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Once-weekly insulin GZR4 versus once-daily insulin degludec in Chinese people with type 2 diabetes: A multicenter, open-label, randomized, phase 2 trial

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ABSTRACT

Background: Insulin GZR4 (GZR4) is a once-weekly insulin currently under development. This phase 2 trial assessed the efficacy and safety of once-weekly (QW) GZR4 versus once-daily (QD) insulin degludec (IDeg) in Chinese people with type 2 diabetes (T2D).

Methods: This 16-week, randomized, open-label, multicenter, treat-to-target phase 2 trial consisted of 2 cohorts: Cohort A enrolled insulin-naïve people; Cohort B enrolled people previously treated with basal insulin. Participants were randomly assigned (1:1) to receive GZR4 or IDeg. The primary outcome was the change in HbA1c from baseline to week 16.

Results: Between August 22, and September 22, 2023, 179 participants were enrolled and allocated to Cohort A (n = 83) and Cohort B (n = 96). The estimated mean change in HbA1c from baseline to week 16 was −1.50 percentage points in the GZR4 group vs −1.48 percentage points in the IDeg group in Cohort A (estimated treatment difference [ETD] of −0.02 percentage points [95% CI −0.34 to 0.30], $p = 0.902$), −1.26 percentage points in the GZR4 group vs −0.87 percentage points in the IDeg group in Cohort B (ETD −0.38 percentage points [95% CI −0.66 to −0.11], $p = 0.007$). At week 16, GZR4 and IDeg group showed a similar proportion of participants achieving HbA1c targets. The treatment-emergent adverse events did not differ between two groups. The incidence of hypoglycemia (mostly level 1) was slightly higher in participants receiving GZR4 than IDeg, particularly in Cohort B. No severe hypoglycemia (level 3) was reported.

Conclusions: In this phase 2 trial, once-weekly GZR4 demonstrated effective glycemic control over 16 weeks in both insulin-naïve patients and those previously treated with basal insulin. The incidence of hypoglycemia was slightly higher with GZR4, particularly in the basal insulin-treated group, though no severe hypoglycemic events were reported. These findings warrant further investigation in larger phase 3 trials, which will utilize an adjusted, more precise molar-dose potency of GZR4 to fully characterize its benefit-risk profile.

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1. Introduction

Therapeutic inertia and poor adherence to daily insulin injection is a substantial challenge in managing type 2 diabetes (T2D) [1,2]. Initiation of conventional daily basal insulin is typically delayed by 10–12 years post-diagnosis, with 23–64% of patients initiating treatment at glycated hemoglobin (HbA1c) levels of ≥9.0%; such a delay is associated with grossly elevated risks of long-term complications [3–6]. To overcome these barriers, a variety of once-weekly insulin formulations have been developed [1,2,7–11]. Once-weekly GLP-1 receptor agonists have been shown to enhance treatment persistence and adherence, as well as improved quality of life and greater patient satisfaction [12] [13], thus supporting the consideration of once-weekly insulins as a preferred option for treatment intensification achieve [9,14,15].

The first once-weekly insulin icodec (Icodec) was approved in China in 2024. In the ONWARDS-2 and ONWARDS-3 trial, the reduction in HbA1c was greater with the Icodec versus (vs) once-daily insulin degludec (IDeg), and 93.7% of the participants preferred the weekly injection frequency [16,17]. Two other weekly insulin preparations, i.e., insulin Efsitora alfa (insulin Efsitora) and insulin GZR4 (GZR4), are currently being investigated in clinical trials [18]. Insulin Efsitora is a fusion protein that combines a single-chain insulin variant with a human IgG2 Fc domain [19]. GZR4 is an acylated insulin analog that protracts time-action through reversible, high-affinity binding to human serum albumin (HSA) by conjugating a 22-carbon fatty diacid side chain and a 12-OEG linker to a modified insulin backbone (A14E, B16H, B25H, B29K, desB30 human insulin) [20]. The unique structural design of GZR4 enables it to bind to and activate insulin receptors even when bound to HSA [20]. In contrast, Icodec exhibits negligible binding affinity for insulin receptors in its albumin-bound state [20]. An ideal once-weekly basal insulin would need to provide fast and effective glycemic control, particularly for those patients switching from once-daily basal insulins to once-weekly insulin to prevent possible transient hyperglycemia during the initial transition period [21]. This is typically achieved through the injection of a one-time loading dose for the first marketed weekly Icodec [22].

GZR4 is a once-weekly basal insulin analog with a half-life of approximately one week following subcutaneous injection [18], providing consistent glucose-lowering coverage over a 7-day period [23]. A previous phase 1b trial indicated that GZR4 reaches steady state rapidly after only 1–2 injections, suggesting a potential benefit for quickly achieving therapeutic insulin concentrations during treatment transitions, without the need for a loading dose [24]. Here, we report the findings of a phase 2, treat-to-target clinical trial designed to investigate and compare the efficacy and safety of once-weekly GZR4 vs once-daily IDeg in T2D patients.

2. Materials and methods

2.1. Trial design

This is a 16-week, randomized, open-label, active-controlled, multicenter, treat-to-target phase 2 trial with two cohorts. Cohort A involved people with T2D inadequately controlled with oral hypoglycemic agents (OHAs), i.e., insulin naïve people; Cohort B involved people with T2D inadequately controlled by a combination of OHAs and basal insulin, i.e., people previously treated with basal insulin. The trial was completed at 30 sites (clinical research centers and hospitals) in China. The trial was conducted in compliance with the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) guidelines and the Declaration of Helsinki. The trial protocol was approved by independent review boards or independent ethics committees at all participating centers. Informed consent was obtained from all participants prior to randomization. The trial was registered at ClinicalTrials.gov (NCT06202079).

2.2. Participants

Eligible participants were adults (aged 18 to 75 years, inclusive) with T2D and a body mass index (BMI) of 18–35 kg/m^2, inclusive, an HbA1c level of 7.5–10.0%, inclusive, and a fasting plasma glucose (FPG) level of ≥7.2 mmol/L at screening. In Cohort A, participants must have received stable doses of metformin, with or without concomitant use of another OHA (e.g., dipeptidyl peptidase-4 inhibitors [DPP4is], α-glucosidase inhibitors, or sodium–glucose cotransporter-2 inhibitors [SGLT2is]), for at least 90 days prior to screening. In Cohort B, participants must have received stable doses of metformin, with or without concomitant use of another one of OHAs (e.g., DPP4is, alpha-glucosidase inhibitors, SGLT2is, or glucokinase activators), along with basal insulin (once- or twice-daily) at a total daily dose of 10–50 units, for at least 90 days prior to screening. Detailed inclusion and exclusion criteria are shown in the supplementary materials (Part 1–2).

2.3. Randomization and masking

In each cohort, eligible participants were randomized 1:1, using a computer-generated random sequence, to receive either once-weekly GZR4 or once-daily IDeg. Randomization was conducted separately for Cohort A and Cohort B. Randomization in Cohort A was stratified by concomitant use of OHA other than metformin at screening. Randomization in Cohort B was stratified by basal insulin type and baseline HbA1c level (<8.5% or ≥8.5%) at screening. Concealment was conducted using an interactive web response system (IWRS), which ensured balance between treatment groups.

This study employed an open-label design due to practical and scientific considerations in comparing an investigational once-weekly insulin with an established daily comparator IDeg. A double-blind approach was not feasible because of apparent differences in delivery devices between treatment arms from different manufacturers. Implementing a double-dummy design would have required daily placebo injections in both groups, increasing injection burden and also contradicting the therapeutic objective of once-weekly dosing. Accordingly, an open-label approach was adopted to preserve operational feasibility and clinical relevance.

To mitigate potential bias, several methodological safeguards were incorporated. Dose titration followed a strict protocol-driven treat-to-target algorithm, minimizing investigator discretion. The primary efficacy endpoint (change in HbA1c) was an objective laboratory measure unlikely to be influenced by lack of blinding. In addition, continuous glucose monitoring (CGM)-derived metrics (e.g., time in range) provided further objective glycemic data for endpoint assessment.

2.4. Procedure

The trial consisted of a 2-week run-in period, a 16-week treatment period, and 4-week safety follow-up (Fig. S1). During the screening period, participants were trained in disease monitoring and management, the use of trial diaries, and trial procedures. Participants were provided with a glucose meter to self-monitor blood glucose (SMBG) and instructed to perform SMBG assessment before breakfast and at any time when hypoglycemia was suspected. Participants were also provided with and trained on Freestyle Libre H CGM system (Abbott) to be worn at the baseline (weeks −2 to −1) and the last 2 weeks of treatment (weeks 15 to 16). GZR4 was administered immediately prior to breakfast on the same day each week. The starting dose of GZR4 was 40 U in Cohort A and 70 U in Cohort B (Table S1). The starting dose of IDeg was 10 U in Cohort A, while in Cohort B, it was equivalent to the previously taken daily basal insulin dose. In this trial, 1 U was defined as 6 nmol of each insulin. GZR4 and IDeg were titrated weekly by the investigator to reach the prebreakfast blood glucose target range of 4.4–7.2 mmol/L. The adjustment algorithm, which was based on the three-preceding patient-measured blood glucose levels, is summarized in Tables S2 and

S3. Background OHAs were continued throughout the trial.

2.5. Outcomes

The primary outcome was the change in HbA1c from baseline to week 16 (tested in a central laboratory). Key secondary efficacy outcomes included the change in FPG from baseline to week 16, HbA1c target attainment rate (≤6.5% and <7.0%), mean blood glucose levels and variability (measured by four 7-point [before breakfast, 2 h after breakfast, before lunch, 2 h after lunch, before dinner, 2 h after dinner and before bedtime] based on SMBG 1 day prior to visits at week 0, 4, 8, 16). The CGM-derived data included proportion of time spent with glucose concentration within the range (TIR, 3.9–10.0 mmol/L), above the range (TAR1, 10.1–13.9 mmol/L; TAR2, >13.9 mmol/L), and below the range (TBR1, 3.0–3.8 mmol/L; TBR2, <3.0 mmol/L) from week 15 to week 16 were also evaluated.

Safety outcomes included treatment-emergent adverse events (TEAEs) and hypoglycemic events. The severity of TEAEs was determined by the investigator based on the Common Terminology Criteria for Adverse Events (CTCAE) V5.0. Hypoglycaemic events were graded based on blood glucose with reference to the American Diabetes Association Standards of Care in Diabetes [25]: level 1, <3.9 mmol/L and ≥3.0 mmol/L; level 2, <3.0 mmol/L; level 3, serious events without specific blood glucose boundaries, hypoglycemia requiring help from others or leading to hospitalization, prolonged hospitalization, life-threatening, or death.

2.6. Statistical analysis

This was an exploratory phase 2 study to estimate the difference in efficacy and safety between GZR4 and IDeg, and was not designed or powered to test formal statistical hypotheses of non-inferiority or superiority. In accordance with the exploratory nature of this phase 2 study, no multiplicity adjustment was made in the analyses of current trial.

The sample size calculation was based on the precision of estimating the mean difference between groups within each cohort, rather than hypothesis testing. The sample size requirement was estimated for the two cohorts independently using PASS software (v21.0), included: 1) mean difference of 0.4% in HbA1c change from baseline to week 16 between the two groups; 2) standard deviation (SD) of HbA1c change from baseline to week 16 at 0.85% in Cohort A, and at 0.89% in Cohort B; 3) power of 80% and two-sided alpha of 0.05; 4) 10% dropout rate. The calculation yielded 80 and 90 patients in Cohort A and B, respectively. The sample size of each cohort was selected to provide preliminary, clinically informative signals in both insulin-naïve and insulin-treated populations to inform the design of subsequent confirmatory trials.

The targeted estimand was defined according to the treatment policy strategy. The primary analysis for the primary efficacy endpoints were analyzed using analysis of covariance (ANCOVA; group and stratification factors as fixed effects, age, and baseline HbA1c as covariates) in a modified intent-to-treat population that included all randomized participants having HbA1c at week 16. Missing data were not imputed. A sensitivity analysis of the primary endpoint was conducted via the ANCOVA model described above, with the modification that missing data at week 16 were imputed via the multiple imputation method. The primary analysis for some secondary efficacy endpoints was analyzed using mixed model repeated measures model (MMRM) and detailed in the supplementary materials. Safety analysis set (SS) were analyzed in a population that included all participants who received at least one dose of the investigational product. All statistical analyses were performed using SAS software version 9.4. Two-side p value of <0.05 was considered statistically significant.

3. Results

3.1. Cohort A

Between 22 August and 22 September 2023, a total of 139 participants were screened, and 83 participants (mean age 57.5 years, 44 men, mean HbA1c 8.18%, mean T2D duration 76 months) were randomized. Of the 83 participants, 42 were randomized to the GZR4 group, and 41 were randomized to the IDeg group. 78 (94%) participants completed the study and 5 (6.0%) withdrew prematurely (Fig. 1). One participant in GZR4 group withdrew due to an AE of the injection site reaction that manifested as erythema. The withdrawal of other participants was necessitated by their need to discontinue participation (Table S4). Demographic and baseline characteristics of the participants in the two groups are shown in Table 1.

The estimated mean HbA1c change from baseline to week 16 was −1.50 percentage points in the GZR4 group and −1.48 percentage points in the IDeg group in the modified intent-to-treat population, with an estimated treatment difference (ETD) of −0.02 percentage points (95% confidence interval [CI], −0.34 to 0.30; $p = 0.902$) (Fig. 2A). Sensitivity analysis via the analysis of ANCOVA model with the modification that missing data at week 16 were imputed via the multiple imputation method also confirmed the robust glucose-lowering effect of GZR4 (Table S5).

All analyses of secondary endpoints were pre-specified as exploratory. At week 16, the proportion of participants who achieved HbA1c target of <7.0% was 59.5% in the GZR4 group and 70.7% in the IDeg group (odds ration [OR] 0.61; 95% CI, 0.23 to 1.67; $p = 0.363$) (Fig. 2B). Nevertheless, the proportion of participants who achieved HbA1c target of ≤6.5% was 38.1% in the GZR4 group and 29.3% in the IDeg group (OR 1.98, 95% CI, 0.71 to 5.50; $p = 0.173$) (Fig. 2B and Table 2). In addition, numerically higher percentages of participants receiving GZR4 than those receiving IDeg reached a HbA1c target of ≤6.5% without clinically significant or severe hypoglycemia (estimated percentage, 38.1% vs 29.3%) (Fig. 2B). Results for HbA1c target attainment (<7.0% and ≤6.5%) without hypoglycemia are shown in Table S6.

The estimated mean reduction in FPG from baseline to week 16 was 2.58 mmol/L in the GZR4 group and 2.71 mmol/L in the IDeg group, with a treatment difference of 0.13 mmol/L (95% CI, −0.47 to 0.73; $p = 0.658$) (Fig. 2C). The estimated mean change in TIR was 31.36%-points in the GZR4 group (71.8% vs 46.7%) and 24.55%-points in the IDeg group (73.1% vs 56.0%), with an ETD of 6.81% (95% CI, −5.94 to 19.55; $p = 0.290$) (Fig. 2D). TAR1 and TAR2 decreased by 22.82% and 11.47% in the GZR4 group versus 18.37% and 7.59% in the IDeg group. Meanwhile, TBR1 and TBR2 increased slightly in the GZR4 group (2.81% and 0.12%) compared with increase of 1.33% and 0.07% in the IDeg group.

The estimated change of mean SMBG from baseline to week 16 was −1.59 mmol/L in the GZR4 group and −2.05 mmol/L in the IDeg group (ETD 0.46 mmol/L, 95% CI, −0.52 to 1.43; $p = 0.354$) (Table 2 and Fig. S2). The mean weekly dose at week 15–16 was 483.6 nmol in the GZR4 group and 994.8 nmol in the IDeg group ($p < 0.001$) (Fig. 2E and Table 2).

A total of 55 participants in Cohort A experienced 161 TEAEs: 108 events in the GZR4 group and 53 in the IDeg group, and the incidence of TEAE for each group were 71.4% (30 participants of 42) and 61.0% (25 of 41), respectively. A total of 15 participants experienced 50 treatment-related AEs (TRAEs): 45 (23.8%, 10 of 42) events in the GZR4 group and 5 (12.2%, 5 of 41) events in the IDeg group (Table 3). Two serious adverse events (SAEs) were reported in two participants (4.8%, 2 of 42) in the GZR4 group (lacunar cerebral infarction [1], unstable angina pectoris [1]), but none were deemed related to the investigational drug. The most common TRAE (excluding hypoglycemic events) was injection site pruritus (3 participants [7.1%], 15 events) in the GZR4 group. TRAEs (injection site erythema, injection site swelling, and injection site pruritus) resulted in drug discontinuation in one participant (2.4%).

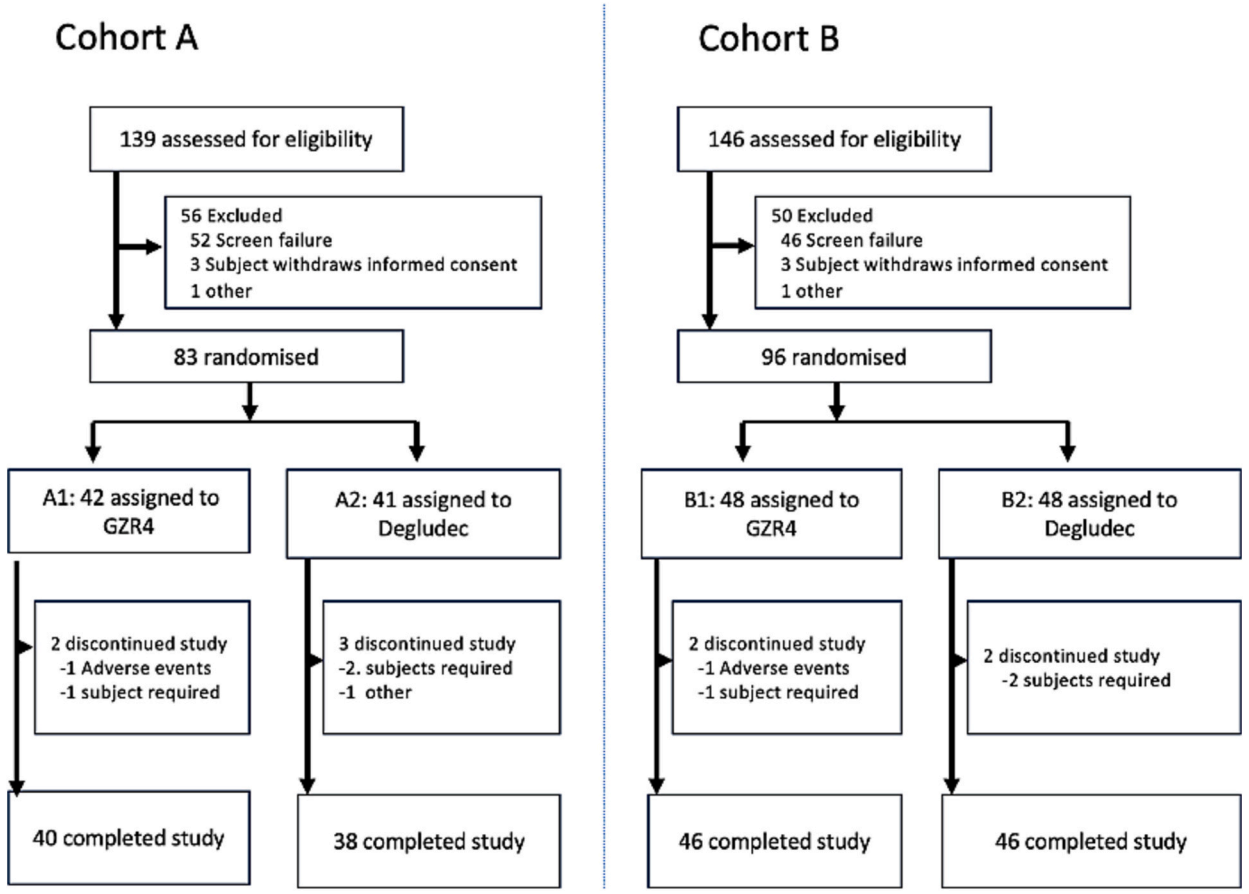

Fig. 1. Flow diagram of participants.

Injection site reactions were observed in 4 participants with 18 events, all of which were grade 1 or 2 according to the CTCAE classification. Of these, 17 events occurred in the GZR4 group (7.1%, 3 of 42) and one event in the IDeg group (2.4%, 1 of 41).

The incidence and rate of hypoglycemic episodes are presented in Table 2. Hypoglycemic events were reported by 20 participants: 17 (40.5%) in the GZR4 group and 3 (7.3%) in the IDeg group. All of them were level 1 hypoglycemia, but only one level 2 hypoglycemia occurred in the GZR4 group. No deaths or severe hypoglycemic episodes were reported. The rate of hypoglycemia alert (level 1) was 6.25 and 0.50 events per patient-year of exposure for GZR4 and IDeg, respectively. The rate of combined clinically significant (level 2) and severe (level 3) hypoglycemia was 0.08 and 0.0 events per patient-year of exposure for GZR4 and IDeg, respectively.

Other safety measures, including clinical laboratory values and immunogenicity, did not indicate any unexpected or concerning safety findings with GZR4 treatment compared with IDeg. Additionally, no statistically significant differences ($p = 0.062$) in body weight gain were noted between GZR4 (1.49 kg) and IDeg (0.70 kg) at week 16, with a treatment difference of 0.79 kg (95% CI −0.04, 1.63).

3.2. Cohort B

In Cohort B, 96 participants (mean age 58 years, 55 men, mean Hb1Ac 8.40%, mean T2D duration 125 months) were randomized to the GZR4 group (n = 48) or the IDeg group (n = 48). Ninety-two (95.8%) participants completed the trial, and 4 (4.2%) withdrew prematurely (1 due to the adverse events of skin reaction and pruritus, and 3 due to participant withdrawal) (Table S4). Demographic and baseline characteristics of the participants in the two groups are shown in Table 1.

The estimated mean HbA1c change from baseline to week 16 was −1.26% in the GZR4 group and −0.87% in the IDeg group in the modified intent-to-treat population, with an ETD of −0.38% (95% CI, −0.66 to −0.11; $p = 0.007$) (Fig. 3A and Tables S2–3). The consistency of the results observed in the sensitivity analysis and in the primary analyses lends support to the robustness of the findings (Table S5).

The proportion of participants who achieved Hb1Ac target of <7% was 52.1% in the GZR4 group and 29.2% in the IDeg group, with a treatment difference of 19.36% (95% CI, 1.30 to 37.41; $p = 0.038$) (Fig. 3B). The proportion of participants who achieved Hb1Ac target of ≤6.5% was 25.0% in the GZR4 group and 10.4% in the IDeg group, with a treatment difference of 13.58% (95% CI, −1.18 to 28.34; $p = 0.074$) (Fig. 3B). In addition, numerically higher percentages of participants receiving GZR4 than those receiving IDeg reached a HbA1c target of ≤6.5% without clinically significant or severe hypoglycemia (estimated percentage, 25% vs 10.4%) (Fig. 3B). Results for HbA1c target attainment (<7.0% and ≤6.5%) without hypoglycemia are shown in Table S6.

The estimated mean reduction in FPG from baseline to week 16 was 2.28 mmol/L and 2.32 mmol/L, respectively (ETD 0.04 mmol/L, 95% CI, −0.51 to 0.60; $p = 0.87$) (Fig. 3C). The estimated mean change in TIR from baseline to week 16 was 24.48% in the GZR4 group (67.0% vs 42.9%) and 21.30% in the IDeg group (65.1% vs 44.0%), with a treatment difference of 3.18% (95% CI, −6.38 to 12.74; $p = 0.510$) (Fig. 3D). TAR1 and TAR2 decreased by 12.78% and 15.55% in the GZR4 group versus 9.87% and 14.49% in the IDeg group. Meanwhile, TBR1 and TBR2 increased slightly in the GZR4 group (3.39% and 0.45%) compared with increase of 2.49% and 0.57% in the IDeg group.

The estimated mean change of SMBG from baseline to week 16 was −2.30 mmol/L in the GZR4 group and −2.01 mmol/L in the IDeg group (ETD −0.29 mmol/L, 95% CI, −1.06 to 0.48; $p = 0.459$). In addition, the SMBG data from the initial treatment period demonstrated that fasting SMBG were lower in GZR4 group than IDeg group (Fig. S4). The mean

Table 1
Demographic and baseline characteristics of the participants.

	Cohort A			Cohort B		
	GZR4 (N = 42)	IDeg (N = 41)	Total (N = 83)	GZR4 (N = 48)	IDeg (N = 48)	Total (N = 96)
Age, years	57.6 (10.92)	57.4 (9.38)	57.5 (10.13)	57.7 (8.97)	58.2 (8.80)	58.0 (8.84)
Male sex, n (%)	23 (54.8)	21 (51.2)	44 (53.0)	27 (56.3)	28 (58.3)	55 (57.3)
Ethnicity, n (%)						
Han	42 (100.0)	40 (97.6)	82 (98.8)	47 (97.9)	46 (95.8)	93 (96.9)
Other	0 (0.0)	1 (2.4)	1 (1.2)	1 (2.1)	2 (4.2)	3 (3.1)
Body weight (kg)	71.06 (15.54)	69.91 (11.76)	70.49 (13.73)	68.73 (10.76)	70.50 (10.05)	69.61 (10.40)
BMI (kg/m^2)	26.35 (3.71)	26.03 (3.35)	26.19 (3.52)	25.16 (2.88)	25.84 (2.88)	25.50 (2.88)
Duration of diabetes, months	79.91 (71.33)	72.24 (51.03)	76.12 (61.88)	129.01 (74.69)	120.82 (75.79)	124.92 (74.96)
FPG (mmol/L)	9.10 (2.21)	9.60 (1.96)	9.35 (2.1)	8.88 (2.22)	8.90 (2.17)	8.89 (2.19)
HbA1c (%)	8.23 (0.65)	8.12 (0.71)	8.18 (0.68)	8.35 (0.69)	8.45 (0.75)	8.40 (0.72)
<8.5%	29 (69.0)	27 (65.9)	56 (67.5)	27 (56.3)	25 (52.1)	52 (54.2)
≥8.5%	13 (31.0)	14 (34.1)	27 (32.5)	21 (43.8)	23 (47.9)	44 (45.8)
Baseline insulin dose- U/day	NA	NA	NA	16.5 (6.7)	17.4 (6.26)	17.0 (6.47)

Data are mean (SD) unless otherwise indicated. Cohort A: insulin-naive participants; Cohort B: participants previously treated with basal insulin. GZR4 = insulin GZR4, IDeg = insulin degludec; BMI = body weight index; FPG = fasting plasma glucose; HbA1c = glycated hemoglobin. 1 U = 6 nmol. NA = Not applicable.

weekly dose at weeks 15–16 was 531.9 nmol in the GZR4 group and 1308.9 nmol in the IDeg group ($p < 0.001$) (Fig. 3E).

A total of 69 participants in Cohort B experienced 165 TEAEs: 34 in the GZR4 group and 35 in the IDeg group, with the incidence of TEAE were 70.8% (34 of 48) and 72.9% (35 of 48), respectively. A total of 14 participants experienced 32 TRAEs: 11 (22.9%,11 of 48) in the GZR4 group and 3 (6.3%, 3 of 48) in the IDeg group. Three SAEs were reported in three participants (3.1%): 2 (4.2%) the GZR4 group (anal fistula and palpitations) and 1 (2.1%) in the IDeg group (cerebral infarction); none were deemed related to the investigational drug. One TRAE (pruritus and skin reaction) in the GZR4 group resulted in drug discontinuation. The most common TRAE (excluding hypoglycemia) was pruritus at the injection site, with a rate of 8.3% (4 participants) and 5 events in the GZR4 group. A total of 12 injection site reactions were observed, all of which occurred in the GZR4 group.

The incidence and rate of hypoglycemic episodes are presented in Table 2. Hypoglycemic events were reported by 37 participants (38.5%): 30 (62.5%) in the GZR4 group and 7 (14.6%) in the IDeg group. The rate of hypoglycemia alert (level 1) was 10.78 and 1.05 events per patient-year of exposure for GZR4 and IDeg, respectively. The rate of combined clinically significant (level 2) and severe (level 3) hypoglycemia was 0.45 and 0.0 events per patient-year of exposure for GZR4 and IDeg, respectively. No deaths or severe hypoglycemic episodes were reported.

Other safety measures, including clinical laboratory values, and immunogenicity, did not indicate any unexpected or concerning safety findings with GZR4 treatment compared with IDeg. Additionally, no statistically significant differences ($p = 0.140$) in body weight gain were noted between GZR4 (0.37 kg) and IDeg (−0.16 kg) at week 16, with a treatment difference of 0.53 kg (95% CI −0.18, 1.23).

4. Discussion

This exploratory treat-to-target phase 2 trial demonstrated that, overall, once-weekly insulin GZR4 provided robust glucose-lowering efficacy in both insulin-naïve patients and those previously treated with daily basal insulin. Notably, in Cohort B, there was a numerically greater reduction in HbA1c with GZR4, along with a numerically higher HbA1c targets achievement. However, the incidence of hypoglycemic events, mostly level 1, was higher in the GZR4 group compared to the IDeg group, yet no severe hypoglycemic events were reported.

The proportion of participants achieving the HbA1c target of <7.0% (52.1% vs 29.2%, $p = 0.038$) and ≤6.5% (25% vs 10.4%, $p = 0.074$) was both numerically higher with GZR4 compared to IDeg in Cohort B. Notably, the results for HbA1c target attainment of ≤6.5% without hypoglycemia was comparable between GZR4 and IDeg group. However, the substantial difference in HbA1c reduction, together with the higher proportion of participants achieving HbA1c target, should be evaluated in the context of its currently accompanied increased hypoglycemia incidence. Additionally, in line with the observed improvements in glucose control as measured by HbA1c, substantial improvements in TIR were also achieved in both cohorts. No statistically significant differences were observed between weekly GZR4 and IDeg, suggesting that both treatments were equally effective for improving the TIR in current trial condition. While GZR4 suggested potential benefits in in several secondary endpoints, including in HbA1c reduction efficacy, these findings should be interpreted with caution due to the absence of multiplicity adjustment and the exploratory design of current trial.

Based on the limited data from previous phase 1 trials, the present phase 2 trial adopted the conventional insulin molar dose conversion of 1 U equivalent to 6 nmol. Thus, under the treat-to-target titration protocol of the current trial, the total weekly molar dose of GZR4 required to achieve protocol-specified glycemic targets was significantly lower than that of IDeg (483.6 vs 994.8 nmol in Cohort A; 531.9 vs 1308.9 nmol in Cohort B). Using an established joint modeling approach [26] that correlates HbA1c response with insulin dose after long-term treatment in patients with T2D, the estimated potency of GZR4 relative to IDeg was 2.01-fold in insulin-naïve participants and 3.20-fold in insulin-treated participants in this phase 2 trial, with an average relative potency of approximately 2.6-fold. This result is basically consistent with the potency estimation from the first-in-human phase 1a single ascending dose clamp study in healthy Chinese participants, where the data indicated that GZR4 displays a 2.8-fold relative potency compared to IDeg [23]. This preliminary potency of GZR4 will be further validated in the ongoing phase 3 clinical trials (NCT06767735, NCT06767748, NCT06767761) and the dedicated steady-state clamp study (NCT07146347).

The unique molecular design of GZR4 determines its distinct pharmacokinetics and pharmacodynamics, which results in the difference in molar dose requirement to reach the same treatment target. While its albumin-binding properties prolong the half-life, a key advantage of GZR4 is its retained bioactivity in the albumin-bound state [20], which is the major existing form within circulation, contributing to a marked enhancement in potency. Mechanistically, the incorporation of an extended linker (12-OEG) increases the special distance between the insulin backbone and the albumin anchor, thereby diminishing steric hindrance and enabling unhindered binding of the HSA coupled insulin backbone to the insulin receptor. The detailed mechanism of action of GZR4, derived from the ongoing research, is scheduled for publication in the near future.

The two groups did not differ in the overall incidence of TEAEs, as well as the incidence of SAEs or severe hypoglycemic events. Injection site reactions, including pruritus, were more prevalent in the GZR4 group. These reactions were typically mild to moderate in severity, which will be further carefully evaluated in the large-scale phase 3 trials with sufficient power and longer treatment duration.

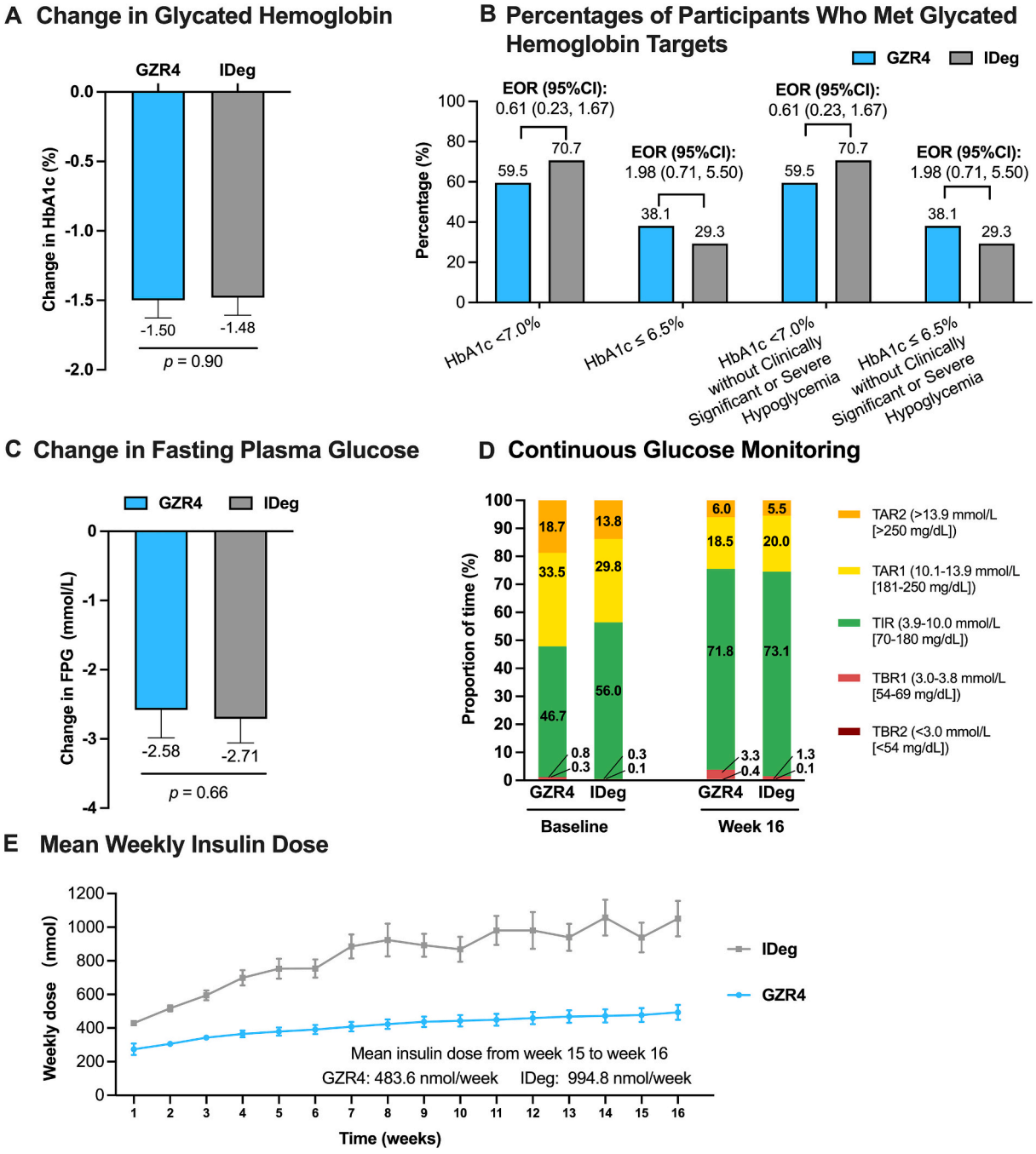

Fig. 2. Efficacy measures in Cohort A (insulin-naïve patients). Panel A: mean change in HbA1c from baseline to week 16. Panel B: at week 16, the proportion of participants who achieved HbA1c target of <7% or ≤6.5% and the proportion of participants who achieved HbA1c target of <7% or ≤6.5% without clinically significant (level 2) or severe (level 3) hypoglycemia. Panel C: mean change in FPG from baseline to week 16. Panel D: TIR, TAR, and TBR at baseline and during the last 2 weeks of treatment (weeks 15 and 16). Panel E: mean weekly insulin dose over the 16-week treatment period. 1 U = 6 nmol. Error bars: standard errors. GZR4 = insulin GZR4, IDeg = insulin degludec, HbA1c = glycated hemoglobin, FPG = fasting plasma glucose, TIR = time in range, TAR = time above range, TBR = time below range.

It is worth noting that the GZR4 group had a higher incidence of hypoglycemia (40.5% vs 7.3% in Cohort A, 62.5% vs 14.6% in Cohort B) and clinically significant (level 2) hypoglycemia in current trial. The higher incidence of overall hypoglycemia observed with GZR4 compared to the comparator, particularly in patients previously treated with basal insulin (Cohort B), constitutes an important exploratory safety finding that requires careful consideration. This can be largely attributed to the relatively aggressive starting dosing and substantial dose titration regimen, especially in Cohort B. The present phase 2 trial used starting doses of 40 U (240 nmol) and 70 U (420 nmol) in insulin naïve and basal insulin switched patients, respectively, with the dose adjustment step by 9 U (54 nmol) or 18 U (108 nmol). These correspond to 103 U and 180 U for starting doses, and 23 U or 46 U for dose adjustments, respectively, according to the aforementioned 2.6-fold potency difference (i.e. 1 U GZR4 equals to 2.33 nmol instead of 6 nmol, which was used in thereafter several phase 3 trials). Therefore, the interpretation of these results should be confined to this exploratory, aggressive starting and titration dose context. On the other hand, the hypoglycemia reporting may have been partially influenced by the current open-label design, with increased vigilance in glucose

Table 2
Key secondary endpoints: change from baseline.

	Cohort A					Cohort B				
	GZR4		IDeg		Treatment difference (95% CI)	GZR4		IDeg		Treatment difference (95% CI)
Endpoint	No. of patients	Change from baseline	No. of patients	Change from baseline		No. of patients	Change from baseline	No. of patients	Change from baseline	
Endpoints assessed as estimated mean change from baseline to week 16										
Fasting plasma glucose – mmol/L	38	−2.58 (−3.17, −1.99)	37	−2.71 (−3.31, −2.12)	0.13 (−0.47, 0.73) $p = 0.658$	44	−2.28 (−2.67, −1.89)	45	−2.32 (−2.71, −1.93)	0.04 (−0.51, 0.60) $p = 0.874$
Mean 7-point self-measured blood glucose – mmol/L	38	−1.59 (−2.57, −0.61)	32	−2.05 (−3.03, −1.06)	0.46 (−0.52, 1.43) ($p = 0.354$)	42	−2.30 (−2.85, −1.74)	44	−2.01 (−2.55, −1.46)	−0.29 (−1.06, 0.48) $p = 0.459$
Body weight - kg	40	1.49 (0.77, 2.21)	38	0.70 (−0.02, 1.41)	0.79 (−0.04, 1 ,63) $p = 0.062$	45	0.37 (−0.13, 0.87)	46	−0.16 (−0.66, 0.34)	0.53 (−0.18, 1.23) $p = 0.140$
Endpoints assessed as estimated mean during the last 2 weeks of treatment										
TIR change from baseline - %	32	31.36 (15.10, 47.61)	33	24.55 (9.38, 39.72)	6.81 (−5.94, 19.55) $p = 0.29$	39	24.48 (17.64, 31.32)	40	21.30 (14.60, 28.01)	3.18 (−6.38, 12.74) $p = 0.51$
Insulin dose - U/ week	40	483.6 (275.82)	38	994.8 (601.68)	$p < 0.001$	46	531.9 (207.9)	46	1308.9 (555.6)	$p < 0.001$

Data are least-square mean (95%CI) or mean (SD). Cohort A: insulin-naive participants; Cohort B: participants previously treated with basal insulin. Analysis was performed using mixed model repeated measures model. GZR4 = insulin GZR4, IDeg = insulin degludec; CI = confidence interval; TIR: time in range. 1 U = 6 nmol.

Table 3
Key safety and adverse events.

	Cohort A				Cohort B			
	GZR4 (N = 42)		IDeg (N = 41)		GZR4 (N = 48)		IDeg (N = 48)	
Events	No. of patients (%)	No. of events (events/ patient-year of exposure)	No. of patients (%)	No. of events (events/ patient-year of exposure)	No. of patients (%)	No. of events (events/ patient-year of exposure)	No. of patients (%)	No. of events (events/ patient-year of exposure)
TEAE	30 (71.4)	108	25 (61.0)	53	34 (70.8)	86	35 (72.9)	79
TRAE	10 (23.8)	45	5 (12.2)	5	11 (22.9)	27	3 (6.3)	5
SAE	2 (4.8)	2	0 (0.0)	0	2 (4.2)	2	1 (2.1)	1
TEAE leading to drug discontinuation	1 (2.4)	1	0 (0.0)	0	1 (2.1)	2	0 (0.0)	0
TEAE leading to death	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0
Adverse events of special interest								
Hypoglycemic events	17 (40.5)	75	3 (7.3)	6	30 (62.5)	150	7 (14.6)	15
Hypoglycemia alert	17 (40.5)	74 (6.25)	3 (7.3)	6 (0.50)	30 (62.5)	144 (10.78)	7 (14.6)	15 (1.05)
Clinically significant or severe hypoglycemia	1 (2.4)	1 (0.08)	0 (0.0)	0 (0.0)	3 (6.3)	6 (0.45)	0 (0.0)	0 (0.0)
Severe hypoglycemia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Injection site reaction	3 (7.1)	17	1 (2.4)	1	6 (12.5)	12	0 (0.0)	0
Injection site reaction-pruritus	3 (7.1)	15	0 (0.0)	0	4 (8.3)	5	0 (0.0)	0

Data were presented as value (proportion). Cohort A: insulin-naive participants; Cohort B: participants previously treated with basal insulin. Safety analysis set. TEAE = treatment-emergent adverse event; N = number of participants; TRAE = treatment-related adverse event; SAE = Serious adverse event. Hypoglycemia alert = level 1 Hypoglycemia, Clinically significant hypoglycemia = level 2 hypoglycemia, Severe hypoglycemia = level 3 hypoglycemia.

monitoring in the investigated GZR4 group. Nevertheless, the majority of hypoglycemic events were mild to moderate, did not lead to study discontinuation, and no level 3 (severe) hypoglycemic events occurred under the current aggressive starting and titration regimen. Overall, the increase in hypoglycemia risk observed with GZR4 and its favorable efficacy should be balanced, reinforcing the need for stringent individualized dose titration approaches and careful patient monitoring in future clinical practice. To mitigate the hypoglycemia risk, a reduced starting dose and more gradual dose titration strategies were explored in the subsequent phase 3 studies based on the redefined molar potency from the collective clinical data (1 U GZR4 equals to 2.33 nmol). These phase 3 studies adopted a starting dose of 72 U (168 nmol) for insulin-naïve participants and a dose calculated as the prior basal insulin dose multiplied by 7 for insulin-treated participants, with both groups following the same dose adjustment of 18 U (42 nmol). The clear benefit-risk profile of GZR4 will be evaluated more carefully in these larger trials of longer duration and in more diverse patient populations.

Both Icodec and insulin Efsitora require a loading dose when switching from once-daily to once-weekly insulin, a step associated with an increased risk of loading dose–induced hypoglycemia and dosing errors [22]. In this trial, blood glucose control remained satisfactory during the treatment transition despite the absence of a loading dose. Omitting the loading dose could simplify the treatment regimen, lower probability of dose transition mistakes and support a smoother transition from daily to weekly basal insulin preparations. Certainly, a direct comparative studies are essential to evaluate the relative efficacy, safety, and practical advantages of emerging once-weekly insulins. Therefore, a phase 3 head-to-head study comparing GZR4 and Icodec is underway to

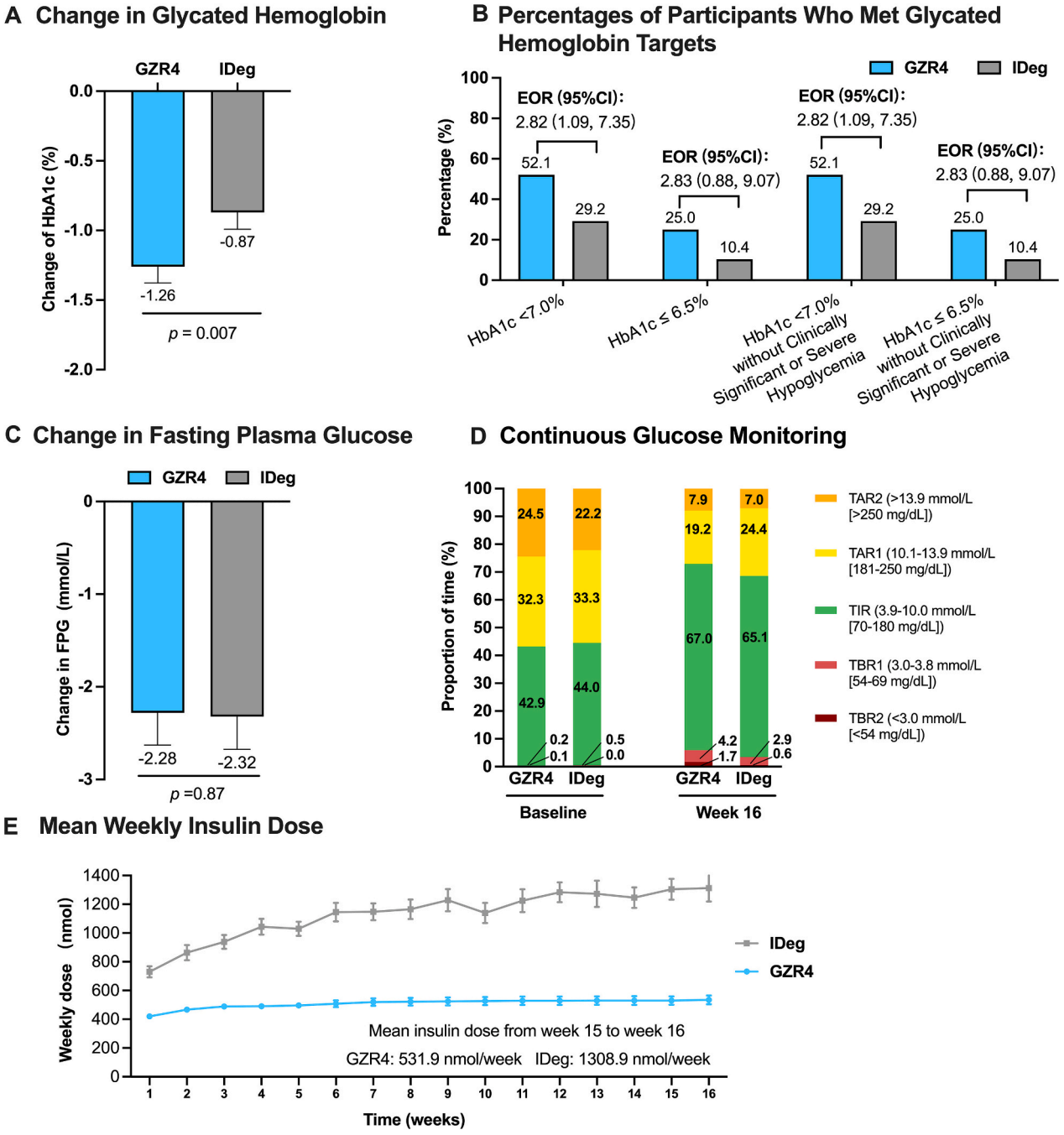

Fig. 3. Efficacy measures in Cohort B (people previously treated with basal insulin). Panel A: mean change in HbA1c from baseline to week 16. Panel B: at week 16, the proportion of participants who achieved HbA1c target of <7% or ≤6.5% and the proportion of participants who achieved HbA1c target of <7% or ≤6.5% without clinically significant (level 2) or severe (level 3) hypoglycemia. Panel C: mean change in FPG from baseline to week 16. Panel D: TIR, TAR, and TBR at baseline and during the last 2 weeks of treatment (weeks 15 and 16). Panel E: mean weekly insulin dose over the 16-week treatment period. 1 U = 6 nmol. Error bars: standard errors. GZR4 = insulin GZR4, IDeg = insulin degludec, HbA1c = glycated hemoglobin, FPG = fasting plasma glucose, TIR = time in range, TAR = time above range, TBR = time below range.

address the concern on efficacy and safety (NCT07165223).

A notable strength of this study is its simultaneous testing of GZR4 in both insulin-naive and insulin-treated people groups. This will allow for the evaluation of the efficacy and safety of GZR4 in two different representative populations, thus facilitating the design of optimal dose settings for various target populations in the phase 3 trials. The current trial has several limitations that need to be noted, including the short duration, smaller sample size, and open-label design. Firstly, the 16-week treatment period is relatively short and does not allow assessment of long-term durability of glycemic control, immunogenicity, or the full safety profile of GZR4. These aspects are being evaluated in ongoing large-scale, longer-duration phase 3 trials (up to 52 weeks; NCT06767735, NCT06767748, NCT06767761), designed to provide confirmatory evidence for comprehensive benefit-risk assessment of GZR4. Secondly, because of the observed high incidence of hypoglycemic events, future studies are needed to test a more refined titration algorithms that optimize the balance between glycemic control and risk of hypoglycemia for GZR4. Thirdly, the present trial enrolled an exclusively Chinese patient population, which may limit generalizability to global populations due to potential ethnic differences in insulin

pharmacokinetics, diabetes pathophysiology, and genetic factors. Evaluation of efficacy and safety in broader multinational cohorts is therefore warranted. Ongoing studies, including a phase 1 euglycemic glucose clamp study in Germany (NCT07146347), form part of the global clinical development program. Finally, as an open-label exploratory trial, there is potential bias in investigator-driven titration and patient-reported outcomes. Although objective endpoints (e.g., HbA1c, CGM metrics) mitigate concerns regarding efficacy assessment, limitations remain for subjective outcomes and generalization of titration patterns. These findings should be interpreted as preliminary estimates generated under conditions of clinical awareness and require confirmation in more controlled settings.

In conclusion, this exploratory phase 2 trial provides preliminary evidence that once-weekly GZR4 offers robust glucose-lowering efficacy in both insulin-naïve and insulin-treated patients with T2D. However, the observed increase hypoglycemia risk underscores the need for further evaluation in larger, longer-term trials to fully characterize the benefit-risk profile of GZR4 and to optimize its starting and dose-titration strategy.

CRediT authorship contribution statement

Liming Chen: Project administration, Investigation. **Xiaolin Dong:** Formal analysis, Data curation. **Qiumei Zhang:** Formal analysis, Data curation. **Huihui Wang:** Formal analysis, Data curation. **Hongyan Zhu:** Formal analysis, Data curation. **Zhifeng Cheng:** Formal analysis, Data curation. **Xiangqun Deng:** Formal analysis, Data curation. **Guang Wang:** Formal analysis, Data curation. **Jingyun Zhang:** Formal analysis, Data curation. **Xuerong Liu:** Formal analysis, Data curation. **Jing Zhao:** Project administration, Investigation, Formal analysis, Data curation. **Chunyue Hao:** Formal analysis, Data curation. **Tian Xie:** Writing – review & editing. **Anshun He:** Writing – review & editing, Writing – original draft. **Yue Li:** Writing – review & editing. **Wei Chen:** Writing – review & editing, Validation, Project administration, Investigation, Formal analysis, Data curation.

Trial registration

ClinicalTrials.gov, NCT06202079; Chinadrugtrials, CTR20232431.

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Declaration of competing interest

L.C., X.D., H.W., H.Z., Z.C., X.D., and G.W. received research funding from Gan & Lee Pharmaceuticals, during the conduct of the study. W.C. is shareholder of Gan & Lee Pharmaceuticals. J.Z., C.H., T.X., A.H., and Y.L. are employees of Gan & Lee Pharmaceuticals.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.metabol.2026.156592.

Data availability

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

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