indicating target engagement and validated the MOA of PCSK9 inhibition. The first-in-human PK data supports the once a day (QD) dosing regime in late stage of clinical development

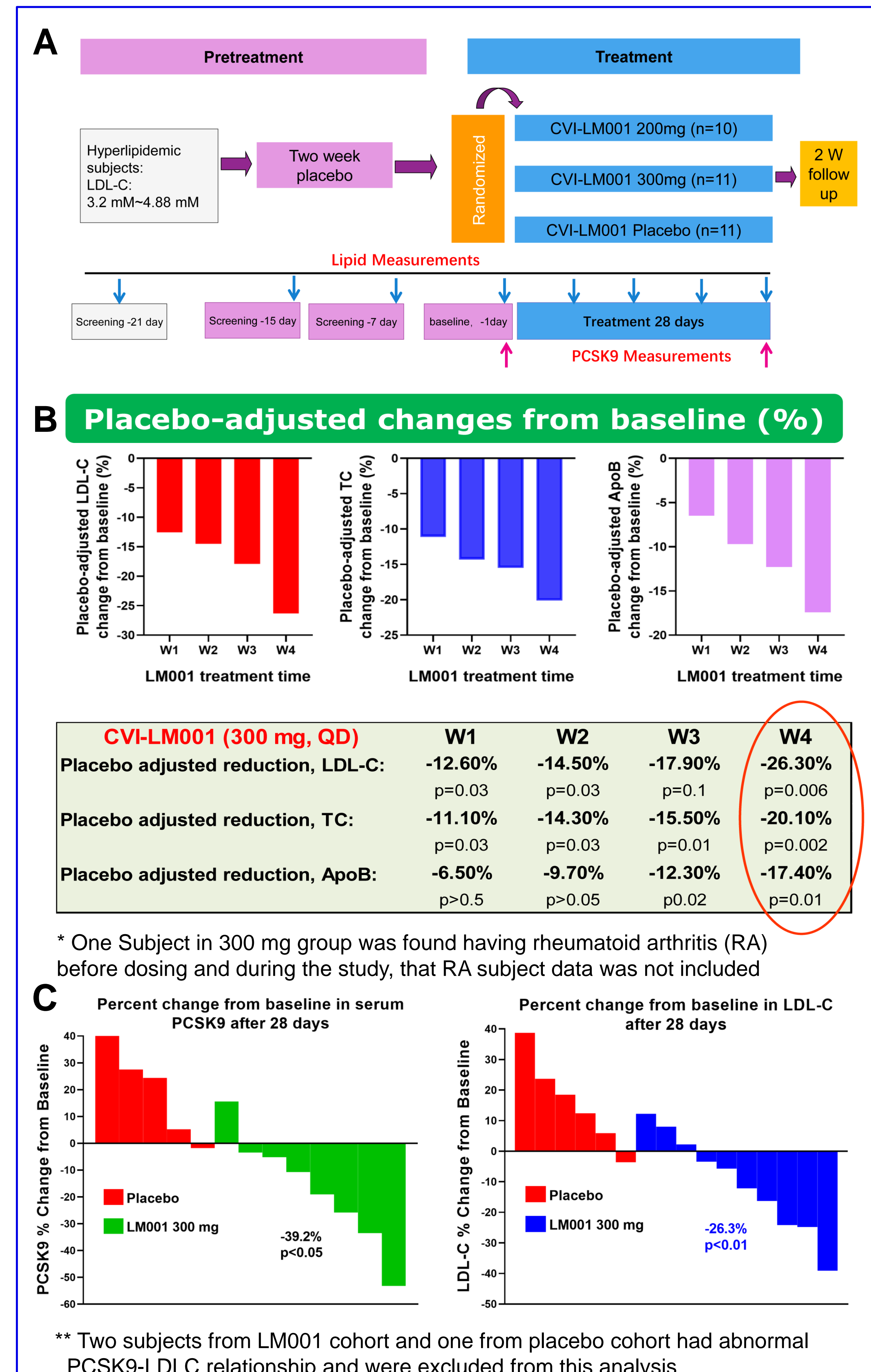


F: CVI-LM001 treatment of 10 days significantly reduced PCSK9 serum levels



Phase 1b Hyperlipidemic Subjects Results

Figure 4. CVI-LM001 28-Day Phase 1b summary: Randomized, double-blind and placebo-controlled trial design (A); benign safety and tolerability profile, no SAEs; Statistically significant reductions in LDL-C, TC and ApoB by 300 mg daily dose (B); CVI-LM001 200 mg dose showed trend in LDL-C and TC reductions; CVI-LM001 300 mg dose reduced PCSK9 serum levels in hyperlipidemic subjects which were consistent with LDL-C lowering (C); Results support a Phase 2 12 week proof-of-concept (POC) study in hyperlipidemic subjects, which is currently undergoing.



CONCLUSION

These studies demonstrate that CVI-LM001, a novel PCSK9 modulator, has the potential to be a new oral cholesterol-lowering drug to treat hypercholesterolemia and NAFLD/NASH.