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Safety, tolerability, pharmacokinetics and pharmacodynamics of GZR4, a novel once-weekly basal insulin, in healthy participants: A randomized trial

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Abstract

Aims: Insulin GZR4 (GZR4), a novel once-weekly basal insulin, has demonstrated a favourable safety and low toxicity profile, as well as notable in vivo glycaemic control effects, in preclinical studies. The study aimed to evaluate the safety, tolerability, pharmacokinetics (PK) and pharmacodynamics (PD) of GZR4 in healthy Chinese participants.

Methods: In this randomized, single-blind, dose-escalation Phase 1a study, healthy male adults aged 18–45 years, with a BMI of 19–24 kg/m^2 were enrolled in five cohorts. Participants in Cohorts 1–4 were randomized 4:1 to receive subcutaneous injections of GZR4 at doses of 1, 3, 6, and 12 nmol/kg or placebo. Participants in Cohort 5 received 0.4 U/kg (2.4 nmol/kg) of insulin degludec (IDeg). Euglycaemic glucose clamps were conducted 24–48 h (Day 2) and 144–168 h (Day 7) after GZR4 administration, and 0–24 h (Day 1) after IDeg administration. The primary endpoints were the safety and tolerability of GZR4.

Results: A total of 43 participants were enrolled, and 42 of them completed the study. No deaths, serious adverse events (SAEs), or discontinuations related to the investigational product were reported. The most common treatment-emergent adverse events (TEAEs) were hypoglycaemia, which occurred exclusively in the 12 nmol/kg GZR4 group. All TEAEs were mild to moderate in severity. The PK parameters of GZR4 increased linearly with the dose from 1 to 12 nmol/kg, and the glucose-lowering effect was sustained for approximately 1 week. The $AUC_{GIR,24\text{-}48h}$ and $AUC_{GIR,144\text{-}168h}$ for the 6 nmol/kg GZR4 dose (54.91 and 37.84 h × mg/kg/min) were comparable with that of IDeg ($AUC_{GIR,0\text{-}24h}$, 40.59 h × mg/kg/min), suggesting that GZR4's potency may be approximately 3.2-times greater than IDeg weekly.

Conclusion: Once-weekly GZR4 demonstrated good safety and tolerability in healthy participants. It exhibited a dose-dependent and sustained glucose-lowering effect over a full week and demonstrated stronger daily glucose-lowering efficacy than once-daily IDeg under similar molar concentrations. These results support further investigation of once-weekly GZR4 for glycaemic control in patients with diabetes.

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KEYWORDS
basal insulin, diabetes, once-weekly, pharmacodynamics, pharmacokinetics

1 | INTRODUCTION

Diabetes mellitus (DM) is a chronic metabolic disorder characterized by hyperglycaemia because of an absolute or relative deficiency in insulin secretion and decreased insulin sensitivity in target tissues.[1] According to the latest data from the International Diabetes Federation (IDF), in 2021, approximately 537 million adults aged 20–79 years were diagnosed with diabetes, which is expected to rise to 643 million by 2030 and 783 million by 2045.[2]

Achieving good glycaemic control is essential for managing diabetes, as it helps prevent or delay the onset and progression of diabetic complications, which can severely impact the quality of life and increase morbidity and mortality.[3,4] At present, the treatment of type 1 diabetes mellitus (T1DM) and advanced type 2 diabetes mellitus (T2DM) predominantly relies on insulin, with basal insulin playing an essential role as an indispensable part of the treatment regimen.[5] Initially, insulin required multiple daily injections because of its relatively short half-life. Efforts have been made to develop insulin formulations with extended half-lives to reduce the frequency of injections.[6,7] Currently, insulin glargine and insulin degludec (IDeg) are widely used long-acting basal insulins administered once daily to maintain stable blood glucose levels.[8–11]

Despite these advances, patients on insulin therapy continue to face many challenges that result in suboptimal glycaemic control. One such challenge is nonadherence to treatment, which has been reported to affect approximately 20%–38% of patients.[12] Reasons for nonadherence may include low socioeconomic status, regimen complexity, the impact of insulin therapy on daily life, forgetfulness, fear and pain associated with injections, and others.[13,14] Additionally, clinical inertia, characterized by the reluctance to initiate insulin therapy, is another challenge to insulin therapy in a significant proportion of patients with T2DM owing to the treatment burden of daily subcutaneous injections,[15,16] resulting in delayed initiation of insulin therapy when oral antidiabetic drugs fail to achieve glycaemic targets. A survey revealed that the need to take insulin at prescribed times every day and the number of daily injections were the two most commonly reported difficulties for patients on insulin treatment, and the majority of patients (92.5%) expressed a strong preference for achieving good glycaemic control with insulin without the need for daily injections.[13] Delaying insulin treatment in T2DM increases the risk and severity of diabetic late-stage complications. It was found that the majority of patients with T2DM initiated treatment intensification more than 1 year (range 0.3–>7.2 years) after a glycated haemoglobin (HbA1c) measurement above the target.[17]

Compared with the once-daily basal insulin, the once-weekly insulin provides the opportunity to address the challenges of the current daily basal insulin therapy. A similarly successful strategy had been witnessed from the development of once-weekly glucagon-like peptide-1 receptor agonists derived from a once-daily dosing regimen, with higher adherence at 360 days (assessed by proportion of days covered (PDC) and proportion of patients with PDC > 80%) observed for once-weekly semaglutide (39.1%) and dulaglutide (43.2%) versus once-daily liraglutide (30.0%).[18] Once-weekly insulin could reduce the frequency of basal insulin injections by approximately 85%, from 365 daily injections to 52 injections per year. This may facilitate insulin initiation and improve treatment adherence and diabetes-related quality of life for individuals with diabetes.[19] In support of this, a survey among patients with T2DM showed the majority of individuals on insulin (73.1%) would be likely to adopt a once-weekly dosing regimen if recommended by their physician.[20] Consequently, basal insulin preparations administered once-weekly have increasingly become a focus of diabetes drug research and development. Among these, insulin icodec (Icodec) has recently obtained regulatory approval in several countries.[21]

Insulin GZR4 (GZR4) is a novel once-weekly basal insulin analog in clinical development. It couples the B29 lysine of a modified insulin backbone (A14E, B16H, B25H, desB30 human insulin) with a 1,22-icosanedioic fatty acid (C22) and a 12-oligoethylene glycol (OEG) spacer. GZR4 exhibits strong human serum albumin (HSA) binding and low insulin receptor affinity. Preclinical studies demonstrate a high safety and low toxicity profile and higher in vivo glycaemic control effects in both T1DM and T2DM diabetic animal models when compared with Icodec or IDeg.[22] These findings support the clinical development of GZR4. The current Phase 1a study evaluated the safety, tolerability, PK, and PD of GZR4 following single ascending subcutaneous doses in healthy male participants.

2 | METHODS

2.1 | Study design and participants

This was a single-centre, single-dose, randomized, single-blind, dose-escalation Phase 1a study, conducted in Bishan Hospital of Chongqing Medical University from 29 August 2022 to 24 March 2023. The study was conducted in full compliance with the International Council for Harmonization for Good Clinical Practice, and the Declaration of Helsinki. The trial was approved by an independent ethics committee (Medical Ethics Committee of the People's Hospital of Bishan District) and registered at https://www.chinadrugtrials.org.cn (CTR20222273). Informed consents were obtained from all participants before any trial-related activities.

Eligible participants were healthy male adults aged 18–45 years (both inclusive), with a body mass index (BMI) of 19.0–24.0 kg/m^2, body weight ≥ 50.0 kg, and HbA1c ≤ 6.0%. Individuals with clinically significant medical history or current diseases related to the endocrine

system, cardiovascular disease, and so forth, as well as those with known severe allergies or known history of allergies to any components of the investigational product (IP) were excluded from participation. Details of inclusion and exclusion criteria are listed in the Supporting Information.

2.2 | Procedures and assessments

The trial consisted of a screening visit (7 days before the treatment period), a treatment period of either 3 (Cohort 5) or 9 (Cohorts 1–4) days' duration, and a follow-up visit. Eligible participants were enrolled and assigned to 1 of 5 cohorts. Participants in Cohorts 1–4 were randomized in a 4:1 ratio to receive different doses of subcutaneous injections of GZR4 (1, 3, 6, 12 nmol/kg) or placebo. Participants in Cohort 5 received 0.4 U/kg (2.4 nmol/kg) of Tresiba® (insulin degludec, IDeg) as a comparator (Figure S1). The selection of GZR4 doses is detailed in the Supporting Information. Randomization was conducted within Cohorts 1–4, using an interactive web response system. In contrast, all participants in Cohort 5 received IDeg with no randomization. The trial was conducted with a single-blind design within Cohorts 1–4 and an open-label design in Cohort 5. Throughout the course of the treatment, participants will be provided with a standard diet.

The primary endpoints were the safety and tolerability of a single dose of GZR4 in healthy participants. The safety assessments included the incidence of treatment-emergent adverse events (TEAEs), such as hypoglycaemic reactions and injection site reactions, clinical laboratory tests, 12-lead electrocardiogram (ECG), vital signs, physical examinations, and local tolerability at the injection site.

Secondary endpoints were the PK/PD profiles, including maximum drug concentration (C_{max}), time to maximum drug concentration (t_{max}), area under the concentration-time curve (AUC) from time zero to the last quantifiable concentration ($AUC_{0\text{-last}}$), maximum glucose infusion rate (GIR_{max}), and AUC of GIR-time (AUC_{GIR}). Details of blood sample collection for PK/PD analysis are provided in the Supporting Information. Plasma GZR4 concentrations were measured by liquid chromatography–tandem mass spectrometry (LC–MS/MS) with an analytical range of 0.5–200 ng/mL. The glucose-lowering effect of GZR4 was assessed using euglycaemic glucose clamps, which were conducted 24–48 h (Day 2) and 144–168 h (Day 7) after GZR4 administration, and 0–24 h (Day 1) after IDeg administration. Details of the clamp methodology are provided in the Supporting Information. The quality of the conducted clamps was high based on derived clamp quality parameters (Table S1).[23,24]

2.3 | Study analysis

No formal sample size calculation was performed for this first-in-human study. The number of participants was based on studies of similar drugs, specifically Icodec,[25,26] and was considered sufficient by the investigator and the sponsor to meet the study's objectives.

Safety analyses were performed using the safety analysis set (SS), which included all recorded data from participants who received the IP. PK/PD analyses were performed using the PK/PD analysis set (PKS/PDS), including data from participants with evaluable PK/PD data. Participants who received a placebo or IDeg were not tested for PK and, therefore, were not included in the PKS. Participants in Cohort 1 were not tested for PD and, therefore, not included in the PDS.

The incidence of TEAEs was summarized according to the System Organ Class (SOC) and Preferred Term (PT) of the Medical Dictionary for Regulatory Activities (MedDRA), and the Common Terminology Criteria for Adverse Events (CTCAE) in terms of relationship to IP and severity. PK parameters were calculated using a non-compartmental model based on actual blood sampling time. For the PK/PD endpoints, the dose–response relationship was assessed using analysis of variance (ANOVA) analyses with log-transformed $AUC_{0\text{-last}}$, C_{max}, and $AUC_{GIR,T}$ as the dependent variable, and log-transformed GZR4 dose as a fixed effect. All other PK/PD endpoints were evaluated descriptively. Calculation of PK/PD results was estimated using Phoenix WinNonlin (version 8.3). The PD effect of GZR4 over a 1-week dosing interval at steady state was predicted for each participant using a pharmacokinetic-pharmacodynamic model, details of which are provided in the Supporting Information. Demographics and baseline characteristics, other PK/PD parameters and safety analyses were analysed using SAS (version 9.4). Descriptive statistics are presented as mean, standard deviation, median, maximum and minimum, while counts and ranks are presented as frequency and percentage.

3 | RESULTS

3.1 | Disposition, demographics, and baseline characteristics

Out of 160 individuals screened, 43 were enrolled in the study. One participant who received a placebo in Cohort 2 withdrew from the study due to toothache. As a result, 42 participants completed the study. The overall disposition is detailed in Figure S2. The demographic and baseline characteristics of the five cohorts, including age, ethnicity, weight and BMI, were generally similar. All participants were male, with the majority (96.6%) identifying as Han ethnicity (Table 1).

3.2 | Safety

A total of 22 participants (51.2%) experienced 34 TEAEs, which were reported in 17 participants (60.7%) in the GZR4 groups, 4 participants (57.1%) in the placebo group, and 1 participant (12.5%) in the IDeg group. This suggests that the incidence of TEAEs in participants receiving GZR4 was similar to that of a placebo. All TEAEs were mild to moderate in severity, and no CTCAE Grade 3 or greater TEAEs were reported. Most TEAEs were determined to be unrelated to IP

TABLE 1 Demographics and baseline characteristics.

	GZR4					
	1 nmol/kg (*N* = 4)	3 nmol/kg (*N* = 8)	6 nmol/kg (*N* = 8)	12 nmol/kg (*N* = 8)	IDeg (*N* = 8)	Placebo (total, *N* = 7)
Age, years	30.3 ± 2.29	29.4 ± 1.80	27.3 ± 2.09	27.6 ± 1.20	29.0 ± 1.98	26.9 ± 2.15
Ethnicity						
Han	4 (100)	8 (100)	8 (100)	8 (100)	8 (100)	6 (85.7)
Other	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (14.3)
Body weight, kg	64.6 ± 3.53	61.0 ± 1.17	65.0 ± 1.91	62.5 ± 1.91	64.4 ± 2.90	64.4 ± 1.78
BMI, kg/m^2	22.1 ± 0.60	21.0 ± 0.21	21.9 ± 0.42	22.1 ± 0.35	22.0 ± 0.49	22.0 ± 0.38

Note: *N*, Total population. Data are presented as mean ± SE or *n* (%).
Abbreviations: BMI, Body mass index; SE, Standard error.

TABLE 2 Summary of adverse events.

	GZR4					
	1 nmol/kg (*N* = 4)	3 nmol/kg (*N* = 8)	6 nmol/kg (*N* = 8)	12 nmol/kg (*N* = 8)	IDeg (*N* = 8)	Placebo (total, *N* = 7)
Any TEAE	3 (75.0) 3	3 (37.5) 3	6 (75.0) 8	5 (62.5) 15	1 (12.5) 1	4 (57.1) 4
Any CTCAE Grade 3 or greater TEAE	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Any hypoglycaemia	0 (0)	0 (0)	0 (0)	5 (62.5) 9	0 (0)	0 (0)
SAE	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
IP-related TEAE	0 (0)	1 (12.5) 1	2 (25.0) 3	5 (62.5) 9	0 (0)	0 (0)
IP-related hypoglycaemia	0 (0)	0 (0)	0 (0)	5 (62.5) 9	0 (0)	0 (0)
Study discontinuation due to TEAE	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (14.3) 1
Injection site reaction	0 (0)	0 (0)	0 (0)	0 (0) 0	0 (0)	0 (0)

Note: *N*, Total population. Data are presented as *n* (%) m, *n* = number of participants, *m* = number of events.
Abbreviations: CTCAE, Common terminology criteria for adverse events; IDeg, Insulin degludec; IP, Investigational product; SAE, Serious adverse event; TEAE, Treatment-emergent adverse event.

(21 events), while 13 events were possibly or probably related to IP. Hypoglycaemia was the most frequently reported TEAE, occurring only in the highest dose group of 12 nmol/kg GZR4 (9 events in 5 participants), and most of them occurred prior to meals (breakfast or lunch) at 3–4 days following GZR4 administration and resolved after treatment with food or a sugar-containing preparation. All reported hypoglycaemic TEAEs were determined to be IP-related and were classified as CTCAE Grade 2. Additionally, four IP-related AEs in three participants were identified. These events included one case of eosinophilia in the 3 nmol/kg GZR4 group, and three events in the 6 nmol/kg GZR4 group, the latter one consisted of one participant with increased blood bilirubin and one participant with nausea and vomiting. All four IP-related AEs were classified as CTCAE Grade 1. No injection site reactions were observed during the study. In addition, no deaths, serious adverse events (SAEs), or IP-related discontinuations were reported. One participant who received the placebo withdrew from the study prematurely owing to a TEAE of toothache that was determined to be unrelated to IP by the investigator. The majority of participants recovered by the end of the study (Table 2).

3.3 | Pharmacokinetics

The PK results included 28 participants. Plasma GZR4 concentrations increased in a dose-dependent manner with dose escalation (Figure 1). The dose-concentration relationship was approximately linear. Peak concentrations were achieved at 22–32 h post-dose, which was slightly later than that of Icodec (12–24 h) in patients with diabetes,[25–27] indicating a relatively longer absorption process. The C_{max} and $AUC_{0\text{-last}}$ of GZR4 increased dose-dependently from 43.15 to 535.75 ng/mL and 5535.8 to 70134.2 h × ng/mL, respectively, over the dose range of 1 nmol/kg to 12 nmol/kg. In addition, the concentrations of GZR4 were still measurable up to 672 h post-dose. The simulated one-week PK profile of GZR4 at steady state is displayed in Figure S3, which demonstrates that GZR4 exposure covered the full one-week dosing interval at steady state.

3.4 | Pharmacodynamics

The PD results included 38 participants enrolled in Cohorts 2–5. After a single subcutaneous injection of GZR4, main PD

parameters, including $GIR_{max,24-48h}$, $AUC_{GIR,24-48h}$, and $AUC_{GIR,144-168h}$, increased with increasing doses (Figure S4). PD parameters are summarized in Table 3. On Day 7 after the single injection, the AUC of GIR-time ($AUC_{GIR,144-168h}$) was approximately 55%, 69%, and 80% of the Day 2 ($AUC_{GIR,24-48h}$) in the 3, 6, and 12 nmol/kg GZR4 groups, respectively. The model-predicted GIR profile across the full one-week after a single administration of GZR4, displayed in Figure S5, highlights the diurnal fluctuation nature of insulin sensitivity. In contrast, the model-predicted GIR profile of GZR4 at steady state, shown in Figure 2A, demonstrates a relatively even daily distribution of glucose-lowering effect over a one-week dosing interval. In particular, at a dose of 6 nmol/kg, the results suggest that the glucose-lowering effect of GZR4 could be sustained for approximately 1 week (Figure 2B). The $AUC_{GIR,\ 24-48h}$ and $AUC_{GIR,144-168h}$ for the 6 nmol/kg dose of GZR4 (54.91 and 37.84 h × mg/kg/min) were comparable to 2.4 nmol/kg of IDeg ($AUC_{GIR,0-24h}$: 40.59 h × mg/kg/min) (Figure 3). These results suggest that the average daily potency of a 6 nmol/kg dose of GZR4 (calculated from the average AUC of Day 2 and Day 7) was nearly equivalent to that of 2.4 nmol/kg of IDeg (16.8 nmol/kg/week), indicating that GZR4's potency may be approximately 3.2-times greater than that of IDeg when adjusted by the AUC_{GIR} ratio.

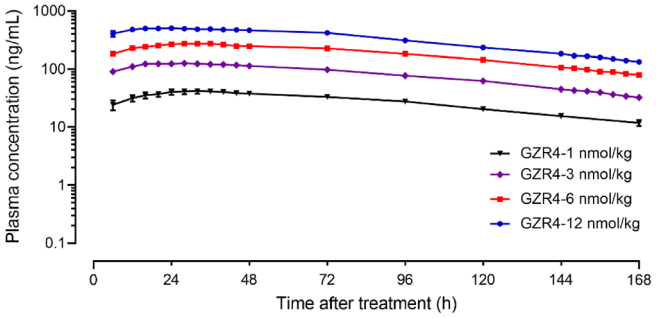

FIGURE 1 Semi-logarithmic transformed mean observed plasma GZR4 concentration-time profiles from 0 to 168 h in healthy participants during a dosing interval of 1 week after a single dose subcutaneous injection. Data are mean ± SE. SE, Standard error.

TABLE 3 Pharmacodynamics parameters of GZR4.

	GZR4				
	3 nmol/kg ($N = 8$)	6 nmol/kg ($N = 8$)	12 nmol/kg ($N = 8$)	IDeg ($N = 8$)[a]	Placebo (total, $N = 6$)
$GIR_{max,24\sim48h}$ (mg/kg/min)	2.14 ± 0.19 (25.70)	2.88 ± 0.25 (25.00)	4.75 ± 0.44 (26.11)	2.55 ± 0.28 (30.98)	0.86 ± 0.02 (6.98)
$T_{GIRmax,24\sim48h}$ (h)	7.5 (2.5, 24.0)[b]	12.5 (6.5, 20.5)[b]	19.0 (4.0, 24.0)[b]	15.5 (10.0, 22.0)	21.5 (16.0, 24.0)[b]
$AUC_{GIR,24\sim48h}$ (h × mg/kg/min)	32.75 ± 2.81 (24.27)	54.91 ± 5.04 (25.95)	83.55 ± 7.66 (25.94)	40.59 ± 5.09 (35.45)	6.49 ± 0.67 (25.12)
$AUC_{GIR,144\sim168h}$ (h × mg/kg/min)	17.98 ± 1.88 (29.64)	37.84 ± 3.49 (26.08)	66.62 ± 5.57 (23.66)	–	6.90 ± 1.29 (45.80)
AUC_{GIR} Ratio (Day 7/Day 2)	~55%	~69%	~80%	–	–

Note: *N*, Total population. Data are presented as mean ± SE (CV) or Median (Min, Max).
Abbreviations: CV, Coefficient of variation; IDeg, Insulin degludec; SE, Standard error.
[a]For IDeg, data are presented on 0-24 h.
[b]Relative to the start time of the clamp.

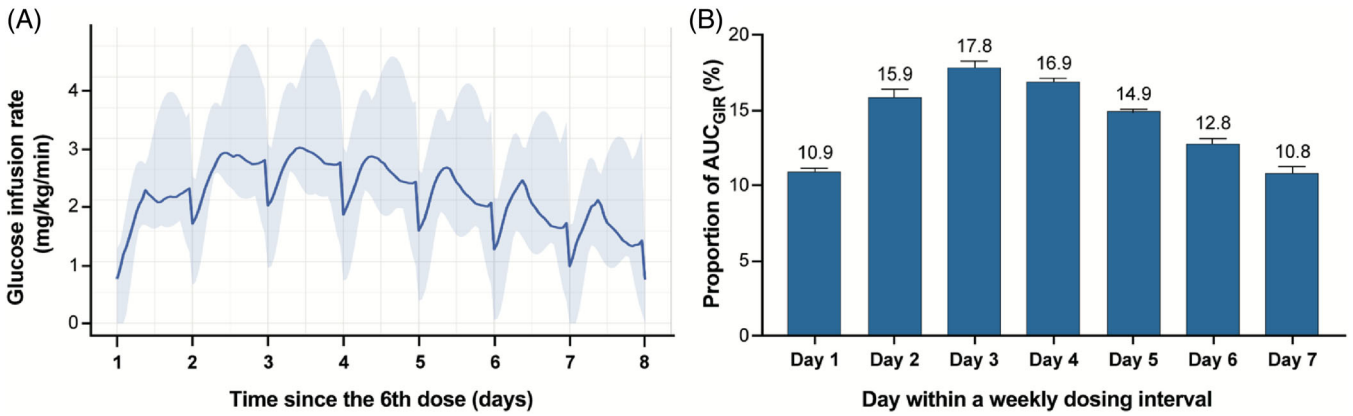

FIGURE 2 Model-predicted GIR profile and distribution of glucose-lowering effect of GZR4 (6 nmol/kg) across 1 week at steady state after six consecutive doses. (A) Model-predicted GIR profiles at steady state. Continuous lines represent the mean, and bands show the 95% prediction interval. (B) Model-predicted daily distribution of glucose-lowering effect across 1 week at steady state. The Y-axis indicates the daily proportion of the AUC_{GIR} for each day of the full week. Data are mean ± SE. AUC, Area under the curve; GIR, Glucose infusion rate; SE, Standard error.

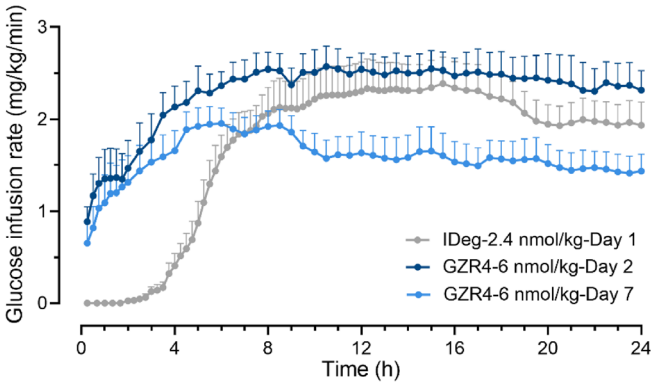

FIGURE 3 Observed GIR profiles following a single dose of GZR4 and IDeg in healthy participants. Data are based on 24-hour GIR profiles from 24 to 48 h (Day 2), and from 144 to 168 h (Day 7) following a single dose of GZR4 (6 nmol/kg) and that from 0 to 24 h (Day 1) following a single dose of IDeg (2.4 nmol/kg) in healthy participants. Data are mean ± SE. GIR, Glucose infusion rate; IDeg, Insulin degludec; SE, Standard error.

4 | DISCUSSION

Basal insulin administered once-weekly has the potential to overcome numerous obstacles associated with the initiation and long-term adherence to insulin therapy. Hence, it has the potential to improve treatment outcomes and quality of life for individuals with diabetes. In this Phase 1a study in healthy Chinese participants, GZR4 was safe and well-tolerated at the doses of 1–12 nmol/kg following a single subcutaneous injection. The antidiabetic effect of GZR4 was demonstrated to last for at least 1 week.

Once-weekly GZR4 was overall safe and well-tolerated in the present study. Owing to the limited sample size and the short duration of this single-dose study, no clear or consistent relationship was found between the occurrence of any TEAEs (or hypoglycaemia) and individual plasma exposure. Consistent with the results observed in other once-weekly insulins, hypoglycaemia was the most common TEAE reported.[25–28] In a separate study involving a single dose administration of insulin BIF, 21 episodes of hypoglycaemia were reported in healthy participants receiving doses of 5 mg or 10 mg.[28] In the present study, nine hypoglycaemic events were reported in 5 participants receiving GZR4. Continuous glucose monitoring was conducted from Day 1 to Day 9 of the treatment period to ensure safety. Two cohorts exhibited a trend towards hypoglycaemia: 2 participants in Cohort 3 (6 nmol/kg: 1 placebo, 1 GZR4) and 9 participants in Cohort 4 (12 nmol/kg: 2 placebo, 7 GZR4). All these participants underwent capillary blood glucose reassessment, but no hypoglycaemic event with a blood glucose level <3.0 mmol/L was confirmed. All 9 reported hypoglycaemic TEAEs were determined to be IP-related, but none were serious. It should also be noted that these events were reported only in participants receiving the highest dose of GZR4 (12 nmol/kg), suggesting that this dose may approach the upper tolerance limit in healthy participants. This resembled the Phase 1 clamp study comparing the PK/PD characteristics of IDeg and insulin glargine, where numerous reported hypoglycaemic events (100 and 95 events in the IDeg and glargine group, respectively) were assumed to be related to the fixed-dose (0.4 U/kg) used in the study.[29]

The euglycaemic clamp technique has been widely recognized as the gold standard for simultaneously assessing the PK and PD properties of insulin formulations.[30,31] Nevertheless, evaluating the glucose-lowering effects of once-weekly insulin by the clamp study is considerably challenging as it is not feasible for participants to remain in a glucose clamp for a whole week. Consequently, clamps are typically conducted two or three times within the weekly dosing interval to assess the glucose-lowering effect of the investigated products.[28,32,33] As shown in the pharmacokinetic data from the initial 1 nmol/kg cohort, the T_{max} of GZR4 was reached between 24 and 48 h. To capture this, euglycaemic clamps in the present study were carried out on Day 2 (24–48 h) to capture the efficacy of the T_{max} and on Day 7 (144–168 h) to capture the weakest efficacy at the end of each dosing interval after a single administration of GZR4. This design enabled the investigation of the anticipated maximal and minimal glucose-lowering capability of GZR4 within a dosing interval.

Single injections of GZR4 displayed a sustained glucose-lowering effect for approximately 1 week in healthy participants. Notably, the ratio of AUC_{GIR} from Day 7 to Day 2 ranged from 55% to 80% across the dose range of 3–12 nmol/kg, with the 12 nmol/kg GZR4 group exhibiting an approximate value of 80% with minimal variation. Moreover, the model-predicted daily distribution of GZR4 exposure after a single dose tended to be evenly distributed over a weekly dosing interval, for instance, 10.8%–17.8% for the 6 nmol/kg dose of GZR4. These results were comparable to those observed in the clamp studies of Icodec in patients with T1DM and T2DM, which were 8.4%–19.6% and 12.0%–16.1%, respectively.[25,26]

The PD profile of GZR4 from the clamp study indicated that a weekly dose of 6 nmol/kg GZR4 was nearly as potent as a daily dose of 2.4 nmol/kg IDeg ($AUC_{GIR,24\text{-}48h}$ and $AUC_{GIR,144\text{-}168h}$ for GZR4 were 54.91 and 37.84 h × mg/kg/min, and $AUC_{GIR,0\text{-}24h}$ for IDeg was 40.59 h × mg/kg/min; AUC ratio for GZR4/IDeg equals 1.14). In contrast, Icodec at a fixed weekly dose of 12 nmol/kg showed markedly lower GIR profiles on Day 2 and Day 7 compared with IDeg at a daily dose of 2.4 nmol/kg.[34] This disparity suggests that GZR4's antidiabetic potency at the same molar concentration may be at least approximately 2-fold greater than that of Icodec; however, it is worth noting that the comparison was made under single and multiple administration, respectively. Nevertheless, the results of the current clamp study are quite consistent with preclinical studies where GZR4 showed comparable reductions in HbA1c at 54 nmol/kg versus Icodec at 162 nmol/kg in streptozotocin-induced T1DM rats, and at 112.5 nmol/kg and 225 nmol/kg in T2DM db/db mice, respectively.[22] One potential explanation for these results was the higher bioactivity of GZR4 relative to Icodec, which was assumed to be greatly associated with the slight variance in their molecular structures. Although these two weekly insulins share the same insulin backbone, GZR4 features an optimized side chain structure with 12 × OEGs as a spacer between a C22 fatty diacid and linker γ-glutamic acid that couples to the insulin backbone, whereas Icodec has 2 × OEGs with a C20 fatty

diacid. During the development of a superior once-weekly basal insulin, it was found that the OEG spacer, which connects the fatty diacid to the insulin backbone, contributes to the potency of acylated insulin. The longer the OEG spacer, the greater the in vivo glucose-lowering efficacy, especially when the number of OEG attempted to 12. This unique molecular design enables GZR4 to retain its relatively stronger insulin receptor binding ability in the presence of HSA. In contrast, Icodec showed almost no binding response under similar conditions, suggesting that the higher in vivo potency of GZR4 might be attributed to its ability to exert activity after binding to albumin in target organs.[22] However, the underlying mechanism still needs further investigation.

While this first-in-human study of GZR4 showed promising results, several limitations were worth noticing. First, the sample size was relatively small, which is typical of most Phase 1 first-in-human studies.[35] Secondly, the study adopted a single-blind design. The glucose input during the clamp test makes it easy for researchers to identify the assigned groups, thus preventing a double-blind design in the study. Additionally, the clamp population in the study were healthy volunteers (HV), who represent an appropriate insulin-sensitive population and have lower intra-individual variability compared with patients with diabetes. Nevertheless, PD data obtained from HV may be confounded by incomplete inhibition of endogenous insulin secretion.[30] However, this was determined to be minimal because mean C-peptide concentrations, which reflect endogenous insulin secretion, were effectively suppressed in all treatment groups. Furthermore, the multiple dosing in the participants, being HV, was limited, and thus, a single injection regimen was adopted. Further PK/PD properties of GZR4 in the target patients with diabetes at steady state will be investigated in the Phase 1b clinical trial (CTR20230491), where multiple injections of GZR4 will be administered to T2DM patients. Finally, it is acknowledged that the present study did not employ a crossover design between GZR4 and IDeg, and that the sample size was relatively small. Therefore, the antidiabetic efficacy results will require further validation in future studies.

5 | CONCLUSION

This study demonstrates that GZR4 has a favourable safety and tolerability profile in healthy Chinese participants. The PK/PD properties of GZR4 suggest its potential as a once-weekly basal insulin with stronger daily glucose-lowering efficacy compared with once-daily IDeg under similar molar concentrations. These findings warrant further investigation of a once-weekly dosing regimen of GZR4 for glycaemic control in patients with diabetes.

AUTHOR CONTRIBUTIONS

WC, RS, LW, MZ, CH, JZ, JP and CT contributed to the study conduct and data analysis. WC, AH, TX, YL, and ZG contributed to the manuscript's writing and editing. WC and CT contributed to the study project management. All authors have read and approved the final manuscript.

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CONFLICT OF INTEREST STATEMENT

WC, CH, JZ, AH, TX, YL, and ZG are Gan & Lee Pharmaceuticals employees. All other authors have no conflicts of interest to declare.

PEER REVIEW

The peer review history for this article is available at https://www.webofscience.com/api/gateway/wos/peer-review/10.1111/dom.16250.

DATA AVAILABILITY STATEMENT

The data supporting the findings of these studies are available on request from the corresponding author, Wei Chen. The data are not publicly available due to privacy or ethical restrictions.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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