

Safety, pharmacokinetics (PK), and pharmacodynamics (PD) of a dual GLP-1/GIP receptor agonist HRS9531 in T2DM patients: A randomized, double-blind, placebo- and open-label positive-controlled phase 1b trial

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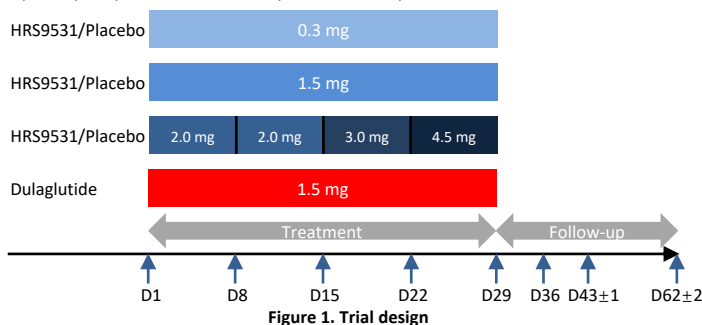
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Introduction

- Accumulating clinical evidence suggests that a dual Glucagon-like peptide 1 (GLP-1)/glucose-dependent insulinotropic polypeptide (GIP) receptor agonist can achieve additive or synergistic effects on glycemic control and body weight loss by regulating both GLP-1 and GIP receptors.¹⁻³
- HRS9531, a novel long-acting dual GLP-1/GIP receptor agonist, effectively lowers blood glucose and body weight in a phase 1 trial with healthy subjects.⁴
- This study assessed the safety, PK, and PD of HRS9531 in T2DM patients.

Methods

- This is a randomized, double-blind, placebo- and open-label positive-controlled phase 1b trial (NCT05516966, **Figure 1**).
- Patients aged 18–65 years with a ≥6-month history of T2DM and prior lifestyle intervention or stable metformin treatment for ≥8 weeks were enrolled.
- Patients were randomized to receive weekly subcutaneous injections of HRS9531 (0.3 mg, 1.5 mg, 4.5 mg [2.0/2.0/3.0/4.5 mg titration]), dulaglutide (1.5 mg), or placebo for 4 weeks.
- The primary endpoints were the safety and tolerability of HRS9531.



Results

Participants

- A total of 63 patients (men/women: 38/25) received the assigned treatments, including 43 patients with HRS9531, 8 patients with dulaglutide, and 12 patients with placebo (**Table 1**).

Table 1. Baseline characteristics

	HRS9531 0.3 mg (N=13)	HRS9531 1.5 mg (N=16)	HRS9531 4.5 mg (N=14)	Dulaglutide (N=8)	Placebo (N=12)
Age, years	54.1±10.5	54.4±10.5	47.4±10.9	48.0±10.6	48.4±14.4
Male	8 (61.5)	9 (56.3)	9 (64.3)	3 (37.5)	9 (75.0)
Weight, kg	74.8±14.3	75.6±15.9	80.3±11.7	79.3±16.5	79.3±14.1
BMI, kg/m ²	27.8±3.3	27.6±3.9	29.0±2.9	29.2±3.6	28.1±3.0
HbA _{1c} , %	8.2±0.6	7.9±0.7	7.7±0.7	7.8±0.6	7.5±0.7
Duration of T2DM, years	5.0±4.0	6.4±5.9	3.4±1.9	5.5±4.5	4.7±4.3
History of metformin	7 (53.8)	7 (43.8)	6 (42.9)	3 (37.5)	6 (50.0)

Data are mean±SD or n (%).

Safety

- Adverse events (AEs) were reported in 84.1% (53/63) of patients, mostly mild.
- Treatment-related AEs (TRAEs) were reported in 42.9% (27/63) of patients (**Table 2**).
- Gastrointestinal AEs (nausea, diarrhea, and vomiting) were dose-related, primarily in the 4.5 mg group of HRS9531 (28.6%, [4/14]).
- There were no severe AEs, serious AEs, AEs leading to treatment discontinuation, or deaths.

Table 2. TRAEs

	HRS9531 0.3 mg (N=13)	HRS9531 1.5 mg (N=16)	HRS9531 4.5 mg (N=14)	Dulaglutide (N=8)	Placebo (N=12)
Total TRAE	6 (46.2)	5 (31.3)	9 (64.3)	2 (25.0)	5 (41.7)
Diarrhea	1 (7.7)	1 (6.3)	3 (21.4)	0	2 (16.7)
Lipase increased	2 (15.4)	0	3 (21.4)	0	2 (16.7)
Decreased appetite	1 (7.7)	0	3 (21.4)	1 (12.5)	1 (8.3)
Vomiting	1 (7.7)	0	2 (14.3)	1 (12.5)	0
Nausea	0	1 (6.3)	2 (14.3)	0	1 (8.3)
Abdominal pain	0	0	2 (14.3)	0	0

Data are n (%). TRAEs occurring in two or more patients in either group are listed.

PK

- The exposure of HRS9531 (C_{max} and AUC) increased with dose escalation within the range of 0.3–4.5 mg (**Figure 2**), with a mean half-life of approximately 1 week.
- The median T_{max} were 72.0–94.8 h after single dosing of HRS9531 and 48.0–71.8 h after the fourth dosing.

PD

- Levels of fasting plasma glucose (FPG), AUC_{0-3h} of glucose, and body weight decreased dose-dependently after HRS9531 treatment (**Table 3**, **Figure 3–5**).
- HRS9531 outperformed placebo in reducing HbA_{1c} and serum LDL cholesterol in a dose-dependent manner (**Table 3**).
- The proportions of patients achieving FPG target (<7 mmol/L) and 2-hour postprandial plasma glucose (2h-PPG) target (<10 mmol/L) on Day 29 in the HRS9531 1.5 mg and 4.5 mg groups were higher than those in the dulaglutide group and placebo group (**Figure 6–7**).

Results

Table 3. The percentage changes from baseline on Day 29

	HRS9531 0.3 mg (N=13)	HRS9531 1.5 mg (N=16)	HRS9531 4.5 mg (N=14)	Dulaglutide (N=8)	Placebo (N=12)
HbA _{1c}	-3.2±3.7	-7.4±5.0	-9.6±3.5	-7.3±4.6	1.7±7.8
FPG	-8.8±16.1	-26.9±22.1	-29.3±12.1	-22.6±26.5	-5.3±9.9
AUC _{0-3h} of glucose	-16.2±11.7	-30.3±26.3	-45.2±7.7	-22.0±21.4	-6.5±14.4
Body weight	-0.3±2.0	-2.6±1.0	-3.0±2.7	-2.2±1.9	-1.0±1.6
Serum LDL cholesterol	-5.1±14.0	-5.4±19.1	-12.5±22.7	-8.1±18.5	-4.7±24.3

Data are mean±SD.

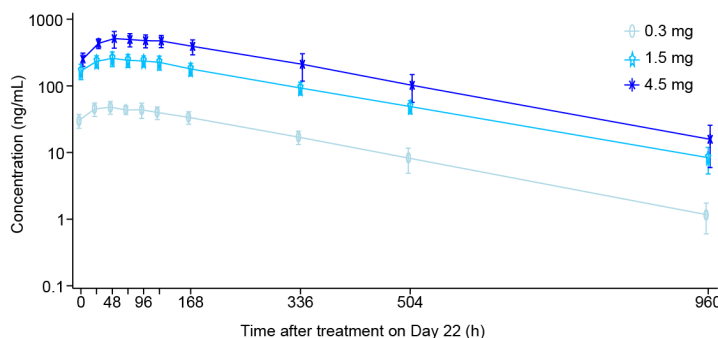


Figure 2. HRS9531 concentration-time curve at steady state (mean ± SD)

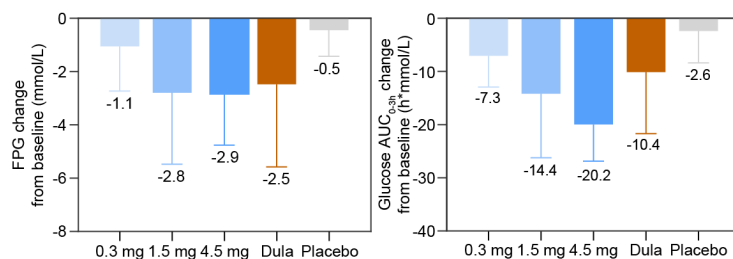


Figure 3. Change from baseline in FPG level at Day 29 (mean ± SD)

Figure 4. Change from baseline in glucose AUC_{0-3h} on Day 29 (mean ± SD)

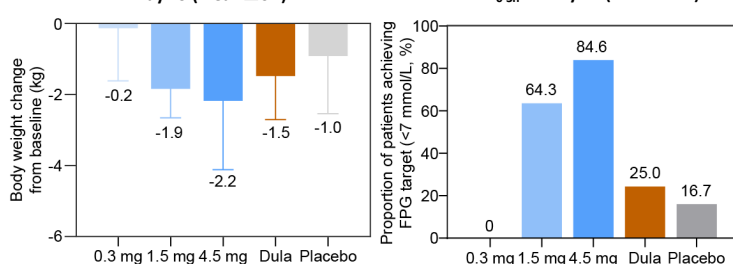


Figure 5. Change from baseline in body weight on Day 29 (mean ± SD)

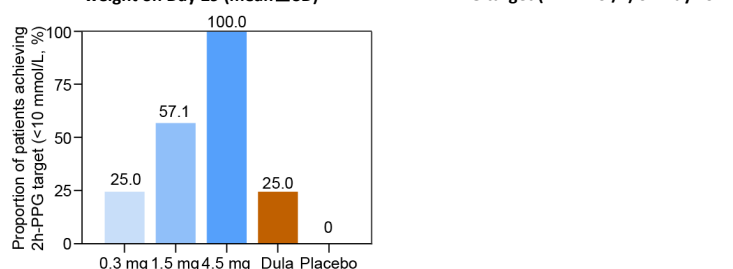


Figure 6. Proportion of patients achieving 2h-PPG target (<10 mmol/L) on Day 29

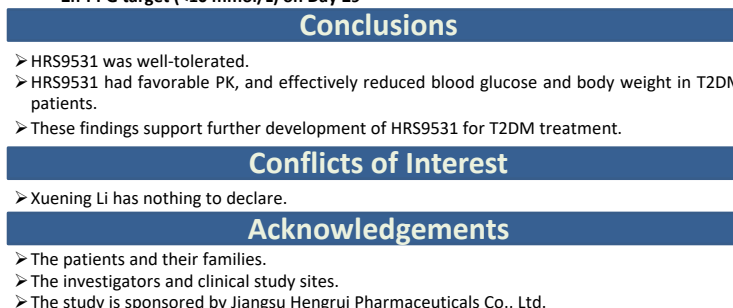


Figure 7. Proportion of patients achieving 2h-PPG target (<10 mmol/L) on Day 29

Conclusions

- HRS9531 was well-tolerated.
- HRS9531 had favorable PK, and effectively reduced blood glucose and body weight in T2DM patients.
- These findings support further development of HRS9531 for T2DM treatment.

Conflicts of Interest

- Xuening Li has nothing to declare.

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