Safiglipron (HRS-7535) for Weight Management in Chinese Adults With Overweight or Obesity: Phase 3 HARBOR-1 Study

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Background

- Obesity is a chronic disease associated with cardiometabolic complications and a substantial disease burden in China.[1]
- Injectable GLP-1 receptor agonists have shown clinically meaningful weight reduction, and oral small-molecule agents offer an alternative route of administration for weight management.[2,3]
- Safiglipron (HRS-7535) is a once-daily oral small-molecule GLP-1 receptor agonist that can be taken without restrictions on meal timing or water intake.
- A phase 2 trial showed weight reduction in Chinese adults with obesity without diabetes, supporting phase 3 evaluation of its efficacy and safety over a longer treatment period.[4]

Objective

- To evaluate the efficacy and safety of once-daily oral safiglipron 120 mg and 180 mg versus placebo in Chinese adults with overweight or obesity without diabetes.

Methods

- HARBOR-1 (NCT06904105) was a randomized, double-blind, placebo-controlled phase 3 trial conducted at 50 sites in China. Adults aged 18–75 years without diabetes and with BMI ≥28 kg/m², or BMI ≥24 kg/m² and ≥1 weight-related complication, were randomized 2:2:1 to safiglipron 120 mg, 180 mg, or placebo once daily for 50 weeks, followed by 2 weeks of safety follow-up. All groups received lifestyle counseling (Figure 1).
- Safiglipron was initiated at 30 mg and increased by 30 mg every 4 weeks to the assigned target dose. Treatment could be taken without restrictions on meal timing or water intake. Dose interruption, delayed titration, and dose reduction were permitted for gastrointestinal intolerance.
- **Coprimary endpoints** were percentage change in body weight and the proportion achieving ≥5% weight reduction at week 44, assessed under the primary treatment-policy estimands. Key secondary endpoints at week 44 were ≥10% and ≥15% weight reduction and change in waist circumference.
- Efficacy was assessed in all randomized participants; safety was assessed in all treated participants.
- A prespecified fixed-sequence procedure controlled multiplicity for the coprimary, key secondary, and selected secondary comparisons. Analysis and missing-data methods are summarized in the figure footnotes.

Figure 1. Study design and participant disposition



Dose modification was permitted for gastrointestinal intolerance.
Participants who discontinued study treatment could remain in the trial for follow-up.

Figure 1 Study design and participant disposition

Participants were randomized 2:2:1 and received once-daily oral treatment with lifestyle counseling. The nominal titration schedule, week 44 coprimary assessment, week 50 treatment completion, and week 52 safety follow-up are shown. Dose modification was permitted for gastrointestinal intolerance; participants who discontinued study treatment could remain in the trial for follow-up. BMI, body mass index.

Results

Participants

- Of 728 adults screened, 556 were randomized: 222 to safiglipron 120 mg, 223 to 180 mg, and 111 to placebo. All randomized participants received study treatment.
- Baseline demographic and clinical characteristics were generally similar across treatment groups (Table 1). Mean age was 34.5 years, 62.1% were women, mean body weight was 94.1 kg, and mean BMI was 34.0 kg/m² (Table 1). Overall, 415 participants (74.6%) completed 50 weeks of treatment.

Table 1 Baseline demographic and clinical characteristics

Characteristic	Safiglipron 120 mg (n=222)	Safiglipron 180 mg (n=223)	Placebo (n=111)	Total (n=556)
Age, years	34.0 (8.2)	35.0 (8.8)	34.8 (8.6)	34.5 (8.5)
Female sex, n (%)	137 (61.7%)	139 (62.3%)	69 (62.2%)	345 (62.1%)
Body weight, kg	93.7 (16.3)	93.7 (14.5)	95.4 (18.2)	94.1 (16.0)
BMI, kg/m²[a]	34.0 (3.3)	33.9 (3.4)	34.4 (3.8)	34.0 (3.5)
BMI category, n (%)				
<32.5 kg/m²	88 (39.6%)	90 (40.4%)	45 (40.5%)	223 (40.1%)
≥32.5 kg/m²	134 (60.4%)	133 (59.6%)	66 (59.5%)	333 (59.9%)
Waist circumference, cm	105.8 (10.7)	105.9 (10.3)	106.7 (12.1)	106.0 (10.8)
HbA1c, %[b]	5.5 (0.3)	5.5 (0.3)	5.5 (0.3)	5.5 (0.3)
Fasting plasma glucose, mmol/L[b]	5.5 (0.7)	5.4 (0.5)	5.5 (0.6)	5.5 (0.6)
Triglycerides, mmol/L	1.9 (1.1)	1.9 (1.0)	2.1 (1.4)	2.0 (1.1)
Total cholesterol, mmol/L	4.8 (0.9)	4.9 (0.9)	4.9 (1.0)	4.9 (0.9)
Systolic blood pressure, mm Hg	119.5 (11.1)	118.4 (11.6)	120.1 (12.8)	119.2 (11.7)
Diastolic blood pressure, mm Hg	82.0 (7.3)	81.2 (7.5)	81.4 (8.9)	81.6 (7.7)
≥1 weight-related complication, n (%)[c]	129 (58.1%)	141 (63.2%)	70 (63.1%)	340 (61.2%)

Data are mean (SD) or n (%). Percentages may not total 100 because of rounding. [a] BMI was calculated as weight in kilograms divided by height in meters squared. [b] Fasting plasma glucose was measured at the central laboratory. Baseline HbA1c used central-laboratory data, with local-laboratory data used when central values were missing. [c] Weight-related complications were based on medical history and coded using MedDRA version 28.0. BMI, body mass index; HbA1c, glycated hemoglobin; MedDRA, Medical Dictionary for Regulatory Activities.

Cardiometabolic outcomes

- At week 50, waist circumference, fasting plasma glucose, triglycerides, and HDL cholesterol showed numerically favorable changes with both doses of safiglipron versus placebo (Table 2).

Table 2 Selected cardiometabolic outcomes at week 50

Change from baseline (95% CI)	Safiglipron 120 mg	Safiglipron 180 mg	Placebo
Waist circumference, cm	−7.60 (−8.56 to −6.64)	−8.83 (−9.77 to −7.90)	−3.31 (−4.62 to −2.00)
FPG, mmol/L	−0.11 (−0.20 to −0.02)	−0.19 (−0.28 to −0.11)	0.15 (0.03 to 0.27)
SBP, mm Hg	−3.34 (−4.74 to −1.93)	−4.20 (−5.58 to −2.81)*	−1.55 (−3.48 to 0.37)
Triglycerides, %	−19.97 (−24.59 to −15.07)	−24.16 (−28.51 to −19.55)	−10.04 (−17.03 to −2.47)
HDL cholesterol, %	9.51 (7.00 to 12.08)	11.69 (9.14 to 14.31)	3.41 (0.21 to 6.72)

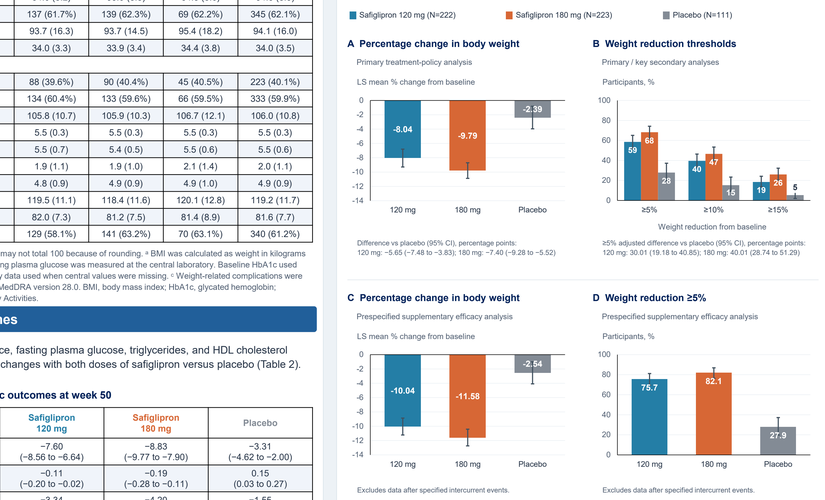
Values are LS mean changes with 95% CIs for waist circumference, FPG, and SBP, and geometric mean percentage changes with 95% CIs for lipids; lipid estimates and CI limits were back-transformed from the natural-log scale. Analyses included all randomized participants. MMRM was used for fasting plasma glucose, systolic blood pressure, and lipids; lipid outcomes were analyzed on the natural-log scale. Waist circumference used ANCOVA, with retrieved-dropout imputation when prespecified treatment-group/intercurrent-event feasibility criteria were met, and copy-reference multiple imputation otherwise, for missing data after treatment discontinuation or weight-altering treatments and missing-at-random imputation otherwise. *The 180-mg versus placebo SBP comparison met the prespecified multiplicity-controlled superiority criterion (LS mean difference, −2.65 mm Hg; 95% CI, −5.01 to −0.29; P=0.0281); the 120-mg comparison did not (−1.78 mm Hg; 95% CI, −4.15 to 0.58; P=0.1389). Week 50 waist circumference and fasting plasma glucose were outside the testing hierarchy; lipid comparisons were nominal. ANCOVA, analysis of covariance; FPG, fasting plasma glucose; HDL, high-density lipoprotein; MMRM, mixed-effects model for repeated measures; SBP, systolic blood pressure.

Body weight outcomes at week 44

At week 44, least-squares (LS) mean percentage changes from baseline in body weight under the primary treatment-policy estimands were −8.04%, −9.79%, and −2.39% with safiglipron 120 mg, 180 mg, and placebo, respectively. Differences versus placebo were −5.65 percentage points (95% CI, −7.48 to −3.83) and −7.40 percentage points (95% CI, −9.28 to −5.52; both P<0.0001). The proportions achieving ≥5% weight reduction were 58.6%, 68.2%, and 27.9%, respectively (Figure 2). Both doses met superiority criteria for all 3 key secondary endpoints at week 44.

The prespecified supplementary efficacy estimand, assuming adherence to assigned protocol treatment and using a hypothetical strategy for specified intercurrent events, supported the primary findings: LS mean percentage changes from baseline in body weight were −10.04%, −11.58%, and −2.54%, respectively (Figure 2C and D).

Figure 2. Efficacy outcomes at week 44



Waist circumference change at week 44 — LS mean (95% CI), cm

120 mg	180 mg	Placebo
−8.03 (−9.25 to −6.82)	−9.04 (−9.98 to −8.09)	−3.71 (−5.13 to −2.29)

Error bars indicate 95% CIs. Coprimary outcomes: body weight change and ≥5% weight reduction. Both doses: P<0.0001 vs placebo for the coprimary outcomes; P<0.001 for all outcomes displayed. P values for supplementary efficacy analyses are nominal. LS, least-squares.

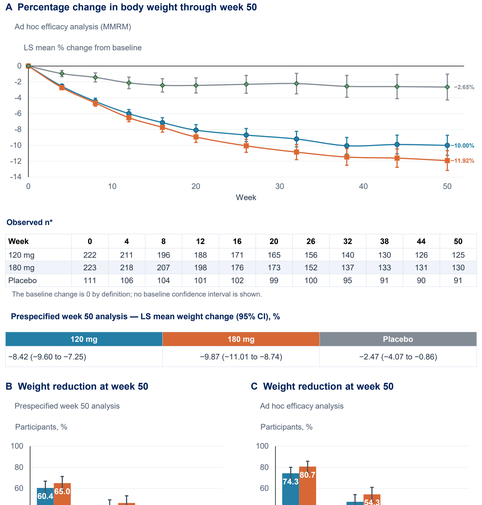
Figure 2 Coprimary and key secondary outcomes at week 44

A, Percentage change from baseline in body weight under the treatment-policy estimand. B, ≥5%, ≥10%, and ≥15% weight reduction. C–D, Prespecified supplementary efficacy estimand. Error bars indicate 95% CIs. All randomized participants were included (222/223/111). Treatment-policy effects were assessed regardless of treatment discontinuation or weight-altering treatments, using ANCOVA and stratified Mantel–Haenszel methods. After these events, the prespecified missing-data procedure specified retrieved-dropout imputation when feasibility criteria were met within treatment-group/intercurrent-event categories, and copy-reference imputation otherwise; other missing data were imputed under a missing-at-random assumption. The supplementary estimand assumed adherence to protocol treatment and used a hypothetical strategy excluding data after treatment discontinuation, weight-altering treatments, or insufficient drug exposure; MMRM estimated weight change and responder status. Primary and key secondary comparisons were multiplicity controlled; supplementary P values were nominal. ANCOVA, analysis of covariance; CI, confidence interval; MMRM, mixed-effects model for repeated measures.

Body weight outcomes through week 50

- For both doses of safiglipron, weight reduction was maintained through week 50. In the prespecified week 50 analysis based on the treatment estimand, LS mean percentage changes in body weight were −8.42%, −9.87%, and −2.47% with safiglipron 120 mg, 180 mg, and placebo, respectively. Both doses were superior to placebo for the 4 prespecified week 50 secondary body weight outcomes (percentage change in body weight and proportions achieving ≥5%, ≥10%, and ≥15% weight reduction) within the fixed-sequence testing procedure. In the ad hoc efficacy-estimand analysis using a hypothetical strategy, corresponding weight changes were −10.00%, −11.92%, and −2.65% (Figure 3).

Figure 3. Weight outcomes through week 50



Error bars indicate 95% CIs.
All estimates in panel A use the same ad hoc MMRM analysis; its week 44 values differ from Figure 2C.
*n: participants with an observed value at the visit and no prior specified intercurrent event.

Figure 3 Weight outcomes through week 50

A, Percentage change from baseline in body weight through week 50 in the ad hoc efficacy-estimand MMRM analysis. B, Proportions achieving ≥5%, ≥10%, and ≥15% weight reduction in the prespecified week 50 secondary analysis. C, The same thresholds in the ad hoc efficacy-estimand analysis. Error bars indicate 95% CIs. Note: The prespecified week 50 analysis used all collected data and was not defined within an estimand framework. The ad hoc analysis used a hypothetical strategy for the intercurrent events described in Figure 2C and D. All estimates in panel A were derived from the same ad hoc MMRM analysis through week 50; its week 44 values differ from the prespecified supplementary analysis in Figure 2C. n denotes participants with a nonmissing observation at each visit and no specified intercurrent event before that visit (week 50: 125/130/91). Prespecified weight comparisons were multiplicity controlled.

Safety

- Treatment-emergent adverse events (TEAEs) occurred in 98.2%, 97.8%, and 91.0% of participants receiving safiglipron 120 mg, 180 mg, and placebo, respectively.
- Nausea and vomiting occurred predominantly during dose escalation.
- All events in the prespecified gastrointestinal TEAE grouping were mild or moderate.
- TEAEs led to treatment discontinuation in 4.1%, 3.1%, and 2.7%, respectively. Serious TEAEs occurred in 3.6%, 2.7%, and 5.4%; no deaths occurred (Table 3).
- Most participants reached their assigned target dose: 188/222 (84.7%) with 120 mg and 163/223 (73.1%) with 180 mg. Among treatment completers, the final dose was the assigned target dose in 130/160 (81.3%) and 115/164 (70.1%), respectively.
- Hypoglycemic events occurred in 8.6%, 9.4%, and 3.6%, respectively, with no severe events.

Table 3 Treatment-emergent adverse events during the 50-week treatment period

Event, n (%)	Safiglipron 120 mg (n=222)	Safiglipron 180 mg (n=223)	Placebo (n=111)
Overall safety summary			
Any TEAE	218 (98.2)	218 (97.8)	101 (91.0)
Treatment-related TEAE	207 (93.2)	208 (93.3)	64 (57.7)
Serious TEAE	8 (3.6)	6 (2.7)	6 (5.4)
Death	0	0	0
TEAE leading to study-treatment discontinuation	9 (4.1)	7 (3.1)	3 (2.7)
Gastrointestinal TEAE leading to study-treatment discontinuation	9 (4.1)	5 (2.2)	1 (0.9)
Prespecified gastrointestinal TEAE grouping	198 (89.2)	195 (87.4)	41 (36.9)
Prespecified adverse events of special interest	0	0	1 (0.9)
Acute pancreatitis	0	0	1 (0.9)
Liver function abnormality	0	0	0
Increased blood calcitonin	0	0	0
Severe hypoglycemia	0	0	0
TEAEs occurring in ≥10% of participants in any group			
Nausea	156 (70.3)	156 (70.0)	18 (16.2)
Vomiting	148 (66.7)	153 (68.6)	5 (4.5)
Diarrhea	82 (36.9)	80 (35.9)	17 (15.3)
Decreased appetite	63 (28.4)	68 (30.5)	13 (11.7)
Upper respiratory tract infection	62 (27.9)	58 (26.0)	37 (33.3)
Abdominal distension	47 (21.2)	41 (18.4)	10 (9.0)
Dizziness	39 (17.6)	43 (19.3)	4 (3.6)
Hyperuricemia	29 (13.1)	38 (17.0)	17 (15.3)
Headache	21 (9.5)	28 (12.6)	6 (5.4)
Constipation	23 (10.4)	23 (10.3)	9 (8.1)
Gastroesophageal reflux disease	21 (9.5)	24 (10.8)	4 (3.6)
Upper abdominal pain	27 (12.2)	17 (7.6)	4 (3.6)
Urinary tract infection	20 (9.0)	24 (10.8)	6 (5.4)
Dyslipidemia	23 (10.4)	14 (6.3)	6 (5.4)
Hyperlipidemia	19 (8.6)	15 (6.7)	12 (10.8)
Positive urine white blood cells	9 (4.1)	14 (6.3)	12 (10.8)
Asthenia	25 (11.3)	12 (5.4)	4 (3.6)

Safety population. Data are n (%); participants were counted once for each event category and preferred term. All events in the prespecified gastrointestinal TEAE grouping (nausea, vomiting, diarrhea, constipation, abdominal distension, and decreased appetite) were mild or moderate. Prespecified adverse events of special interest included liver function abnormality, acute pancreatitis, increased blood calcitonin, and severe hypoglycemia; these categories are distinct from individual laboratory abnormalities listed as TEAEs. Hypoglycemic events reported in the text include potential symptomatic events without a corresponding glucose measurement. TEAE, treatment-emergent adverse event.

Conclusions

- Once-daily oral safiglipron 120 mg and 180 mg achieved clinically meaningful weight reduction compared with placebo, meeting both coprimary and all 3 key secondary endpoints at week 44, with weight reduction maintained through week 50.
- Favorable changes in selected cardiometabolic measures supported the weight findings.
- Gastrointestinal adverse events were frequent but mild or moderate in the prespecified grouping, and treatment discontinuation due to adverse events was infrequent.

References

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