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 small molecule modulators that can reduce PCSK9 gene expression and increase circulating LDL-C (the low-density lipoprotein cholesterol) by engaging SNAPShot mechanisms in hepatocytes. Among them, the lead compound CVI-LM001 is advanced to Phase 2a to treat hypercholesterolemia 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 UCP2 and 3.5-fold and decreased circulating PCSK9 levels by 10% of control at the highest dose, which was accompanied by significant reductions in serum LDL-C. In a double-blind, randomized Phase 1a study conducted in healthy volunteers with normal lipids, 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 warrants 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 receptors (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, delivering robust efficacy and benefits in ASCVD patients. However, PCSK9 inhibitors require subcutaneous administration and the cost of therapies 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 by independent hepatic actions 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 (HFD) 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. Subsequently, 12 males or females, 18-45 years of age, were selected to receive 100, 200, or 300 mg 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 patients (males or females, 18-65 years) received 200 mg (n=10), 300 mg (n=10) or 400 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 lipids levels including total cholesterol (TC), LDL-C, and ApoB were measured.

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