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

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ABSTRACT

In hypercholesterolemic patients on stable moderate-intensity (MI) or high-intensity (HI) statin therapy:

- Characteristics gemcabe's safety and tolerability
- Determine gemcabe’s additive impact to statins on serum biomarkers
- Atherosclerotic: LDL-C, non-HDL-C, ApoB, TG
- Inflammatory: hsCRP, Serum Amyloid A (SAA)

Aims of ROYAL-1 Study:

- In hypercholesterolemic patients on stable moderate-intensity (MI) or high-intensity (HI) statin therapy:
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- Inflammatory: hsCRP, Serum Amyloid A (SAA)

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

GOOD SAFETY AND TOLERABILITY PROFILE

- Overall, gemcabe 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 gemcabe group and 24 of 51 patients (47.1%) in the placebo group who were 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 strata.
- There was no modification of statin and gemcabe combination.
- There were no transaminase elevations > 3 x ULN and no clinically significant CK elevations.

ROYAL-1 DEMOGRAPHICS AND BASELINE CHARACTERISTICS

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

GEMCABENE IMPACTS MULTIPLE PARAMETERS

Atherosclerotic Markers

- LDL-C
- Non-HDL-C
- ApoB
- TG

Inflammatory Markers

- hsCRP

Screening Phase

<table>
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<tr>
<th>Group</th>
<th>LDL-C mg/dL</th>
<th>Non-HDL-C mg/dL</th>
<th>ApoB mg/dL</th>
<th>TG mg/dL</th>
<th>hsCRP mg/L</th>
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<td>Placebo</td>
<td>127</td>
<td>180</td>
<td>53</td>
<td>155</td>
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<td>40 mg</td>
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<td>167</td>
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<tr>
<td>80 mg</td>
<td>116</td>
<td>159</td>
<td>44</td>
<td>120</td>
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</table>

Discussion

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

Nearly 20% of hypercholesterolemic patients in the US receive no low or low intensity (≤10 mg) statin therapy. These patients were not represented in ROYAL-1. In prior studies, gemcabe demonstrated robust reductions in 30-40% of 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 as low intensity lowering (18% vs. 23%), including 5-10% more on the most potent statin, rosuvastatin 40 mg. In an analysis of published phase II studies and in combination with other therapies, from completed clinical studies, showed a mean LDL-C reduction of 21%.

Gemcabe given on top of steady-state statins has shown a statin-intensity dependent effect. We believe this is related to these factors related to gemcabe's mechanism of action (1): Gemcabe synergizes the activity of the LDL-C receptor to reduce intracellular LDL-C formation. Reduction of intracellular LDL-C production would allow basal LDL-C receptor levels to more efficiently remove an existing existing statin (2). Gemcabe inhibits hepatic cholesterol synthesis and decreases VLDL, potentially leading to lower hepatic production of APOB, which in turn reduces hepatic production of VLDL. Statins inhibit cholesterol synthesis and upregulate LDL receptor expression to effect LDL-C reduction (3). Gemcabe would be expected to further lower LDL-C by decreasing hepatic APOB production and lowering hepatic VLDL synthesis. Statins inhibit cholesterol synthesis and upregulate LDL receptor expression to effect LDL-C reduction (4). Gemcabe would also be expected to lower LDL-C by decreasing hepatic APOB production and lowering hepatic VLDL synthesis. Statins inhibit cholesterol synthesis and upregulate LDL receptor expression to effect LDL-C reduction (5). Gemcabe would be expected to lower LDL-C by decreasing hepatic APOB production and lowering hepatic VLDL synthesis.

Evidence suggests that other atheroprotective lipoproteins beyond LDL-C may impact the residual cardiovascular risk of patients and that lowering of ApoB may be associated with improved clinical outcomes in patients with hypercholesterolemia. The results of the current ROYAL-1 study, cholesterol synthesis is already markedly inhibited, the LDL receptor is highly expressed and gemcabe would have little additional cholesterol synthesis effect and would still maintain an ability to reduce intracellular LDL-C production. We plan to test these hypotheses in future human lipoprotein kinetic studies.

We believe that atherosclerotic and inflammatory markers in combination with other therapies, from completed clinical studies, showed a mean LDL-C reduction of 21%.

CONCLUSIONS

Gemcabe as an add-on therapy to the highest doses of background statins was well-tolerated and showed LDL-C reductions of 30-40% in patients on no or low-intensity statin therapy, which may impact clinical endpoints. In patients with hypercholesterolemia, despite being on MI and HI statins, gemcabe produced significant reductions in both atherosclerotic and inflammatory markers without evidence of increased muscle or liver toxicities.

- 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 higher cardiovascular risk.
- The safety, tolerability and efficacy on both atheroprotective lipoproteins and hsCRP are supportive of Phase 3 development.

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