Effect of Bofanglutide on the Pharmacokinetics of Metformin in Healthy Participants

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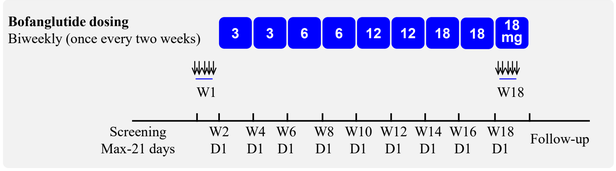
Introduction/Objective

- Bofanglutide (also known as GZR18) is a novel biweekly GLP-1 analog under phase 3 development for the treatment of type 2 diabetes, overweight/obesity, and obesity-related obstructive sleep apnea[1,2].
- Given that metformin is frequently co-prescribed or used concomitantly with GLP-1 analog, it is clinically essential to evaluate the potential pharmacokinetic (PK) interaction between bofanglutide and metformin.
- This trial evaluated the effect of steady-state bofanglutide on the PK of metformin in healthy participants.

Methods

Study design

- In this open-label, fixed-sequence, phase 1 trial, eligible participants were adults aged 18–50 years, with a body weight of ≥50 kg and a body mass index (BMI) ≥ 24.0 and ≤ 33.0 kg/m^2 at screening.
- Participants received escalating biweekly subcutaneous bofanglutide (3, 6, 12 mg, each for 4 weeks) followed by 18 mg for 6 weeks. Metformin (500 mg twice daily for 2.5 days) was administered alone or in combination with bofanglutide at week 5 of the 18 mg dose.



Endpoints

- ***Primary***: Metformin area under the plasma concentration–time curve over the 12-hour dosing interval at steady state ($AUC_{0\text{-}tau}$), and maximum plasma concentration (C_{max}).
- ***Secondary***: Time to reach C_{max} (T_{max}), elimination half-life ($t_{1/2}$), apparent total clearance (CL/F), and apparent volume of distribution (V_z/F); safety and tolerability; pharmacodynamics (changes in body weight, etc.).

Results

Participant disposition, demographics and baseline characteristics

- Thirty-two out of the 127 screened participants were enrolled and exposed to the treatment in the trial. Twenty-eight participants completed the trial. Four participants withdrew from the trial prematurely.
- At baseline, the mean age of participants was 32.7 years, 17 (53.1%) were male, and the mean BMI was 27.8 kg/m² (Table 1).

Metformin Exposure with or without bofanglutide

- Co-administration of bofanglutide resulted in comparable overall metformin exposure but a reduced metformin C_{max} (Table 2, Figure 1).
- The geometric mean ratios (GMRs) of $C_{max,ss}$ and $AUC_{0\text{-}tau}$ (with versus [vs.] without bofanglutide) were 0.72 (90% confidence interval [CI] , 0.61-0.84) and 0.94 (90% CI, 0.84-1.05), respectively (Figure 2).

Clinical Efficacy

- Bofanglutide markedly reduced body weight, waist circumference and triglycerides (Figure 3).

Safety

- Bofanglutide with or without metformin was well tolerated, with all treatment-emergent adverse events being Grade 1–2 in severity;
- The most frequently reported adverse events were gastrointestinal, primarily vomiting and nausea;
- Two participants reported two episodes of grade 1 hypoglycemia, both considered related to bofanglutide (Table 3) .

Conclusion

- Bofanglutide was well tolerated in participants receiving metformin with/without bofanglutide.
- Bofanglutide had no clinically meaningful effect on overall metformin exposure, indicating that metformin dose adjustment is unnecessary when co-administered with bofanglutide.

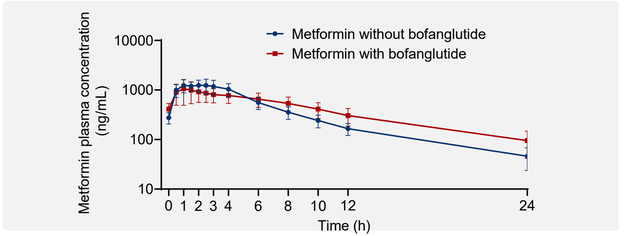


Figure 1. Semi-log plasma concentration-time profiles of metformin with and without bofanglutide. Data are presented as mean ± Standard deviation.

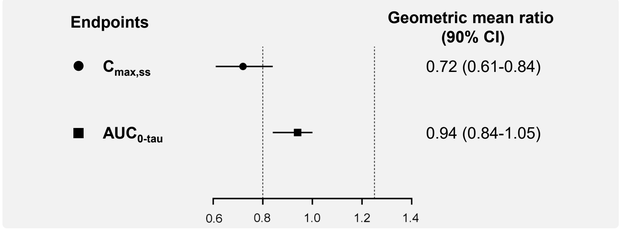


Figure 2. Geometric mean ratios and 90% CIs for $C_{max,ss}$ and $AUC_{0\text{-}tau}$ before and during bofanglutide treatment. The vertical dashed lines represent the prespecified equivalence interval of 0.8-1.25. CI= confidence interval.

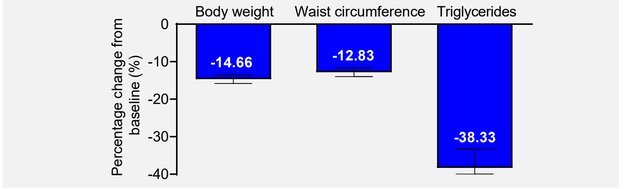


Figure 3. Percentage changes from baseline in body weight, waist circumference and triglycerides at end of treatment. Data are presented as mean ± standard error.

Table 1. Demographics and baseline characteristics

Characteristics	Total (N=32)
Age (years)	32.7 (6.4)
Sex (Male), n (%)	17 (53.1)
Ethnicity (Han), n (%)	31 (96.9)
Weight (kg)	75.9 (9.0)
Height (cm)	165.1 (8.5)
BMI (kg/m²)	27.8 (1.1)

Data are presented as Mean (SD) unless otherwise stated. SD= Standard deviation.

Table 2. Pharmacokinetic parameters of metformin

PK parameters	Metformin N=32	Metformin with bofanglutide N=28
$C_{max,ss}$ (ng/mL)	1468.0 (470.9)	1145.2 (536.8)
$AUC_{0\text{-}tau}$ (ng*h/mL)	7855.7 (1731.6)	7698.2 (2377.3)
$t_{1/2}$ (h)	6.2 (2.0)	6.9 (2.1)
T_{max} (h)[a]	1.5 (1.0, 2.5)	1.0 (1.0, 2.5)

Data are presented as Mean (SD) unless otherwise stated. [a] Median (Q1, Q3).

Table 3. Summary of adverse events (AEs)

Event	Total (N=32)
TEAE	30 (93.8) 333
Grade 1	20 (62.5) 314
Grade 2	10 (31.3) 19
Grade 3 or higher	0 (0) 0
Bofanglutide-related TEAE	30 (93.8) 252
Metformin-related TEAE	15 (46.9) 44
SAE	0 (0) 0
TEAE leading to trial discontinuation	1 (3.1) 1
GIAE	
Vomiting	18 (56.3) 67
Nausea	16 (50.0) 29
Hypoglycemia	2 (6.3) 2
Injection site reaction	7 (21.9) 27

TEAE= Treatment-emergent adverse event; SAE= Serious adverse event; GIAE= Gastrointestinal adverse event.

References

1. Linong Ji, et al. Signal Transduct Target Ther. 2026 Feb 27;11(1):73.
2. Linong Ji, et al. Cell Rep Med. 2026 Apr 21;7(4):102743.

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