An Oral, Rising, Multiple-Dose Tolerance, Pharmacokinetic, and Pharmacodynamic Study of Gemcabene in Healthy Volunteers

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ABSTRACT

Background: Gemcabene is a novel lipid-regulating compound being developed as an adjunct to diet and statin therapy for the treatment of dyslipidemia. Gemcabene was administered in a randomized, double-blind, rising, multiple-dose safety, tolerance, pharmacokinetic, and pharmacodynamic study in healthy subjects[a].

Methods: Fifty healthy subjects (34 men and 16 women), with a mean age of 39.7 years and mean baseline LDL-C of 116.7 mg/dL were randomized to either gemcabene 50, 150, 300, 450, 600/750, or 900 mg or placebo once daily for 29 days in six rising-dose cohorts.

Results: Forty-seven subjects completed the study. Gemcabene significantly lowered total cholesterol by 18-21%, low-density lipoprotein-cholesterol (LDL-C) by 26-32%, and apolipoprotein B (ApoB) by 8-21% from both baseline and placebo at the 450, 750/600, and 900 mg doses (Table 1). Gemcabene was rapidly absorbed with dose proportional increases in maximum plasma concentration (Cmax) and area under plasma concentration time curve from 0 to 24 hours (AUC(0-24)) values. Elimination half-life values were independent of dose and averaged 32-41 hours. Multiple doses of gemcabene up to 900 mg for 29 days were generally well-tolerated. There were no treatment-related serious adverse events. Adverse events reported were generally mild to moderate in intensity.

Table 1. Pharmacodynamic Changes

Dose (mg)	N	Total Cholesterol	LDL-C	ApoB	HDL-C	TG
0	8	-4.54	-3.21	-5.39	-9.39[a]	7.21
50	8	-4.28	-3.17	-14.53[a]	-5.72	-6.19
150	8	0.76	1.67	-0.83	2.94[b]	-5.19
450	8	-17.67[a,b]	-26.39[a,b]	-8.26[a]	2.44[b]	-11.48
750/600	8	-18.32[a,b]	-32.48[a,b]	-16.89[a,b]	9.91[a,b]	12.51
900	7	-20.54[a,b]	-28.06[a,b]	-21.13[a,b]	-3.53	-20.37

Least-square means
[a] Significantly different from baseline, p≤0.05
[b] Significantly different from placebo, p≤0.05

Conclusions: Gemcabene exposure increased proportional with dose, was well tolerated, and was observed to significantly lower total cholesterol, LDL-C, and ApoB at once daily doses of 450 to 900 mg. Gemcabene is being developed as an oral, lipid-altering agent to be used as an adjunctive therapy for the treatment of dyslipidemia, including the rare indication of HoFH.

INTRODUCTION

Gemcabene is a novel lipid-regulating compound being developed as an adjunct to diet and statin therapy for the treatment of dyslipidemia. Gemcabene's dual mechanism of action is designed to enhance the clearance of very low-density lipoproteins (VLDLs) in the plasma and inhibit the production of fatty acids and cholesterol in the liver. Gemcabene has been tested as monotherapy and in combination with statins and other drugs in 895 subjects, which includes healthy volunteers and patients, across 18 Phase 1 and Phase 2 clinical trials and has demonstrated promising evidence of efficacy, safety and tolerability. Gemphire is developing gemcabene as a treatment for patients who are unable to reach their lipid-lowering goals including (1) homozygous familial hypercholesterolemia (HoFH), a rare genetic lipid disorder which results in elevated LDL-C usually due to mutations in both alleles, a pair of genes on a chromosome responsible for a specific trait, of the LDL-receptor gene; (2) heterozygous familial hypercholesterolemia (HeFH), a more prevalent genetic lipid condition which results in elevated LDL-C usually due to a mutation in one allele of the LDL-receptor gene; and (3) atherosclerotic cardiovascular disease (ASCVD).

STUDY DESIGN

The 1027-003[a] study was an oral, randomized, double-blind, rising, multiple-dose tolerance, pharmacokinetic, and pharmacodynamic study of gemcabene capsules in 50 healthy volunteers. Subjects had to be men or naturally menopausal or surgically sterile women 18 to 55 years of age in general good health.

Five groups, each consisting of 10 subjects were to receive gemcabene (50 mg to 900 mg QD) or placebo over four weeks according to the double-blind randomized dosing schedule (Table 2). Blinding was maintained within each group by administering the same number of capsules to all subjects.

Primary values measured were $AUC_{0\text{-}24}$ and C_{max}. Pharmacodynamic endpoints measured were TC, LDL-C, HDL-C, TGs, ApoB, and ApoA1.

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METHODS

Pharmacokinetic parameter values were calculated for each subject using noncompartmental analysis of plasma and urine concentration-time data. Nominal sample collection times were used for pharmacokinetic analysis. C_{max} and times for these to occur (T_{max}) were recorded as observed. C_{min} was recorded as the minimum concentration observed in the dosing interval. AUC values were estimated using the linear trapezoidal rule.

The pharmacodynamic data were analyzed with a repeated measures analysis of variance (ANOVA) model.

Table 2: Dosing Schedule

Groups	Days 1 to 29
Group1	
8 subjects	50 mg Gemcabene
2 subjects	Placebo
Group 2	
8 subjects	150 mg Gemcabene
2 subjects	Placebo
Group 3	
8 subjects	450 mg Gemcabene
2 subjects	Placebo
Group 4	
8 subjects	750/600 mg Gemcabene
2 subjects	Placebo
Group 5	
8 subjects	900 mg Gemcabene
2 subjects	Placebo

PATIENT CHARACTERISTICS / DISPOSITION

Fifty healthy subjects (34 men and 16 women), with a mean age of 39.7 years. The majority (49) of the subjects were white. Forty-seven subjects received all scheduled doses of gemcabene or placebo. Two subjects randomized to the placebo group and one subject randomized to the 900 mg gemcabene group were withdrawn from the study. One subject randomized to the placebo group withdrew from the study due to an adverse event.

Table 3 presents the mean baseline lipid values for each of the dose groups.

Table 3. Baseline Lipid Values

Dose (mg)	N	Total Cholesterol (mg/dL)	LDL-C (mg/dL)	ApoB (mg/dL)	HDL-C (mg/dL)	TG (mg/dL)
0	8	201.3	121.4	94.5	49.0	154.3
50	8	198.6	119.6	87.8	52.1	134.1
150	8	164.8	99.1	83.4	38.9	134.4
450	8	203.9	128.9	89.4	47.8	135.8
600/750	8	190.8	127.4	92.9	42.4	104.6
900	7	184.4	107.5	80.0	56.6	101.2

Least square means

PHARMACOKINETIC PROFILE

Mean plasma gemcabene concentration-time profiles on Days 8 and 29 are shown in Figure 1. Gemcabene is rapidly absorbed following oral administration, with median time to maximum plasma concentrations (Tmax) occurring within 2 hours of dosing for the majority of doses tested. As shown in Figure 2, steady state concentrations were achieved within 6 days of repeated dose administration.

Figure 1: Mean Plasma Concentration-Time Profiles

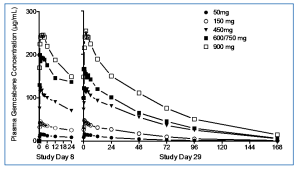
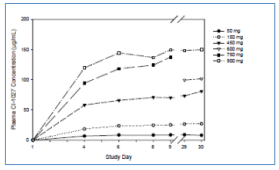


Figure 2: Mean Trough Plasma Concentrations



PHARMACOKINETIC PARAMETERS

Increases in maximum plasma concentration (Cmax) and AUC were approximately dose proportional following multiple-dose administration (Figure 3). The $t_{1/2}$ was independent of dose and averaged 32.1 hours to 41.2 hours for doses ranging from 50 mg to 900 mg QD (Table 4).

Figure 3: Individual and Mean AUC (0-24) Values

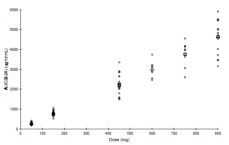


Table 4: Plasma Pharmacokinetic Parameters (Mean, CV%)

Dose (mg)	N	C_{max} (ng/mL)	T_{max} (h)	$AUC_{(0\text{-}24)}$ (µg·hr/mL)	$t_{1/2}$ (h)	Cl_0/F (L/hr)	V_z/F (mL)
50	8	17.8 (29)	1.58 (117)	272 (31)	32.1 (19.2)	0.199 (28.3)	9190 (34.7)
150	8	40.2 (19)	0.87 (54.2)	706 (17)	32.9 (14.5)	0.193 (15.9)	9020 (10.3)
450	8	128 (26)	2.17 (87.9)	2310 (29)	36.5 (23.7)	0.210 (29.6)	10600 (19.2)
600[a]	8	186 (17)	1.21 (94.8)	3010 (14)	35.6 (24.0)	0.203 (13.3)	10200 (17.3)
900	7	267 (21)	2.38 (74.3)	4660 (21)	41.2 (20.3)	0.202 (24.8)	11600 (14.2)

Note: Data are from Day 29 of dosing (last dose).
a. Subjects were initially dosed with 750 mg daily; the dose was reduced to 600 mg starting on Day 12 to 15 through Day 29 as preliminary Day 8 data incorrectly indicated that plasma concentration exceeded the upper limits for C_{max} and AUC defined in the protocol.
$AUC_{0\text{-}24}$ = area under the plasma concentration-time curve from time 0 to 24 hours; Cl_0/F = apparent oral clearance; C_{max} = maximum plasma concentration; CV = coefficient of variation; $t_{1/2}$ = terminal elimination half-life; T_{max} = time to maximum plasma concentration; V_z/F = apparent volume of distribution.
Source: Report 1027-003, Appendix C2, Table 4 (Abel et al., 2000)

PHARMACODYNAMIC (LDL-C LOWERING) DOSE RESPONSE

As presented in Figure 4, gemcabene significantly lowered LDL-C, with a mean percent change of approximately -30% from 450 mg to 900 mg. While Figure 4 might suggest an effective dose may be 450 mg to 900 mg, a closer review of dose response by exposure (mg/kg/day) suggests the 600 mg dose would be the most appropriate dose covering the range of 6-12 mg/kg/day for the broadest subject population (Table 5).

As presented in Figure 5 and 6, gemcabene LDL-C lowering exceeds 25% when AUC(0-24) values are greater than 2500 hr*µg/mL with limited additional LDL-C lowering above 5000 hr*µg/mL.

Figure 4: Mean % LDL-C Change from Baseline (by Dose)

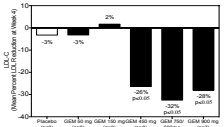


Figure 5: Mean % LDL-C Change from Baseline (by AUC)

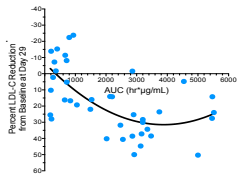


Figure 6: Mean % LDL-C Change from Baseline (by mg/kg/day)

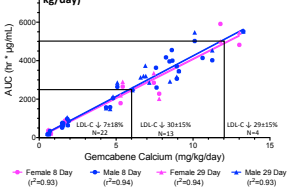


Table 5. Dose Selection (by mg/kg/day)

	40 KG	50 KG	60 KG	70 KG	80 KG	90 KG	100 KG
300 MG	8	6	5	4	4	3	3
600 MG	15	12	10	9	8	7	6
900 MG	23	18	15	13	11	10	9

SAFETY

The study demonstrated that multiple oral doses of gemcabene for 4 weeks QD was well tolerated in healthy subjects. In general, frequency and intensity of adverse events did not increase with dose. The most frequently reported adverse events in gemcabene-treated subjects were headache (43% and 60% in the combined gemcabene group and the placebo group, respectively), infection (15% and 10%, respectively), nausea (15% and 10%, respectively), asthenia (13% and 0%, respectively), photosensitivity reaction (13% and 20%, respectively), rhinitis (13% and 10%, respectively), diarrhea (10% and 20%, respectively), flatulence (10% and 0%, respectively), dizziness (8% and 10%, respectively), and pharyngitis (8% and 0%, respectively).
There were no SAEs reported. One subject in the placebo group withdrew due to headache. There were no treatment-related changes in physical examinations, vital signs, ECGs, or clinical laboratory assessments. Several subjects had mild elevations in BUN (blood urea nitrogen) with normal creatinine during the study. All returned to normal or baseline by closeout. These findings were considered to be unrelated to the study drug.

CONCLUSIONS

Gemcabene is rapidly absorbed following oral administration, with Tmax occurring within 2 hours of dosing. Both Cmax and AUC were approximately dose proportional following both single- and multiple-dose administration and steady state concentrations were achieved within 6 days of repeated dose administration. Multiple dosing QD resulted in a consistent t1/2 of approximately 32 to 41 hours, and minimal accumulation was observed following 4 weeks of dosing. Gemcabene's primary route of elimination is renal.

Gemcabene was well tolerated and was observed to significantly lower total cholesterol, LDL-C, and ApoB at once daily doses of 450 to 900 mg. Gemcabene is being developed as an oral, lipid-altering agent to be used as an adjunctive therapy for the treatment of dyslipidemia, including the rare indication of HoFH.

REFERENCES

[a] 1027-003 - An Oral, Rising, Multiple-Dose Tolerance, Pharmacokinetic and Pharmacodynamic Study of Gemcabene Capsules in Healthy Volunteers (clinicaltrials.gov identifier: NCT02587364)