A First-in-Human Single Ascending Dose Study of GSBR-1290, a Novel Small Molecule GLP-1 Receptor Agonist, in Healthy Volunteers

INTRODUCTION

- Type 2 Diabetes Mellitus (T2DM) and obesity incidences are rising globally (IDF, 2021). The GLP-1 receptor molecular pathway has been extensively validated, with several glucagon-like peptide 1 receptor agonists (GLP-1 RAs) in use for T2DM and chronic weight management (CKD).
- The currently available GLP-1 RAs are peptides that mimic the action of GLP-1 at its receptor; however, there is a need for GLP-1 RAs that can maintain effective concentrations throughout the dosing interval, can be stored easily (no refrigeration) and administered easily (orally with food). If any, restrictions regarding food/fluid intake and concurrent medications
- GSBR-1290 is a potent small molecule GLP-1RA that can be orally administered. In nonclinical models, GSBR-1290 increased glucose-dependent insulin secretion and suppressed food intake with similar efficacy to the injectable peptide GLP-1 RA liraglutide (Mao et al, ADA 2023, Poster 760)

METHODS

- The objective of this first-in-human study was to evaluate the safety and pharmacokinetic (PK) profile of GSBR-1290 through single ascending doses (SAD) in healthy volunteers.
- Population and Correlation
- The study was designed and conducted in accordance with the Declaration of Helsinki and Good Clinical Practice (GCP). The study protocol was approved by the respective institutional review board (IRB) or independent ethics committee (IEC).
- Approximately 24 healthy male and female volunteers (18 to 55 years inclusive) were randomized 3:1 to receive a single oral dose of GSBR-1290 or placebo (3:1). Single dose escalation proceeded at 1, 10, 15 (fasted/fed), 30, 60 and 90 mg of GSBR-1290 (Figure 1).

RESULTS

- At higher GSBR-1290 dose levels, there was predominantly a decrease in the mean change from baseline over time
- These changes in a healthy participant population are not clinically significant and may be due to physiologic variation
- There were no changes in QTcF (data not shown)
- The most common TEAE was nausea (60% for GSBR-1290 vs 17% in placebo), followed by vomiting (30% for GSBR-1290 vs 1% in placebo) and headache (5% for GSBR-1290 vs 25% in placebo)
- Other GI-related side effects captured in the study were decreased appetite, diarrhea and abdominal pain
- There was an apparent treatment and dose-related trend in the incidence of GI TEAEs

DISCLOSURES

- No SAEs and no clinically significant changes in labs
- Dose-response observed in the percent of participants experiencing AE, and tolerability profile consistent with GLP-1RA class
- These data support further clinical development in a multiple ascending dose study in individuals with T2DM and participants living with obesity or diabetes (currently ongoing)

CONCLUSIONS AND DISCUSSION

- GSBR-1290 was generally safe and well-tolerated in this Phase 1 SAD study with healthy participants
- No SAs and no clinically significant changes in labs
- Dose-response observed in the percent of participants experiencing AEs, and tolerability profile consistent with GLP-1RA class
- These data support further clinical development in a multiple ascending dose study in individuals with T2DM and participants living with obesity or diabetes (currently ongoing)

TABLE 1: SAD Baseline Demographics

<table>
<thead>
<tr>
<th>Statistic Sub-group</th>
<th>GSBR-1290 (N = 36)</th>
<th>Placebo (N = 12)</th>
<th>% of Participants with TEAEs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender, Male (%)</td>
<td>45.0%</td>
<td>33.3%</td>
<td>50.0%</td>
</tr>
<tr>
<td>Female (%)</td>
<td>50.0%</td>
<td>66.6%</td>
<td>50.0%</td>
</tr>
<tr>
<td>Age (years)</td>
<td>22.50 ± 1.50</td>
<td>25.00 ± 1.50</td>
<td>50.0%</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>22.50 ± 2.00</td>
<td>25.00 ± 2.00</td>
<td>50.0%</td>
</tr>
<tr>
<td>Diabetes duration</td>
<td>2 ± 1</td>
<td>3 ± 1</td>
<td>50.0%</td>
</tr>
<tr>
<td>Family History</td>
<td>No</td>
<td>No</td>
<td>50.0%</td>
</tr>
<tr>
<td>Medication</td>
<td>No</td>
<td>No</td>
<td>50.0%</td>
</tr>
<tr>
<td>Other (No, %)</td>
<td>100%</td>
<td>100%</td>
<td>50.0%</td>
</tr>
</tbody>
</table>

FIGURE 1: Study Design

- Participants were well-balanced across the treatment groups: female (60%), 100%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 10%
- Study Design

FIGURE 2: Mean Plasma Concentrations of GSBR-1290

- C(max) and AUC increased with dose of GSBR-1290 across the dose range (Figure 2)
- There was minimal amount of GSBR-1290 excreted unchanged in urine (< 0.1% of the dose, data not shown)
- Reduced systemic exposure of GSBR-1290 when administered in the fast state, with 50% relative bioavailability

FIGURE 3: Phase 1 Tolerability

- Treatment emergent adverse events (TEAEs) were higher than placebo, with the majority as mild to moderate (Figure 3)
- Consistent with GLP-1RA class, TEAEs were driven by GI related side effects
- No SAEs and no clinically significant changes in labs
- Dose-response observed in the percent of participants experiencing AEs, and tolerability profile consistent with GLP-1RA class
- These data support further clinical development in a multiple ascending dose study in individuals with T2DM and participants living with obesity or diabetes (currently ongoing)