# Effects of Mild or Moderate Renal Impairment on Pharmacokinetics and Safety of Once-weekly Insulin GZR4

Jie Pan[1], Wei Zhao[2], Huaying Shen[1], Jing Zhao[3], Chunyue Hao[3], Tian Xie[3], Anshun He[3], Jingjing Wang[3], Jerzy Kolaczynski[4], Haiya Wu[4], Wei Chen[3]

[1]The Second Affiliated Hospital of Soochow University, Suzhou, China ; [2]The First Affiliated Hospital of Shandong First Medical University, Jinan, China; [3] Gan & Lee Pharmaceuticals, Beijing, China; [4] Gan & Lee Pharmaceuticals USA Corp, Bridgewater, USA.

1745-P ADA 2026

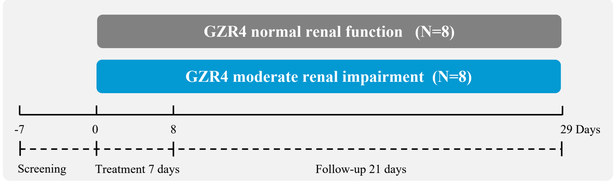
## Introduction/Objective

- Once-weekly (QW) insulin aims to reduce treatment burden by lowering injection frequency, potentially enhancing treatment acceptance and adherence[1-2].
- Insulin GZR4 (GZR4) is a novel QW basal insulin analog in phase 3 development.
- Renal impairment may influence the pharmacokinetics (PK) of insulin in individuals.
- The objective of this trial was to investigate the effects of mild or moderate renal impairment on the PK, safety, and tolerability of GZR4.

## Methods

### Study design

- In this open-label, single-dose, parallel-group trial, 16 adults (body mass index [BMI] 18.5-27.9 kg/m$^2$) were allocated to two groups: normal renal function (NRF, estimated glomerular filtration rate [eGFR] 90 to <130 mL/min; n=8) and moderate renal impairment (MRI, eGFR 30 to <60 mL/min; n=8). Following a single subcutaneous administration of 3 nmol/kg GZR4, blood samples were collected up to 672 h post-dose.
- An additional group of individuals with mild renal impairment (eGFR 60 to <90 mL/min; n=8) was to be recruited if the $AUC_{0\text{-}inf}$ ratio of GZR4 between individuals with normal and moderately impaired renal function was outside the pre-defined threshold.



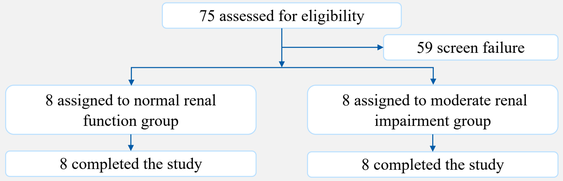

### Endpoints

- The primary endpoint was the PK parameters: area under the plasma concentration–time curve (AUC) from time zero to the time of the last measurable concentration ($AUC_{0\text{-}last}$) and maximum plasma concentration ($C_{max}$). Secondary endpoints included the PK parameters ($T_{max}$, $AUC_{0\text{-}168h}$), safety and immunogenicity.

## Results

### Subject disposition

- A total of 75 participants assessed for eligibility and 16 were included. Eight participants were assigned to each group and completed the study.




### Demographics and baseline characteristics

- Twelve (75%) participants were male. Mean age was 43.4±6.8 years old. Mean eGFR was 108.0 mL/min in the normal renal function group and 46.0 mL/min in moderate renal impairment group. Other variables were well-balanced at baseline (Table 1).

### Pharmacokinetics

- The mean $C_{max}$ of GZR4 was comparable between two groups (MRI, 122 ng/mL versus [vs.] NRF, 118 ng/mL). The MRI group exhibited a 13% higher GZR4 exposure compared to the NRF group ($AUC_{0\text{-}last}$: 19924 vs. 17680 ng*h/mL; $AUC_{0\text{-}inf}$: 20076 vs. 17770 ng*h/mL)(Table 2, Figure 1).
- The estimated geometric mean difference ratio (90% CI) for $C_{max}$, $AUC_{0\text{-}last}$, and $AUC_{0\text{-}inf}$ were 101.22% (80.43%, 127.39%), 113.18% (96.42%, 132.86%), and 113.45% (96.69%, 133.12%), respectively. Based on these results, the contingency of recruiting individuals with mild renal impairment was not implemented.

### Safety Profile

- The safety profiles of the two groups were comparable, with one hypoglycemia (CTCAE 5.0 level 1) reported in the MRI group, which recovered following glucose treatment. No serious adverse events occurred. Only one participant with NRF developed anti-GZR4 antibodies (titer: 100) at the end of follow-up (Day 29) (Table 3).

**Table 1. Demographics and baseline characteristics**

| Characteristics | Normal renal function, N=8 | Moderate renal impairment, N=8 | Total, N=16 |
|---|---|---|---|
| Age (years) | 43.6 (6.0) | 43.1 (7.9) | 43.4 (6.8) |
| Sex (Male), n (%) | 6 (75.0) | 6 (75.0) | 12 (75.0) |
| Ethnicity (Han), n (%) | 8 (100.0) | 8 (100.0) | 16 (100.0) |
| Height (cm) | 165.2 (6.1) | 166.6 (6.1) | 166.0 (6.0) |
| Weight (kg) | 64.5 (5.5) | 65.2 (6.7) | 65.9 (6.0) |
| BMI (kg/m$^2$) | 23.6 (1.5) | 23.5 (1.9) | 23.5 (1.7) |
| eGFR (mL/min) | 108.0 (12.9) | 46.0 (10.1) | 76.9 (33.9) |

Data were presented as Mean (SD) or n (%).
BMI=body mass index; eGFR= estimated glomerular filtration rate.

**Table 3. Summary of adverse events (AEs)**

| Event | Normal renal function, N=8 | | Moderate renal impairment, N=8 | |
|---|---|---|---|---|
| | No. of patients (%) | No. of events | No. of patients (%) | No. of events |
| TEAE | 3 (37.5) | 7 | 7 (87.5) | 19 |
| Grade 1 | 3 (37.5) | 7 | 6 (75.0) | 12 |
| Grade 2 | 0 (0.0) | 0 | 2 (25.0) | 4 |
| Grade 3 and above | 0 (0.0) | 0 | 2 (25.0) | 3 |
| TRAE | 2 (25.0) | 3 | 4 (50.0) | 11 |
| Grade 1 | 2 (25.0) | 3 | 3 (37.5) | 5 |
| Grade 2 | 0 (0.0) | 0 | 1 (12.5) | 3 |
| Grade 3 and above | 0 (0.0) | 0 | 2 (25.0) | 3 |
| Hypoglycemia | 0 (0.0) | 0 | 1 (12.5) | 1 |
| SAE | 0 (0.0) | 0 | 0 (0.0) | 0 |
| TEAE leading to discontinuation from the study | 0 (0.0) | 0 | 0 (0.0) | 0 |

TEAE=treatment-emergent adverse event; TRAE= treatment-related adverse event;
SAE=serious adverse event. According to Common terminology criteria for adverse event (CTCAE 5.0).

**Table 2. PK parameters after single dose of 3 nmol/kg GZR4 in individuals with moderate renal impairment and normal renal function.**

| PK parameters | Normal renal function, N=8 | Moderate renal impairment, N=8 |
|---|---|---|
| $C_{max}$ (ng/mL) | 118 ± 22.7 (19.3%) | 122 ± 36.4 (29.8%) |
| $T_{max}$ (h) | 32.00 (23.92, 72.00) | 32.00 (24.00, 72.00) |
| $AUC_{0\text{-}last}$ (ng•h/mL) | 17680 ± 3451 (19.5%) | 19924 ± 3339 (16.8%) |
| $T_{last}$ (h) | 504.0 (503.9, 672.4) | 672.0 (503.5, 672.2) |
| $AUC_{0\text{-}inf}$ (ng•h/mL) | 17770 ± 3450 (19.4%) | 20076 ± 3354 (16.7%) |
| $AUC_{0\text{-}168h}$ (ng•h/mL) | 13747 ± 2327 (16.9%) | 14795 ± 3278 (22.2%) |
| CL/F (L/h) | 90.5 ± 18.7 (20.7%) | 78.7 ± 15.4 (19.6%) |
| $V_z$/F (L) | 9071 ± 1521 (16.8%) | 8769 ± 2042 (23.3%) |

Data were presented as Mean ± SD (CV%) or Median (minimum, maximum). $C_{max}$=maximum plasma concentration; $T_{max}$=Time to reach $C_{max}$; $AUC_{0\text{-}last}$=area under the plasma concentration–time curve (AUC) from time zero to the time of the last measurable concentration; CL/F=apparent total clearance; $V_z$/F=apparent volume of distribution.

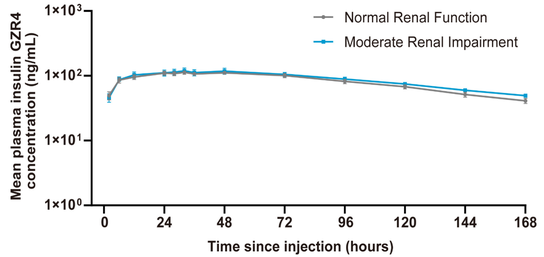



**Figure 1.** Mean (SE) GZR4 plasma concentration-time plots during a 1 week after a single subcutaneous injection of 3 nmol/kg GZR4 injection in individuals with moderate renal impairment and normal renal function.

## Conclusion

- Moderate renal impairment had no significant impact on the exposure and safety of GZR4.
- No specific dose adjustment of GZR4 is required in individuals with mild or moderate renal impairment.

**References**

1. Almigbal, T. H. *et al.* Clinical Inertia in the Management of Type 2 Diabetes Mellitus: A Systematic Review. *Medicina (Kaunas)* **59**, doi:10.3390/medicina59010182 (2023).
2. Chen L. *et al.* Once-weekly insulin GZR4 versus once-daily insulin degludec in Chinese people with type 2 diabetes: A multicenter, open-label, randomized, phase 2 trial. Metabolism. 2026 Jun;179:156592. doi: 10.1016/j.metabol.2026.156592

Note: Data of all figure were presented as mean (SE).

This work was supported by Gan & Lee Pharmaceuticals and was registered with ClinicalTrials.gov (NCT06547502).