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Efficacy and safety of gemcabene as add-on to stable statin therapy in hypercholesterolemic patients

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BACKGROUND: Ezetimibe added to statin therapy further reduces LDL-C and clinical atherosclerotic cardiovascular disease compared to statin alone. However, the number of effective and safe oral agents for patients not at LDL-C goal is limited. In prior clinical trials, gemcabene reduced LDL-C and was generally well-tolerated in nearly 900 patients treated for up to 12 weeks.

OBJECTIVE: To evaluate the LDL-C lowering and safety of gemcabene as add-on to stable statin therapy in hypercholesterolemic patients.

METHODS: This was an 8-week, double-blind, placebo-controlled, randomized, phase 2 study in men and postmenopausal women ≥18 and ≤65 years of age with LDL-C ≥130 mg/dL (3.4 mmol/L) while on low-intensity to high-intensity stable statin (the majority on moderate intensity) therapy. Sixty-six patients were randomized 1:1:1 to gemcabene 300 mg, 900 mg, or placebo QD.

RESULTS: Gemcabene 300 mg and 900 mg produced a mean percent change in LDL-C of −23.4 ± 4.7% ($P = .005$) and −27.7 ± 4.3% ($P < .001$), respectively, vs −6.2 ± 4.3% for placebo. The median percent change in CRP was −26.1% ($P = .196$) and −53.9% ($P < .001$) for gemcabene 300 mg and 900 mg, respectively, vs −11.1% for placebo. Gemcabene 300 mg and 900 mg were well-tolerated with no significant difference in AEs compared to placebo.

CONCLUSIONS: Gemcabene as add-on to stable statin therapy demonstrated additional dose-dependent and statistically significant reductions in LDL-C of >20% and CRP >40% compared to placebo. The results support gemcabene-continued development for patients requiring LDL-C lowering beyond that provided by background statin therapy.

Introduction

Low-density lipoprotein cholesterol (LDL-C) lowering is one of the most validated and modifiable of known risk factors for reducing cardiovascular events. It is also the basis of virtually all national and international guidelines for reducing the burden of clinical atherosclerotic

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cardiovascular disease (ASCVD).[1–5] Based on numerous cardiovascular outcome trials over the last 25 years, a robust relationship between absolute lowering in LDL-C and cardiovascular disease (CVD) has been established whereby each 1.0 mmol/L (38.7 mg/dL) lowering in LDL-C reduces the incidence of major coronary events, coronary revascularizations, and ischemic stroke by approximately 20%.[3] Although the majority of the data were derived from statin trials, the recent IMPROVE-IT trial confirmed the LDL-C/ASCVD relationship when a non-statin, ezetimibe was added to high-dose simvastatin and compared to simvastatin alone to achieve further LDL-C lowering.[6]

Most guidelines for the prevention of CVD recommend lowering of LDL-C to <100 mg/dL (<2.59 mmol/L) for patients considered at high coronary heart disease risk and <70 mg/dL (<1.81 mmol/L) in patients with established CVD.[7,8] The only major departure from these treatment-targeted guidelines is the 2013 American College of Cardiology/American Heart Association (ACC/AHA) guidelines, which focus on individual patient risk and maximizing statin therapy while de-emphasizing LDL-C goals.[8] Guidelines from other organizations in the United States such as the National Lipid Association and the American Association of Clinical Endocrinologists continue to emphasize the NCEP-ATP III treatment goals for LDL-C levels.[9,10]

Statins, as the first line therapy, are very effective at lowering LDL-C; however, many patients do not achieve LDL-C targets with statins alone.[11,12] In addition, a small but significant percentage of patients are unable or unwilling to tolerate effective doses of statins.[13] Secondary oral agents used to achieve additional LDL-C reduction are often limited by tolerability, side effects, or efficacy; these include bile acid sequestrants, fibrates, nicotinic acid, and ezetimibe.[14–17] Other agents such as lomitapide, an oral microsomal triglyceride transfer protein inhibitor,[18] and mipomersen, an anti-sense apolipoprotein B synthesis inhibitor administered by subcutaneous injection,[19,20] are approved only for the rare patient population with homozygous familial hypercholesterolemia (HoFH). Both these lipid-altering agents carry a "boxed" warning for risk of hepatotoxicity and are administered under a risk evaluation and mitigation strategy program. The recently approved proprotein convertase subtilisin/kexin type 9 monoclonal antibody inhibitors, while being the most effective LDL-C lowering class to enter routine practice, are very expensive for broad market use and require parenteral administration every 2 or 4 weeks.[21–23] Therefore, there remains a need for more effective, well-tolerated and safe oral agents to lower LDL-C levels.

Gemcabene (administered as 6, 6'-oxybis [2, 2-dimethyl-4-hexanoic acid] monocalcium salt) is a lipid-regulating compound with a novel mechanism of action that enhances the clearance of very low density lipoprotein (VLDL) via the reduction of hepatic apolipoprotein C-III (apoC-III) messenger RNA (mRNA).[24–26] In the early 2000s, seven phase 2 studies were conducted, with the results from six of these studies never being published. Integration of the data supports gemcabene as being generally well tolerated across various patient populations with significant lowering of LDL-C, apolipoprotein B (apoB), and C-reactive protein (CRP) in hypercholesterolemia patients, and significant lowering of triglycerides (TG) and increases in high-density lipoprotein cholesterol (HDL-C) in hypertriglyceridemic patients. To date, gemcabene has been administered to 895 healthy subjects and patients and has been observed to be well tolerated in doses up to 900 mg once daily (QD) for up to 12 weeks.[27,28]

In 2011 gemcabene was in-licensed by Gemphire Therapeutics Inc. for continued development. Herein, we report data from the first study assessing gemcabene when added to previously prescribed background statins; an 8-week, double-blind, placebo-controlled study evaluating the efficacy and safety of gemcabene in patients whose LDL-C remained ≥ 130 mg/dL (3.4 mmol/L) while on stable statin therapy.

Methods

The study was conducted in compliance with good clinical practices. The study protocol, amendments, and subject-informed consent documents were approved by site-specific Institutional Review Boards, and the informed consent was signed by all participants before performance of any study-related activity.

Study subjects

From August 2000 to April 2002, patients entered into a run-in phase of up to 12 weeks whereby other lipid-lowering agents (fibrates, niacin, and fish oils) were discontinued and statin doses were stabilized. Patients on stable statin monotherapy (>3 months) and who met the eligibility criteria were randomized to an 8-week treatment phase (NCT02571257). Major inclusion criteria included men and postmenopausal women 18 to 65 years old and LDL-C ≥ 130 mg/dL (3.4 mmol/L). Patients were excluded if they had TGs > 400 mg/dL, creatine kinase [CK] > 3 × the upper limit of normal (ULN); body mass index > 35 kg/m^2; uncontrolled diabetes mellitus (HbA1C > 10%); renal dysfunction (blood urea nitrogen [BUN] or creatinine > 2 × ULN); or hepatic dysfunction (aspartate aminotransferase [AST] or alanine aminotransferase [ALT] > 2 × ULN); myocardial infarction, severe or unstable angina pectoris, coronary angioplasty, coronary bypass graft, or any other major cardiovascular event resulting in hospitalization in the previous month; or a history of gall stones or gall bladder disease.

Study design

This was an 8-week, double-blind, placebo-controlled, randomized, multicenter, phase 2 study in