

Efficacy and safety of injectable ribupatide (HRS9531) in Chinese participants with obesity and polyendocrine metabolic ovarian syndrome (PMOS): a multicenter, randomized, double-blind, phase 2 trial

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BACKGROUND

- Ribupatide (HRS9531), a novel GLP-1/GIP dual receptor agonist, has demonstrated weight loss in overweight/obesity, but its effects in polyendocrine metabolic ovarian syndrome (PMOS) remain uncharacterized.
- This multicenter, randomized, double-blind, placebo-controlled phase 2 trial evaluated the efficacy and safety of different doses of ribupatide in Chinese participants with obesity and PMOS.

METHODS

- Participants with PMOS were randomized (1:1:1:1) to once-weekly subcutaneous (sc) ribupatide 1 mg, 2 mg, 4 mg or placebo for 32 weeks (**Figure 1**).
- Primary endpoint: percent change in body weight from baseline to week 32; treatment-policy estimand (ANCOVA).

Inclusion criteria:

- Women aged 18 to 40 years;
- PMOS diagnosed per Chinese criteria: Oligomenorrhea/amenorrhea/irregular bleeding (required) + hyperandrogenism or , polycystic ovarian morphology (PCOM), after exclusion of other causes.
- BMI ≥ 28.0 kg/m².

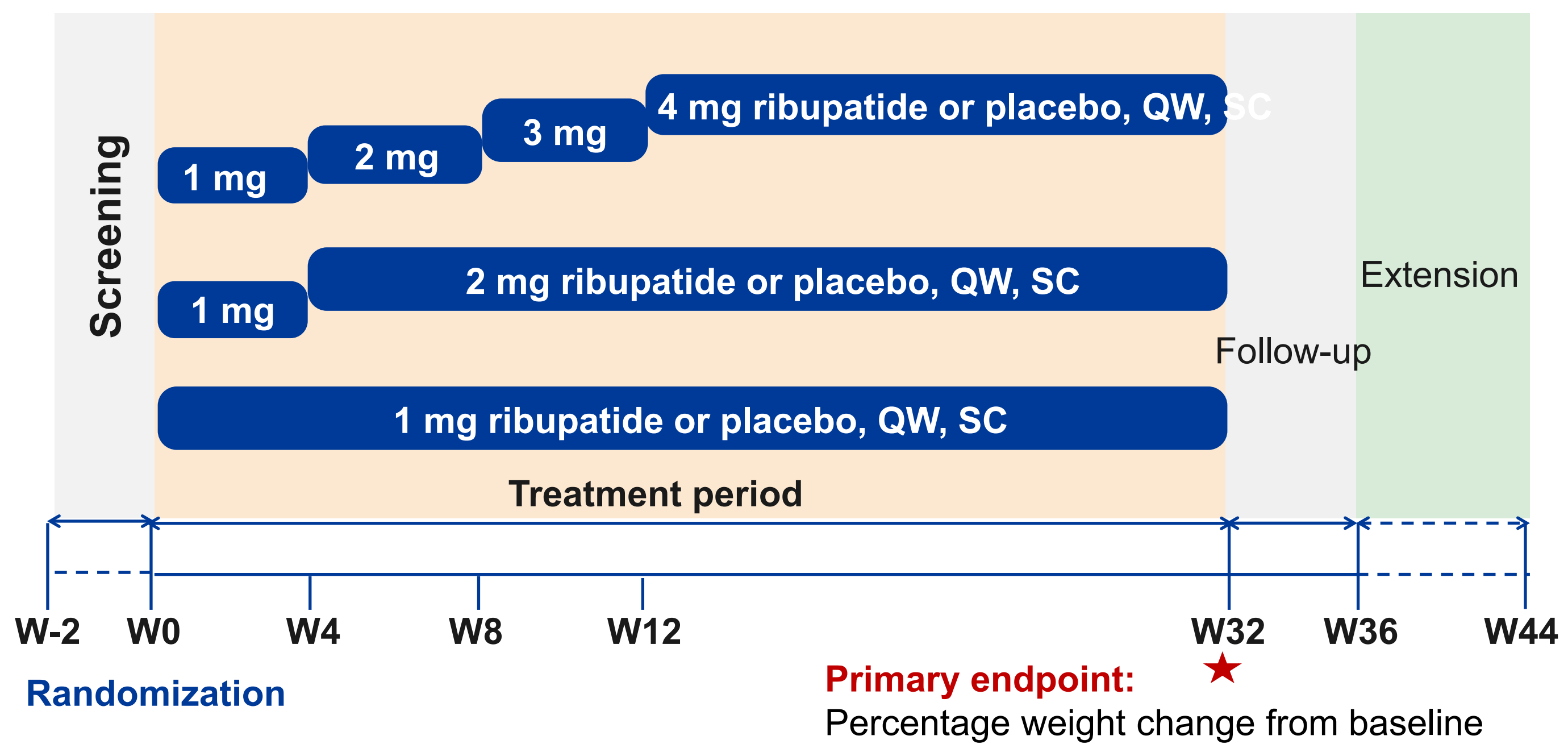


Figure 1. Study design

RESULTS

Baseline characteristics

- A total of 158 participants were randomized, and all received at least one dose of study drug; Treatment was discontinued in 12 participants (7.6%).
- Baseline demographic and clinical characteristics were well balanced across the four treatment groups (**Table 1**).

RESULTS

Table 1. Baseline characteristics

	Ribupatide			Placebo	Total
	1 mg (n = 39)	2 mg (n = 39)	4 mg (n = 40)	(n = 40)	(N = 158)
Age, year	28.4 (4.7)	27.2 (5.4)	27.7 (5.4)	28.8 (5.6)	28.0 (5.3)
Weight, kg	84.4 (10.4)	88.1 (11.9)	85.4 (10.3)	84.7 (10.2)	85.6 (10.7)
BMI, kg/m ²	33.0 (3.8)	33.6 (4.2)	32.8 (3.1)	32.7 (3.3)	33.0 (3.6)
Waist circumference, cm	102.4 (9.7)	101.9 (10.5)	99.3 (8.6)	100.2 (8.6)	100.9 (9.4)
Duration of PMOS, year	4.1 (5.1)	3.8 (4.4)	3.4 (4.3)	3.7 (4.2)	3.7 (4.5)
Menstrual frequency, cycles/12 weeks	1.5 (1.0)	1.2 (0.9)	1.1 (0.8)	1.2 (1.0)	1.2 (0.9)
SHBG, nmol/L	21.0 (8.8)	18.0 (7.3)	20.1 (9.0)	21.5 (9.3)	20.2 (8.7)
FAI	9.8 (6.0)	13.0 (7.8)	10.2 (5.8)	9.7 (8.3)	10.7 (7.1)
HOMA-IR	6.1 (4.3)	6.9 (8.3)	10.7 (24.3)	6.2 (4.5)	7.5 (13.4)
TT, nmol/L	1.7 (0.6)	2.0 (0.7)	1.7 (0.5)	1.7 (0.5)	1.8 (0.6)

Data are mean (SD). BMI, body mass index; SHBG, sex hormone-binding globulin; FAI, free androgen index; HOMA-IR, homeostatic model assessment of insulin resistance; TT, total testosterone. Menstrual frequency was assessed over the 12 weeks prior to informed consent.

Primary endpoint

- **Treatment policy estimand (ANCOVA):** LS mean weight change at week 32 was -10.0%, -15.1%, -20.2% vs -2.6% (placebo); all p < 0.0001.
- Sensitivity analysis (**hypothetical strategy, MMRM**): consistent with primary analysis (**Figure 2**).

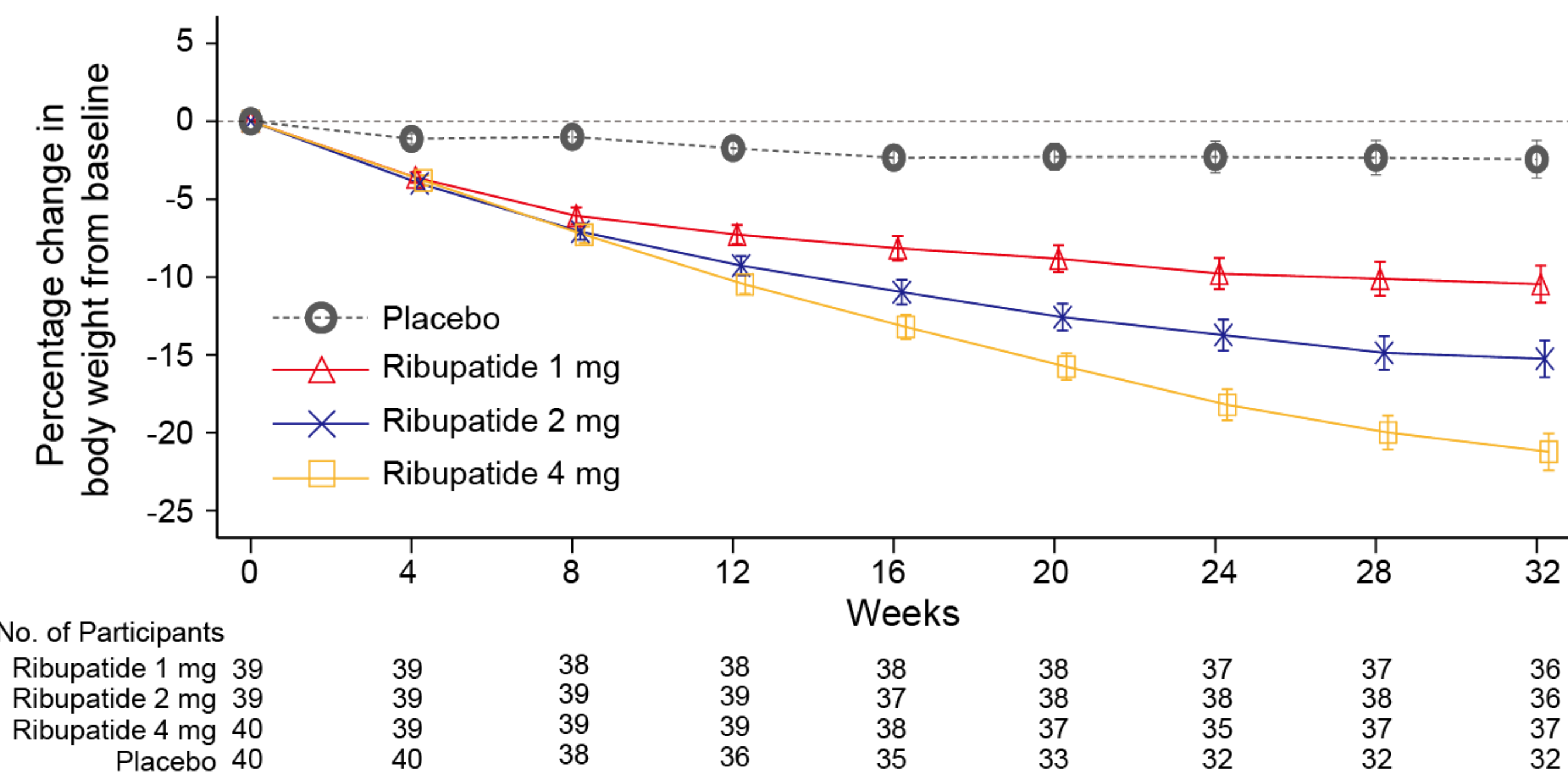


Figure 2. Percentage weight change at week 32

ANCOVA, analysis of covariance; MMRM, mixed-effects model for repeated measures

Other efficacy endpoints

- Menstrual frequency improved dose-dependently: up to 0.9 more cycles over 12 weeks (4 mg) vs 0.2 fewer with placebo (nominal p < 0.0001) (**Table 2**).

RESULTS

Table 2. Menstrual-related endpoints

	Ribupatide			Placebo
	1 mg (n = 39)	2 mg (n = 39)	4 mg (n = 40)	(n = 40)
Menstrual frequency change from baseline at week 32, LSMean (SE), cycles/12 weeks	0.3 (0.2)	0.5 (0.1)	0.9 (0.1)	-0.2 (0.2)
≥3 menstrual cycles of 21-35 days during weeks 12-32, n (%)	11 (28.2)	11 (28.2)	12 (30.0)	3 (7.5)
Regular menstrual cycles at week 32, n (%)	8 (20.5)	5 (12.8)	6 (15.0)	2 (5.0)
Regular ovulation at week 32, n (%)	5 (12.8)	1 (2.6)	3 (7.5)	1 (2.5)

- **≥5% weight loss:** up to 97.5% (4 mg) vs 17.5% (**Table 3**);
- **HOMA-IR** improved dose-dependently (GMR 0.36–0.65 vs 1.11);
- **FAI** reduced dose-dependently (–6.09 to –3.41 vs +0.02).

Table 3. Metabolic and other endpoints

	Ribupatide			Placebo
	1 mg (n = 39)	2 mg (n = 39)	4 mg (n = 40)	(n = 40)
Percentage weight loss ≥5%, n (%)	24 (61.5)	34 (87.2)	39 (97.5)	7 (17.5)
Percentage weight loss ≥10%, n (%)	18 (46.2)	27 (69.2)	34 (85.0)	2 (5.0)
Percentage weight loss ≥15%, n (%)	14 (35.9)	18 (46.2)	28 (70.0)	1 (2.5)
Percentage weight loss ≥20%, n (%)	5 (12.8)	10 (25.6)	19 (47.5)	0
GMR of HOMA-IR at week 32 to baseline (95% CI)	0.65 (0.51, 0.84)	0.60 (0.47, 0.76)	0.36 (0.28, 0.45)	1.11 (0.86, 1.44)
FAI change from baseline, LSMean (SE)	-3.41 (0.74)	-3.91 (0.73)	-6.09 (0.71)	0.02 (0.75)

LSMean, least squares mean; SE, standard error; CI, confidence interval; GMR, geometric mean ratio;

Safety endpoints

- Incidences of adverse events (AEs) were comparable across all groups (**Table 4**).
- No serious TRAEs, no AESI, and no AEs leading to treatment discontinuation occurred.

Table 4. Adverse events

	Ribupatide			Placebo
	1 mg (n = 39)	2 mg (n = 39)	4 mg (n = 40)	(n = 40)
Any AE	34 (87.2)	35 (89.7)	37 (92.5)	34 (85.0)
Mild	28 (71.8)	23 (59.0)	33 (82.5)	27 (67.5)
Moderate	5 (12.8)	12 (30.8)	4 (10.0)	6 (15.0)
Severe	1 (2.6)	0	0	1 (2.5)
TRAE	22 (56.4)	26 (66.7)	31 (77.5)	15 (37.5)
Gastrointestinal Adverse Events (≥10% in Any Group)				
Diarrhea	8 (20.5)	7 (17.9)	7 (17.5)	0
Nausea	4 (10.3)	5 (12.8)	12 (30.0)	1 (2.5)
Vomiting	3 (7.7)	6 (15.4)	7 (17.5)	1 (2.5)

Data are n (%). AE, adverse event; TRAE, treatment-related adverse event.

CONCLUSIONS

- Injectable ribupatide 1, 2, 4 mg significantly reduced body weight in a dose-dependent manner, by up to 20.2% at week 32.
- Injectable ribupatide 1, 2, 4 mg improved menstrual frequency, regularity, insulin resistance, and hyperandrogenism in Chinese women with obesity and PMOS.
- Injectable ribupatide 1, 2, 4 mg showed a favorable safety profile with no new safety signals identified.

ACKNOWLEDGEMENT

- We sincerely thank all the participants and their families for their valuable contribution to this study.
- This study was sponsored by Jiangsu Hengrui Pharmaceuticals Co., Ltd.

