Efficacy and Safety of Oral Ribupatide (HRS9531) in Chinese Adults with Obesity: A Phase 2 Trial

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Introduction

- Dual GLP-1/GIP receptor agonists are emerging as a key therapeutic option in obesity treatment [1].
- Ribupatide (HRS9531) is a novel dual GLP-1/GIP receptor agonist peptide. Its once-weekly **subcutaneous** injection has showed compelling weight loss efficacy in a previously reported phase 3 trial [2].
- This randomized, multicenter, double-blind, placebo-controlled phase 2 study (NCT06841445) aims to evaluate the efficacy and safety of **oral** ribupatide in Chinese adults with obesity without diabetes.

Methods

- In this study, participants without diabetes (BMI of 28−40 kg/m^2, age 18-65 years) were randomized 1:1:1:1 to once-daily (QD) oral ribupatide 10 mg, 25 mg, or 50 mg groups (achieved via titration) or placebo group for 26 weeks (**Figure 1**).
- The primary endpoint was the percentage change in body weight from baseline at week 26.

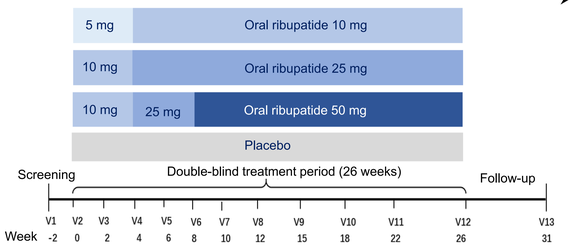

Figure 1. Study design

Results

Participants

- A total of 166 (61 [36.7%] male, 105 [63.3%] female) participants were enrolled and received at least one post-randomization dose of the study treatment, and 151 participants completed treatment.
- The mean baseline body weight and BMI were 92.6 kg and 33.3 kg/m^2.

Efficacy

- Based on hypothetical estimand at week 26, least squares (LS) mean weight loss from baseline were -6.9%, -12.1%, and -12.1% for oral ribupatide 10, 25, and 50 mg, compared to -2.3% for placebo (p=0.0027, p<0.0001 and p<0.0001). The 50 mg group exhibited steeper weight loss compared to the 25 mg group after week 8 without observed reduction plateau in both groups through week 26. (**Figure 2**).

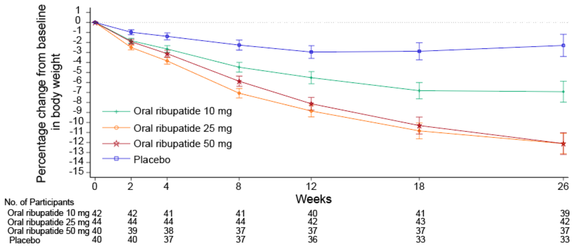

Figure 2. Percentage change in body weight from baseline to week 26 (LS mean [SE])

- For waist circumference, the mean reduction from baseline reached up to -10.8 cm in the oral ribupatide 25 mg and 50 mg groups at week 26, versus -2.6 cm in the placebo group **(Figure 3).**

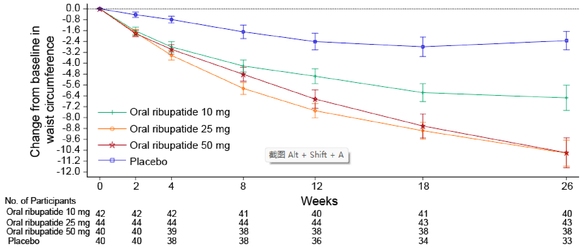

Figure 3. Mean (SE) change in waist circumference from baseline to week 26

Results

- At week 26, the mean change from baseline in BMI reached -4.0 kg/m^2 in the oral ribupatide 25 mg and 50 mg groups, versus -0.7 kg/m^2 in the placebo group **(Figure 4).**

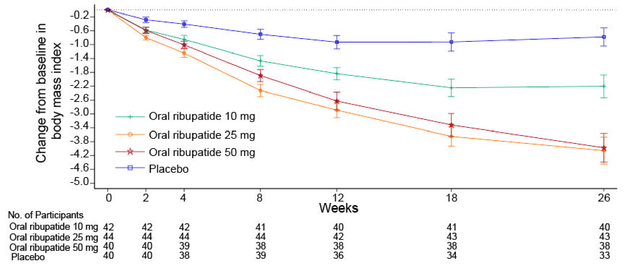

Figure 4. Mean (SE) change in body mass index from baseline to week 26

- At Week 26, oral ribupatide was associated with greater proportions of participants achieving ≥5%, ≥10%, and ≥15% weight reduction, and greater reductions in body weight, blood pressure, triglycerides, and uric acid levels compared with placebo **(Table 1).**

Table 1. Other efficacy outcomes at week 26

	Oral ribupatide 10 mg QD (N=42)	Oral ribupatide 25 mg QD (N=44)	Oral ribupatide 50 mg QD (N=40)	Placebo (N=40)
Pts with ≥5% body weight reduction, n (%)	25 (59.5)	34 (77.3)	31 (77.5)	7 (17.5)
Pts with ≥10% body weight reduction, n (%)	13 (31.0)	26 (59.1)	21 (52.5)	2 (5.0)
Pts with ≥15% body weight reduction, n (%)	2 (4.8)	17 (38.6)	15 (37.5)	1 (2.5)
Body weight, kg, LS mean (SE)	-6.1 (1.0)	-11.1 (1.0)	-10.6 (1.0)	-1.7 (1.0)
SBP, mmHg, LS mean (SE)	-6.1 (1.4)	-6.4 (1.3)	-5.1 (1.4)	-3.9 (1.5)
DBP, mmHg, LS mean (SE)	-3.8 (1.0)	-4.2 (1.0)	-3.7 (1.0)	-0.2 (1.1)
Triglycerides, geometric mean ratio (week 26 / baseline) [95%CI]	0.9 (0.8, 1.0)	0.8 (0.7, 0.8)	0.8 (0.7, 0.9)	1.0 (0.9, 1.1)
Blood uric acid, μmol/L, LS mean (SE)	-32.8 (9.9)	-46.7 (9.5)	-53.7 (10.2)	-5.2 (10.9)

Pts, participants; SBP, systolic blood pressure; DBP, diastolic blood pressure.

Results

Safety

- Treatment-emergent adverse events (TEAEs) were reported in 80.0% to 84.1% of participants across ribupatide dose groups, compared with 80.0% in the placebo group (**Table 2**).
- The majority of TEAEs were mild to moderate in severity, the most common gastrointestinal adverse events (GIAEs) with oral ribupatide were nausea, diarrhea, and vomiting. Most GIAEs occurred during the initial titration period and were transient. Importantly, no GIAEs led to treatment discontinuation or dose reduction.

Table 2. Treatment-emergent adverse events

	Oral ribupatide 10 mg QD (N=42)	Oral ribupatide 25 mg QD (N=44)	Oral ribupatide 50 mg QD (N=40)	Placebo (N=40)
Any TEAEs	35 (83.3)	37 (84.1)	32 (80.0)	32 (80.0)
Mild	28 (66.7)	27 (61.4)	26 (65.0)	24 (60.0)
Moderate	7 (16.7)	9 (20.5)	6 (15.0)	8 (20.0)
Severe	0	1 (2.3)	0	0
SAEs*	1 (2.4)	2 (4.5)	0	1 (2.5)
TEAEs leading to treatment discontinuation	0	0	1 (2.5)#	0
GIAEs$^{\Delta}$ with ≥5% frequency in any arm				
Nausea	5 (11.9)	10 (22.7)	8 (20.0)	3 (7.5)
Diarrhea	2 (4.8)	9 (20.5)	2 (5.0)	2 (5.0)
Vomiting	1 (2.4)	5 (11.4)	3 (7.5)	0
Constipation	1 (2.4)	0	2 (5.0)	1 (2.5)
Hypoglycemia	0	1 (2.3)	1 (2.5)	0
Severe	0	0	0	0

Data are n (%). TEAE, treatment-emergent adverse event; SAE, serious adverse event; GIAE, gastrointestinal adverse event.
* SAEs were reported in the oral ribupatide 10 mg group (one pharyngeal mass, unrelated to study drug), the 25 mg group (one cholelithiasis and acute cholecystitis, possibly related to study drug; and one benign ovarian germ cell teratoma, unrelated to study drug), and the placebo group (one ectopic pregnancy, unrelated to study drug).
# One participant in oral ribupatide 50 mg group discontinued treatment due to ventricular extrasystoles and ventricular tachycardia (unrelated to study drug).
$^{\Delta}$ GIAEs were defined based on a predefined list of preferred terms, including nausea, diarrhea, vomiting, and constipation only.

Conclusions

- In Chinese adults with obesity without diabetes, oral ribupatide with titration regimens (1-2 steps) showed clinically significant body weight reduction compared to placebo over the 26-week treatment period.
- Oral ribupatide also showed metabolic benefits beyond weight loss, along with a favorable safety profile and a low incidence of gastrointestinal adverse events (e.g., vomiting).

References: [1] Neumiller JJ, et al. Diabetes Care. 2025 Feb 1;48(2):177-181. [2] (2025), Oral Abstracts. Obesity (Silver Spring), 33: 6-70.

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