60th Annual Meeting
European Association for the Study of Diabetes
9 - 13 September 2024
Madrid, Spain
EASD 2024

Efficacy and safety of HRS9531, a novel dual GLP-1/GIP receptor agonist, in patients with type 2 diabetes mellitus (T2DM): a randomized, double-blind, placebo-controlled phase 2 trial

Jiajun Zhao[1], Meng Zhao[1], Weihong Song[2], Dongji Wang[3], Xianghua Zhang[4], Yuan Hui[5], Yanqin Zhou[6], Yibing Lu[7], Hong Chen[8], Lei Zhang[8], Xiaojing Cui[8], Jingjing Wang[8]

[1]Shandong First Medical University Affiliated Provincial Hospital, Jinan, China; [2]Chenzhou No. 1 People's Hospital, Chenzhou, China; [3]LianyungangHospital of TCM, Lianyungang, China; [4]Yueyang Central Hospital, Yueyang, China; [5]The First People's Hospital of Lianyungang, Lianyungang, China; [6]Pingxiang Second People's Hospital, Pingxiang, China; [7]The Second Affiliated Hospital of Nanjing Medical University, Nanjing, China; [8]Jiangsu Hengrui Pharmaceuticals Co., Ltd., Shanghai, China

Disclosure

- Dr. Hong Chen is an employee of Jiangsu Hengrui Pharmaceuticals.
- Prof. Jiajun Zhao declares no potential conflicts of interest.

Background

- Accumulating clinical evidence suggests that a dual glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) receptor agonist can achieve additive or synergetic effects on glycemic control and body weight loss.[1-3]
- **HRS9531 is a novel agonist of both GLP-1 and GIP receptors.**
  - Superior GLP-1R agonist potency and weaker GIPR agonist potency compared to GT2020170-1*
  - Similar GLP-1R agonist potency compared to GT2020170-2*
- A clinical study conducted in healthy participants showed that HRS9531 had linear pharmacokinetics and a half-life of 7–8 days, supporting its **once-weekly** dosing regimen.[4]
- HRS9531 demonstrated preliminary efficacy in glycemic control and weight loss, with good tolerability after 4 weeks of treatment in patients with T2DM in a phase 1 trial.[5]

Potency assays (*preclinical*)		HRS9531	GT2020170-1	GT2020170-2
EC_{50} (nM)	GLP-1 activity	0.005	0.013	0.003
	GIP activity	0.0017	0.0009	>1
Insulin secretion		Comparable		

*GT2020170-1 and GT2020170-2 were synthesized based on publicly available data on tirzepatide and semaglutide, respectively, and served as internal controls in this study.

1. Marso, et al. *N Engl J Med* 2016; 375: 311–22. 2. Tuttle, et al. *Lancet Diabetes Endocrinol* 2018; 6: 605–17. 3. Rosenstock, et al. *Lancet* 2021; 398: 143–55. 4. He. et al. Diabetes 2023; 72; 763-P. 5. Zhao. et al. *Diabetes Res Clin Pract* 2024; IDF23-0198.

Objective and Study Design

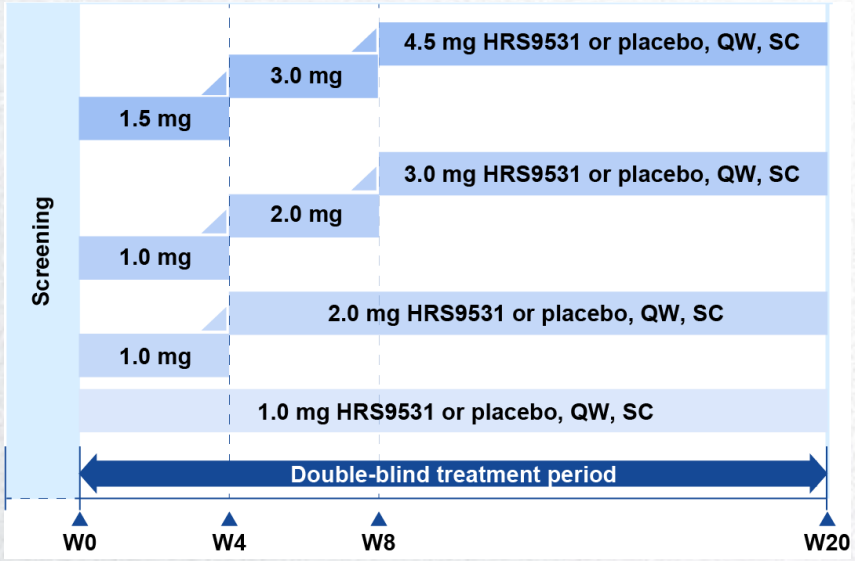
- **Objective:** To evaluate the efficacy and safety of HRS9531 compared with placebo in T2DM patients.
- This is a multicenter, randomized, double-blind, placebo-controlled **phase 2 trial (NCT05966272)**.

Key Inclusion:

- Aged 18–65 years
- History of T2DM ≥ 6-month
- HbA_{1c} of 7.5%–10.5%
- BMI of 22–40 kg/m^2
- Lifestyle intervention or stable metformin treatment for at least 8 weeks

Primary endpoint:

- Change in HbA1c from baseline to week 20



Abbreviations: BMI, body-mass index; QW, once a week; SC, subcutaneous injection.

Baseline Characteristics

- A total of 199 eligible patients (from 37 hospitals in China) were randomized and received assigned treatment.
- The baseline demographics and clinical characteristics were generally balanced across the four doses of HRS9531 and the placebo group.

	HRS9531 1.0 mg (N=40)	HRS9531 2.0 mg (N=41)	HRS9531 3.0 mg (N=39)	HRS9531 4.5 mg (N=40)	Placebo (N=39)	Total (N=199)
Age, years	47.7±10.9	45.5±9.5	45.1±10.4	46.4±10.6	51.8±9.2	47.3±10.3
Male	26 (65.0)	31 (75.6)	26 (66.7)	31 (77.5)	20 (51.3)	134 (67.3)
Weight, kg	77.3±12.7	83.3±17.3	82.9±20.4	78.7±12.8	75.4±14.6	79.5±16.0
BMI, kg/m^2	28.1±3.6	28.9±4.3	29.0±4.5	28.3±3.4	28.0±3.7	28.5±3.9
HbA_{1c}, %	8.5±0.9	8.5±0.8	8.7±0.8	8.2±0.8	8.4±0.9	8.5±0.9
FPG, mmol/L	9.5±2.3	9.4±1.7	10.1±2.6	9.3±1.8	9.7±2.1	9.6±2.1
Duration of T2DM, years	4.2±3.1	4.6±4.1	5.0±3.9	3.6±3.2	5.2±4.8	4.5±3.9
Metformin use	21 (52.5)	21 (51.2)	20 (51.3)	21 (52.5)	19 (48.7)	102 (51.3)

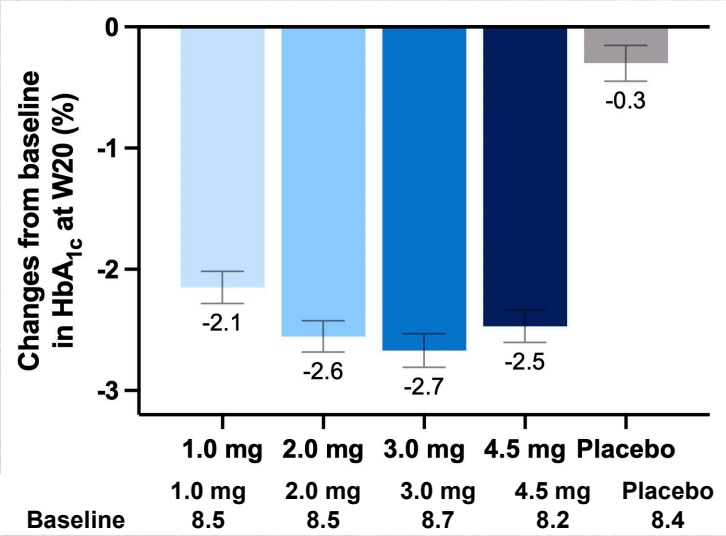
Data are mean ± SD or n (%).

Abbreviations: FPG, fasting plasma glucose.

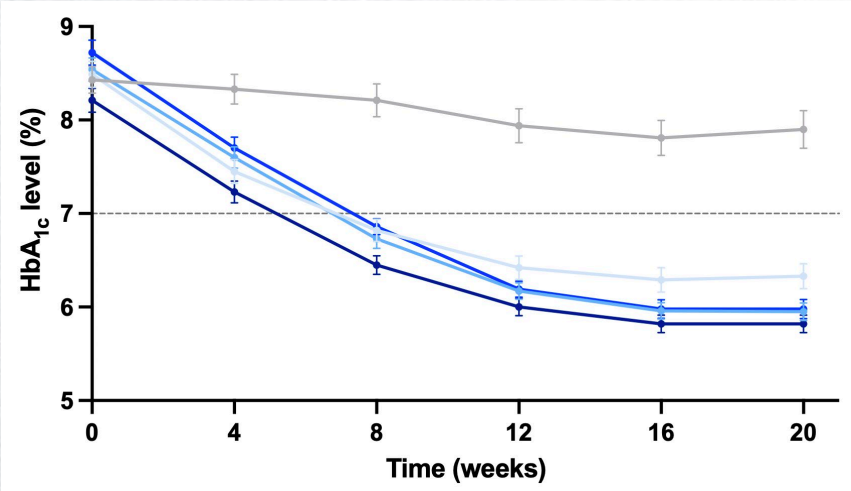
Primary Endpoint (HbA_{1c} Reduction)

- At week 20, HbA_{1c} reductions in the four doses group of HRS9531 were all greater than that in the placebo group ($p<0.0001$ for all comparisons with placebo).

Changes from baseline in HbA_{1c} level



HbA_{1c} level over time

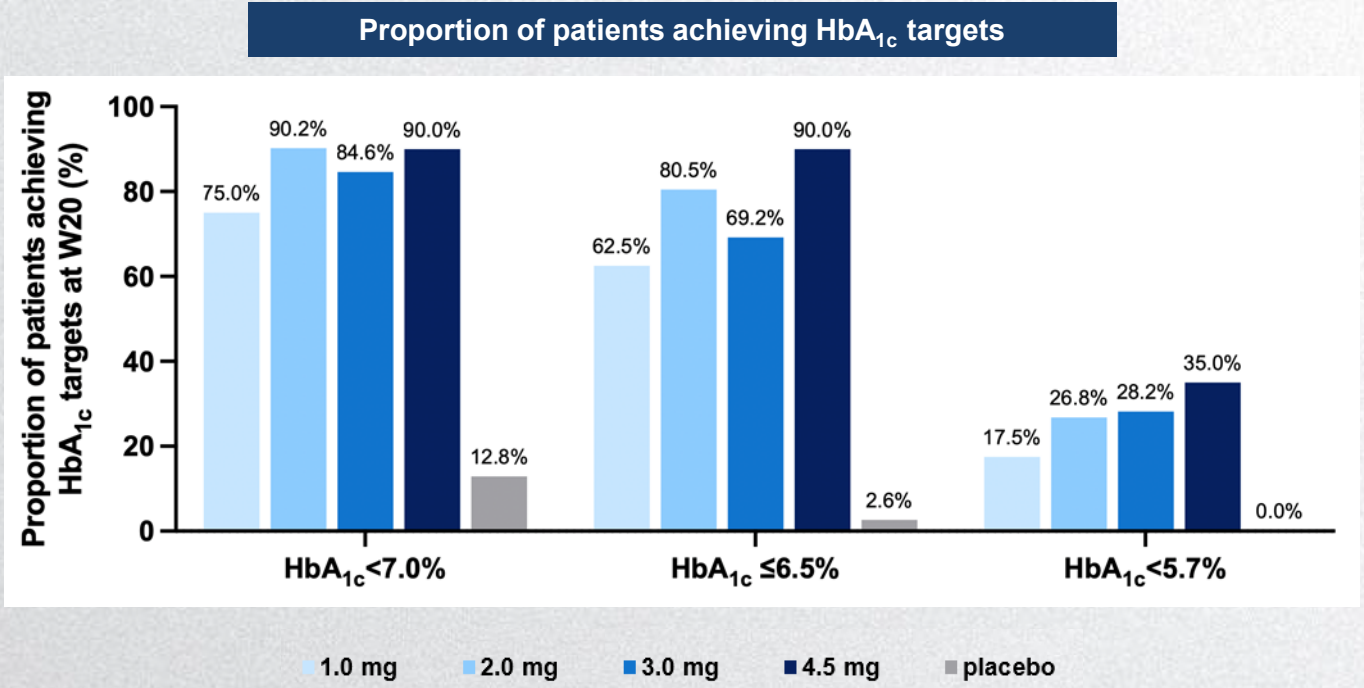


Data presented are LSMean
Error bars indicate SE

1.0 mg 2.0 mg 3.0 mg 4.5 mg placebo

HbA_{1c} Targets Proportions

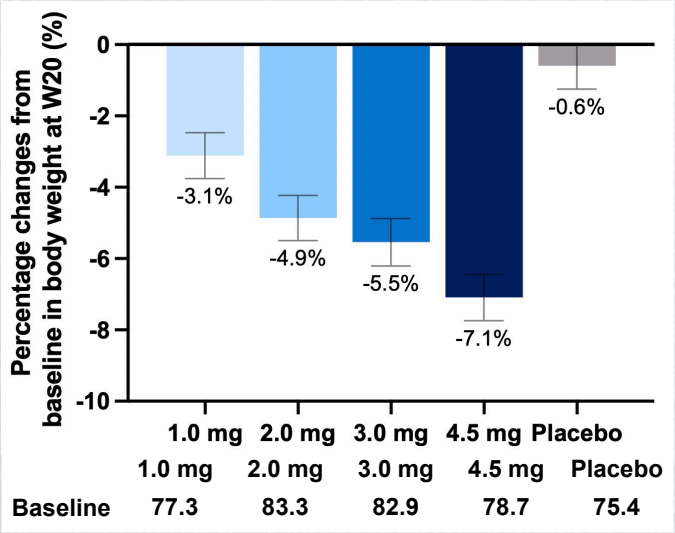
- The proportions of patients achieving targets of HbA_{1c} <7.0%, ≤6.5%, and <5.7% at week 20 in the four doses group of HRS9531 were all higher than those in the placebo group.



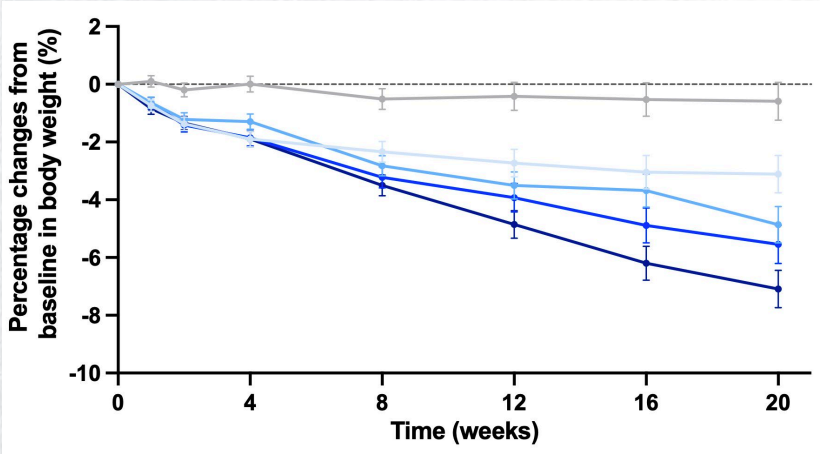
Body Weight Reduction

- Body weight reductions from baseline to week 20 in four doses group of HRS9531 were all greater than the placebo group.

Percentage changes from baseline in body weight



Percentage changes from baseline in body weight over time



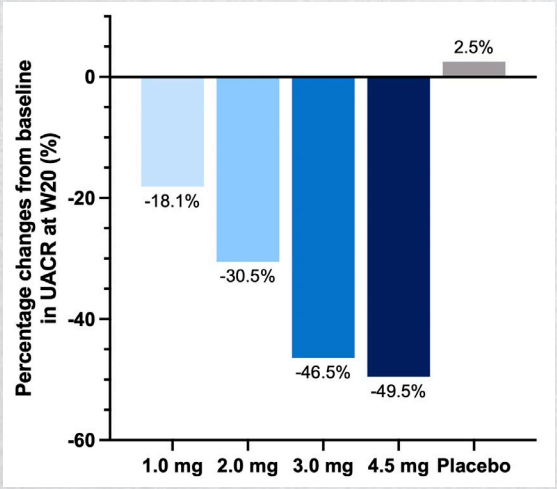
Data presented are LSMean
Error bars indicate SE

1.0 mg 2.0 mg 3.0 mg 4.5 mg placebo

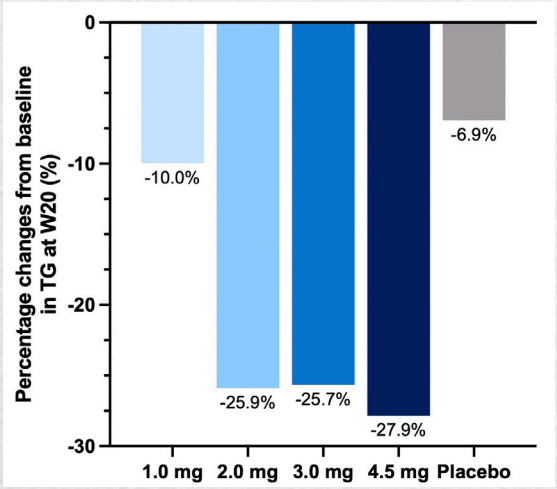
Other Efficacy Endpoints

- All doses of HRS9531 were superior to placebo at week 20 in the reductions of urinary albumin creatinine ratio (UACR), triglyceride (TG), and systolic blood pressure (SBP).

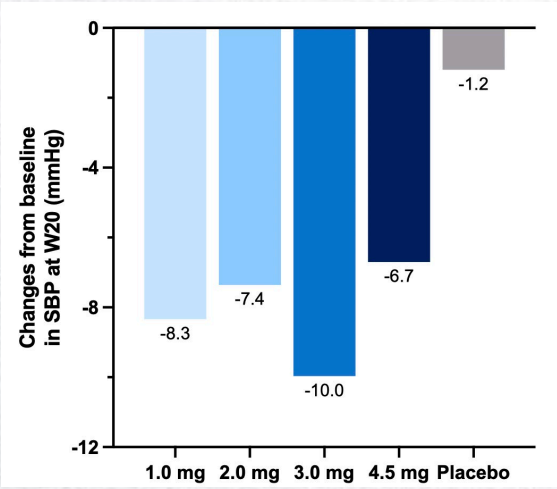
Geometric percentage changes from baseline in UACR



Geometric percentage changes from baseline in TG



Changes from baseline in SBP



Data presented are LSMean

1.0 mg 2.0 mg 3.0 mg 4.5 mg placebo

Safety

- Most adverse events (AEs) in HRS9531 groups were mild or moderate.
- The most common treatment-related gastrointestinal AEs were diarrhea, nausea, and abdominal distension.
- No clinically significant (<3 mmol/L) or severe hypoglycemia were reported.

	HRS9531 1.0 mg (N=40)	HRS9531 2.0 mg (N=41)	HRS9531 3.0 mg (N=39)	HRS9531 4.5 mg (N=40)	Placebo (N=39)
AE	30 (75.0)	35 (85.4)	32 (82.1)	34 (85.0)	30 (76.9)
Treatment-related gastrointestinal AEs occurring in ≥5% of patients in any dose group of HRS9531					
Diarrhea	6 (15.0)	10 (24.4)	10 (25.6)	14 (35.0)	2 (5.1)
Nausea	4 (10.0)	7 (17.1)	9 (23.1)	9 (22.5)	0
Abdominal distension	2 (5.0)	1 (2.4)	3 (7.7)	6 (15.0)	0
Vomiting	2 (5.0)	1 (2.4)	3 (7.7)	3 (7.5)	0
Flatulence	1 (2.5)	1 (2.4)	0	2 (5.0)	0
Abdominal discomfort	0	2 (4.9)	0	2 (5.0)	0
Abdominal pain	1 (2.5)	0	0	2 (5.0)	0
Gastroesophageal reflux disease	0	0	0	3 (7.5)	1 (2.6)
Hypoglycemia					
Grade 2–3	0	0	0	0	0

Data are n (%).

Conclusions

HRS9531 demonstrated superior glycemic and weight control, and other metabolic benefits compared to placebo in patients with T2DM at week 20.

- HbA_{1c} reduction
  - ✓ Maximum LSMean change: HRS9531 (-2.7%) vs placebo (-0.3%); all one-sided $p<0.0001$
- Body weight reduction
  - ✓ Maximum LSMean percentage change: HRS9531 (-7.1%) vs placebo (-0.6%)
- UACR, TG, and SBP improvements.

HRS9531 had an acceptable safety profile and a low risk of hypoglycemia.

Acknowledgements

- Patients and their families;
- Investigators and research personnel from all study sites;
- Staff at Jiangsu Hengrui Pharmaceuticals Co., Ltd. who participated in this trial.