diabetesresearchandclinicalpractice 231 (2026) 113061

Contents lists available at ScienceDirect

Diabetes Research and Clinical Practice

journal homepage: www.journals.elsevier.com/diabetes-research-and-clinical-practice

A phase 1b, randomized, open-label study of once-weekly insulin GZR4 in patients with type 2 diabetes mellitus

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ARTICLE INFO

Keywords:
Once-weekly Insulin
GZR4
Type 2 diabetes mellitus
Glycemic control
Pharmacokinetics
Hypoglycemia

ABSTRACT

Aims: To investigate the safety, tolerability, pharmacokinetics, and pharmacodynamics of multiple ascending doses of GZR4 in patients with type 2 diabetes mellitus (T2DM).
Methods: This randomized, active-controlled, phase 1b trial was conducted in adults with T2DM on stable daily basal insulin therapy. Eligible participants were randomized in 3:1 ratio within three cohorts to receive either a fixed once-weekly dose of GZR4 or once-daily insulin degludec (IDeg) subcutaneously for six weeks. Primary endpoints were incidence of adverse events (AEs), serious adverse events (SAEs), and hypoglycemia.
Results: The most commonly reported treatment-emergent AE across all treatment groups was hypoglycemia. No SAEs or severe hypoglycemia was observed. At steady state, the mean C_{max} of GZR4 was 289.0 ± 17.1 to 1,016.0 ± 262.4 ng/mL; mean $AUC_{GZR4,\ 0\text{-}168h}$ ranged from 34,449.6 ± 2,055.7 to 137,064.2 ± 41,496.5 h.ng/mL. Mean change in FPG from baseline to week 6 was −1.77 ± 0.20 to −2.75 ± 0.71 mmol/L for GZR4 groups and −1.12 ± 0.36 mmol/L for IDeg group; corresponding change in HbA1c was −0.38 ± 0.64 % to −0.76 ± 0.14 % versus −0.13 ± 0.21 %.
Conclusions: GZR4 was safe and well tolerated in patients with diabetes in present trial with pharmacokinetic and pharmacodynamic profiles enabling once-weekly dosing.

1. Introduction

Type 2 diabetes mellitus (T2DM) has emerged as a global public health crisis, currently affecting over 400 million individuals and contributing substantially to premature mortality and morbidity worldwide [1–3]. Although a range of oral antidiabetic drugs, and incretin-based therapeutics (both oral and injectable) are available, insulin is eventually required in a remarkable group of patients with T2DM due to progressive decline in pancreatic β-cell function. Among insulin regimens, basal insulin is typically recommended for insulin initiation [4,5]. The development of basal insulin analogs, such as insulin glargine, insulin detemir, and insulin degludec [IDeg], has represented significant progress in diabetes care by offering a more sustained and stable glycemic control [6–11].

Despite these advancements, optimal basal insulin therapy remains a clinical unmet need. The current available daily injections can be inconvenient and uncomfortable for patients [12–14], and often requires frequently dosing and titration adjustments, which may further complicate treatment [6]. The barriers may affect treatment adherence thereby jeopardizing the long-term glycemic control [15,16]. These limitations highlight a pressing need for novel basal insulin regimens that can reduce injection frequency while maintaining effective and sustained glycemic control [17].

Once-weekly basal insulin analogs have emerged as a promising regimen to address above limitations, as they seem to be at least equally efficacious in glycemic management and safe comparable to daily insulin injections in people with T2DM [18]. Insulin icodec (Icodec), the only marketed once-weekly insulin has shown non-inferior efficacy and

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https://doi.org/10.1016/j.diabres.2025.113061
Received 19 November 2025; Received in revised form 12 December 2025; Accepted 17 December 2025
Available online 18 December 2025

safety relative to traditional once-daily basal insulins in head-to-head clinical trials [19,20]. While once-weekly basal insulin formulations present promising therapeutic advantages, their dosing protocols raise clinically relevant concerns. For example, to address the lag in reaching the glucose-lowering steady state, initial one-time loading dose was employed in clinical trials with weekly insulin icodec and insulin Efsitora alfa [21]. Although current evidence indicates no increased hypoglycemia risk during treatment initiation with these protocols, the integration of loading doses fundamentally diverges from traditional basal insulin titration strategies, necessitating rigorous healthcare provider training and patient counseling to reconcile this conceptual shift [21]. These challenges highlight the unmet need for once-weekly insulin engineered with intrinsically optimized pharmacokinetic (PK) and pharmacodynamic (PD) properties. Specifically, once-weekly insulin can more closely mimic endogenous basal insulin distribution patterns to eliminate dependence on loading doses while preserving therapeutic efficacy.

Insulin GZR4 (GZR4), a novel ultra-long-acting insulin analog designed for once-weekly subcutaneous administration, has demonstrated a prolonged glucose-lowering effect in preclinical studies [22]. In the first-in-human phase 1a trial conducted in healthy participants, GZR4 exhibited favorable safety, tolerability, and PK and PD profiles that support its potential for once-weekly administration [23]. Additionally, model-based simulations indicated a uniform glucose-lowering effect of GZR4 over the entire weekly dosing interval, providing additional support for its potential as a once-weekly basal insulin analog [23]. The present phase 1b trial was designed to further investigate the safety, tolerability, pharmacokinetics, and pharmacodynamics of GZR4 in individuals with T2DM following 6 consecutive administrations using a multiple dose-escalation design.

2. Methods

2.1. Study participants

The study enrolled adult participants aged 18 to 65 years with a confirmed diagnosis of T2DM for more than three months. Eligible participants had a body mass index (BMI) between 18.5 and 35 kg/m^2, with a HbA1c level ranging from 6.5 % to 10.0 % [48–86 mmol/mol] (both inclusive) and FPG levels of $\leq$ 13.9 mmol/L at screening. Participants were required to be on stable daily basal insulin ($\geq$ 0.1 U/kg/day) for at least two months prior to enrollment, with or without concomitant oral antidiabetic drugs, which were to be maintained at stable doses for at least one month prior to screening.

2.2. Study design and procedures

This study was a randomized, open label, phase 1b clinical trial conducted across three centers in China between March 22, 2023, and November 1, 2023: Bishan Hospital of Chongqing Medical University, Beijing Luhe Hospital Capital Medical University, and The Second Affiliated Hospital of Xingtai Medical College. This study was conducted in accordance with the ethical principles in the Declaration of Helsinki. The study protocol (ClinicalTrials. gov, NCT06553248) was approved the independent Institutional Review Boards of each participating center before patient enrolment. All participants provided written informed consent.

Thirty-six participants discontinued their prior basal insulin regimen on Day 1 (D1) and were assigned to one of three GZR4 dose cohorts: 6 nmol/kg/week, 8 nmol/kg/week, and 12 nmol/kg/week. Within each cohort, participants were randomized in 3:1 ratio to receive either GZR4 (n = 9) or IDeg (n = 3) (unit-to-unit switch from the previous daily basal insulin dose). Participants in 6 and 8 nmol/kg/week dose cohorts had been on a prior basal insulin dose of 0.1–0.3 U/kg/day, while those in the 12 nmol/kg/week cohort had received $\geq$ 0.3 U/kg/day. Based on data from a previous phase 1a single-dose study and PK modeling, a loading dose was not required for GZR4 to achieve steady-state concentrations. The trial was designed to assess the safety, tolerability, pharmacokinetics, and pharmacodynamics of GZR4, over a 6-week treatment period, followed by a 28-day follow-up. Throughout the study, participants were instructed to maintain a diabetes-specific diet and adhere to appropriate lifestyle interventions for diabetes management. The consumption of caffeinated beverages was prohibited, and participants were strictly advised to avoid smoking, alcohol intake, or any other activities that could potentially interfere with pharmacokinetic assessments or safety evaluations.

2.3. Study endpoints

The study endpoints were designed to evaluate the safety, pharmacokinetics, pharmacodynamics, and immunogenicity of GZR4. The primary endpoint focused on safety, including the incidence of adverse events (AEs) and serious adverse events (SAEs), as well as changes or abnormalities in laboratory tests (hematology, biochemistry, coagulation, and urinalysis), 12-lead electrocardiograms (ECGs), vital signs, physical examinations, injection site reactions, and the frequency and severity of hypoglycemia. Hypoglycemic events were classified in accordance with the American Diabetes Association definitions: Level 1 hypoglycemia: 3.9 mmol/L-3.0 mmol/L; Level 2 hypoglycemia: below 3.0 mmol/L; and Level 3 hypoglycemia: serious events without specific blood glucose boundaries, hypoglycemia requiring assistance from others, or leading to hospitalization, prolonged hospitalization, life-threatening situations, or death.

Secondary endpoints assessed the PK of GZR4, including parameters such as the area under the plasma concentration–time curve (AUC) at various intervals, maximum plasma concentration (C_{max}), trough plasma concentration (C_{trough}), time to maximum concentration (T_{max}). The steady state of GZR4 was considered achieved when there were no significant differences in C_{trough} between consecutive time points. PK analysis samples were collected in GZR4 groups pre-administration on Day 1, 15, 22, 29, and 36; and collected 168 h and 672 h post-administration at specified time points on Day 1 and Day 36, respectively.

PD endpoints included change in FPG, HbA1c, and glycated albumin (GA) from baseline to week 6. In addition, a seven-point self-monitoring of blood glucose (SMBG) profile was performed by all participants on Day 1 (baseline), 2, 36, 37, and 42 to calculate the percentage of them achieving a glycemic target of 3.9–10.0 mmol/L, which was calculated from the number of SMBG values reaching the target divided by seven. Continuous glucose monitoring (CGM) was performed pre-treatment (one week before the first administration) and post-treatment (one week after the last administration) to assess the percentage of time with glucose levels within target range (TIR; 3.9–10.0 mmol/L [70–180 mg/dL]), time above range (TAR; > 10.0 mmol/L [> 180 mg/dL]), and time below range (TBR; < 3.9 mmol/L [< 70 mg/dL]). Immunogenicity was evaluated in participants receiving GZR4 by collecting samples for determination of serum anti-drug antibodies (ADA) specific for GZR4 and their titers.

2.4. Statistical analyses

No formal sample size calculation was conducted in this trial. The sample size was decided based on the consensus of the investigators and sponsors, considering it sufficient to achieve the study objectives. The target enrollment of 12 participants in each cohort was set to ensure adequate control and was deemed adequate to provide descriptive statistics for primary and secondary endpoints.

PK and PD analyses were conducted on the full analysis set (FAS), including all randomized participants who received at least one dose of the investigational product and had at least one evaluable PK or PD parameter. Analysis sets were defined as follows: Safety Analysis Set (SS) included participants receiving at least one dose for AE and laboratory

parameter analysis. Per Protocol Set (PPS) included FAS participants without major protocol deviations. PK-PPS and PD-PPS included participants with evaluable PK and PD data, respectively.

Assessed safety variables were listed and summarized using standard descriptive statistics. Immunogenicity was assessed by summarizing ADA positivity rates across treatment groups, with positive cases listed.

PK data were analyzed descriptively, including plasma concentration–time curves, AUC, and C_{max}. Dose proportionality was evaluated using ANOVA on log-transformed parameters, with 90 % confidence intervals (CI) for dose-normalized geometric means. For the PD analysis parameters such as FPG, HbA1c, and TIR were summarized descriptively. All analyses were performed using SAS version 9.4 and Phoenix WinNonlin version 8.3.

3. Results

3.1. Baseline characteristics

A total of 78 participants were screened, of whom 36 (46.2 %) were met the inclusion criteria and were subsequently randomized (Fig. 1). Baseline characteristics of the randomized participants are summarized in Table 1. Most participants were aged 40 years or older and were predominantly male (66.7 %, 33.3 %, 55.6 %, and 44.4 %, respectively). The mean (± standard deviation [SD]) duration of diabetes ranged from 41.3 ± 19.1 to 105.6 ± 48.4 months. Most participants were of Han ethnicity, comprising 88.9 % to 100 % of each cohort. No statically significant differences in baseline demographic or clinical characteristics were observed among the treatment groups (Table 1).

Table 1
Demographics and baseline characteristics.

	Cohort 1 GZR4 (6 nmol/kg/week) (N = 9)	Cohort 2 GZR4 (8 nmol/kg/week) (N = 9)	Cohort 3 GZR4 (12 nmol/kg/week) (N = 9)	Degludec (total) (N = 9)
Sex (Male)	6 (66.7)	3 (33.3)	5 (55.6)	4 (44.4)
Age (years)	53.1 ± 10.66	53.4 ± 5.46	51.9 ± 9.45	57.8 ± 5.63
Ethnicity (Han)	8 (88.9)	8 (88.9)	9 (100)	8 (88.9)
Body weight (kg)	68.93 ± 9.01	73.07 ± 14.22	71.29 ± 9.89	70.74 ± 9.76
BMI (kg/m^2)	25.6 ± 2.36	27.3 ± 2.70	26.5 ± 3.41	26.8 ± 2.34
Duration of T2DM (months)	42.9 ± 24.02	41.3 ± 19.08	105.6 ± 48.37	41.4 ± 37.29
Baseline insulin dosage (U/kg/week)	1.2 ± 0.25	0.97 ± 0.18	2.53 ± 0.63	1.66 ± 0.82

Data were presented as the mean ± standard deviation (SD) or n (%). BMI = Body mass index, T2DM = Type 2 diabetes mellitus. N = number of participants in a treatment group.

3.2. Safety

The overall completion rates in the GZR4 cohorts were 100 % (9/9) for both the 6 and 8 nmol/kg/week, and 88.9 % (8/9) for the 12 nmol/

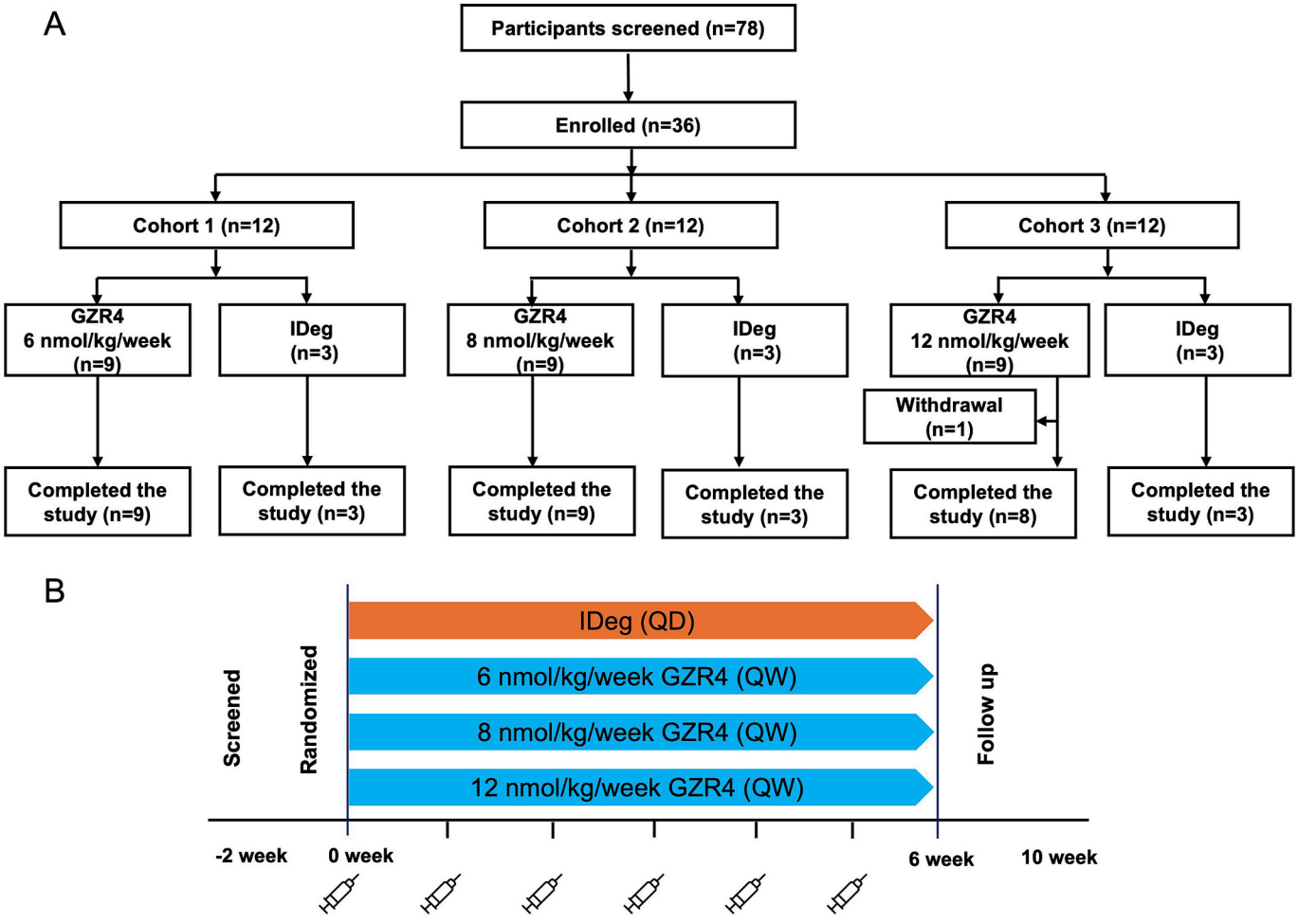

Fig. 1. Flow diagram of the study participants. (A) Participant disposition. (B) Study design. People with T2DM and previously treated with basal insulin; QW: once-weekly fixed doses of GZR4 (6, 8, 12 nmol/kg/week); QD: once-daily insulin degludec equal to participant's daily basal insulin dose prior to enrollment.

kg/week cohort. One participant in the 12 nmol/kg/week cohort discontinued the study due to a treatment-emergent adverse event (TEAE) of level 2 hypoglycemia. The incidence of TEAEs was 77.8 % (7/9) in the 6 nmol/kg/week GZR4 cohort, and 100 % (9/9) in the 8 nmol/kg/week GZR4, 12 nmol/kg/week GZR4, and IDeg groups, respectively (Table 2). No SAEs occurred in any treatment group. All TEAEs were either resolved or recovering by the end of the study.

Hyperglycemia and hypoglycemia were the most commonly reported TEAEs in this study. Level 1 and 2 hyperglycemia (level 1: FPG $\leq$ 13.9 mmol/L and $\geq$ 10.1 mmol/L [$\leq$ 250 mg/dL and $\geq$ 180 mg/dL]; level 2: FPG $>$ 13.9 mmol/L [$>$ 250 mg/dL]), were reported in 5 (55.6 %), 7 (77.8 %), 8 (88.9 %), and 8 (88.9 %) receiving 6, 8, 12 nmol/kg/week GZR4 and IDeg, respectively. Hypoglycemia was reported in all groups: occurring in 66.7 % (6/9) of participants in the 6 nmol/kg/week GZR4 cohort, 77.8 % (7/9) in the 8 nmol/kg/week GZR4 cohort, 55.6 % (5/9) in the 12 nmol/kg/week GZR4 cohort, and 33.3 % (3/9) in the IDeg group. No level 3 hypoglycemia was reported. Injection site reactions were reported in 33.3 % (3/9) of participants in the 8 nmol/kg/week GZR4 cohort but were absent in the 6 and 12 nmol/kg/week GZR4 cohorts, or in the IDeg group.

3.3. Pharmacokinetics

Following the final dose of GZR4 at PK steady state, $C_{GZR4,max}$ (mean $\pm$ standard error [SE]) was 289.0 $\pm$ 17.1 ng/mL, 676.7 $\pm$ 110.5 ng/mL, and 1,016.0 $\pm$ 262.4 ng/mL in the 6, 8, and 12 nmol/kg/week cohorts, respectively. $T_{GZR4,max}$ values at steady state were approximately 32 h in the 6 nmol/kg/week cohort, 28 h in the 8 nmol/kg/week cohort, and 36 h in the 12 nmol/kg/week cohort. The PK profile was shown in Fig. 2 and the PK parameters was summarized in Table S1.

The linear regression analysis of the log-transformed PK parameters ($AUC_{GZR4,\ 0\text{-}168h}$ and $C_{GZR4,max}$) versus the log-transformed GZR4 doses confirmed a positive linear relationship between the PK parameters and the doses after the first administration across the dose ranges of 6, 8, 12 nmol/kg/week. The slope (β) for $AUC_{GZR4,\ 0\text{-}168h}$ and $C_{GZR4,max}$ was 0.93 (90 % CI 0.66–1.19) and 0.99 (90 % CI 0.70–1.28), both within a predefined determination interval of 0.68–1.32 and 0.49–1.52, respectively, indicating approximate dose proportionality. Following the last administration, a same linear regression analysis including two additional PK parameters $AUC_{GZR4,\ 0\text{-last}}$ and $AUC_{GZR4,\ 0\text{-}\infty}$ was also conducted. Across the dose ranges of 6, 8, 12 nmol/kg/week, a positive linear relationship between the log-transformed $C_{GZR4,max}$ and the log-transformed GZR4 doses was observed (β = 1.24 [90 % CI 0.59–1.89]), within the predefined interval of 0.49–1.52. However, no obvious dose-proportional PK relationship was observed for $AUC_{GZR4,\ 0\text{-}168h}$, $AUC_{GZR4,\ 0\text{-last}}$, and $AUC_{GZR4,\ 0\text{-}\infty}$ following multiple administrations.

The results demonstrated that GZR4 reached steady state with a relatively few (1–2 doses) administrations (Fig. S1). In the 6 and 8 nmol/kg/week GZR4 cohorts, comparisons of trough plasma concentrations on Day 8, 15, and 22 revealed no statistically significant differences ($p > 0.05$), indicating that steady state was reached by Day 8. Similarly, in the 12 nmol/kg/week GZR4 cohort, no significant differences ($p > 0.05$) were observed between C_{trough} values on Day 15, 22 and 29, demonstrating that steady state was achieved by Day 15.

Table 2
key safety endpoints and adverse events across different treatment groups.

	GZR4 (6 nmol/kg/week) N = 9 (SS)	GZR4 (8 nmol/kg/week) N = 9 (SS)	GZR4 (12 nmol/kg/week) N = 9 (SS)	Degludec (total) N = 9 (SS)
TEAEs, n (%) m	7 (77.8) 86	9 (100) 75	9 (100) 136	9 (100) 57
IP related TEAEs, n (%) m	6 (66.7) 65	8 (88.9) 34	6 (66.7) 59	4 (44.4) 5
Any SAE, n (%) m	0 (0) 0	0 (0) 0	0 (0) 0	0 (0) 0
IP related SAEs, n (%) m	0 (0) 0	0 (0) 0	0 (0) 0	0 (0) 0
TEAEs leading to study discontinuation, n (%)	0 (0)	0 (0)	1 (11.1)	0 (0)
IP related TEAEs leading to study discontinuation, n (%) m	0 (0)	0 (0)	1 (11.1)	0 (0)
TEAEs leading to death, n (%)	0 (0)	0 (0)	0 (0)	0 (0)
IP related TEAEs leading to death, n (%)	0 (0)	0 (0)	0 (0)	0 (0)
Hypoglycemia, n (%) m	6 (66.7) 53	7 (77.8) 19	5 (55.6) 44	3 (33.3) 3

N = number of participants in a treatment group; n = number of participants experiencing adverse events; %= the proportion of participants experiencing adverse events; m = number of adverse events; SAE = serious adverse event; SS = safety analysis set; TEAE = treatment-emergent adverse event; IP = investigational product.

3.4. Pharmacodynamics

Following the 6-week treatment period, GZR4 demonstrated robust glucose-lowering effects, as evidenced by reductions in mean HbA1c, FPG, and GA across all dose cohorts (Fig. 3 and S2). GZR4 produced dose-dependent reduction in FPG from baseline, with mean $\pm$ SE of 1.77 $\pm$ 0.20 mmol/L, 2.03 $\pm$ 0.66 mmol/L, and 2.75 $\pm$ 0.71 mmol/L in the 6, 8, and 12 nmol/kg/week GZR4 dose cohorts, respectively, compared with a reduction of 1.12 $\pm$ 0.36 mmol/L in IDeg group. Greater reductions in HbA1c were observed with GZR4, ranging from 0.38 $\pm$ 0.64 % to 0.76 $\pm$ 0.14 %, compared with 0.13 $\pm$ 0.21 % in the IDeg group. Mean changes in GA ranged from −0.7 $\pm$ 0.96 % to −1.6 $\pm$ 0.88 % in GZR4 cohort, versus an increase of 0.3 $\pm$ 0.78 % in the IDeg group (Fig. S2).

The robust glucose-lowering efficacy of GZR4 was further supported by SMBG data collected at baseline and on Day 36. On Day 36, the mean (±SE) percentage of participants achieving glycemic targets increased by 11.1 $\pm$ 3.9 %, 10.9 $\pm$ 10.0 %, and 9.7 $\pm$ 8.9 % in the 6, 8, and 12 nmol/kg/week GZR4 cohorts, respectively, whereas a mean decrease of 6.4 $\pm$ 7.8 % was observed in the IDeg group.

CGM data further confirmed these finding. From baseline to Day 36, the GZR4 group exhibited a mean (±SE) increase in TIR of 15.6 $\pm$ 5.6 % to 16.2 % $\pm$ 5.7 %, compared with a 4.3 % $\pm$ 5.5 % increase in the IDeg group. TAR decreased by 15.6 $\pm$ 5.5 % to 20.7 % $\pm$ 6.7 % in the GZR4 group, compared with a 3.4 % $\pm$ 5.5 % decrease in the IDeg group. Meanwhile, TBR increase slightly in the GZR4 group, ranging from 1.3 $\pm$ 1.1 % to 4.4 % $\pm$ 2.5 %, compared with a decrease of 0.89 % $\pm$ 1.3 % in the IDeg group.

3.5. Immunogenicity analysis

At baseline (Day 1), all participants in each GZR4 cohort tested negative for ADA. By Day 71 ($\pm$ 1), ADA positivity was observed in 11.1 % (1/9) of participants in the 6 nmol/kg/week GZR4 cohort, 55.6 % (5/9) in the 8 nmol/kg/week GZR4 cohort, and 33.3 % (3/9) in the 12 nmol/kg/week GZR4 cohort. Among the 9 participants who tested ADA-positive, one participant in the 8 nmol/kg/week GZR4 cohort exhibited an ADA titer of 200, while the remaining 8 participants across all dose groups had an ADA titer of 100.

4. Discussion

This phase 1b study demonstrated that GZR4, a novel once-weekly basal insulin analog, was safe and well tolerated in patients with T2DM previously treated with daily basal insulin. In addition to its favorable safety profile, GZR4 showed a robust glucose-lowering effect across all employed doses, along with PK profiles suitable for once-weekly administrations. In contrast, modest improvements in glucose control were observed in participants receiving once-daily IDeg at doses

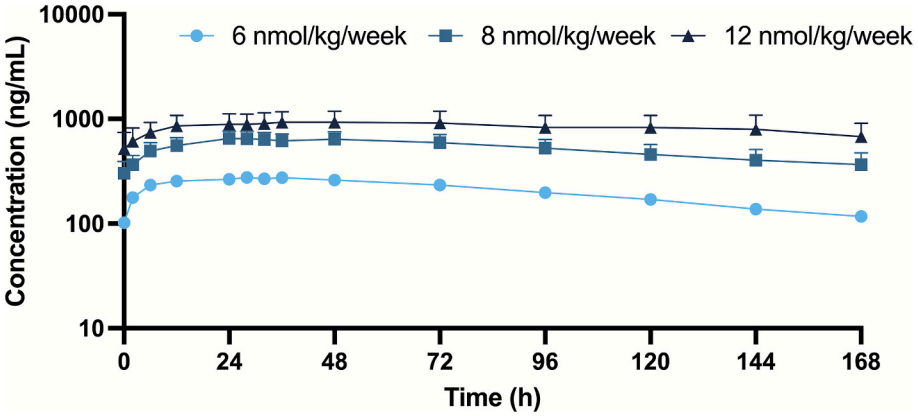

Fig. 2. Semi-logarithmic Plot of GZR4 Plasma Concentration after Last Dose. Data were presented as the mean ± standard error (SE).

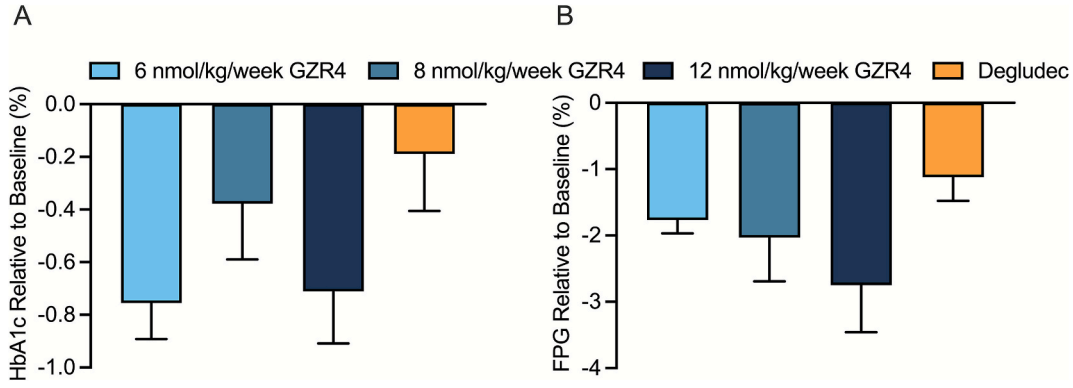

Fig. 3. Glucose-lowering Effect of GZR4 and Insulin Degludec (IDeg). (A) The changes in glycated hemoglobin (HbA1c) and (B) fasting plasma glucose at week 6. Data were presented as the mean ± standard error (SE).

representing unit-to-unit switch from the previous daily basal regimen. These findings highlight the potential of GZR4 as an effective and convenient once-weekly insulin.

In contrast to other once-weekly basal insulins like Icodec, which generally requires 3–4 weeks to reach steady state [24]. GZR4 reaches the pharmacokinetic steady state relatively rapidly, approximately within 1–2 weeks. When the insulin concentration reaches approximately 90 % of the steady-state concentration (after approximately 3 times of $t_{1/2}$), then the clinically relevant steady state is usually considered to be achieved for insulin medicines [21]. Once a steady state is reached, insulin levels will not accumulate further significantly as long as similar doses are administered at intervals appropriate to the half-life of insulins [21]. The rapid attainment of steady state for GZR4 may be attributed to an integrated effect of the half-life, the weekly dose, and the frequency of dosing, and also its higher potency which means relative lower concentration is required to agonize the insulin receptor [21], although the detailed mechanism of action requires further investigation. Nevertheless, this unique PK profile of GZR4 makes it particularly beneficial for patients switching from once-daily basal insulins to once-weekly insulin regimens, as it significantly reduce the risk of transient hyperglycemia and potentially eliminates the need for an additional 50 % once-time loading dose [25]; thereby alleviating the concerns about late-emerging hypoglycemia [26].

The PD analysis revealed that GZR4 provided robust glycemic control across multiple endpoints. In the 12 nmol/kg/week GZR4 cohort, the change in FPG was −2.75 ± 0.71 mmol/L, significantly higher than the change of −1.12 ± 0.36 mmol/L observed in the IDeg group. Despite the relatively short treatment duration, clinically meaningful reductions in HbA1c were also noticed. The 6 nmol/kg/week GZR4 cohort achieved a mean change of −0.76 ± 0.14 % on HbA1c, compared with −0.13 ± 0.21 % in the IDeg group. However, a clear dose–response relationship for the HbA1c reduction was not observed in the GZR4 group. This may be attributed to several factors, including the fixed dosing regimen specified in the study protocol, short treatment duration, and substantial heterogeneity in participants' baseline daily basal insulin doses and glycemic control.

In the present study, both GA and TIR were evaluated. While HbA1c remains the cornerstone for assessing long-term glycemic control, GA offers a complementary measure reflecting average glucose over a shorter period (approximately 2–3 weeks), and TIR provides a direct, dynamic assessment of daily glucose excursions. GZR4 demonstrated substantial improvements in GA compared to IDeg group. Furthermore, the 12 nmol/kg/week cohort exhibited a pronounced increase in TIR from baseline to week 6 (16.22 % ± 5.70 %), substantially exceeding the modest improvement observed in the IDeg group (4.33 % ± 5.51 %). These improvements in TIR were consistent with the proportion of participants achieving the self-measured glycemic target (3.9–10.0 mmol/L). These data demonstrate that improvements in GA and TIR paralleled the reduction in HbA1c across treatment groups, further confirmed the robust effect of GZR4 on glycemic control. Together, the PD results underscore GZR4′s potential to deliver consistent and sustained glycemic control in patients with T2DM.

The safety profile of GZR4 was similar to those observed in other basal insulins' clinical trials, with glycemia related events being the most commonly reported TEAEs. In current trial, the incidence of TEAE in each GZR4 cohort was similar to that observed in the IDeg group, and no SAEs related to the investigational products were reported. Hypoglycemic events were generally mild to moderate in severity across all GZR4 dose cohorts. The observed higher incidence of hypoglycemia with GZR4 compared with IDeg was apparently attributable to the fixed

dosing regimen used in this study, as opposed to a treat-to-target titration strategy in the phase 2 and 3 trials, and also associated with the significant differences in glucose-lowering potency between the two insulins. The potency of GZR4 was not yet determined in current trial and unit definition for GZR4 was artificially claimed to be the same as insulin degludec, i.e., 1 U = 6 nmol. The evaluation of the unit potency of GZR4 will conduct in the further clinical trials. The relatively lower rate of hypoglycemia observed in the 12 nmol/kg/week cohort compared with the 6 and 8 nmol/kg/week cohorts may be attributed to its higher mean baseline weekly insulin dose. This suggests that these patients had greater pre-existing insulin requirement or exposure. Additional contributing factors likely include individual variability in insulin sensitivity and the influence of limited sample size on random variation. In addition, injection site reactions for GZR4 were minimal and manageable, further supporting its favorable tolerability. These results suggest that GZR4 has an acceptable safety profile, however, future phase 2–3 studies should evaluate individualized dosing strategies to mitigate hypoglycemia risk, particularly at higher doses.

The strengths of this trial include its randomized, multicenter design, the low treatment discontinuation rate (one participant discontinued treatment in the highest dose 12 nmol/kg/week cohort), and the design allowing for comprehensive assessment of glucose lowering effect with parameters such as HbA1c, FPG, SMBG profiles, and internationally accepted CGM metrics [27]. Nonetheless, several limitations should be acknowledged. The open-label design of the study may have introduced potential bias in outcome assessment. The six-week treatment duration was insufficient to evaluate the long-term safety, efficacy, and immunogenicity of GZR4. The fixed-dose approach may have contributed to variability in glycemic outcomes and increased the incidence of hypoglycemia. Additionally, the homogenous study population, consisting exclusively of Chinese participants, may limit the generalizability of these findings to other ethnic groups. Given the influence of genetic, metabolic, and lifestyle factors on insulin responsiveness, future studies should aim to include more ethnically and geographically diverse populations to better establish the global applicability of GZR4.

Overall, the data from this phase 1b study provided critical insights for the PK and PD profiles of GZR4, which informed the design of subsequent clinical studies. Another phase 2 treat to target study (ClinicalTrials.gov identifier: NCT06202079) had been completed to characterize the dose titration strategies for GZR4 in patients with T2DM, including both insulin-naïve and basal insulin-switched individuals, and to evaluate the efficacy and safety of GZR4 in the absence of one-time loading dose. This phase 2 trial results suggest effective glycemic control and similar safety of GZR4 versus IDeg in a broad patient population with T2DM, and ADA positivity exhibited no substantial influence on glycemic control. Thus, several phase 3 studies are currently ongoing to confirm the observed clinical benefits and molar efficacy of GZR4 in comparison to current marketed daily basal insulins, and the marketed weekly insulin icodec (ClinicalTrials.gov identifier: NCT07165223, NCT07165223, NCT06767748, NCT06767761).

5. Conclusion

Once-weekly GZR4 was generally safe and well tolerated in this phase 1b trial, with no serious adverse events and a manageable safety profile. Its pharmacokinetic and pharmacodynamic characteristics support the feasibility of once-weekly dosing regimen to achieve stable and sustained glycemic control. These findings underscore GZR4′s potential as a convenient and effective once-weekly basal insulin treatment option for individuals with diabetes. Further clinical development of GZR4 is warranted to confirm its long-term efficacy and safety in larger, more diverse populations, with dose titration strategies designed to optimize glycemic management and clinical outcomes.

Data sharing

The data generated during the current study are available from the corresponding author on request.

Funding

This trial was sponsored and funded by Gan & Lee Pharmaceuticals. The sponsor was involved in study design and data collection only.

CRediT authorship contribution statement

Xuhong Wang: Writing – review & editing, Investigation, Formal analysis, Data curation. **Ye Hu:** Formal analysis, Data curation. **Chengyong Tang:** Investigation, Formal analysis, Data curation. **Chenghu Huang:** Investigation, Formal analysis, Data curation. **Fengxue Guo:** Investigation, Formal analysis, Data curation. **Wei Chen:** Writing – review & editing, Validation, Project administration, Investigation, Formal analysis, Data curation.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgment

The authors would like to thank all investigators and study site personnel who were involved in the conduct of this trial but not listed as authors. The authors would also like to thank Dr. Zhong-Ru Gan for his contribution to this trial and Dr. Jerzy W. Kolaczynski, Dr. Anshun He and Tian Xie for their contribution on the drafting and revision of the manuscript.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.diabres.2025.113061.

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