# CVI-LM001, a First-in-class Novel Oral PCSK9 Modulator, Lowers Plasma LDL-C and Reduces Circulating PCSK9 in Preclinical Animal Models and in Hyperlipidemic Human Subjects

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## ABSTRACT (Control Number 12579)

CVI Pharmaceuticals has discovered a series of novel PCSK9 small molecule modulators that can reduce PCSK9 gene expression and increase LDLR abundance by PCSK9 dependent and independent mechanisms in hepatocytes. Among them, the lead compound CVI-LM001 is advanced to Phase 2 stage to treat hypercholesterolemic patients. Here we report that in hyperlipidemic hamsters, treatment with CVI-LM001 (40, 80 and 160 mg/kg, QD) for 4 weeks dose-dependently increased liver LDLR protein levels up to 3.5-fold and decreased circulating PCSK9 levels to 10% of control at the highest dose, this was accompanied by significant reductions in serum LDL-C. In a double-blind, randomized Phase 1a study conducted in healthy volunteers with normal lipid levels, compared to baseline, we observed a 36.4% ($p<0.001$) reduction in serum PCSK9 levels after 10 days of oral treatment with CVI-LM001 (300 mg, QD). Moreover, in a Proof of Mechanism Phase 1b study conducted in subjects with elevated LDL-C, compared with placebo cohort, treatment with CVI-LM001 (300 mg, QD) for 28 days significantly reduced serum LDL-C (-26.3% $p<0.01$), TC (-20.1%, $p<0.01$), Apo B (-17.4%, $p=0.01$) and PCSK9 (-39.2%, $p<0.05$). CVI-LM001 had a benign safety profile and was well tolerated in 105 treated healthy volunteers and 33 treated hyperlipidemic subjects. In addition, CVI-LM001 exhibited excellent pharmacokinetics properties with peak concentrations occurred approximately 1-1.5h post-dose. Mean half-lives ranged from 32 to 45h after single dosing and 62 to 68h following multiple dosing. These studies, for the first time, demonstrate that CVI-LM001, a novel PCSK9 modulator, has the potential to be a new oral cholesterol-lowering drug and warrant further development.

## INTRODUCTION

Hypercholesterolemia is a major risk factor for atherosclerotic cardiovascular disease (ASCVD) and lowering low-density lipoprotein cholesterol (LDL-C) levels via upregulation of hepatic LDL receptor (LDLR) has demonstrated CVD benefits. More recently, monoclonal antibodies targeting PCSK9, a LDLR degradation protein, has emerged as a new therapeutic approach for lowering LDL-C levels, offering robust efficacy and benefits in ASCVD patients. However, PCSK9 inhibitors require subcutaneous injections and the cost of therapy is high. CVI Pharmaceuticals is a clinical stage biopharmaceutical company developing first-in-class novel oral drugs for CVD and NAFLD/NASH.

CVI-LM001 is a First-in-class oral lipid lowering drug candidate under development by CVI Company and it is discovered through phenotypical screening targeted to PCSK9/LDLR pathway. CVI-LM001 has unique dual mechanism of actions to reduce LDL-C and attenuate hepatic steatosis via AMPK activation. It has shown robust pharmacological effects in various animal models including hyperlipidemic hamsters.

## METHODS

Effects of CVI-LM001 on circulating lipids, serum PCSK9 and hepatic lipids and gene expression 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 40 mg/kg, 80 mg/kg or 160 mg/kg, or 100 mg/kg fenofibrate, or vehicle once daily.

Double-blind, randomized single ascending-dose (100-800 mg per day) and multiple ascending-dose (MAD) studies were conducted to assess the safety, 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 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.

## Preclinical Study Results

**Figure 1.** Significant reductions of serum TC, LDL-C, TG and hepatic cholesterol and triglycerides by oral treatment of HFHCD-fed golden Syrian hamsters with 40 mg/kg, 80 mg/kg and 160 mg/kg CVI-LM001 or vehicle for 4 weeks (n=10-12 per group). Fenofibrate at 100 mg/kg was used as a reference compound **(A).** HPLC separations of lipoprotein-cholesterol **(B)** or triglyceride **(C)** fractions of pooled serum samples from vehicle or CVI-LM001 40 mg/kg treatment group further confirmed the reductions of LDL-C and TG by CVI-LM001 treatment. Statistical significance was assessed by comparing each treatment group with vehicle by one-way ANOVA.

**A**

| Compounds | Serum TC | Serum LDL-C | Serum TG | Liver TC | Liver TG |
|---|---|---|---|---|---|
| LM001, 40 mg/kg | Reducing 31.0%, p<0.05 | Reducing 22.2%, p<0.05 | Reducing 52.2%, p<0.01 | Reducing 15.0%, p<0.01 | Reducing 48%, p<0.01 |
| LM001, 80 mg/kg | Reducing 34.4%, p<0.05 | Reducing 27.6%, p<0.01 | Reducing 52.1%, p<0.01 | Reducing 13.4%, p<0.05 | Reducing 37%, p<0.05 |
| LM001, 160 mg/kg | Reducing 43.9%, p<0.01 | Reducing 42.6%, p<0.001 | Reducing 52.1%, p<0.01 | Reducing 20.3%, p<0.001 | Reducing 49%, p<0.01 |
| Fenofibrate, 100 mg/kg | Reducing 51.9%, p<0.01 | Reducing 57.7%, p<0.001 | Reducing 79.7%, p<0.001 | Reducing 12.9%, p<0.05 | Reducing 30%, p=0.08 |

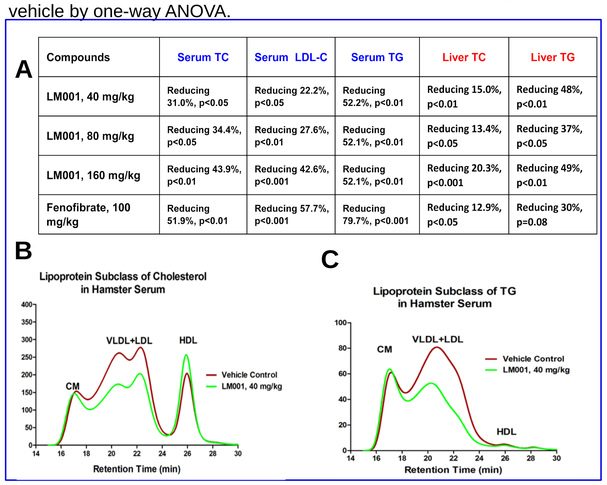



**Figure 2. Hepatic gene expression analysis provided direct evidence demonstrating the mechanism of action (MOA) of CVI-LM001 in upregulating LDLR and inhibiting PCSK9 expression as well as AMPK activation.**

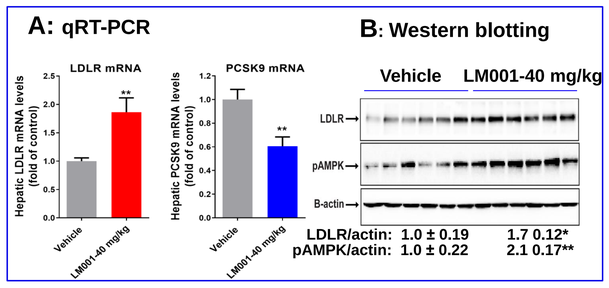
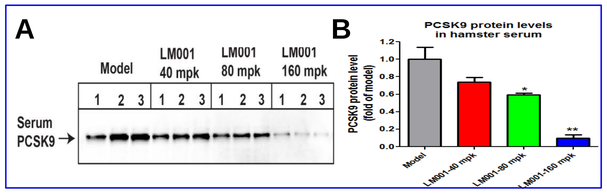


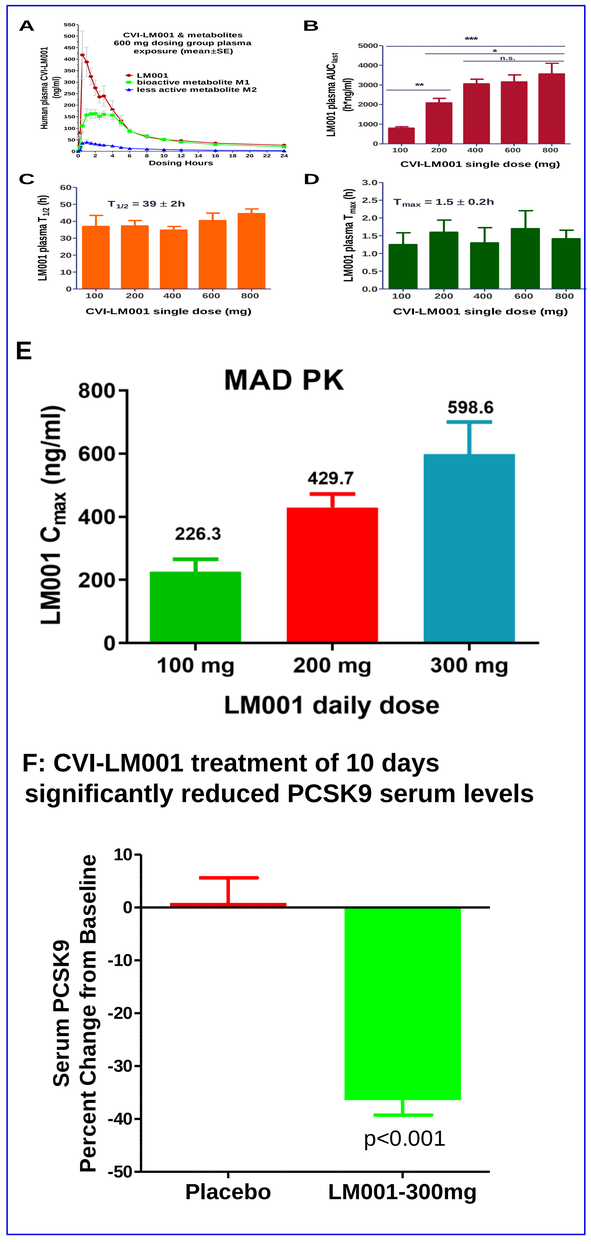

**Figure 3. Detection of serum PCSK9 demonstrated the dose-dependent effect of CVI-LM001 in lowering serum PCSK9 levels.**
**(A)** Three serum samples from vehicle and LM001 treatment group were pooled, and 20 µL of pooled serum was used for conducting PCSK9 immunoprecipitation and Western blotting.
**(B)** Quantitative results of IP. Values are mean ± SEM of 3 samples per group. * $p < 0.05$ and ** $p < 0.01$ compared to vehicle group.




## Phase 1a Healthy subjects MAD Results

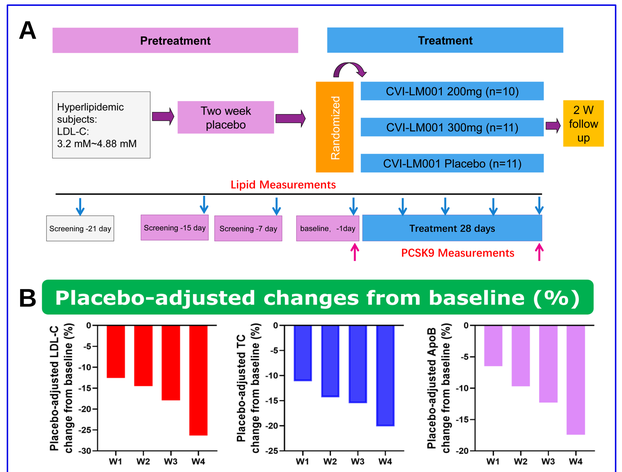
**Figure 4. CVI-LM001 Phase Ia Clinical Highlights:**

- 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



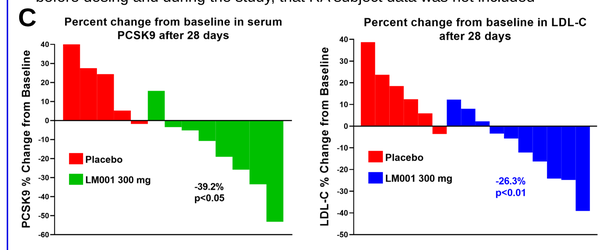

## Phase 1b Hyperlipidemic Subjects Results

**Figure 5. CVI-LM001 28-Day Phase Ib 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.




| CVI-LM001 (300 mg, QD) | W1 | W2 | W3 | W4 |
|---|---|---|---|---|
| Placebo adjusted reduction, LDL-C: | -12.60% | -14.50% | -17.90% | -26.30% |
| | p=0.03 | p=0.03 | p=0.1 | p=0.006 |
| Placebo adjusted reduction, TC: | -11.10% | -14.30% | -15.50% | -20.10% |
| | p=0.03 | p=0.03 | p=0.01 | p=0.002 |
| Placebo adjusted reduction, ApoB: | -6.50% | -9.70% | -12.30% | -17.40% |
| | p>0.5 | p>0.05 | p0.02 | p=0.01 |

* One Subject in 300 mg group was found having rheumatoid arthritis (RA) before dosing and during the study, that RA subject data was not included




** Two subjects from LM001 cohort and one from placebo cohort had abnormal PCSK9-LDLC relationship and were excluded from this analysis

## CONCLUSION

**We demonstrate that CVI-LM001, a novel PCSK9 modulator, has the potential to be a new oral LDL-cholesterol lowering drug to treat hypercholesterolemia.**