Safiglipron (HRS-7535) Effect on Glycaemic Status in Prediabetes of Obese and Overweight Participants with Comorbidity: HARBOR-1 Subgroup Analysis

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Background

- **Prediabetes**, typically defined as blood glucose levels above normal but below diabetes thresholds, is associated with an increased risk of developing type 2 diabetes mellitus (T2DM)[1].
- **Glucagon-like peptide-1 receptor agonists (GLP-1RAs)**, as a class of therapeutic agents, can improve glycemia through glucose-dependent insulin secretion and glucagon suppression, slowing of gastric emptying, and reduction of caloric intake and bodyweight[2].
- **Safiglipron (HRS-7535)** is a once-daily oral small-molecule GLP-1RA in development for T2DM and chronic weight management[3]. HARBOR-1 has evaluated the efficacy and safety of safiglipron in Chinese adults with overweight/obesity without diabetes.
- **This ad hoc analysis of HARBOR-1** aimed to assess the efficacy and safety of safiglipron (120 mg or 180 mg, once daily, orally) on glycemic status in prediabetes and normoglycemia subgroups of the main analysis population of HARBOR-1 (Chinese adults with overweight/obesity and without diabetes).

Study design

- This was an ad hoc exploratory subgroup analysis of a multicenter, randomized, double-blind, placebo-controlled phase 3 trial (HARBOR-1, NCT06904105) conducted in China. The main study enrolled adults without diabetes who had a BMI ≥ 28.0 kg/m², or a BMI ≥ 24.0 kg/m² with at least one weight-related comorbidity. Eligible participants were randomized 2:2:1 to once-daily safiglipron 120 mg, 180 mg, or placebo for 50 weeks, with step-wise dose titration (**Figure 1**).
- Participants from the main study were stratified according to baseline glycemic status, defined by HbA1c levels per ADA criteria[4], into a prediabetes subgroup (HbA1c 5.7-6.4%) and a normoglycemia subgroup (HbA1c < 5.7%).
- The outcomes of interest were defined as the changes from baseline in HbA1c and FPG at week 50 among participants with prediabetes receiving safiglipron compared to placebo. We also assessed reversion to normoglycemia, progression from baseline normoglycemia to HbA1c ≥ 5.7%, changes in bodyweight, and insulin resistance by HOMA-IR and TyG index.
- All analyses were exploratory; P-values are nominal and were not adjusted for multiple comparisons.

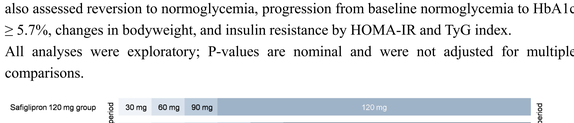


Figure 1. Study design

Results

Participants

This ad hoc analysis included 556 participants from the main study with available baseline HbA1c data, stratified by HbA1c into prediabetes (5.7-6.4%, N = 167) and normoglycemia (<5.7%, N = 389). Participants receiving safiglipron 120 mg, 180 mg, and placebo included 71, 60, and 36 in the prediabetes subgroup, and 151, 163, and 75 in the normoglycemia subgroup.

Baseline characteristics

Baseline characteristics were generally similar between the safiglipron groups and the placebo group among prediabetes participants, and likewise in normoglycemia participants (**Table 1**).

Table 1. Baseline characteristics

Characteristics	Prediabetes (HbA1c 5.7%-6.4%)			Normoglycaemia (HbA1c <5.7%)		
	Safiglipron 120 mg (N=71)	Safiglipron 180 mg (N=60)	Placebo (N=36)	Safiglipron 120 mg (N=151)	Safiglipron 180 mg (N=163)	Placebo (N=75)
Age, years	36.0 (8.0)	36.4 (10.3)	37.0 (10.3)	33.1 (8.2)	34.4 (8.2)	33.7 (7.5)
Male, n (%)	31 (43.7)	27 (45.0)	15 (41.7)	54 (35.8)	57 (35.0)	27 (36.0)
Bodyweight, kg	96.7 (17.6)	97.9 (14.4)	97.1 (17.4)	92.4 (15.5)	92.2 (14.3)	94.6 (18.6)
BMI, kg/m²	34.4 (3.6)	34.7 (3.5)	35.1 (4.0)	33.8 (3.2)	33.6 (3.3)	34.1 (3.8)
BMI group						
<32.5 kg/m², n (%)	27 (38.0)	17 (28.3)	12 (33.3)	61 (40.4)	73 (44.8)	33 (44.0)
≥32.5 kg/m², n (%)	44 (62.0)	43 (71.7)	24 (66.7)	90 (59.6)	90 (55.2)	42 (56.0)
HbA1c, %	5.89 (0.17)	5.88 (0.17)	5.89 (0.22)	5.30 (0.22)	5.30 (0.25)	5.31 (0.20)
FPG, mmol/L	5.89 (0.90)	5.72 (0.51)	5.78 (0.58)	5.29 (0.45)	5.31 (0.44)	5.37 (0.53)
HOMA-IR, geometric mean (geometric SD)	7.58 (1.83)	6.90 (1.70)	7.04 (1.89)	5.45 (1.73)	4.95 (1.76)	5.34 (1.74)
HOMA-β, geometric mean (geometric SD)	258.90 (1.73)	252.06 (1.66)	250.05 (1.79)	269.33 (1.65)	238.55 (1.69)	249.99 (1.58)
Triglyceride-glucose index	7.44 (0.56)	7.44 (0.51)	7.56 (0.53)	7.24 (0.51)	7.24 (0.50)	7.29 (0.59)

Data are mean (SD), n (%), or geometric mean (geometric SD). Percentages were calculated using the number of participants in each baseline HbA1c category and treatment group as the denominator.

Efficacy

- **HbA1c and FPG changes from baseline at Week 50 among prediabetic participants**

  At Week 50, based on an ad hoc analysis using an efficacy estimand in which data after intercurrent events were excluded (intercurrent events included premature discontinuation of study treatment and insufficient drug exposure), among participants with baseline prediabetes, the LS mean changes in HbA1c (%) were −0.29% and −0.38% for the safiglipron 120 mg and safiglipron 180 mg groups, vs -0.01% for placebo, with corresponding placebo-adjusted differences of −0.29% (p = 0.0003) and −0.38% (p < 0.0001) (**Figure 2A**). Reductions in FPG were also observed with both safiglipron doses (-0.53 mmol/L and -0.47 mmol/L vs -0.03 mmol/L for placebo). The corresponding placebo-adjusted differences were −0.49 mmol/L (p = 0.0011) and −0.44 mmol/L (p = 0.0039), respectively (**Figure 2B**).

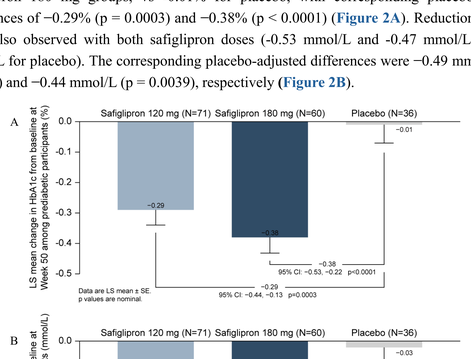


Figure 2. Effects of safiglipron on glycemic markers in baseline prediabetes. (A) Change in HbA1c (%) from baseline at Week 50. (B) Change in FPG (mmol/L) from baseline at Week 50. Analyses were ad hoc (efficacy estimand). Data after intercurrent events were excluded. Intercurrent events include premature discontinuation of study treatment and insufficient drug exposure. A REML-based MMRM included treatment group, visit, randomization stratification factors (sex; BMI at Visit 2 [<32.5 vs ≥32.5 kg/m²]), and treatment-by-visit interaction as fixed effects, with a UN, alternatively, CS covariance matrix. Covariates: baseline HbA1c (A) and baseline FPG (B). Values are LS mean changes with SE; differences versus placebo are LS mean differences. All p values are two-sided, nominal, and unadjusted for multiplicity.

- **Reversal of prediabetes and progression from normoglycemia at Week 50**

  A total of 42 participants (59.2%) in the 120 mg safiglipron group, 45 participants (75.0%) in the 180 mg safiglipron group, and 8 participants (22.2%) in the placebo group achieved normoglycemia from a prediabetic baseline at Week 50 (differences vs placebo: 36.9 pp for 120 mg, p = 0.0005; 52.8 pp for 180 mg, p < 0.0001) (**Figure 3A**). Progression from normoglycemia at baseline to HbA1c ≥ 5.7% at Week 50 occurred in 5 participants (3.3%) in the 120 mg safiglipron group, 3 (1.8%) in the 180 mg safiglipron group, and 9 (12.0%) in the placebo group (**Figure 3B**).

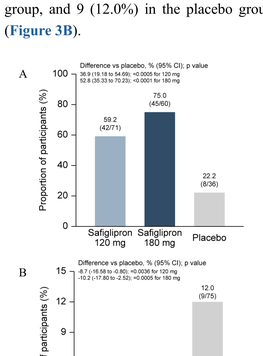


Figure 3. Reversal of prediabetes and progression from normoglycemia by HbA1c level at Week 50. (A) Proportions reaching normoglycemia from prediabetic baseline. (B) Proportions progressing from normoglycemia at baseline to HbA1c ≥ 5.7%. Data after intercurrent events were excluded. Missing values were imputed using a REML-based MMRM with baseline HbA1c as a covariate; treatment group, visit, randomization stratification factors (sex and BMI at Visit 2 [<32.5 vs ≥32.5 kg/m²]), and treatment-by-visit interaction as fixed effects; and a UN or, alternatively, CS covariance matrix. Responder status was derived after imputation. CIs for proportions used the Clopper-Pearson method. Between-group differences are percentage-point differences based on normal approximation; p values were from logistic regression with treatment group, randomization stratification factors, and baseline HbA1c as fixed effects. Analyses were ad hoc; all p values are two-sided, nominal, and were not adjusted for multiplicity.

- **Bodyweight change from baseline at Week 50 among prediabetic participants**

  At Week 50, based on an ad hoc analysis using an efficacy estimand in which data after intercurrent events were excluded (intercurrent events included premature discontinuation of study treatment and insufficient drug exposure), LS mean percentage changes in bodyweight were −9.10%, −11.97%, and −1.56% with safiglipron 120 mg, 180 mg, and placebo, respectively. The placebo-adjusted differences were −7.54 and −10.41 pp (**Figure 4A**). The proportions of baseline prediabetic participants, achieving ≥5%, ≥10%, ≥15% bodyweight loss, were 69.0%, 36.6%, 16.9% with safiglipron 120 mg; 78.3%, 55.0%, 30.0% with safiglipron 180 mg; 13.9%, 8.3%, 2.8% with placebo at Week 50 (**Figure 4B**).

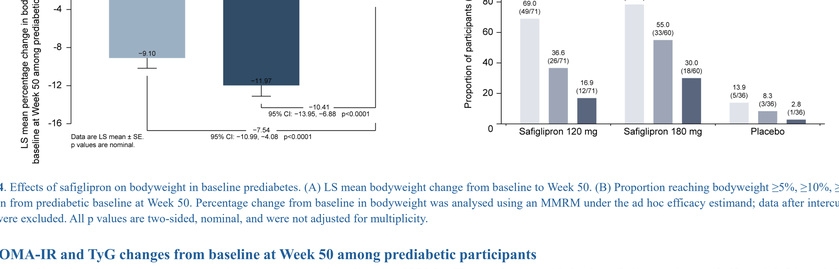


Figure 4. Effects of safiglipron on bodyweight in baseline prediabetes. (A) LS mean bodyweight change from baseline to Week 50. (B) Proportion reaching bodyweight ≥5%, ≥10%, ≥15% reduction from prediabetic baseline at Week 50. Percentage change from baseline in bodyweight was analysed using an MMRM under the ad hoc efficacy estimand; data after intercurrent events were excluded. All p values are two-sided, nominal, and were not adjusted for multiplicity.

- **HOMA-IR and TyG changes from baseline at Week 50 among prediabetic participants**

  For insulin-related parameters, geometric mean ratio to baseline for HOMA-IR was lower with both safiglipron doses (0.63 and 0.54 vs 0.87 for placebo) at Week 50 among prediabetic participants (**Figure 5A**). LS mean change in TyG index also decreased with safiglipron (-0.39 and -0.43 vs -0.15 for placebo) at Week 50 among prediabetic participants (**Figure 5B**). Together with the HbA1c and FPG findings in Figure 2, these exploratory results suggest possible benefits of safiglipron on glycemic and insulin-related parameters.

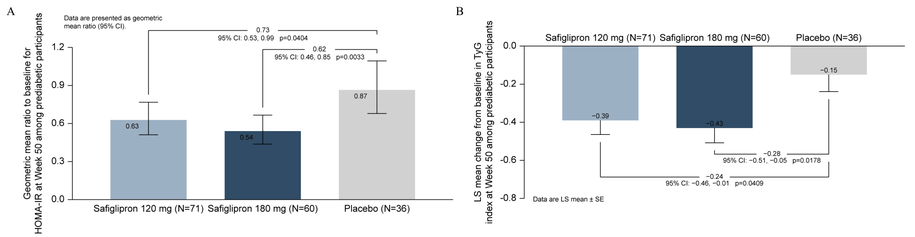


Figure 5. Ad hoc analysis of safiglipron versus placebo on insulin-related parameters at Week 50 among prediabetic participants. (A) Geometric mean ratio to baseline for HOMA-IR. (B) LS mean change in TyG index. Analyses were ad hoc and used the efficacy estimand; data after intercurrent events were excluded. Differences versus placebo are LS mean differences for TyG index; HOMA-IR ratios versus placebo are geometric mean ratios. All p values are two-sided, nominal, and were not adjusted for multiplicity.

Safety

The safety profile in prediabetic and normoglycemic participants was consistent with main analysis. Adverse events were mainly gastrointestinal and mostly mild to moderate.

Conclusion

- In this ad hoc subgroup analysis, 50-week safiglipron improved HbA1c, FPG, HOMA-IR, and TyG index in participants with prediabetes, with more participants reverting to normoglycemia and fewer progressing from normoglycemia to HbA1c ≥5.7% than with placebo.
- These findings suggest potential benefits of safiglipron for preventing glycemic deterioration in at-risk adults and warrant prospective confirmation.

References

1. *Nat. Rev. Dis. Primer* **11**, 49 (2025). 2. *BMJ* **384**, e076410 (2024).
3. *Nat. Med.* (2026). 4. *Diabetes Care* **49**, S27–S49 (2026).

Abbreviations

ADA: American diabetes association; BMI: body-mass index; CI: confidence interval; CS: compound symmetry; FPG: fasting plasma glucose; GLP-1RAs: glucagon-like peptide-1 receptor agonists; HbA1c: hemoglobin A1c; HOMA-β: homeostatic model assessment of β-cell function; HOMA-IR: homeostatic model assessment of insulin resistance; LS: least squares; MMRM: mixed model for repeated measures; pp: percentage points; REML: restricted maximum likelihood; SD: standard deviation; SE, standard error; T2DM: type 2 diabetes mellitus; TyG, triglyceride glucose index; UN: unstructured.

Trial registration: ClinicalTrials.gov NCT06904105.
Funding: The study was supported by Jiangsu Hengrui Pharmaceuticals.

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