Pharmacokinetic and Pharmacodynamic Profiles of GZR102 Injection, a Novel Once-Weekly Fixed-Ratio Combination of Insulin GZR4 and GLP-1 Analog Bofanglutide

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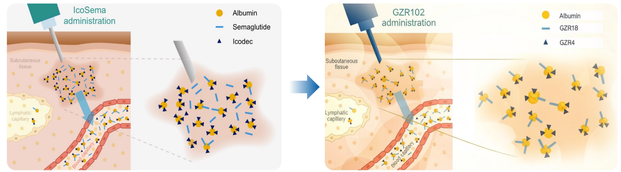
Introduction/Objective

- Fixed-ratio combinations (FRCs) of basal insulin and a GLP-1 receptor agonist (RA) deliver both agents in a single injection, improving treatment convenience.
- IcoSema (an FRC of basal insulin icodec and semaglutide) caused more gastrointestinal side effects than monotherapy, mainly because human serum albumin (HSA) binding competition raises semaglutide levels[1].
- There remains an unmet need for optimized once-weekly FRCs that preserve the intrinsic pharmacokinetic (PK) and pharmacological properties of each component while minimizing drug-drug interactions and maintaining efficacy and tolerability.
- GZR102 injection (GZR102) is a novel once-weekly FRC of insulin GZR4 and the GLP-1 analog bofanglutide (GZR18)[2-3].
- GZR102 is designed to preserve the PK characteristics of the individual components while delivering complementary glycemic control and metabolic benefits in people with Type 2 Diabetes Mellitus (T2DM).



Methods

- ***In vitro pharmacology***: Potential pharmacological interactions between GZR4 and GZR18 were assessed using in-cell western blotting, reporter gene assays, and HSA binding studies.
- ***Pharmacokinetic analysis:*** PK profiles of GZR102 and corresponding individual components were characterized following a single dose administration to Sprague Dawley (SD) rats and Bama Miniature Pigs.
- ***Efficacy:*** The efficacy of GZR102 was evaluated in diet-induced obese (DIO) and *db/db* mouse models following subcutaneous administration for 30 days at multiple dose levels.

Results

- Relative potency sustained close to 100% across tested ratios, indicating minimal pharmacological interference between GZR4 and GZR18 (Table 1). No apparent competition for albumin binding between GZR4 and GZR18 in the GZR102 combination was detected (Figure 1).
- GZR102 preserved the PK profiles of both GZR4 and GZR18 in SD rats and Bama Miniature pigs (Figure 2).
- GZR102 manifested enhanced glucose-lowering and body weight-reducing effects in DIO and *db/db* mice (Figure 3). In DIO mice, GZR102 decreased random glucose, improved glucose tolerance, and reduced body weight by 13-25% (Figure 3 A-C). In *db/db* mice, GZR102 achieved superior glycemic control with greater numerical reductions in HbA_{1c} (1.2% to 1.6%） versus (vs.) GZR4 (0.3%) or GZR18 (0.9%) alone (Figure 3 D-F).

Table 1. Drug-drug interaction between GZR4 and GZR18 in the combinations

In-cell Western blotting assay		**GZR4:GZR18 mass ratio of 1:3**	**GZR4:GZR18 mass ratio of 1:0.8**	**GZR4:GZR18 mass ratio of 1:0.2**	**GZR4:GZR18 mass ratio of 1:0.05**	
	Relative Potency*	87%	99%	100%	93%	
Reporter Gene assay		**GZR4:GZR18 mass ratio of 1:0.625**	**GZR4:GZR18 mass ratio of 1:0.77**	**GZR4:GZR18 mass ratio of 1:0.83**	**GZR4:GZR18 mass ratio of 1:5**	**GZR4:GZR18 mass ratio of 1:20**
	Relative Potency#	118%	110%	109%	97%	99%

Using the In-cell Western blotting assay, the potency of different concentrations of a mixture containing GZR18 and GZR4 relative to GZR4 alone was measured to assess the effect of GZR18 on the GZR4-induced activation of the hIR signaling pathway, reflecting the interaction between GZR18 and GZR4. *Relative potency = potency of each combination/potency of GZR4.

Using the Reporter gene assay, the potency of different concentrations of a mixture containing GZR4 and GZR18 relative to GZR18 alone was measured to assess the effect of GZR4 on the GZR18-induced activation of the GLPR signaling pathway, reflecting the interaction between GZR18 and GZR4. #Relative potency = potency of each combination / potency of GZR18.

Conclusion

- GZR102 preserved the PK characteristics of GZR4 and GZR18 without observed meaningful pharmacological interference.
- GZR102 demonstrated complementary/synergistic glycemic control and metabolic benefits including body weight reduction.
- These findings support the further clinical development of GZR102 as a once-weekly FRC.

References

1. Westergaard, L. et al. Clin Drug Investig. 2024 doi: 10.1007/s40261-024-01405-8
2. Chen L. *et al*. Metabolism. 2026. doi: 10.1016/j.metabol.2026.156592;
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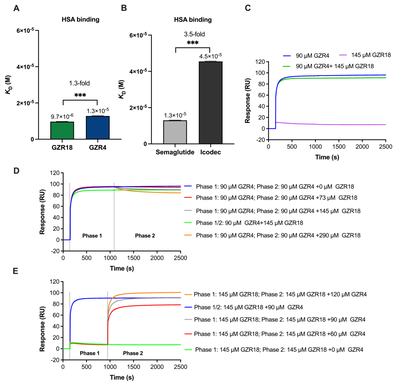


Figure 1. The competition binding assay of GZR4 and GZR18 to HSA

A. HSA binding affinity of GZR4 and GZR18 were determined by SPR assay and expressed as K_D (mean ± standard error of mean[SEM], n=5), a lower K_D value indicates a higher binding affinity;

B. HSA binding affinity of Icodec and semaglutide (mean ± SEM, n=5) ***p<0.001;

C. Sensograms showing the HSA binding profiles of binding affinity to HSA of 90 μM GZR4, 145 μM GZR18, GZR102, respectively; Differences in RU likely reflected differences in molecular weight, concentration, and HSA binding characteristics;

D. Binding affinity to HSA of 90 μM GZR4 in absence of GZR18 or in the presence of various concentration of GZR18 (73, 145, 290 μM) during the coinjection Phase 2;

E. Binding affinity to HSA of 145 μM GZR18 in the absence of GZR4 or in the presence of difference concentration of GZR4 (60, 90, 120 μM) during the coinjection Phase 2.

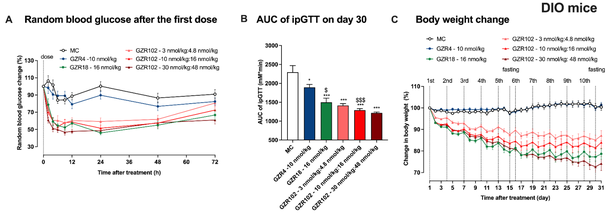


Figure 3. The pharmacodynamic effects of GZR102 in DIO mice and *db/db* mice.

A. Effects of GZR102 on random blood glucose in DIO mice after the first dose (n=8);

B. Area under the curve (AUC) of intraperitoneal glucose tolerance test (ipGTT) in DIO mice on day 30 (n=8);

C. Body weight change in different groups (n=8) over time;

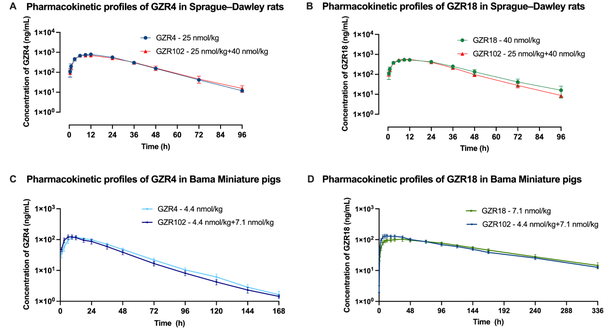


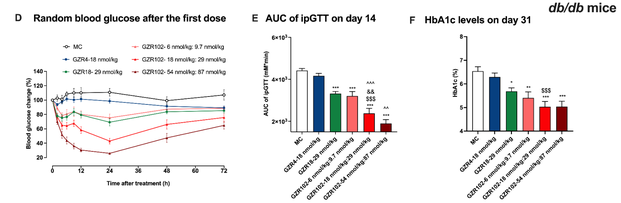
Figure 2. The PK profile of GZR102 was comparable to its individual components at equivalent doses in SD rats and Bama miniature pigs.

A. Semi-logarithmic pharmacokinetic profiles of GZR4 in SD rats after single subcutaneous administration of GZR102 or GZR4;

B. Semi-logarithmic pharmacokinetic profiles of GZR18 in SD rats after single subcutaneous administration of GZR102 or GZR18 (mean ± SEM, n=10) ;

C. Semi-logarithmic pharmacokinetic profiles of GZR4 in Bama Miniature Pigs after single subcutaneous administration of GZR102 (equivalent to 4.4 nmol/kg GZR4 and 7.1 nmol/kg GZR18) or GZR4 (equivalent to 4.4 nmol/kg);

D. Semi-logarithmic pharmacokinetic profiles of GZR18 in Bama Miniature Pigs after single subcutaneous administration of GZR102 (equivalent to 4.4 nmol/kg GZR4 and 7.1 nmol/kg GZR18) or GZR18 (7.1 nmol/kg)(mean ± SEM, n=6).



D. Effects of GZR102 on random blood glucose in *db/db* mice after the first dose (n=10);

E. AUC of ipGTT on day 14 (n=10);

F. HbA_{1c} levels on day 31 (n=10). All data were expressed as "Mean ± SEM". *p<0.05, **p<0.01, ***p<0.001 vs. MC; $$$p$<0.01, $$$$p$<0.001 vs. GZR4: &&$p$<0.01 vs. GZR18; ^$p$<0.05, ^^$p$<0.01, ^^^$p$<0.001 vs. low-dose GZR102.

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