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

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760-P

ABSTRACT

- Peptidic glucagon-like peptide 1 receptor agonists (GLP-1RAs) 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 utility 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 Gαs 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 in 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 (Coll et al, ADA 2023)

INTRODUCTION

Smaller and Improved Medicines

Peptide or Biologic Challenges

- Generally not orally available
- Higher total costs
- Limited stability, cold supply chain

Oral Small Molecule Opportunities

- Orally available, better patient compliance
- Lower costs
- Stable, no cold-chain requirements

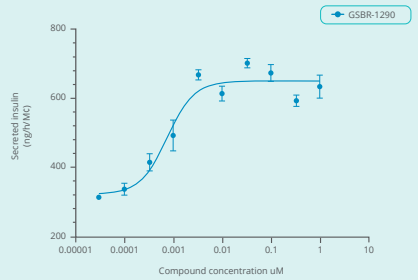
RESULTS

TABLE 1: GSBR-1290 *In Vitro* Characteristics

Assays	GSBR-1290	Exendin-4
***In vitro* potency**		
hGLP-1R cAMP, EC_{50}, nM	< 0.1	< 0.1
hGLP-1R binding, Ki, nM	< 10	< 10
Biased signaling		
hGLP-1R β-arrestin2, EC_{50}, nM / E_{max}, %	> 10000 / < 10	2.85 / 103
Cross species activities		
Human, NHP, rat, mouse, dog	+, +, –, –, –	+, +, +, +, +

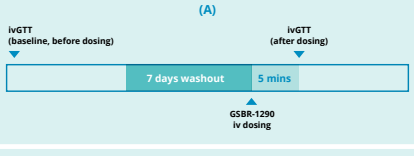
- GSBR-1290 potently binds to and activates hGLP-1R and has biased signal to Gα-cAMP signal
- GSBR-1290 only activates human and monkey GLP-1R among other species

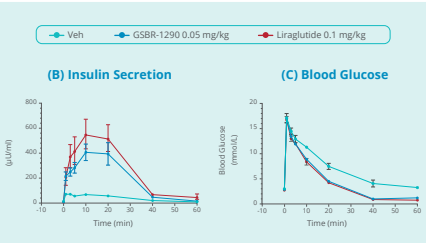
FIGURE 1: GSBR-1290 Induced Insulin Secretion in EndoC-bH5 Cell

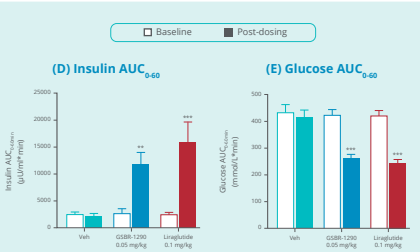


- EndoC-bH5 is a cell line derived from human pancreatic β cells. Robust glucose stimulated insulin secretion was observed (Hamza Olleik et al, Diabetes 2022)
- GSBR-1290 dose dependently induced insulin secretion in EndoC-bH5 cells

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







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

**P ≤ 0.01; ***P ≤ 0.001 vs baseline; 2 way ANOVA, Šídák's multiple comparisons test.

FIGURE 3 (A): GSBR-1290 Repeated Oral Dosing NHP Efficacy Study

(A)

- A repeat oral dosing study (3 dosing groups) in healthy NHP was designed

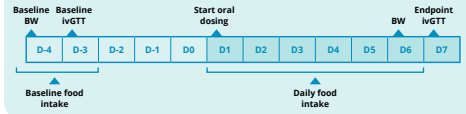


FIGURE 3 (B–F): GSBR-1290 Repeated Oral Dosing ivGTT: Insulin Secretion and Glucose Clearance

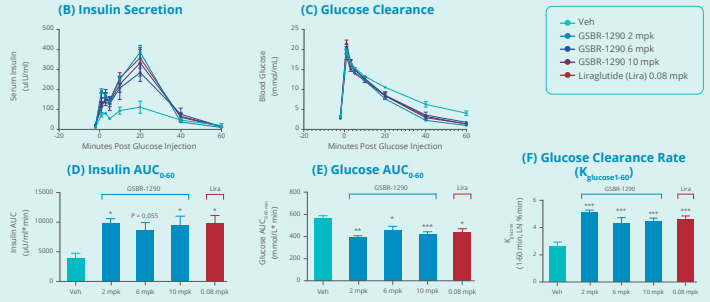
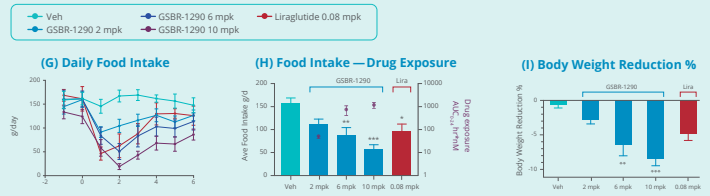


FIGURE 3 (G-I): GSBR-1290 Repeated Oral Dosing Efficacy: Food Intake Reduction and Body Weight Loss



- GSBR-1290 at 2 mg/kg reached maximal insulin secretion and glucose clearance during the ivGTT study on day 7
- GSBR-1290 induced dose (drug exposure) dependent food intake and body weight reduction with more than 8% body weight reduction at top dose (10mpk)

*P ≤ 0.05, **P ≤ 0.01, ***P ≤ 0.001 vs Veh; Ordinary one-way ANOVA; Dunnett's multiple comparisons test.

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

1. Diabetes 2022;71(Supplement 1):254-LB. Hamza Olleik; Bruno Bianchi. Bruno Bianchi. EndoC- βH5 Human Beta Cells — A Unique "Thaw and Go" Model for Accelerating Diabetes Research with Highly Functional and Ready-to-Use Human Beta Cells. **2.** Coll, B et al. A first-in-human single ascending dose study of GSBR-1290, a novel small molecule GLP-1 receptor agonist, in healthy volunteers. ADA 2023, poster #760.

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