Discovery of GSBR-1290, a Highly Potent, Orally Available, Novel Small Molecule GLP-1 Receptor Agonist

ABSTRACT

• Peptidic glucagon-like peptide 1 receptor agonists (GLP-1Rs) are established treatments for patients with Type 2 Diabetes Mellitus (T2DM) and obesity. However, the need for injection and cold chain storage may limit the use of most peptidic GLP-1RAs. An oral small molecule GLP-1RA that offers enhanced bioavailability and stability could be more convenient and accessible to patients. Here we report the discovery of GSBR-1290, a highly potent, orally available, novel small molecule GLP-1RA and the characterization of its in vitro and in vivo pharmacology profiles.

• GSBR-1290 is a small molecule GLP-1RA with high binding affinity to human GLP-1R. GSBR-1290 strongly activated GLP-1R Gs-cAMP pathway without inducing measurable β-arrestin recruitment signaling, which indicates it is a fully biased agonist. The insulin secretion stimulation effect of GSBR-1290 was evaluated in a functional human pancreatic beta cell line, in which GSBR-1290 showed dose dependent induction of insulin secretion. The in vivo efficacy of GSBR-1290 on insulin secretion, glucose control and food intake were evaluated in nonhuman primates (NHPs). In an acute intravenous glucose tolerance test (ivGTT), a single dose of GSBR-1290 strongly induced insulin secretion and glucose clearance. In a repeated dosing study, GSBR-1290 administered orally once daily for 7-day demonstrated robust increase in insulin secretion and glucose clearance in ivGTT and a dose dependent reduction of food intake and body weight. Overall, GSBR-1290 demonstrated potent in vivo efficacy stimulating insulin secretion, improving glucose tolerance, and reducing food intake and body weight.

• In conclusion, GSBR-1290 is a highly potent, orally available, fully biased GLP-1RA. Human clinical trials are underway to further evaluate GSBR-1290 as a potential therapy for T2DM and obesity.

INTRODUCTION

TABLE 1: GSBR-1290 In Vitro Characteristics

<table>
<thead>
<tr>
<th>Assay Type</th>
<th>GSBR-1290</th>
<th>EndoC-bH5</th>
</tr>
</thead>
<tbody>
<tr>
<td>In vitro potency</td>
<td>+, +, +, –, –, –, +</td>
<td>+, +, +, +, +</td>
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<tr>
<td>TcGlu-P1 AMP, EC50 (μM)</td>
<td>&lt; 0.1</td>
<td>0.1</td>
</tr>
<tr>
<td>TcGlu-1 binding, % ILM</td>
<td>&gt; 100</td>
<td>10</td>
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<tr>
<td>Biased signaling</td>
<td>+, +, +, +, +, +, +, +</td>
<td>+, +, +, +, +, +, +, +</td>
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<tr>
<td>Cross species activities</td>
<td>Human, NHP, rat, mouse, dog</td>
<td>Human, NHP, rat, mouse, dog</td>
</tr>
</tbody>
</table>

• GSBR-1290 potently binds to and activates hGLP-1R and has biased signal to Gs-cAMP signal
• GSBR-1290 only activates human and monkey GLP-1R among other species

RESULTS

• GSBR-1290 induced dose (drug exposure) dependent food intake and body weight reduction
• GSBR-1290 induced glucose dependent insulin secretion in EndoC-bH5 cells

FIGURE 1: GSBR-1290 Induced Insulin Secretion in EndoC-bH5 Cell

• Strong insulin secretion and glucose clearance effect during ivGTT post single dose injection of GSBR-1290

FIGURE 2 (A-E): GSBR-1290 Single Dose NHP ivGTT Study

• GSBR-1290 is a highly potent, orally available, fully biased GLP-1RA

FIGURE 3 (B-F): GSBR-1290 Repeated Oral Dosing ivGTT: Insulin Secretion and Glucose Clearance

• GSBR-1290 is a highly potent, orally available, fully biased GLP-1RA and has biased signal to Gs-cAMP signal

FIGURE 3 (G-I): GSBR-1290 Repeated Oral Dosing Efficacy: Food Intake Reduction and Body Weight Loss

• GSBR-1290 is a highly potent, orally available, fully biased GLP-1RA

CONCLUSIONS AND DISCUSSION

• GSBR-1290 is a highly potent, orally available, fully biased small molecule GLP-1R agonist
• GSBR-1290 induced glucose dependent insulin secretion in EndoC-bH5 cells, indicating a proper target engagement in physiological relevant insulin secreting cells
• GSBR-1290 showed good efficacy in stimulating insulin secretion and inhibiting daily food intake in NHP efficacy studies
• Ph1 SAD study with GSBR-1290 has been completed (Coll et al, ADA 2023)

REFERENCES

• Ting Mao, Qinghua Meng, Haihui Zhang, Jianqiang Zhang, Songting Shi, Zhibo Guan, Xinglong Jiang, Fang Zhang, Hui Lei, Xichen Lin

Structure Therapeutics Inc, South San Francisco, CA, United States