Drug Design Principles and Pharmacokinetics/Pharmacodynamics of GSBR-1290, a Small Molecule GLP-1RA

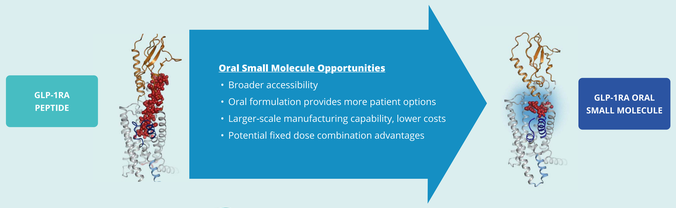
Ke (Mike) Liu,[1] Olivier Barriere,[2] Amparo de la Peña,[2] Carlos Fernandez Teruel,[2] Leo Seman,[1] Blai Coll,[1] Huibin Yue,[1] Mark Bach,[1] Aline Barth[1]

[1]Structure Therapeutics Inc.; [2]Clinical Pharmacology and Pharmacometrics Solutions, Simulations Plus, Inc.

INTRODUCTION

- Obesity has reached worldwide epidemic proportions, with more than 70% of adults in the United States living with overweight or obesity. Nearly 80% of people with type 2 diabetes mellitus (T2DM) are also living with either overweight or obesity
- Selective glucagon-like peptide receptor agonists (GLP-1RAs) are a class of incretin peptides modeled after naturally occurring GLP-1, whose functions include appetite reduction and decreased gastric motility
- Using structure-based drug discovery, GSBR-1290 was designed to be a potent, orally available, safe, non-peptide small molecule GLP-1RA, which is currently under development for the treatment of T2DM and chronic weight management
- Pharmacokinetic (PK) properties of GSBR-1290 include 24 hour drug exposure coverage above an efficacy threshold after QD dosing, together with a low risk of off-target safety effects
- Clinical PK and efficacy GSBR-1290 data were analyzed using population PK (popPK) and PK/pharmacodynamic (PD) modeling approaches to support its continued development

MAKING MEDICINES ACCESSIBLE FOR ALL



GLP-1RA ORAL SMALL MOLECULE ASPIRATIONAL TARGET PRODUCT PROFILE

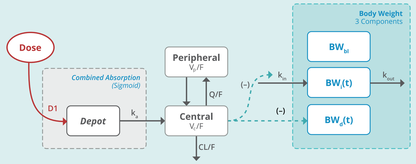
- Highly potent, non-peptide, full GLP-1R agonist with minimal β-arrestin signaling engagement
- Weight loss comparable to injectable GLP-1RA peptides
- Designed for ~24 hour drug exposure to enable QD dosing in a large patient population
- Clean 6 and 9 month GLP-tox studies with large safety margin (≥ 150 fold at 120 mg)
- Ability to modulate PK properties aimed at optimized tolerability
- Scalability in commercial manufacturing

METHODS

- GSBR-1290 was evaluated using data from participants in Phase 1 and 1b/2a trials
  - GSBR-1290-01: a Phase 1, randomized, double-blind, placebo-controlled, first-in-human study of the safety, tolerability, PK, and PD of single-ascending doses of GSBR-1290 in healthy volunteers. Doses up to 90 mg were administered to study participants
  - GSBR-1290-02: a Phase 1b/2a, randomized, double-blind, placebo-controlled multiple ascending dose (MAD) study in which dose levels with different titration steps were evaluated in overweight/obese participants with and without T2DM. In Part 1, doses up to 90 mg were administered for 4 weeks in T2DM participants; In Part 2, doses up to 120 mg were administered for 12 weeks in healthy overweight/obese participants
  - GSBR-1290-03: a Phase 1, randomized, double-blind, placebo-controlled, ethnobridging study of the safety, tolerability, PK, and PD of multiple-ascending doses of GSBR-1290 in healthy Japanese and non-Japanese participants. Doses up to 60 mg were administered for 4 weeks
  - GSBR-1290-05: a two-part, Phase 1, randomized study to evaluate the safety, tolerability, PK, comparative bioavailability, and dose titration of multiple-ascending doses of GSBR-1290 in healthy overweight/obese participants. In Part 1, 10 mg capsule or tablet were administered at single dose in a crossover design; In Part 2, doses up to 120 mg were administered as tablets for 12 weeks
- Several models were developed, including: popPK model, PK/PD model and exposure-response (ER) model for weight loss. The modeling and simulation were performed with software NONMEM (version 7.3)
- A 2-compartment popPK model was built and used to explore covariates. The PK model included a combined absorption term composed of a zero-order absorption which estimates the absorption duration (D1) into a depot compartment, followed by a first-order absorption, managed by a rate constant (k_a) from the depot compartment, and linear elimination **(Figure 1)**
- The efficacy PK/PD model was consistent with GLP-1RA mode of action, consisting of a combined indirect and direct response model to account for the time delay between the weight loss response and GSBR-1290 concentration **(Figure 1)**.[1] For long-term projections, we used data from other GLP-1R agonists[1,2]
- The exposure-response relationships were visualized using quantile plots with model prediction overlays. An E_{max} model was developed to describe the correlation between C_{avg} and body weight reduction

RESULTS

FIGURE 1. **Schematic for the PK/PD Model**



PK: CL/F = apparent clearance; D1= zero-order absorption duration of infusion; k_a = first-order absorption rate constant; Q/F = apparent intercompartmental clearance; V_c/F = apparent central volume of distribution; V_p/F = apparent peripheral volume of distribution.

PD: BW_{ss} = estimated individual body weight at baseline; $BW_i(t)$ = body weight direct response model; $BW_d(t)$ = body weight indirect response model; k_{in} = input response rate; k_{out} = elimination response rate.

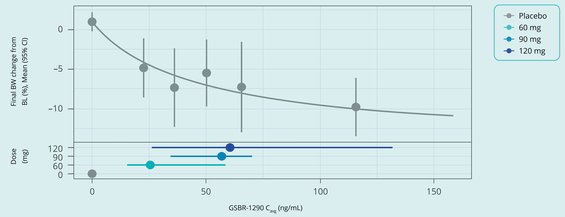
TABLE 1. **Demographic Characteristics of Participants Included in Analysis Dataset**

		Study GSBR-1290				
Participant Characteristic		**Ph1 SAD**	**Ph1b/2a MAD**	**Japanese Ethnobridging**	**Capsule to Tablet PK**	
N		**(N = 48)**	**(N = 88)**	**(N = 18)**	**(N = 70)**	**Overall (N = 224)**
Race, N (%)	**White / Caucasian**	32 (66.7%)	63 (71.6%)	6 (33.3%)	53 (75.7%)	154 (68.8%)
	Black /African American	0 (0%)	11 (12.5%)	0 (0%)	15 (21.4%)	26 (11.6%)
	Asian	9 (18.8%)	0 (0%)	12 (66.7%)	1 (1.4%)	22 (9.8%)
	American Indian/ Alaska Native	2 (4.2%)	2 (2.3%)	0 (0%)	1 (1.4%)	5 (2.2%)
	Native Hawaiian/ Pacific Islander	2 (4.2%)	3 (3.4%)	0 (0%)	0 (0%)	5 (2.2%)
	Other / Missing	3 (6.3%)	9 (10.2%)	0 (0%)	0 (0%)	12 (5.4%)
Ethnicity, N (%)	**Hispanic**	12 (25.0%)	38 (43.2%)	5 (27.8%)	50 (71.4%)	105 (46.9%)
	Japanese	0 (0%)	0 (0%)	12 (66.7%)	0 (0%)	12 (5.4%)
	Other	36 (75.0%)	50 (56.8%)	1 (5.6%)	20 (28.6%)	107 (47.8%)
Sex, N (%)	**Female**	29 (60.4%)	44 (50.0%)	12 (66.7%)	34 (48.6%)	119 (53.1%)
	Male	19 (39.6%)	44 (50.0%)	6 (33.3%)	36 (51.4%)	105 (46.9%)
Baseline Age (y)	**Mean (SD)**	30.9 (8.4)	45.7 (13.1)	41.2 (9.7)	44.0 (11.9)	41.7 (12.9)
	Median	30.0	45.6	42.5	42.0	39.0
Baseline BW (kg)	**Mean (SD)**	70.9 (12.7)	91.9 (14.8)	60.5 (6.8)	85.3 (11.5)	82.8 (16.4)
	Median	68.9	88.6	59.6	82.7	81.9
Baseline BMI (kg/m^2)	**Mean (SD)**	24.5 (3.1)	31.8 (3.1)	22.6 (1.9)	30.0 (2.3)	28.9 (4.3)
	Median	24.1	31.1	23.1	29.7	29.5
Baseline eGFR ($mL/min/1.73\ m^2$)	**Mean (SD)**	92.4 (13.8)	99.0 (26.5)	121 (26.8)	96.8 (18.8)	98.6 (23.0)
	Median	91.3	95.0	113	91.1	94.5
Baseline BW Categorization, N (%)	**Healthy**	38 (79.2%)	0 (0%)	18 (100%)	1 (1.4%)	57 (25.4%)
	Overweight	6 (12.5%)	26 (29.5%)	0 (0%)	39 (55.7%)	71 (31.7%)
	Obese	4 (8.3%)	62 (70.5%)	0 (0%)	30 (42.9%)	96 (42.9%)

One participant had missing race and was set as "Other." T2DM participants from study 02 were excluded from this analysis. **BMI** = body mass index; **BW** = body weight; **eGFR** = estimated glomerular filtration rate; **N** = number of participants

The exposure response (ER) analysis showed that efficacy is driven by exposure, consistent with published ER analysis results from other GLP-1RAs[3,4]

FIGURE 2. **Quantile Plot of GSBR-1290 Exposure and Body Weight Reduction**

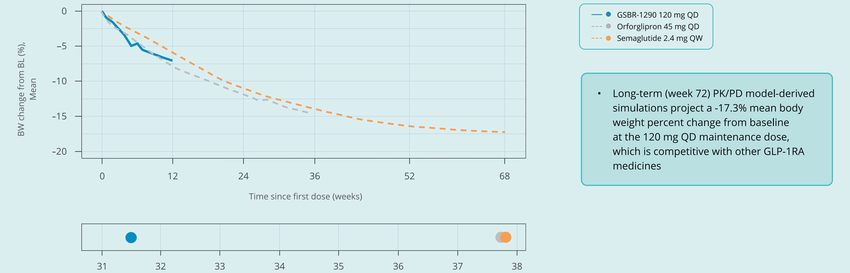


Limitations:
- Model had data up to only 12 weeks with limited number of data points above 100 ng/mL, contributing to uncertainty on the fit
- The separation between the quantile data points is due to the abundance of data points at each exposure; there were few participants with highly variable data for the highest C_{avg}, therefore the trending should be interpreted with caution
- Higher BW reduction is expected with longer duration and higher dose levels

Top panel: data are mean values of body weight % change from baseline with 95% confidence interval (CI) of the mean vs C_{avg} grouped into 5 quantiles. A value of 0 exposure was assigned to participants treated with placebo. C_{avg} = AUC/dosing interval; **BL** = Baseline. The black line represents an E_{max} model fit to the data. **Bottom panel:** horizontal lines represent median and 95% exposure (C_{avg}) ranges for each dose level. **Data Source:** GSBR-1290-02 (Phase 2a) cohort 4 and GSBR-1290-05 (Capsule to tablet PK study) Part2 Cohort 1, 2 and 3.

RESULTS

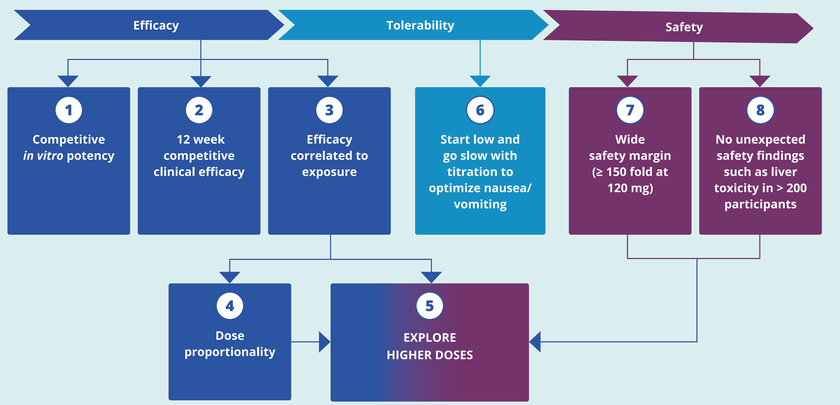
FIGURE 3. **BW Change From Baseline (%) for GSBR-1290, compared to other GLP-1RAs[1,2]**



- Long-term (week 72) PK/PD model-derived simulations project a -17.3% mean body weight percent change from baseline at the 120 mg QD maintenance dose, which is competitive with other GLP-1RA medicines

Data for orforglipron and semaglutide up to 36 and 68 weeks respectively, were digitized from the literature. Orforglipron data represents the least-square means and semaglutide data represents the mean. **Data Source:** Study GSBR-1290-02 (Phase 2a) Cohort 4. **BL** = Baseline
No head-to-head study has been conducted evaluating GSBR-1290 against the other product candidates included herein. Differences exist between study designs and conditions, and caution should be exercised when comparing data across studies.

CONCLUSIONS



- **GSBR-1290 was designed to optimize risk/benefit resulting in a compound with strong pharmacological properties supportive of QD dosing with broad safety margins**
- **Efficacy is driven by exposure, consistent with published exposure-response analysis results from other GLP-1RAs[3,4]**
- **Modeling projects potential for competitive long-term efficacy, at maintenance doses of 120 mg QD**
- **The generally dose proportional PK profile and the wide safety margins support the assessment of higher doses, while optimizing tolerability with appropriate dose titration. Potential additional efficacy could position GSBR-1290 as best-in-class**

ABBREVIATIONS

BL = baseline; **BMI** = body mass index; **BW** = body weight; C_{avg} = AUC/dosing interval; **CI** = confidence interval; **eGFR** = estimated glomerular filtration rate; E_{max} maximum effect model; **ER** = exposure-response; **GLP-1RA** = glucagon-like peptide receptor agonists; **GLP-tox** = good laboratory practice toxicology studies; **N** = number of participants; **NONMEM** = nonlinear mixed effects modeling; **PD** = pharmacodynamic; **PK** = pharmacokinetic; **PopPK** = population PK; **QD** = once daily; **QW** = once weekly; **SD** = standard deviation; **T2DM** = type 2 diabetes mellitus

REFERENCES

1. Strathe A, Horn DB, Larsen MS, et al. A model-based approach to predict individual weight loss with semaglutide in people with overweight or obesity. *Diabetes Obes Metab.* 2023 Nov;25(11):3171-3180. **2.** Wharton S, Blevins T, Connery L, et al. Daily Oral GLP-1 Receptor Agonist Orforglipron for Adults with Obesity. *N Engl J Med.* 2023 Sep;7;389(10):877-888. **3.** Petri KCC, Ingwersen SH, Flint A, et al. Exposure-response analysis for evaluation of semaglutide dose levels in type 2 diabetes. *Diabetes Obes Metab.* 2018;20(9):2238-2245. **4.** Wilding JP, Overgaard RV, Jacobsen LV, et al. Exposure-response analyses of liraglutide 3.0 mg for weight management. *Diabetes Obes Metab.* 2016 18(5):491-9.

Structure Therapeutics and the Structure Therapeutics logo are trademarks owned by the Structure Therapeutics. © 2024 Structure Therapeutics, Inc. 11/24