Efficacy and Safety of HRS9531, a Novel Dual GLP-1/GIP Receptor Agonist, in Obese Adults: A Phase 2 Trial

Lin Zhao[1], Dan Zhu[2], Dexue Liu[3], Tianrong Pan[4], Dongji Wang[5], Yuan Hui[6], Hongwei Ling[7], Hanqing Cai[8], Meifang Zeng[9], Yue Zuo[9], Yuqi Sun[9], Yike Wang[9], Xiaoying Li[1]

[1]Department of Endocrinology and Metabolism, Zhongshan Hospital, Fudan University, Shanghai, China; [2]Cardiovascular Medicine, Peking University Third Hospital, Beijing, China; [3]Endocrinology Department, The First Affiliated Hospital of Nanyang Medical College, Nanyang, China; [4]Department of Endocrinology, The Second Hospital of Anhui Medical University, Hefei, China; [5]Department of Endocrinology and Metabolism, Lianyungang Hospital of TCM, Lianyungang, China; [6]Department of Endocrinology, The First People's Hospital of Lianyungang, Lianyungang, China; [7]Department of Endocrinology and Metabolism, The Affiliated Hospital of Xuzhou Medical University, Xuzhou, China; [8]Department of Endocrinology, The Second Hospital of Jilin University, Changchun, China; [9]Clinical Research & Development, Jiangsu Hengrui Pharmaceuticals Co., Ltd., Shanghai, China

American Diabetes Association. 84TH SCIENTIFIC SESSIONS ORLANDO, FL | HYBRID | JUNE 21-24, 2024

1861-LB

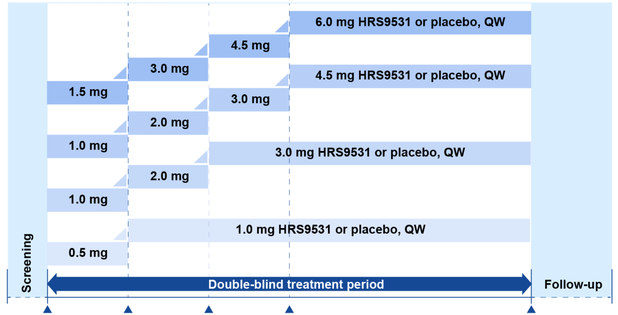
ZHONGSHAN HOSPITAL FUDAN UNIVERSITY

Introduction

- Growing clinical data indicates that a dual agonist targeting GLP-1 and GIP receptors may produce additive or synergetic effects for reducing body weight and improving glycemic control through the modulation of both GLP-1 and GIP receptors.[1-5]
- HRS9531, a novel dual GLP-1 and GIP receptor agonist, has shown prominent efficacy in weight loss and glycemic control in both healthy subjects and participants with type 2 diabetes in phase 1 trials.[6-7]
- This phase 2 study evaluated the efficacy and safety of HRS9531 in obese adults without diabetes.

Methods

- This is a randomized, double-blind, placebo-controlled phase 2 study (NCT05881837, **Figure 1**).
- Adults aged 18–65 years with a BMI of 28–40 kg/m^2 were randomized (4:1) to receive once-weekly subcutaneous injections of HRS9531 or placebo across four dose cohorts (1.0 mg, 3.0 mg, 4.5 mg, and 6.0 mg) for 24 weeks (24W).
- The primary endpoint was the percentage change in body weight from baseline to W24.



The analysis of the primary endpoint was performed using mixed-effects model for repeated measures (MMRM) based on the restricted maximum likelihood (REML) method. If a subject discontinued treatment or used prohibited drug or treatment before the primary endpoint, treatment policy estimand was used to continue to incorporate the observed data in the analysis

Figure 1. Trial design

Results

Participants

- A total of 249 participants were enrolled in this study (**Table 1**).
- Among them, 240 (96.4%) participants had completed the 24 weeks double-blind treatment period.

Results

Table 1. Baseline characteristics

	HRS9531 1.0 mg (N=50)	HRS9531 3.0 mg (N=51)	HRS9531 4.5 mg (N=50)	HRS9531 6.0 mg (N=49)	Placebo (N=49)	Total (N=249)
Age, years	32.7 (8.3)	34.9 (8.8)	34.9 (7.0)	33.3 (7.9)	35.3 (9.3)	34.2 (8.3)
Male, n (%)	24 (48.0)	24 (47.1)	24 (48.0)	24 (49.0)	24 (49.0)	120 (48.2)
Weight, kg	91.9 (12.1)	91.7 (14.3)	92.8 (13.4)	90.0 (13.4)	91.3 (15.2)	91.5 (13.6)
BMI, kg/m^2	32.2 (2.8)	33.0 (3.3)	32.3 (3.2)	31.9 (2.9)	31.9 (3.0)	32.3 (3.0)
WC, cm	103.1 (10.2)	105.1 (8.7)	103.7 (9.6)	103.4 (9.6)	104.2 (9.7)	103.9 (9.5)
HbA1c, %	5.3 (0.4)	5.3 (0.4)	5.3 (0.4)	5.4 (0.3)	5.3 (0.3)	5.3 (0.3)
SBP, mmHg	119.0 (9.7)	119.6 (13.5)	117.4 (9.1)	120.0 (13.3)	119.2 (13.2)	119.0 (11.5)
HOMA-IR	4.9 (2.6)	5.7 (3.8)	4.9 (2.4)	5.1 (4.4)	5.6 (5.5)	5.1 (3.4)
TG, mmol/L	1.6 (0.8)	1.9 (0.8)	1.7 (0.9)	2.0 (1.1)	1.7 (0.9)	1.8 (0.9)

Data are mean (SD) unless otherwise specified.
WC, waist circumference; SBP, systolic blood pressure; TG, triglycerides.

Efficacy

- The least-squares mean (LS Mean) percentage change from baseline at W24 in body weight was -5.4% (95% CI -7.3% to -3.5%), -13.4% (-15.2% to -11.5%), -14.0% (-15.9% to -12.1%), and -16.8% (-18.8% to -14.9%) in the HRS9531 1.0 mg, 3.0 mg, 4.5 mg, and 6.0 mg groups, respectively, compared to -0.1% (-2.1% to 1.8%) in the placebo group (P<0.0001 for all comparisons with placebo; **Figure 2**).
- The proportion of participants achieving ≥5% body weight reduction from baseline at W24 was 52.0%, 88.2%, 92.0%, 91.8% in the four HRS9531 groups (placebo: 10.2%; **Figure 3**).
- The LS Mean changes from baseline at W24 in the waist circumference and systolic blood pressure in the HRS9531 groups reached up to -12.7 cm and -8.3 mmHg, respectively (placebo: -1.8 cm and -0.4 mmHg; **Figure 4, Table 2**).
- HRS9531 also outperformed placebo in improving glycemic control and reducing triglyceride levels at W24 (**Table 2**).

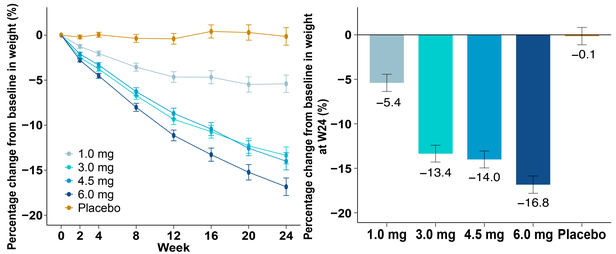
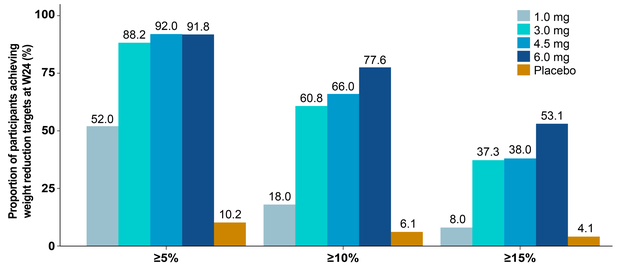


Figure 2. Percentage change in body weight from baseline (LS Mean [SE])

Results



Missing value was imputed by using non-response imputation.

Figure 3. Proportion of participants achieving weight reduction targets at W24

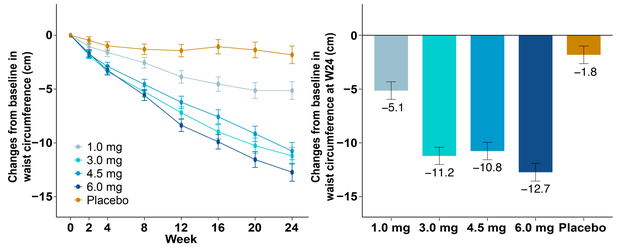


Figure 4. Changes in waist circumference from baseline (LS Mean [SE])

Table 2. The changes from baseline at W24

	HRS9531 1.0 mg (N=50)	HRS9531 3.0 mg (N=51)	HRS9531 4.5 mg (N=50)	HRS9531 6.0 mg (N=49)	Placebo (N=49)
SBP, mmHg*	-4.5 (1.4)	-8.1 (1.4)	-8.3 (1.4)	-7.9 (1.5)	-0.4 (1.4)
DBP, mmHg*	-1.3 (0.9)	-4.6 (0.9)	-3.6 (0.9)	-4.1 (0.9)	-0.7 (0.9)
HbA1c, %*	-0.2 (0.0)	-0.3 (0.0)	-0.4 (0.0)	-0.4 (0.0)	0.1 (0.0)
HOMA-IR*	-0.6 (0.3)	-2.2 (0.3)	-1.7 (0.3)	-2.4 (0.3)	-0.2 (0.3)
TG, %#	-6.6% (38.1)	-29.2% (25.1)	-28.9% (24.9)	-39.0% (24.1)	8.1% (41.6)
ALT, %#	-15.7% (49.1)	-16.6% (70.6)	-33.9% (27.7)	-28.8% (46.3)	18.1% (63.8)
Uric acid, %#	-14.1% (13.0)	-17.4% (16.3)	-20.3% (14.5)	-22.0% (14.3)	-5.1% (15.5)

*Data are value changes from baseline at W24 and presented in LS Mean (SE).
#Data are percentage changes from baseline at W24 and presented in mean (SD).
SBP, systolic blood pressure; DBP, diastolic blood pressure; TG, triglycerides; ALT, alanine aminotransferase.

Results

Safety

- Most adverse events (AEs) were mild or moderate in severity, and the most common AEs were nausea, diarrhea, decreased appetite, and vomiting, occurring primarily during dose escalation (**Table 3**).
- No serious AEs (SAEs) were treatment-related and no participants discontinued treatment due to treatment-related AEs (TRAEs).

Table 3. Adverse events

	HRS9531 1.0 mg (N=49)	HRS9531 3.0 mg (N=51)	HRS9531 4.5 mg (N=50)	HRS9531 6.0 mg (N=49)	Placebo (N=49)
Any AE	34 (69.4)	42 (82.4)	39 (78.0)	44 (89.8)	38 (77.6)
SAE	0	2 (3.9)	1 (2.0)	0	3 (6.1)
AEs leading to treatment discontinuation	1 (2.0)	1 (2.0)	0	0	1 (2.0)
Treatment-related SAE	0	0	0	0	0
TRAEs leading to treatment discontinuation	0	0	0	0	0
Gastrointestinal disorders with ≥5% frequency in any arm					
Nausea	7 (14.3)	14 (27.5)	16 (32.0)	16 (32.7)	4 (8.2)
Diarrhea	5 (10.2)	17 (33.3)	15 (30.0)	15 (30.6)	4 (8.2)
Vomiting	3 (6.1)	10 (19.6)	10 (20.0)	14 (28.6)	1 (2.0)
Abdominal distension	1 (2.0)	9 (17.6)	3 (6.0)	4 (8.2)	0
Eructation	0	2 (3.9)	2 (4.0)	4 (8.2)	0
Dyspepsia	0	4 (7.8)	1 (2.0)	1 (2.0)	0
Abdominal pain	0	1 (2.0)	3 (6.0)	1 (2.0)	0

Data are n (%). One patient in the 1.0 mg group did not receive HRS9531 treatment and was not included in the safety analysis.

Conclusions

- HRS9531 effectively reduced body weight, blood pressure, blood glucose, and triglycerides, with a favorable safety profile.
- These data support further clinical development of HRS9531 for obesity treatment.

Conflict of interest

- Lin Zhao has nothing to declare.

Acknowledgements

- The participants and their families, investigators, and clinical study sites.
- The study is sponsored by Jiangsu Hengrui Pharmaceuticals Co., Ltd.

References: 1. Nauck, et al. Lancet Diabetes Endocrinol 2016; 4: 525–36; 2. Holst, et al. Physiol Rev 2007; 87: 1409–39; 3. Marso, et al. N Engl J Med 2016; 375: 311–22; 4. Tuttle, et al. Lancet Diabetes Endocrinol 2018; 6: 605–17; 5. Rosenstock, et al. Lancet 2021; 398: 143–55; 6. He, et al. Diabetes 2023;72(Supplement_1):763-P; 7. Zhao, et al. Diabetes Res Clin Pract 2024, 209:111436.

Contact: Lin Zhao, MD (zhao.lin@zs-hospital.sh.cn)