Usefulness of Gemcabene in Homozygous Familial Hypercholesterolemia (from COBALT-1)

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Homozygous familial hypercholesterolemia (HoFH) is a rare genetic disorder characterized by severely elevated plasma low-density lipoprotein-cholesterol (LDL-C), and premature atherosclerotic cardiovascular disease. Depending on residual LDL receptor (LDLR) function, most HoFH patients respond modestly to statins, ezetimibe, and proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors. However, LDL-C typically remains markedly elevated necessitating additional therapies, including apheresis. Gemcabene is a novel lipid-lowering agent with a mechanism of action independent of the LDLR, which has previously demonstrated the ability to reduce levels of LDL-C on top of maximally tolerated statins. The present study (COBALT-1) assessed efficacy, tolerability, and safety of gemcabene as an adjunctive therapy to current lipid-lowering treatment for familial hypercholesterolemia patients. Eight patients with either a clinical or genetic diagnosis of HoFH on stable standard of care, including statins, ezetimibe, and PCSK9 inhibitors, were treated with gemcabene in an open-label study for 12 weeks. DNA analysis for mutations in the *LDLR*, apolipoprotein B, and *PCSK9* genes was performed. Patients received 300 mg gemcabene for the first 4 weeks, 600 mg for the next 4 weeks, and 900 mg for the final 4 weeks. All patients completed the 12-week study. Mean change from baseline in LDL-C was −26% (p = 0.004) at Week 4 (300 mg), −30% (p = 0.001) at Week 8 (600 mg), and −29% (p = 0.001) at Week 12 (900 mg). In conclusion, the COBALT-1 study demonstrates gemcabene has potential to significantly reduce LDL-C levels when used as an adjunctive therapy to current lipid-lowering treatment for familial hypercholesterolemia patients. **(Am J Cardiol 2019;124:1876−1880)**

Homozygous familial hypercholesterolemia (HoFH) is a very severe form of hypercholesterolemia, defined clinically by low-density lipoprotein-cholesterol (LDL-C) >500 mg/dl (12.95 mmol/L) and either skin or tendon xanthoma expressed before 10 years or clinical heterozygous FH (HeFH) in both parents. Untreated HoFH is associated with very early atherosclerotic cardiovascular disease (ASCVD).[1−3] HoFH world prevalence is estimated at 1 in 160,000 to 300,000.[1,4−7] Most HoFH patients carry mutations in the LDL receptor (LDLR) gene, although other genes are also involved.[8] Reductions in LDL-C in HoFH with agents acting through LDLR-related mechanisms, particularly statins and PCSK9 inhibitors, is variable, with response generally related to the residual LDLR activity.[9−11] Mean reductions of 20% are also achieved with ezetimibe.[12] Despite current therapies, including apheresis, mipomersen or lomitapide, few phenotypic HoFH patients achieve optimal LDL-C levels.[13,14] Gemcabene reduced LDL-C in animal models of HoFH and in early phase human studies, suggesting mechanisms independent of LDLR.[15−17] In this study, we evaluated the safety and efficacy of gemcabene as an add-on therapy to current lipid-lowering regimens in patients with HoFH.

Methods

Adult patients with HoFH were diagnosed by DNA analysis or by clinical phenotype; a history of untreated LDL-C >500 mg/dl (12.95 mmol/L), or > 300 mg/dl (7.77 mmol/L) on maximally tolerated lipid-lowering therapy, together with either appearance of xanthoma before 10 years of age, or evidence of HeFH in both parents. Eligibility was also based on LDL-C >130 mg/dl (>3.37 mmol/L) and a triglyceride (TG) value of ≤400 mg/dl (≤4.52 mmol/L) whereas on a stable, low-fat, low-cholesterol diet in combination with statins, ezetimibe and/or PCSK9 inhibitors. Patients receiving apheresis, lomitapide or mipomersen within 2 months of the screening visit were excluded. The full inclusion/exclusion criteria are given in Table S1 (in the online-only Data Supplement).

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See page 1880 for disclosure information.

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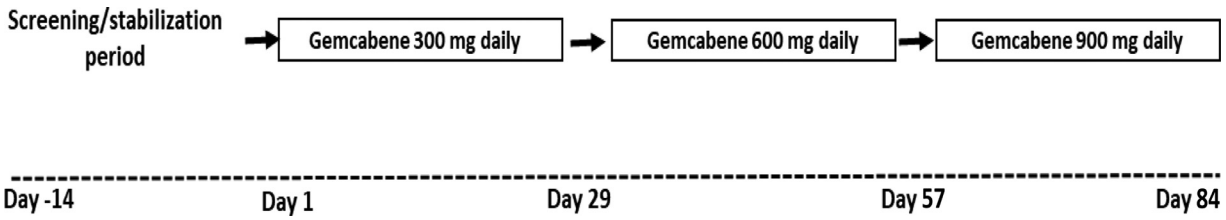

Figure 1. COBALT-1 trial design. In all 8 patients, dose of study drug gemcabene was successfully escalated from 300 mg/day to 600 mg/day to 900 mg/day. Data for primary and secondary end points were calculated every 14 days.

This 12 week, open-label, dose-finding study comprised 3 consecutive 4-week periods where gemcabene increased from a 300 mg to 600 mg to 900 mg dose once daily. There were no interruptions in dosing between treatment periods, and patients were instructed to take the study drug in the morning 30 to 60 minutes before breakfast. Patients maintained their baseline diet and background lipid-lowering therapy throughout the trial (Figure 1).

The trial was funded by Gemphire (Livonia, MI) and managed by Medpace Inc. (Cincinnati, Ohio) at 9 clinical sites in the United States, Canada, and Israel. The trial was registered on clinicaltrials.gov (NCT02722408). The Institutional Review Board at each site approved the protocol; all patients signed written consent forms before the study. Total study duration was up to 18 weeks and consisted of a Screening Visit, a Treatment Period, and a Follow-up Visit. During the treatment period, patients visited the site on Day 1 and at Weeks 2, 4, 8, and 12 for assessments, which included side effects, dietary compliance, concomitant lipid drugs, other prescription drugs, vital signs, physical examination, and 12-lead electrocardiograms (ECGs). Laboratory tests included fasting lipid, routine safety, and pharmacokinetic measurements.

The primary efficacy end points were absolute and percent change in LDL-C levels determined by Friedewald[18] and confirmed by ultracentrifugation[19] from baseline to Week 4 (300 mg), Week 8 (600 mg), and Week 12 (900 mg). Secondary efficacy end points included percent changes from baseline to Week 12 in total-C, TG, high-density lipoprotein cholesterol (HDL-C), non−HDL-C, very-low density lipoprotein cholesterol, Apo B, Apo AI, Apo AII, Apo E, and Apo CIII. The primary safety end point was the incidence of treatment-emergent adverse events (AEs); other safety end points included laboratory abnormalities and changes in ECG parameters. AEs were coded using the *Medical Dictionary for Regulatory Activities*, version 15.[20,21] Lipid and apolipoprotein analyses, including measurement of LDL-C by preparative ultracentrifugation and safety tests, were performed by Medpace Reference Laboratories, accredited by the College of American Pathology and part III certified by Lipid Standardization Program of Centers for Disease Control and Prevention (https://www.medpace.com/labs/central-lab/accreditations). Gemcabene pharmacokinetics were measured by Medpace Bioanalytical Laboratory. All patients, including those previously diagnosed by genetics, were genotyped by Progenika Inc. (Medford, Massachusetts) to identify, or confirm, mutations in *LDLR, APOB, PCSK9,* and *LDLRAP1* genes. Targeted next-generation sequencing was conducted at the London Regional Genomics Centre (www.lrgc.ca) using established protocols[22] to identify a broader range of mutations in *LDLR, APOBçPCSK9, LDLRAP1,* and other genes implicated in FH such as *STAP1, APOE, LIPA, ABCG5*, and *ABCG8*, in addition to 17 other genes implicated in monogenic dyslipidemias.

In the Statistical analysis, the baseline values for lipid parameters were the average of screening and Day 1 values. Absolute and percent changes for LDL-C were calculated from baseline to the end for each 4 week period. All other secondary efficacy variables were analyzed similar to LDL-C. Statistical analyses in this open-label, single-arm study were descriptive with the exception of a longitudinal analysis conducted with a mixed-effects model to estimate additional drug benefit with increasing dose using SAS (SAS Institute Inc., Cary, North Carolina). Safety end points were reported over the entire duration of the trial as patient incidence.

Results

A total of 8 patients were randomized to the treatment phase with the first patient screened on June 16, 2016, and the last patient completing on July 13, 2017. The baseline characteristics, lipids, and background lipid-lowering therapy are shown in Table S2 (in the online-only date supplement). Three patients had null mutations in both *LDLR* alleles with <2% LDLR function. Although phenotypically HoFH, 5 patients had a single pathogenic mutation of *LDLR, APOB,* or *PCSK9* (gain-of-function) and were considered genetically HeFH although several had variants of unknown effect in the sequenced genes.

The percent changes in LDL-C from baseline, the primary efficacy measure, are shown for each patient in Table 1 and Figure 2. In all patients (n = 8), the mean percent and absolute changes in LDL-C by Friedewald[18] from

Table 1
Individual LDL-C response

Patient number	Baseline LDL-C (mg/dl)	Percent (%) change in LDL-C on gemcabene		
		300 mg	600 mg	900 mg
1	137.5	−28.7%	−32.4%	−28.7%
2	194.5	−18.3%	−22.9%	−32.6%
3	261	−55.2%	−49.8%	−52.5%
4	303	−36.6%	−50.5%	−53.5%
5	601	−1.0%	−1.3%	−16.6%
6	430	+0.5%	+1.6%	+5.6%
7	260	−32.3%	−37.3%	−30.0%
8	623	−30.0%	−44.3%	−24.2%

LDL-C = low-density lipoprotein cholesterol.

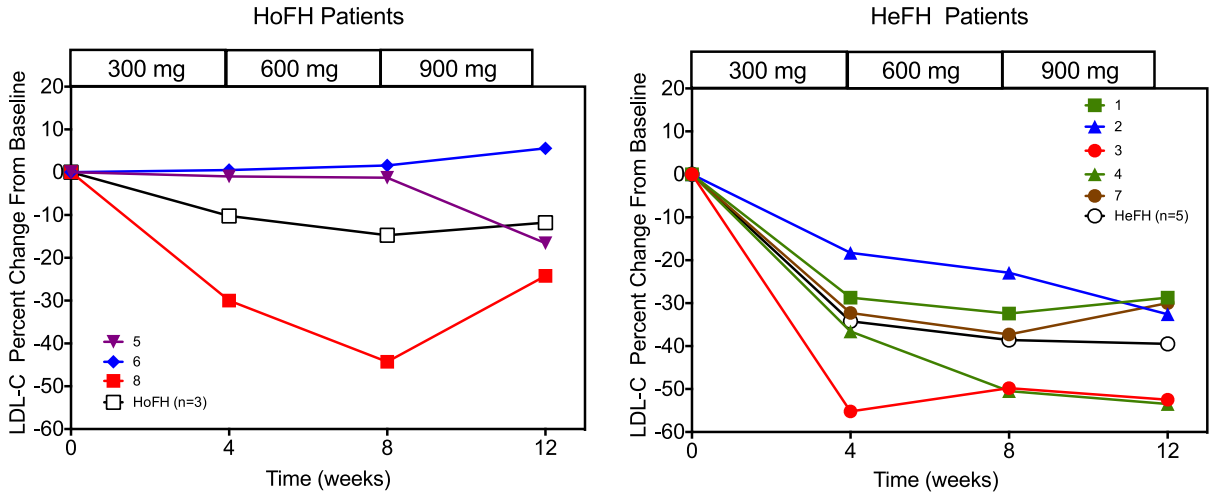

Figure 2. Individual patient LDL-C over time by genotype.

baseline were −26% (p = 0.004; range −55% to +1%) and −82 mg/dl (p = 0.056), at Week 4 (300 mg); −30% (p = 0.001; range −51% to +2%) and −100 mg/dl (p = 0.022) at Week 8 (600 mg); and −29% (p = 0.001; range -54% to +6%), and −95 mg/dl (p = 0.029) at Week 12 (900 mg). LDL-C values were confirmed by ultracentrifugation.[19] Variability in response was seen across all severities of genetic mutations. HoFH (n = 3) with LDLR receptor-negative activity (mean baseline LDL-C 551 mg/dl [14.25 mmol/L]) and HeFH (n = 5) LDL-C changes in response to gemcabene are shown in Table 2.

The all-patient group showed a mirrored statistically significant lowering of other atherogenic lipids and lipoproteins (non−HDL-C, Apo B, and Apo E) to that observed for LDL-C in Table 3. This was also observed in both the HeFH and HoFH patient subsets in Figure 3 and Table S3 (in the online-only Data Supplement). Other lipid parameters such as HDL-C, Apo AI, Apo AII, Apo CIII, and TG did now show meaningful changes.

For safety, the most common AEs were diarrhea and headache with 7 of the 8 patients reporting one or more AE. The incidence of AEs did not increase over time and/or with increasing dose. Four patients reported at least 1 treatment-related AE. The majority of treatment-related AEs were mild, with 1 patient, experiencing an AE of moderate intensity. No patient withdrew from the study due to an AE, and no patient had a serious AE or death during the study (Table S4 in the online-only Data Supplement). No patients had creatine kinase elevations >5 times the upper limit of normal or liver enzymes (alanine aminotransferase or

Table 2
Mean % change in LDL-C for all patients and by genotype

		300 mg gemcabene Day 28	600 mg gemcabene Day 56	900 mg gemcabene Day 84
All patients				
Percent change from baseline	No. of patients	8	8	8
	LS mean (SE)	−25.54 (8.30)	−29.94 (8.30)	−29.41 (8.30)
	95% CI	(−42.41, −8.67)	(−46.81, −13.07)	(−46.28, −12.54)
	p value	0.0041	0.0010	0.0012
HeFH (single mutant *LDLR, APOB,* or PCSK9 allele)				
Percent change from baseline	No. of patients	5	5	5
	LS mean (SE)	−33.97 (6.16)	−38.33 (6.16)	−39.22 (6.16)
	95% CI	(−46.88, −21.07)	(−51.23, −25.42)	(−52.12, −26.32)
	p value	<0.0001	<0.0001	<0.0001
HoFH (two mutant *LDLR* alleles)				
Percent change from baseline	No. of patients	3	3	3
	LS mean (SE)	−9.78 (10.19)	−14.27 (10.19)	−11.36 (10.19)
	95% CI	(−32.50, 12.94)	(−36.98, 8.45)	(−34.08, 11.36)
	p value	0.3601	0.1920	0.2912

Baseline lipid measurements were defined as the average of the last 2 fasting measurements prior to the first dose of study drug. Least-squares means, SEs, CIs, and p values were from a mixed-effects model for repeated-measures analysis with change or percent change in LDL-C as the dependent variable, visit as a fixed effect, and patient as a random effect.

Auto-regressive variance-covariance structure was used.

CI = confidence interval; HeFH = heterozygous familial hypercholesterolemia; HoFH = homozygous familial hypercholesterolemia; LDL-C = low-density lipoprotein cholesterol; LDLR = low-density lipoprotein receptor; LS = least-squares; No. = number; SE = standard error.

Table 3
Mean percent change in other lipids and lipoprotein parameters in all patients

Variable	Baseline (mg/dl)	Percent change from baseline		
		300 mg Week 4	600 mg Week 8	900 mg Week 12
Non HDL-C	378.1	−23.87**	−27.33**	−26.59**
Total-C	423.4	−21.53**	−24.85**	−24.79**
Apo B	221.3	−17.95	−23.98*	−21.58*
Apo E	6.68	−19.57*	−23.01*	−19.20*

*p <0.05; **p <0.01.

aspartate aminotransferase) >3 times the upper limit of normal There was a slight, nonsignificant increase from baseline in serum creatinine of 0.061 mg/dl, 0.130 mg/dl, and 0.124 mg/dl associated with the 300, 600, and 900 mg doses of gemcabene, respectively.

Discussion

Patients in the current gemcabene trial were treated at entry on statins and/or ezetimibe and/or PCSK9 inhibitors. Gemcabene was well tolerated with no significant clinical or laboratory safety signals in this high-risk population. This is similar to previous experience with the drug in non-FH patients whereby gemcabene has been well tolerated in combination with the highest doses of statin therapy, with no drug-drug interaction, and no evidence of liver or muscle toxicity in 25 studies with over 1,100 patients exposed. The mean percent change of 30% in LDL-C achieved with gemcabene 600 mg in the COBALT-1 study is similar to that achieved with statins, ezetimibe, and PCSK9 inhibitors; and, importantly, this change was observed on top of the LDL-C lowering already achieved with these standard of care therapies. Among patients with genetically confirmed HoFH, 3 were characterized as LDLR negative with <2% of normal LDLR activity. These patients present minimal or reduced response to current therapies, including statins and PCSK9 inhibitors, with many requiring LDL apheresis or sophisticated, invasive or expensive investigational therapies.[23,24] In the 3 LDLR negative patients having participated to the present study, one showed a 44.3% reduction in LDL-C at a dose of 600 mg, another one presented a 16.6% reduction at 900 mg whereas one had no response (Figure 2), suggesting that gemcabene has the potential to importantly decrease LDL-C even among LDLR negative patients, a feature consistent with a LDLR-independent mechanism of action. COBALT-1 thus demonstrates the importance of a lipid modulating treatment with a mechanism independent of the *LDLR* in patients who are unable to utilize this pathway. In comparison, the 2 enrolled LDLR negative patients in the HoFH TESLA A study with evolocumab had either no response or an *increase* in LDL-C.[25]

LDL-C is a well-accepted surrogate end point by regulatory agencies with 17 lipid-lowering agents having been approved based on this over the last 3 decades.[26] Although many of these agents, or mechanisms, have subsequently been shown in large long-term placebo-controlled ASCVD outcome trials to reduce events, none have done so in specific HoFH or HeFH populations. Although most LDL-C-lowering agents, such as most statins, ezetimibe, and the PCSK9 inhibitor evolocumab, approved for broad use have also been approved for treatment of HoFH, some, as lomitapide and mipomersen, have been approved for use only in HoFH.[27]

As the risk in ASCVD risk has been well established to be related to the absolute, not percent, reduction in LDL-C with a mean baseline LDL-C of 351 mg/dl, the decrease in LDL-C of 100 mg/dl with gemcabene 600 mg would be expected to translate into a significant reduction in ASCVD risk in these patients.[28] In addition, gemcabene showed an almost 1:1 decrease in Apo B, Apo E, and non−HDL-C with that of LDL-C, indicating a decrease in overall atherogenic burden.

In summary, the COBALT-1 study provides evidence of clinically important reductions in LDL-C in HoFH and HeFH patients on existing statin, ezetimibe and/or PCSK9 inhibitor therapy and supports the continued study of gemcabene alone or in combination with other approved treatment for patients with severe LDL-C elevations due to HoFH or HeFH.

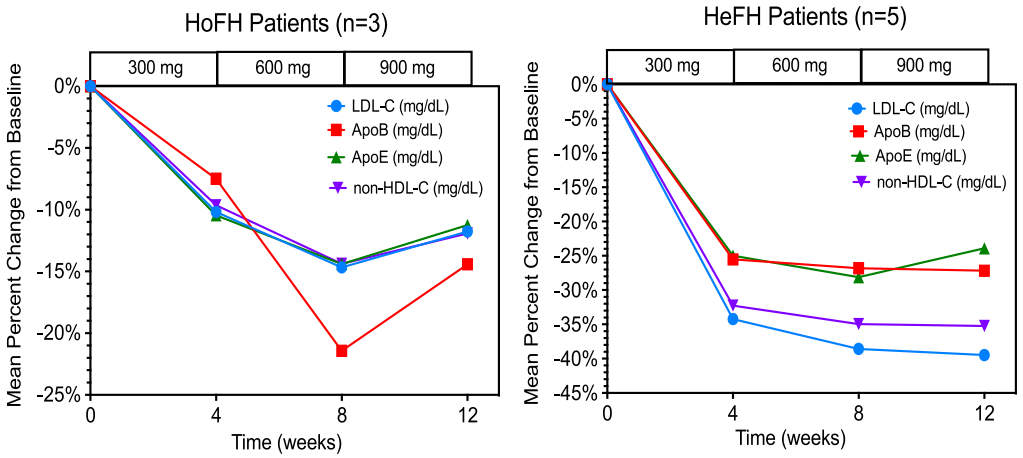

Figure 3. Mean percent change in LDL-C and atherogenic biomarkers by genotype.

Disclosures

Gaudet, Durst and Lepor were investigators in the COBALT-1 trial. They have no financial interest in Gemphire Therapeutics Inc. Bisgaier, Masson, Bakker-Arkema, and Golden have ownership interest in Gemphire Therapeutics Inc. Bisgaier and Bakker-Arkema are employed by Gemphire Therapeutics Inc. Kastelein, Stein, and Hegele are consultants for Gemphire Therapeutics Inc. Gemphire participated in study design, data collection and interpretation, and writing the report.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.amjcard.2019.09.010.

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