Efficacy and Safety of HRS9531, a Dual GLP-1/GIP Receptor Agonist, in Chinese Adults Living with Overweight or Obesity Without Diabetes

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Introduction and Objective

- Use of dual glucagon-like peptide-1/glucose-dependent insulinotropic polypeptide receptor agonists (GLP-1/GIP RAs) for chronic weight management is increasing.[1]
- HRS9531, a dual GLP-1/GIP RA, demonstrated potential for glycemic control and weight loss.[2]
- Once-weekly subcutaneous administration of HRS9531 demonstrated significant reduction in body weight in adults living with overweight or obesity in two Phase 2 studies:
  - Study HRS9531-201: Demonstrated 16.8%* mean weight loss from baseline in the 6 mg group at Week 24 (NCT05881837).[3]
  - Study HRS9531-203: Demonstrated 22.8%* mean weight loss from baseline in the 8 mg group at Week 36 (NCT06054698).[4]

This Phase 3 study (HRS9531-301) evaluated the efficacy and safety of HRS9531 versus placebo as an adjunct to lifestyle intervention in Chinese adults living with overweight or obesity.

1. Neumiller JJ, et al. Diabetes Care. 2025 Feb 1;48(2):177-181; **2.** Kun He, et al. Diabetes 20 June 2023; 72 (Supplement_1): 763–P; **3.** Xiaoying Li, et al. Diabetes 2024;73(Supplement_1):1861-LB (* treatment policy estimand); **4.** Jiaqiang Zhou, et al. Diabetes 20 June 2025; 74 (Supplement_1): 874–P (* treatment polciy estimand).

HRS9531-301 Phase 3 Study Design

48-week, Multicenter, Randomized, Double-Blind, Placebo-Controlled (NCT06396429)

Randomization:

3:1:3:1:3:1

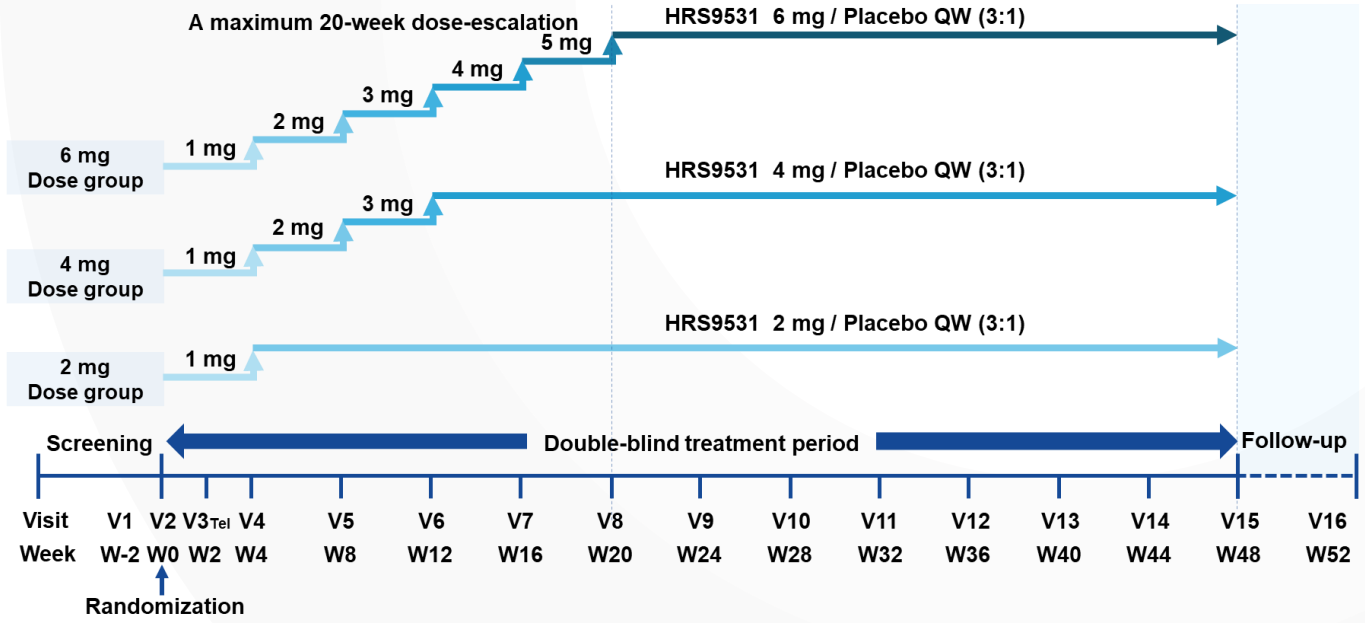
- 2, 4, or 6 mg HRS9531 vs matching placebo

Resulting in 1:1:1:1

- 2, 4, or 6 mg HRS9531 vs combined placebo

Population:

- BMI ≥ 28.0 kg/m^2 or ≥ 24 kg/m^2 with at least 1 weight-related comorbidity without diabetes (HbA1c < 6.5%)



Co-primary Endpoints:

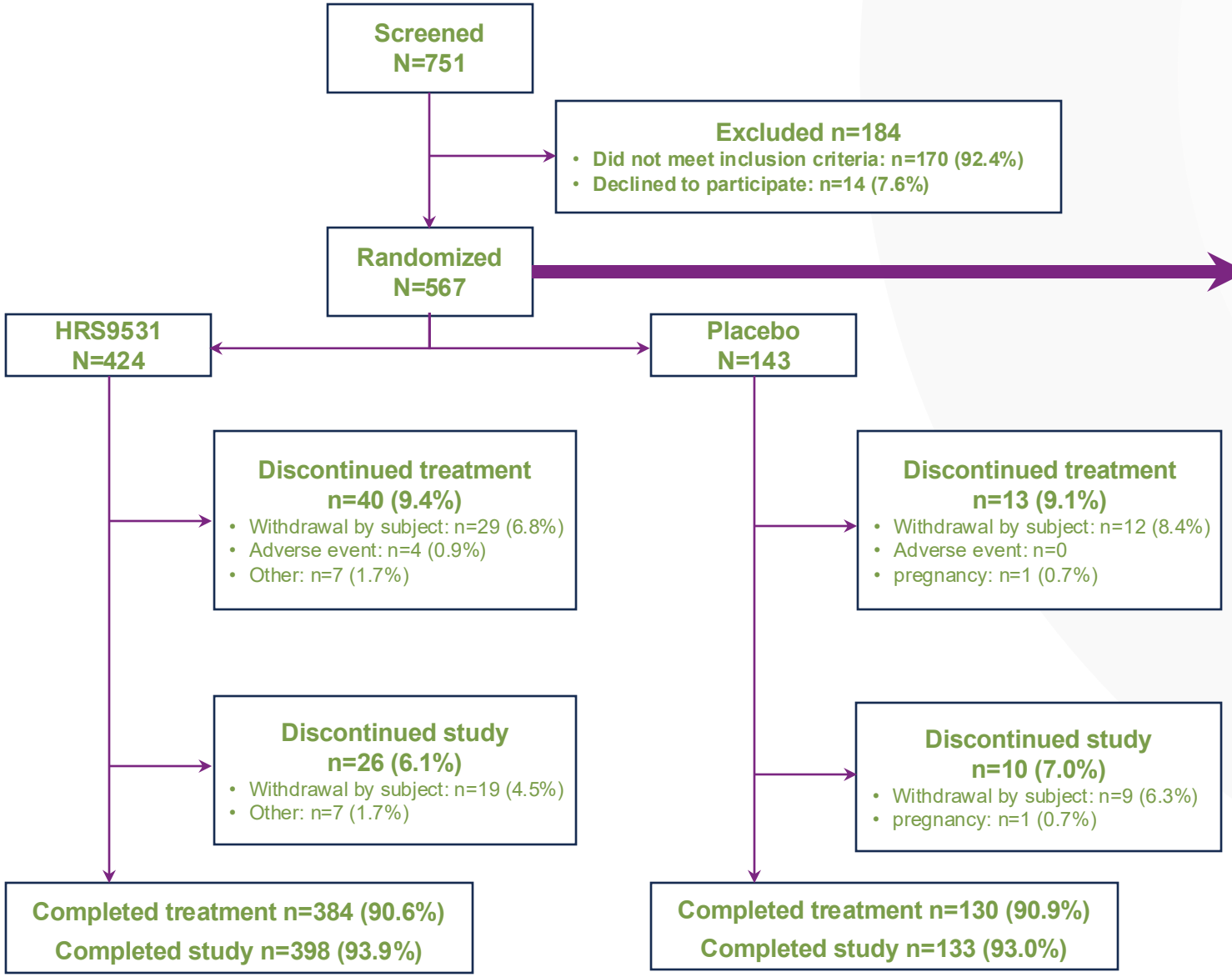
- Percent change in body weight from baseline at Week 48
- Participant proportion achieving ≥ 5% weight reduction from baseline at Week 48

Secondary Endpoints:

- Participant proportion achieving ≥ 10%,15%, and 20% weight reduction from baseline at Week 48
- Change from baseline at Week 48 in waist circumference and BMI
- Change from baseline at Week 48 in blood pressure, lipids, HbA1c, HOMA-IR, hsCRP, etc.

W = week; QW = once per week; BMI = body mass index; HbA1c = glycated hemoglobin A1c; HOMA-IR = homeostatic model assessment of insulin resistance.

Participant Disposition and Baseline



Baseline demographics and characteristics were generally balanced

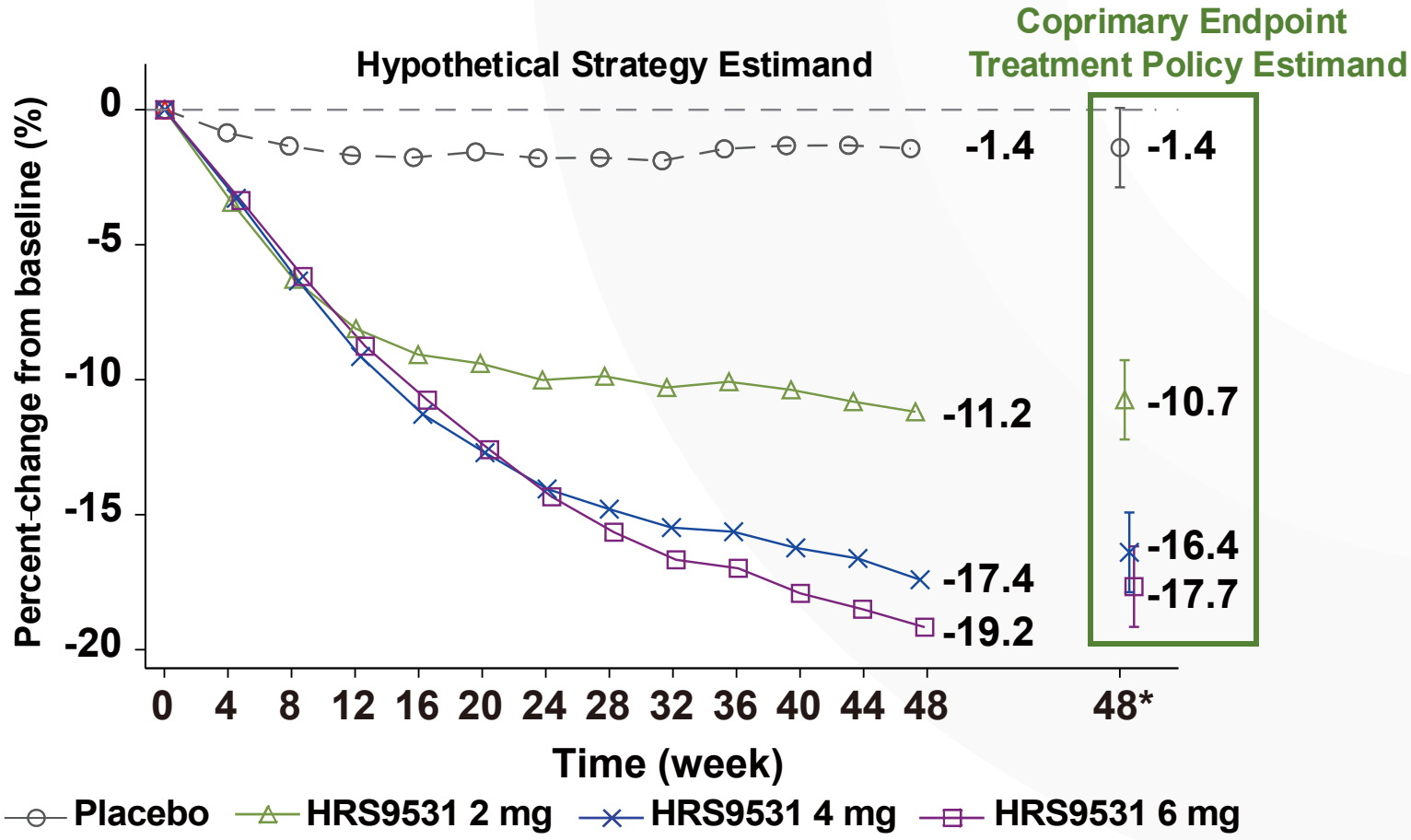
Baseline

Age: 34.4 (8.4) years
Female, n (%): 309 (54.5%)
Weight: 93.0 (17.3) kg
BMI: 33.3 (4.5) kg/m^2
Waist Circumference: 105.8 (11.5) cm
HbA1c: 5.5 (0.4)%
FPG: 5.2 (0.6) mmol/L
Triglycerides*: 1.6 (1.6) mmol/L
Total cholesterol*: 4.8 (1.2) mmol/L
SBP: 119 (11) mmHg
DBP: 81 (8) mmHg

Data are mean (SD) and *data are geometric mean (Geometric SD).
BMI = body mass index; FPG = fasting plasma glucose; HbA1c = glycated hemoglobin A1c; SBP = systolic blood pressure; DBP = diastolic blood pressure

Co-Primary Endpoint: Percent Change in Body Weight

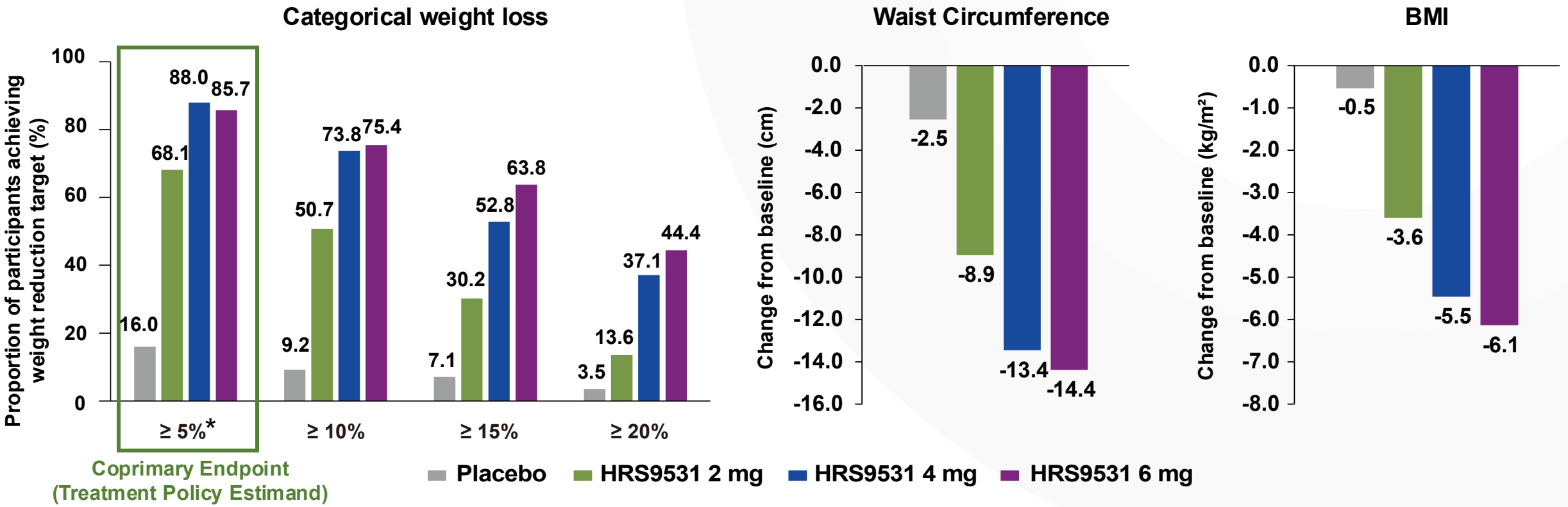
- Body weight continued decreasing in a dose-dependent manner in HRS9531 groups.
- No plateau observed at Week 48 in the 4 mg and 6 mg groups.



All HRS9531 groups vs placebo $P < 0.0001$.
The main graphic data are least square mean performed with MMRM, and 48* data are least square mean performed with ANCOVA.

Co-Primary and Secondary Endpoints

- HRS9531 had larger participant proportions in achieving weight reduction targets from baseline at Week 48.
- Decrease in waist circumference and BMI from baseline in HRS9531 groups was also observed compared to the placebo group at Week 48.

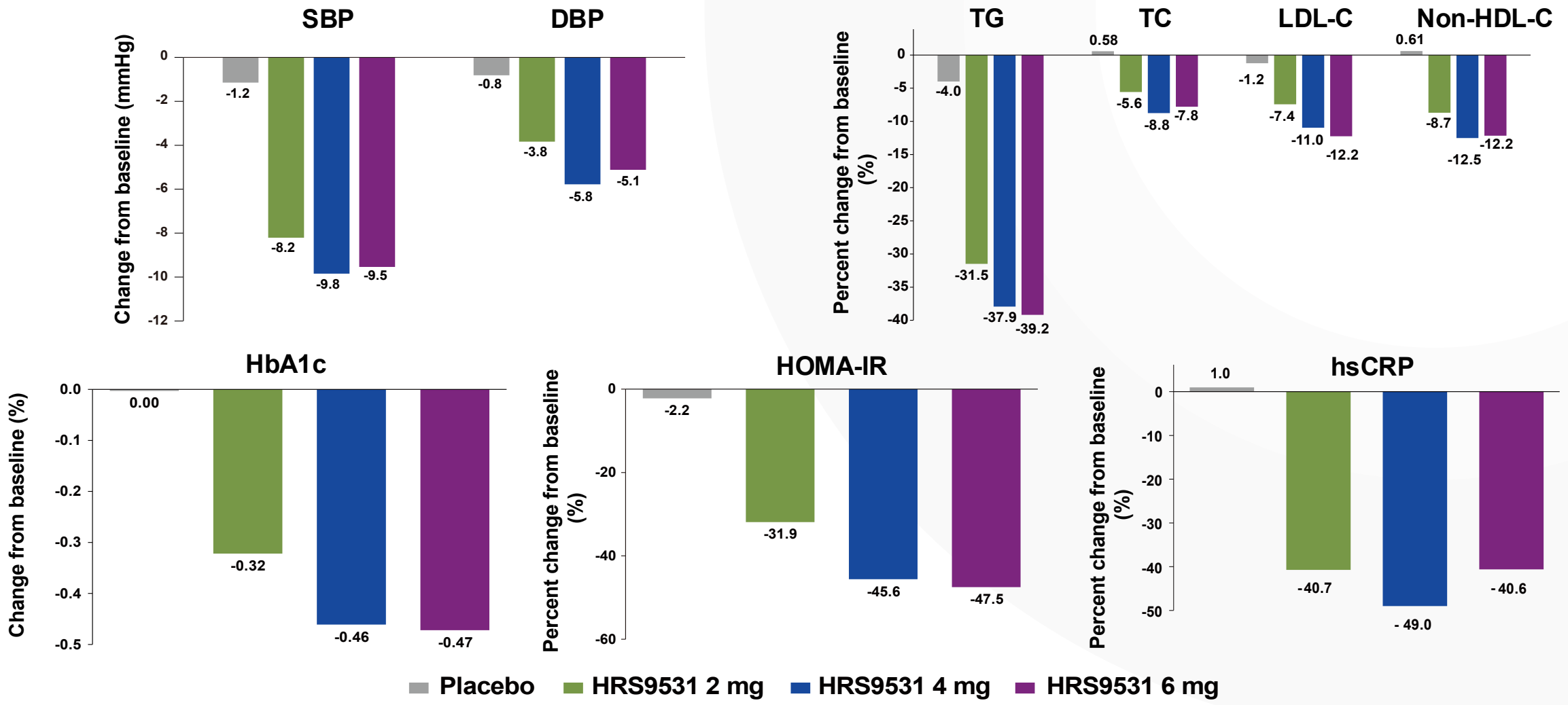


* The coprimary estimand 2 (treatment policy estimand) used the Mantel-Haenszel test.
* All HRS9531 groups vs placebo P < 0.0001.

The analysis of waist circumference from baseline was performed by ANCOVA model and the analysis of BMI from baseline was performed by MMRM model.
Data are least square mean. BMI, body mass index

Improvement in Cardiometabolic Risk Factors

- All HRS9531-treated groups improved cardiometabolic risk factors over baseline compared to placebo at Week 48.



Data are least square mean. The analysis of blood pressure and HbA1c from baseline were performed using MMRM model. The analysis of serum lipid levels, HOMA-IR and hsCRP were performed with natural logarithm transformation using MMRM model. SBP, systolic blood pressure; DBP, diastolic blood pressure; TG, triglyceride; TC, total cholesterol; LDL-C, low density lipoprotein cholesterol; HbA1c, glycated hemoglobin A1c; HOMA-IR, homeostatic model assessment of insulin resistance; hsCRP, high sensitivity C reactive protein.

Safety of HRS9531 Treatment

Among treatment completers, proportion of participants achieving the target dose* in HRS9531 2, 4, 6 mg, and placebo group were 99.2%, 92.2%, 85.8%, and 99.2%, respectively.

- Majority of TEAEs were mild and moderate in severity.
- SAEs were generally balanced among treatment groups.

TEAE, n (%)	Placebo (N=143)	HRS9531 2 mg (N=142)	HRS9531 4 mg (N=141)	HRS9531 6 mg (N=141)
Any TEAEs	128 (89.5)	130 (91.5)	129 (91.5)	132 (93.6)
Mild	75 (52.4)	78 (54.9)	70 (49.6)	72 (51.1)
Moderate	52 (36.4)	51 (35.9)	54 (38.3)	57 (40.4)
Severe	1 (0.7)	1 (0.7)	5 (3.5)	3 (2.1)
SAEs	8 (5.6)	2 (1.4)	7 (5.0)	6 (4.3)
TEAEs leading to death	0	0	0	0
TEAEs leading to permanent discontinuation	0	1 (0.7)	1 (0.7)	2 (1.4)
TEAEs leading to dose reduction	0	2 (1.4)	16 (11.3)	28 (19.9)
TEAEs leading to temporary interruption	4 (2.8)	9 (6.3)	16 (11.3)	16 (11.3)

Data are n (%).
* The definition of achieving the target dose was the last actual dose given to the participant was greater than or equal to the target maintenance dose of the dose group specified in the protocol.
N, number of participants in safety set; n, number of participants in category; TEAE, treatment-emergent adverse event; SAEs, serious adverse events.

Safety of HRS9531 Treatment

- The most common TEAEs were gastrointestinal AEs, including diarrhea, nausea, and vomiting.
- There was a trend of increasing incidence with dose in HRS9531 groups for gastrointestinal disorders and decreased appetite compared to the placebo, while other TEAEs was similar across treatment groups.
- HRS9531 demonstrated a safety profile consistent with those reported for the injectable GLP-1 or GLP-1/GIP receptor agonist class.

TEAE, n (%)	Placebo (N=143)	HRS9531 2 mg (N=142)	HRS9531 4 mg (N=141)	HRS9531 6 mg (N=141)
TEAEs ≥ 10% frequency in any treatment groups				
Diarrhea	10 (7.0)	42 (29.6)	45 (31.9)	50 (35.5)
Nausea	7 (4.9)	23 (16.2)	24 (17.0)	38 (27.0)
Decreased appetite	5 (3.5)	28 (19.7)	28 (19.9)	35 (24.8)
Vomiting	3 (2.1)	20 (14.1)	27 (19.1)	34 (24.1)
Upper respiratory tract infection	28 (19.6)	20 (14.1)	21 (14.9)	27 (19.1)
Hyperuricemia	28 (19.6)	21 (14.8)	11 (7.8)	18 (12.8)
Urinary tract infection	18 (12.6)	13 (9.2)	13 (9.2)	18 (12.8)
Abdominal pain upper	1 (0.7)	3 (2.1)	8 (5.7)	15 (10.6)
Hyperlipidemia	19 (13.3)	13 (9.2)	10 (7.1)	12 (8.5)

Data are n (%).
N, number of participants in safety set; n, number of participants in category; TEAE, treatment-emergent adverse event.

Conclusion

- In Chinese adults living with overweight or obesity without diabetes (baseline BMI 33.3 kg/m^2 and female proportion 54.5%), once-weekly subcutaneous administration of HRS9531 induced mean body weight loss up to 17.7% under treatment policy estimand or 19.2% under hypothetical strategy estimand from baseline at Week 48.
- Up to 88% of participants achieved a weight reduction of at least 5% under the treatment policy estimand at Week 48.
- HRS9531 also showed waist circumference and BMI reduction up to 14.4 cm and 6.1 kg/m^2, respectively, at Week 48.
- HRS9531 improved cardiometabolic risk factors including blood pressure, lipids, glucose, insulin resistance and hsCRP.
- HRS9531 demonstrated a safety profile consistent with those reported for the injectable GLP-1 or GLP-1/GIP receptor agonist class.

Acknowledgements

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