Comparable Glycemic Control of Once-Weekly Insulin GZR4 Relative to Once-Daily Insulin Degludec in Insulin-naïve Chinese Subjects with T2D

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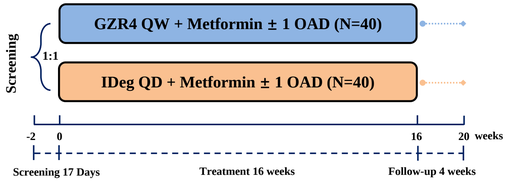
Objective

- Once-weekly (QW) insulin aims to reduce treatment burden by lowering injection frequency, potentially enhancing treatment acceptance and adherence, addressing a substantial challenge of poor adherence to daily insulin injection in managing diabetes[1-2].
- This trial evaluated the efficacy and safety of a novel QW insulin analog GZR4 versus once-daily (QD) insulin degludec (IDeg) in insulin-naïve subjects with T2D inadequately controlled by oral antidiabetic drugs (OADs).

Methods

Study design

In this open-label, treat-to-target phase 2 trial, 83 eligible subjects with HbA1c between 7.5% and 10.0% were randomized in a 1:1 ratio to receive either GZR4 or IDeg treatment for 16 weeks.



Endpoints

Primary: change in HbA1c from baseline to week 16 .

Secondary: proportion of achieving HbA1c target (<7.0% and ≤6.5%), change in fasting plasma glucose (FPG), incidence of treatment-emergent adverse events (TEAEs) and hypoglycemia.

Results

Subject disposition

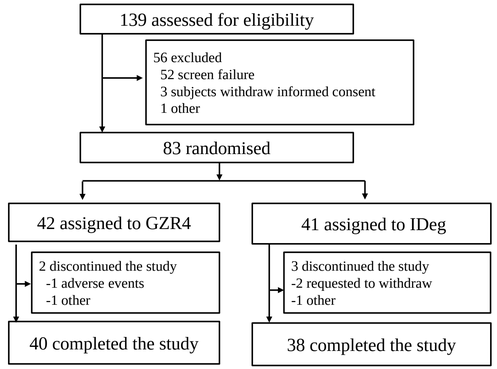


Table 1. Demographics and baseline characteristics

Characteristics	GZR4, N=42	IDeg, N=41	GZR4 vs IDeg, *p* value
Age (years)	57.6 (10.9)	57.4 (9.4)	*p*=0.79
Sex (Male), n (%)	23 (54.8)	21 (51.2)	-
Race (Han), n (%)	42 (100.0)	40 (97.6)	-
Weight (kg)	71.1 (15.5)	69.9 (11.8)	*p*=0.69
Diabetes duration (months)	79.9 (71.3)	72.2 (51.0)	*p*=0.57
Baseline HbA1c (%)	8.23 (0.65)	8.12 (0.70)	*p*=0.46
Baseline FPG (mmol/L)	9.10 (2.21)	9.60 (1.96)	*p*=0.28

Data were presented as Mean (SD) or n (%).

The Least-square mean (LSM) change in HbA1c was comparable between GZR4 and IDeg groups (−1.50% versus -1.48%, *p* = 0.902). The GZR4 group showed a similar proportion of subjects achieving HbA1c targets and a similar reduction in FPG compared to the IDeg group. However, the total weekly insulin dosage required at steady state was half that of the IDeg group (80.6 vs 165.8 U/week, *p*<0.001).

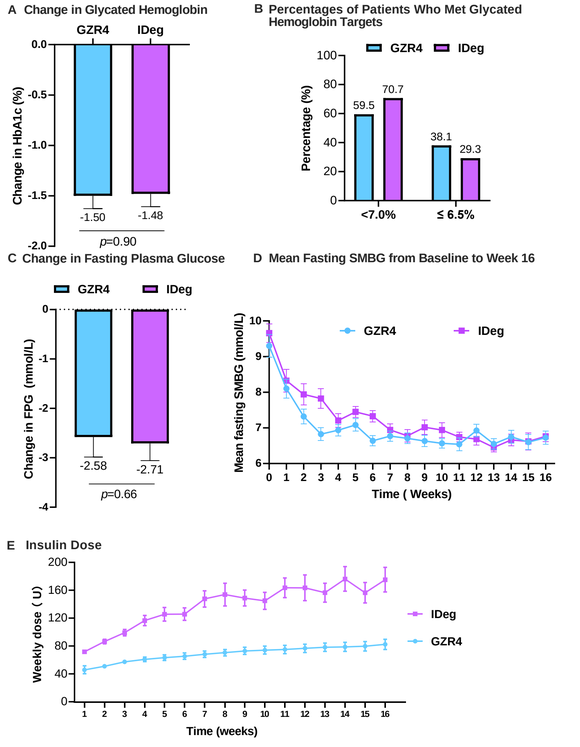


Figure 1. Efficacy of GZR4 in insulin-naïve patients. Panel A shows the mean change in HbA1c from baseline to week 16 in GZR4 and IDeg group. Panel B shows estimated proportion of subjects who achieved a HbA1c target of <7% or ≤ 6.5% after 16 weeks. Panel C shows the mean change in FPG from baseline to week 16 among subjects who received either once-weekly insulin GZR4 or once-daily IDeg. Panel D shows mean fasting self-measured blood glucose (SMBG) from baseline to week 16. Data are observed mean values. Panel E shows the mean weekly insulin dose over the treatment in insulin-naïve patients. 1U= 6 nmol.

TEAEs were mild and similar between groups, with low and comparable rates of level 2 hypoglycemia. No serious adverse events (SAEs) or level 3 hypoglycemia were deemed related to GZR4.

Table 2. Summary of adverse events (AEs)

	GZR4, N=42		IDeg, N=41	
Event	No. of patients (%)	No. of events	No. of patients(%)	No. of events
TEAE	30 (71.4)	108	25 (61.0)	53
TEAE related to IMP	10 (23.8)	45	5 (12.2)	5
SAE	2 (4.8)	2	0 (0.0)	0
TEAE leading to discontinuation from the study	1 (2.4)	1	0 (0.0)	0
TEAE leading to death	0 (0.0)	0	0 (0.0)	0
Hypoglycemic event	17 (40.5)	75	3 (7.3)	6
Level 1 hypoglycemia	17 (40.5)	74	3 (7.3)	6
Level 2 hypoglycemia	1 (2.4)	1	0 (0.0)	0
Level 3 hypoglycemia	0 (0.0)	0	0 (0.0)	0
Injection site reaction	3 (7.1)	17	1 (2.4)	1

SAE=serious adverse event; TEAE=treatment-emergent adverse event; IMP=investigational medicinal product

Conclusion

- GZR4 demonstrated comparable efficacy and safety profiles to QD IDeg in insulin-naïve subjects with T2D, with a lower weekly insulin dosage.
- GZR4 is promising to be a safe and effective weekly insulin in diabetes management.

References

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2. XING, W. *et al.* 823-P: Molecular and Pharmacological Properties of GZR4, a Once-Weekly Insulin Analog. *Diabetes* **73**, doi:10.2337/db24-823-P (2024)

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

This work was supported by Gan & Lee Pharmaceuticals and was registered with ClinicalTrials.gov (NCT06202079).

Superior Glycemic Control Achieved with Once-Weekly Insulin GZR4 Compared to Once-Daily Insulin Degludec in Insulin-treated Chinese Subjects with T2D

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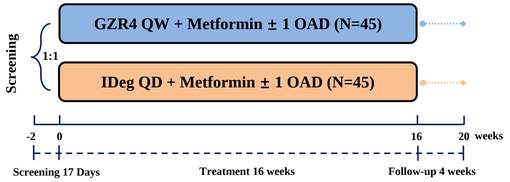
Objective

- Despite the availability of once-daily (QD) insulin, adherence and persistence on insulin therapy are lower than desired.
- Once-weekly (QW) insulins have emerged as a research focus due to their potential to enhance treatment acceptance and adherence by reducing injection frequency[1-2].
- GZR4 provides basal insulin coverage over a full week after a single subcutaneous injection[3].
- This trial studied the efficacy and safety of a novel QW insulin analog GZR4 versus QD insulin degludec (IDeg) in basal insulin-treated T2D subjects inadequately controlled by oral antidiabetic drugs (OADs).

Methods

Study design

In this open-label, treat-to-target phase 2 trial, 96 eligible subjects with HbA1c from 7.5 to 10.0% were randomized in a 1:1 ratio to receive either GZR4 or IDeg treatment for 16 weeks.



Endpoints

Primary: change in HbA1c from baseline to week 16 .

Secondary: proportion of achieving HbA1c target (<7.0% and ≤6.5%), change in fasting plasma glucose (FPG), incidence of treatment-emergent adverse events (TEAEs) and hypoglycemia.

Results

Subject disposition

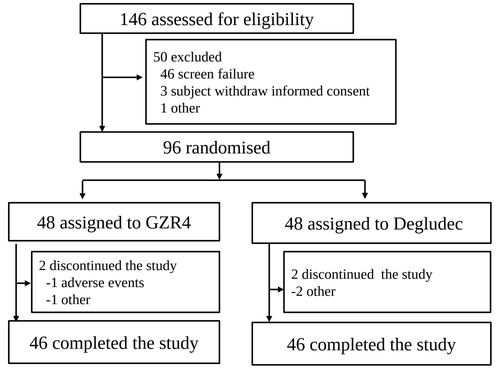


Table 1. Demographics and baseline characteristics

Characteristics	GZR4, N=48	IDeg, N=48	GZR4 vs IDeg, *p* value
Age (years)	57.7 (9.0)	58.2 (8.8)	*p*=0.78
Sex (Male), n (%)	27 (56.3)	28 (58.3)	-
Race (Han), n (%)	47 (97.9)	46 (95.8)	-
Weight (kg)	68.7 (10.8)	70.5 (10.1)	*p*=0.40
Diabetes duration (months)	129.0 (74.7)	120.8 (75.8)	*p*=0.60
Baseline HbA1c (%)	8.35 (0.69)	8.45 (0.75)	*p*=0.50
Baseline FPG (mmol/L)	8.88 (2.22)	8.90 (2.17)	*p*=0.97

Data were presented as Mean (SD) or n (%).

The Least-square mean (LSM) change in HbA1c was significantly lower in the GZR4 group than that of the IDeg group (−1.26% versus −0.87%, *p*< 0.01). The proportion of subjects achieving HbA1c target of <7% was higher in the GZR4 group. The GZR4 group showed a strikingly lower weekly insulin dosage at steady state than that of the IDeg group (88.7 versus 218.2 U/week, *p*<0.001).

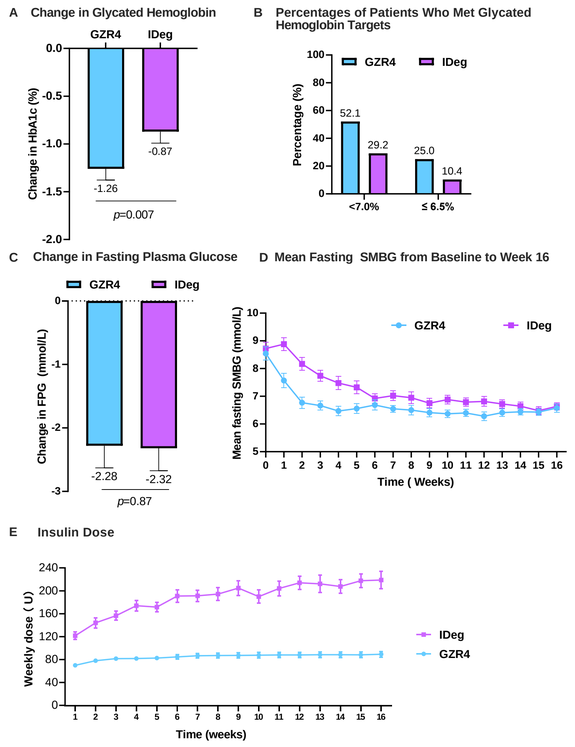


Figure 1. Efficacy of GZR4 in insulin-treated patients. Panel A shows the mean change in HbA1c from baseline to week 16 in GZR4 and IDeg group. Panel B shows estimated proportion of subjects who achieved a HbA1c target of < 7% or ≤ 6.5% after 16 weeks. Panel C shows the mean change in FPG from baseline to week 16 among subjects who received either once-weekly insulin GZR4 or once-daily IDeg. Panel D shows mean fasting self-measured blood glucose (SMBG) from baseline to week 16. Panel E shows the mean weekly insulin dose over the treatment in insulin-treated patients. 1U = 6 nmol.

Incidences of TEAE were similar between the two treatment groups. The GZR4 group showed a slightly higher level 2 hypoglycemia incidence than that of the IDeg group. Three serious adverse events (SAEs) were reported in three patients (3.1%): 2 (4.2%) in the GZR4 group and 1 (2.1%) in the IDeg group; none were related to the investigational medicinal product.

Table 2. Summary of adverse events (AEs)

	GZR4, N=48		IDeg, N=48	
Event	No. of patients (%)	No. of events	No. of patients(%)	No. of events
TEAE	34 (70.8)	86	35 (72.9)	79
TEAE related to IMP	11 (22.9)	27	3 (6.3)	5
SAE	2 (4.2)	2	1 (2.1)	1
TEAE leading to discontinuation	1 (2.1)	2	0 (0.0)	0
TEAE leading to death	0 (0.0)	0	0 (0.0)	0
Hypoglycemic event	30 (62.5)	150	7 (14.6)	15
Level 1 hypoglycemia	30 (62.5)	144	7 (14.6)	15
Level 2 hypoglycemia	3 (6.3)	6	0 (0.0)	0
Level 3 hypoglycemia	0 (0.0)	0	0 (0.0)	0
Injection site reaction	6 (12.5)	12	0 (0.0)	0

SAE=serious adverse event; TEAE=treatment-emergent adverse event; IMPs=investigational medicinal products

Conclusion

- GZR4 demonstrated superior HbA1c reduction after 16 weeks of treatment in insulin-treated subjects with T2D.
- The glycemic control of GZR4 was well controlled under condition of no loading dose.
- GZR4 is promising to be a safe and effective QW basal insulin in diabetes management.

References

1. Lingvay, I. *et al*. Once-Weekly Insulin Icodec vs Once-Daily Insulin Degludec in Adults With Insulin-Naive Type 2 Diabetes: The ONWARDS 3 Randomized Clinical Trial. JAMA , (2023).
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3. Tang C *et al*. Safety, tolerability, pharmacokinetics and pharmacodynamics of GZR4, a novel once-weekly basal insulin, in healthy participants: A randomized trial. Diabetes Obes Metab. 2025 May;27(5):.

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

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