Gemcabene Add-on Therapy to High- and Moderate-Intensity Statin Stratums in Hypercholesterolemic Patients (ROYAL-1, a Phase 2b Study)

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ABSTRACT

Introduction: Recent cardiovascular event outcome trials (CVOT) with ezetimibe and a proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor added to statins demonstrated benefit from additional LDL-C reduction. Despite availability of approved injectable PCSK9 inhibitors, there still remains a need for novel, efficacious, safe, well-tolerated, and cost-effective oral LDL-C lowering therapies. Gemcabene (GEM) has been shown to significantly lower LDL-C, non-HDL-C, ApoB, and hsCRP further in hypercholesterolemic patients when added to background statin therapy. GEM neither interacts pharmacokinetically nor has shown increased adverse effects with statins.
Hypothesis: GEM added to high- or moderate-intensity statin +/-ezetimibe therapy will provide additional LDL-C reduction for patients not at goal.
Methods: High-risk patients including those with heterozygous familial hypercholesterolemia or atherosclerotic cardiovascular disease on appropriate diet and stable statin therapy for at least 12 weeks and LDL-C ≥ 100 mg/dL (2.59 mmol/L) and triglycerides < 500 mg/dL (5.65 mmol/L) were randomized into a 12-week, placebo-controlled, parallel-group, double-blind study to assess the efficacy of GEM 600 mg QD on LDL-C and other lipoproteins and hsCRP. Safety and tolerability were also evaluated. The patients were stratified by high- or moderate-intensity statin therapy, with or without ezetimibe, with a target of 52 patients (26 GEM; 26 placebo) in each stratum. The study (NCT02634151) enrolled 105 patients (53% women, 77% Caucasian, mean age 61 years). Mean baseline LDL-C for all patients was approximately 134 mg/dL (3.48 mmol/L) with most patients in the high-intensity statin stratum on atorvastatin and most patients in the moderate-intensity stratum on either simvastatin or atorvastatin.
Results: Data for the full cohort was previously reported. Data by statin-intensity stratum (high and moderate) including LDL-C, non-HDL-C, ApoB, and hsCRP as well as safety and tolerability will now be reported.
Conclusion: The trial and data analysis by statin-intensity stratification, including efficacy and safety, will be completed in October 2017 in time for presentation at the American Heart Association Scientific Sessions.

GEMCABENE BACKGROUND

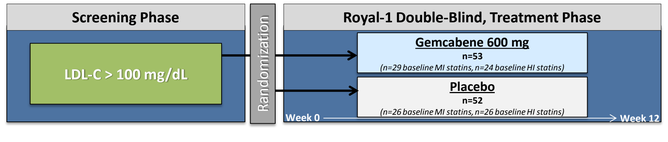
- ***Twenty completed Phase 1 and 2 studies*** (approx. 1300 subjects; **956 treated with gemcabene**) demonstrated safety and efficacy.
- Gemcabene has been ***well tolerated***. Most treatment-emergent adverse events (AEs) were mild to moderate. In prior studies, none of the 10 reported SAEs were related to gemcabene. There were no deaths.
- Gemcabene's ***MOA is complimentary to approved therapies*** and enhances apoB containing remnant lipoprotein clearance through the VLDL remnant receptor (Syndecan-1) by increasing the activity of this receptor by the inhibition of sulfatase 2 expression. In addition, gemcabene reduces apoCIII protein levels that otherwise blocks VLDL remnant clearance.[3]
- Gemcabene's enhanced syndecan-1 mediated clearance supports the observed ***lowering of atherogenic particles*** in our clinical trials. Enhanced apoB containing remnant lipoprotein clearance through the VLDL remnant receptor reduces non-HDL containing lipoproteins and reduces their conversion to LDL.
- Gemcabene has demonstrated a mean ***LDL-C lowering of 21% (range 17-40%)*** accompanied by mirrored lowering in apoB and non-HDL-C.[4]
- Gemcabene reduces inflammation with consistent ***lowering of hsCRP of 40% (range 35-53%).[4]***
- Gemcabene reduces TG levels by 39% and 60% in patients with baseline TGs >200 mg/dL and >500 mg/dL.[6]
- Previously reported, top-line data for ROYAL-1 showed **gemcabene produced a mean percent change of 17% in LDL-C** (vs 5% for placebo) and a **median percent change of 40% in hsCRP** (vs 6% for placebo)

ROYAL-1

Aims of ROYAL-1 Study:

In hypercholesterolemic patients on stable moderate-intensity (MI) or high-intensity (HI) statin therapy:
- Characterize gemcabene's safety and tolerability
- Determine gemcabene's additive impact to statins on serum biomarkers:
  - Atherogenic: LDL-C, non-HDL-C, apoB, apoE, TG
  - Inflammatory: hsCRP, Serum Amyloid A (SAA)

A total of 105 hypercholesterolemic patients, including ASCVD or HeFH, were randomized 1:1 to either gemcabene 600 mg or placebo with 50 (24 gemcabene 600 mg; 26 placebo) patients on baseline high-intensity (HI) statins (atorvastatin 40 mg or 80 mg QD; or rosuvastatin 20 mg or 40 mg QD) and 55 (29 gemcabene 600 mg; 26 placebo) patients on baseline moderate-intensity (MI) statins (atorvastatin 10 mg or 20 mg QD; rosuvastatin 5 mg or 10 mg QD; or simvastatin 20 or 40 mg QD). Baseline LDL-C was 127 mg/dL and 134 mg/dL in the MI statin and HI statin stratum, respectively.



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GOOD SAFETY AND TOLERABILITY PROFILE

- Overall, gemcabene was well tolerated with a profile consistent with earlier studies.
- There were no SAEs and no deaths reported in the study.
- 33 of 54 patients (61.1%) in the gemcabene group and 24 of 51 patients (47.1%) in the placebo group who reported at least one AE during the study. The most prevalent AEs were those associated with infections.
- Reported AEs were similar for the MI and HI statin stratums.
- There was no difference in myalgias between placebo and gemcabene groups.
- There were no transaminase elevations > 3 x ULN and no clinically significant CK elevations.

ROYAL-1 DEMOGRAPHICS AND BASELINE CHARACTERISTICS

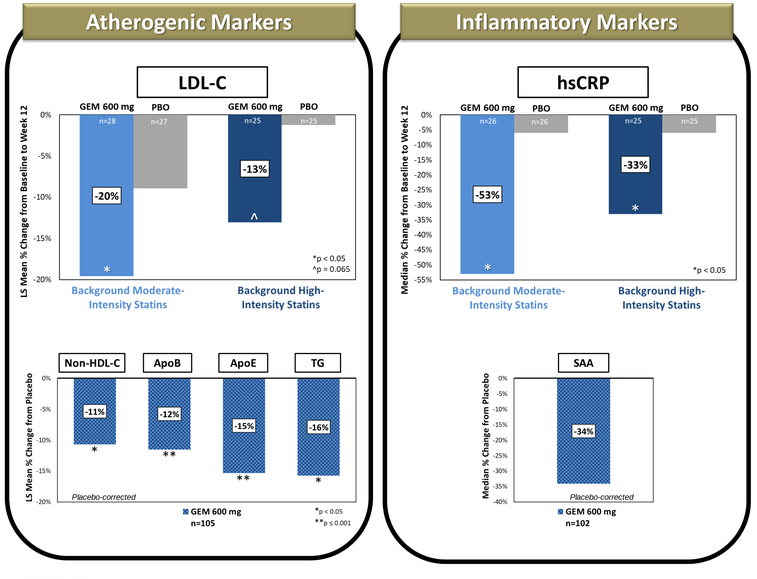
Characteristic	Gemcabene 600mg N=53	Placebo N=52	Total N=105
Age	62.7	59.0	60.8
Female n(%)	29 (55%)	27 (52%)	56 (53%)
BMI (kg/m2)	30.2	31.0	30.6
Moderate Intensity Statin Stratum n(%)	29 (55%)	26 (50%)	55 (52%)
High Intensity Statin Stratum n(%)	24 (45%)	26 (50%)	50 (48%)
Mixed Dyslipidemia TGs≥200 mg/dL	10 (19%)	8 (15%)	18 (17%)

Baseline Lipid Values	Gemcabene 600mg N=53	Placebo N=52	Total N=105	Mixed Dyslipidemia N=18
LDL-C (mg/dL)	134	126	130	146
Non-HDL-C (mg/dL)	162	154	158	193
TC-C (mg/dL)	217	206	211	238
TG(mg/dL)*	142	139	140	247
VLDL-C (mg/dL)	28	28	28	47
HDL-C (mg/dL)	55	52	53	46
ApoB (mg/dL)	108	100	104	127
ApoE (mg/dL)	4.3	4.2	4.3	4.6
hsCRP(mg/L)	1.5	1.7	1.7	3.9
SAA(mg/L)	5.1	5.8	5.8	6.5

- 38% of HI statin patients receiving gemcabene were on highest doses of atorvastatin or rosuvastatin
- 62% of MI statin patients receiving gemcabene were on highest atorvastatin, rosuvastatin or simvastatin dose for this stratum

**87 (83%) of subjects had baseline TGs <200mg/dL. In prior studies, gemcabene was shown to significantly impact TG levels when above 200 mg/dL.*

GEMCABENE IMPACTS MULTIPLE PARAMETERS



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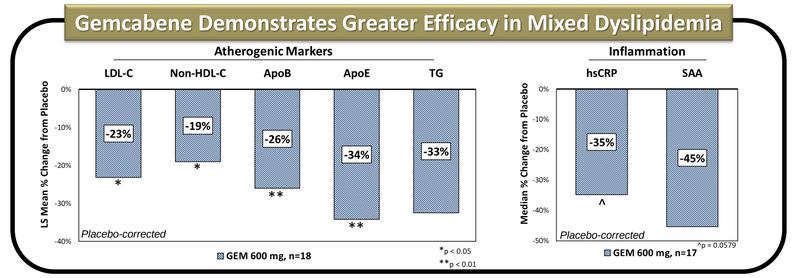
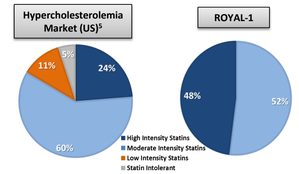
GEMCABENE LOWERS ATHEROGENIC BURDEN AND INFLAMMATION IN CARDIOMETABOLIC PATIENTS

- Cardiometabolic patients, including those with mixed dyslipidemia, have elevated sulphatase-2 levels and reduced Syndecan-1 mediated clearance of atherogenic particles, indicative of reduced remnant receptor activity.
- Given gemcabene's mechanism of action, a pre-defined analysis was performed in patients with mixed dyslipidemia (LDL-C ≥ 100 mg/dL and triglycerides ≥ 200 and < 500 mg/dL).
- Ten gemcabene 600 mg patients and 8 placebo patents (50% women) with a baseline mean LDL-C of 142 mg/dL and TGs of 247 mg/dL and a BMI of 34 kg/m^2 were analyzed.



DISCUSSION

ROYAL-1 was designed to largely address the safety of gemcabene in patients on the highest doses of statins. In patients with hypercholesterolemia, despite being on MI and HI statins, gemcabene produced significant reductions in both atherogenic and inflammatory markers without evidence of increased muscle or liver toxicities.



Nearly 20% of hypercholesterolemic patients in the US receive no or low intensity (LI) statin therapy; these patients were not represented in ROYAL-1. In prior studies, gemcabene demonstrated LDL-C reductions of 30-40% in patients on no or low intensity statin therapy. In ROYAL-1, the percentage of patients on HI statins was more than double that of the overall hypercholesterolemic population on lipid lowering therapy (48% vs. 23%), including 5-fold more on the most potent statin, rosuvastatin 40 mg.[5] An integrated analysis of gemcabene efficacy, inclusive of all background therapies, from completed clinical studies, showed a mean LDL-C reduction of 21%. Gemcabene given on top of steady-state statins has shown a statin-intensity dependent effect. We believe this is related to three factors related to gemcabene's mechanism of action: 1) Gemcabene enhances the clearance of VLDL remnants leading to reduced intravascular LDL-C formation. 2) Reduction of intravascular LDL-C production would allow basal LDL receptor levels to more effectively remove an existing smaller LDL-C pool. 3) Gemcabene blocks hepatic cholesterol and triglyceride synthesis, likely reducing hepatic VLDL production. Statins inhibit cholesterol synthesis and upregulate LDL receptor expression to effect LDL-C reduction. The more potent the statin, the greater the effect on these processes. We believe the smaller percent reduction of LDL-C lowering when statin intensity increases may be due to a lesser effect that gemcabene can have on reducing hepatic cholesterol production. Low-intensity statins have not optimized the effects on hepatic cholesterol synthesis and LDL receptor expression, and therefore, gemcabene shows greater LDL-C lowering by enhancing the clearance of atherogenic precursors via the remnant receptor as well as adding additional inhibition of hepatic cholesterol synthesis. At the highest statin levels, as in the current ROYAL-1 study, cholesterol synthesis is already markedly inhibited, the LDL receptor is highly expressed and gemcabene would have limited additional hepatic cholesterol synthesis effects, but would still maintain the ability to reduce intravascular LDL-C production. We plan to test these hypotheses in future human lipoprotein kinetic studies.

Evidence supports that other atherogenic lipoproteins beyond LDL-C may impact the residual CV risk of patients and that lowering of ApoB and non-HDL-C may be better correlates to improving CV outcomes. A recent Mendelian randomization analysis suggested that the clinical benefit of lowering LDL-C may be related to the reduction in ApoB-containing lipoprotein particles.[1] Consistent with the mechanism of action of gemcabene, patients with mixed dyslipidemia showed a greater reductions in LDL-C, non-HDL-C, ApoB, ApoE and TG of 23%, 19%, 26%, 34% and 33%, respectively.

The CANTOS study reported that canakinumab, when added to statins, further decreases hsCRP, without modulating LDL-C or other lipids, providing proof-of-concept for CV risk reduction by reducing inflammation. Thus, agents such as gemcabene, that reduce both atherogenic lipoproteins and hsCRP may have a greater CV risk benefit than seen by lipid reduction alone.

CONCLUSIONS

Gemcabene as an *add-on therapy to the highest doses of background statins* was well-tolerated and showed LDL-C decreases within the range observed in earlier trials:

- **No evidence of muscle or liver related toxicities.**
- **Decreased atherogenic burden with mirrored lowering in non-HDL-C, apoB and apoE.**
- **Decreased inflammation as observed with decreased serum hsCRP.**
- **Even greater effects were observed in a cardiometabolic population, patients with mixed dyslipidemia, who have a particularly high atherogenic particle burden.**
- **The safety, tolerability and efficacy on both atherogenic lipoproteins and hsCRP are supportive of Phase 3 development.**