Effect of Renal Impairment on the Pharmacokinetics and Safety of Bofanglutide

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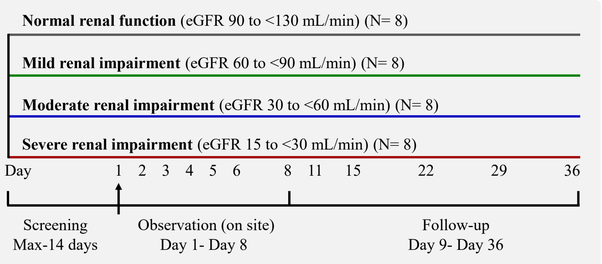
Introduction/Objective

- Bofanglutide (also known as GZR18) is a novel biweekly GLP-1 analog in phase 3 development for the treatment of type 2 diabetes, overweight/obesity, and obesity-related obstructive sleep apnea[1-3].
- This trial evaluated the pharmacokinetics (PK) and safety of bofanglutide in participants with renal impairment (mild, moderate, or severe) versus matched controls with normal renal function.

Methods

Study design

- In this open-label, parallel-group, single-dose, phase 1 trial, eligible participants were adults aged 18–75 years, with a body weight of ≥50 kg and a body mass index (BMI) between 20.0 and 40.0 kg/m^2 at screening.
- Participants were classified into groups of various degrees of renal function based on estimated glomerular filtration rate (eGFR) values calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation. All participants received a single subcutaneous dose of 3 mg bofanglutide.



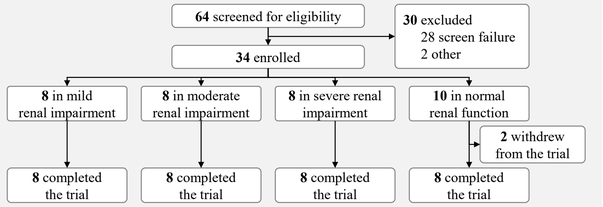
Endpoints

- ***Primary***: Area under the plasma concentration–time curve (AUC) from time zero to the time of the last measurable concentration ($AUC_{0\text{-last}}$), AUC from time zero to infinity ($AUC_{0\text{-inf}}$), and maximum plasma concentration (C_{max}).
- ***Secondary***: Time to reach C_{max} (T_{max}), elimination half-life ($t_{1/2}$), and apparent total clearance after subcutaneous administration (CL/F); safety and tolerability; immunogenicity.

Results

Participant disposition

- Sixty-four participants were screened for eligibility. Eight each were allocated to four groups with different degrees of renal impairment (mild, moderate, severe and normal). A total of 32 participants completed the trial.



Demographics and baseline characteristics

- General baseline parameters were comparable across the four groups. Mean eGFR values were 104.0, 74.1, 48.4 and 24.7 mL/min in normal, mild, moderate, and severe renal impairment groups, respectively (Table 1).

Pharmacokinetics

- Exposure of bofanglutide was generally similar across the normal renal function group and different degrees of renal impairment (Figure 1, Table 2).
- The geometric least-squares (LS) mean ratios for C_{max}, $AUC_{0\text{–last}}$, and $AUC_{0\text{–inf}}$ were all close to 1, with the 90% confidence interval (CI) generally falling within the prespecified equivalence range of 0.80–1.25, except for a few upper bounds that slightly exceeded limit, up to 1.28 (Figure 2).
- No significant relationship between eGFR and bofanglutide exposure was observed (Table 3).

Safety

- Bofanglutide was well tolerated, with treatment-emergent adverse events (TEAEs) mostly being Grade 1 or 2 in severity. One SAE (diarrhea) was reported which was deemed unrelated to the investigational product by the investigator;
- The most frequently reported adverse events were gastrointestinal, including nausea and vomiting;
- No participants developed anti-bofanglutide antibodies during the trial.

Table 1. Demographics and baseline characteristics

Characteristics	Normal renal function N=8	Mild renal impairment N=8	Moderate renal impairment N=8	Severe renal impairment N=8
Age (years)	48.0 (2.8)	43.1 (7.3)	44.6 (5.8)	48.4 (7.5)
Sex (Male), n (%)	5 (62.5)	6 (75.0)	4 (50.0)	6 (75.0)
Ethnicity (Han), n (%)	8 (100)	8 (100)	8 (100)	8 (100)
Weight (kg)	63.3 (3.3)	63.9 (8.3)	60.0 (4.5)	63.0 (7.6)
BMI (kg/m^2)	23.3 (1.4)	23.0 (2.0)	22.4 (0.8)	22.9 (1.7)
eGFR (mL/min)	104.0 (4.5)	74.1 (9.4)	48.4 (8.5)	24.7 (5.2)

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

Table 2. Pharmacokinetic parameters

PK parameters	Normal renal function N=8	Mild renal impairment N=8	Moderate renal impairment N=8	Severe renal impairment N=8
C_{max} (ng/mL)	341 (75.8)	353 (58.7)	334 (85.0)	349 (65.8)
$AUC_{0\text{-last}}$ (ng*h/mL)	96244 (20076)	103544 (16637)	102596 (15146)	101028 (16387)
$AUC_{0\text{-inf}}$ (ng*h/mL)	99373 (21228)	107683 (18965)	106773 (15681)	104585 (18304)
T_{max} (h)[a]	24 (24, 48)	48 (24, 72)	48 (24, 72)	48 (24, 120)
$t_{1/2}$ (h)	155 (14.1)	171 (21.6)	173 (11.2)	156 (27.3)

Data are presented as Mean (SD) unless otherwise stated. a Median (range).

Table 3. Linear regression and Pearson correlation analysis of the effect of eGFR on pharmacokinetic parameters

PK parameters	Linear regression analysis			Pearson correlation analysis	
	Slope (β)	90% CI	P	Correlation coefficient (r)	P
C_{max} (ng/mL)	-0.08	-0.78, 0.63	0.855	-0.04	0.810
$AUC_{0\text{-last}}$ (ng*h/mL)	-52.54	-205.05, 99.96	0.563	-0.13	0.464
$AUC_{0\text{-inf}}$ (ng*h/mL)	-57.49	-222.52, 107.54	0.559	-0.13	0.459
CL/F (L/h)	0.00[a]	0.00, 0.00	0.499	0.15	0.409

[a] The slope and confidence interval for CL/F were each <0.001 and are reported as 0.00.

Table 4. Summary of adverse events

Event	Normal renal function N=8	Mild renal impairment N=8	Moderate renal impairment N=8	Severe renal impairment N=8
TEAE	7 (87.5) 22	8 (100) 28	7 (87.5) 20	8 (100) 27
Grade 1	7 (87.5) 16	8 (100) 17	7 (87.5) 14	8 (100) 19
Grade 2	5 (62.5) 6	7 (87.5) 10	3 (37.5) 5	5 (62.5) 8
Grade 3 or higher	0 (0) 0	1 (12.5) 1	1 (12.5) 1	0 (0) 0
SAE	0 (0) 0	0 (0) 0	1 (12.5) 1	0 (0) 0
Death	0 (0) 0	0 (0) 0	0 (0) 0	0 (0) 0
TEAE leading to trial discontinuation	0 (0) 0	0 (0) 0	0 (0) 0	0 (0) 0
GIAE				
Nausea	6 (75.0) 6	7 (87.5) 7	3 (37.5) 3	3 (37.5) 3
Vomiting	4 (50.0) 4	4 (50.0) 4	4 (50.0) 4	3 (37.5) 3
Hypoglycemia	0 (0) 0	0 (0) 0	0 (0) 0	0 (0) 0
Injection site reaction	0 (0) 0	0 (0) 0	0 (0) 0	0 (0) 0

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

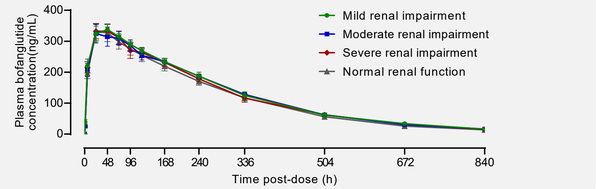


Figure 1. Mean plasma concentration-time profiles of bofanglutide after a single subcutaneous dose of 3mg. Data are presented as mean ± standard error.

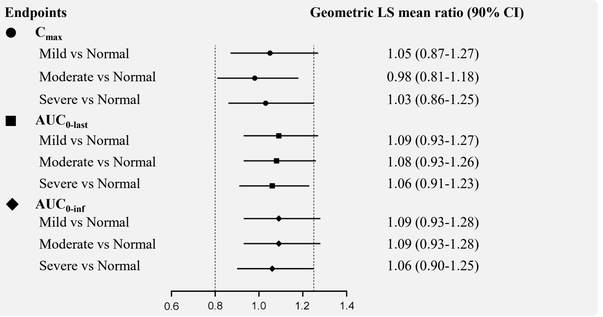


Figure 2. Comparison of geometric LS mean ratios and 90% CIs for C_{max}, $AUC_{0\text{-last}}$ and $AUC_{0\text{-inf}}$ between participants with various degrees of renal impairment and those with normal renal function. The vertical dashed lines represent the prespecified equivalence interval of 0.8-1.25. LS= Least-squares; CI= confidence interval.

Conclusion

- Bofanglutide was well tolerated in participants across all stages of renal function, from normal to severe renal impairment.
- No clinically relevant effects of renal impairment on bofanglutide PK were observed. Therefore, dose adjustment is not required for individuals with renal impairment receiving bofanglutide.

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.
3. Ming Liu, et al. Ann Intern Med. In press.

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