

Oral small-molecule GLP-1 receptor agonist safiglipron (HRS-7535) in early type 2 diabetes: a randomized, double-blind, placebo-controlled trial

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on behalf of the OUTSTAND-1 Study Group**

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No competing interests reported.



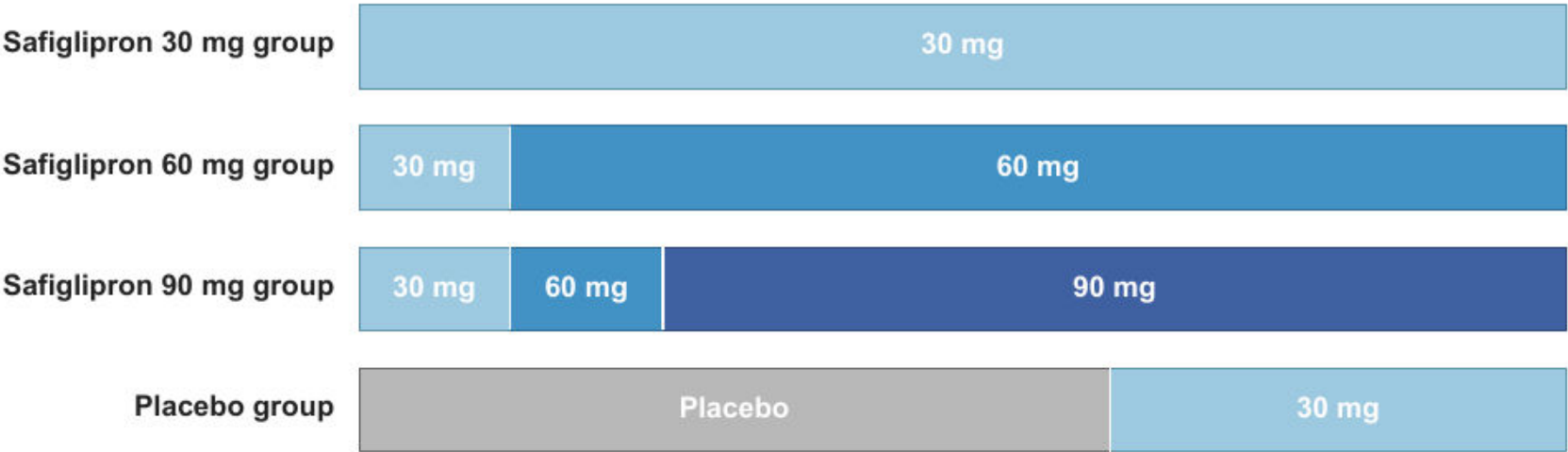
Study Design and Baseline Characteristics

Background: Safiglipron (HRS-7535) is a once-daily oral small-molecule GLP-1 receptor agonist administered without fasting or dietary restrictions.

Design: Phase 3, multicenter, randomized, double-blind, placebo-controlled trial at 46 sites in China.

Population (N=284)

- Chinese adults with type 2 diabetes managed with diet and exercise alone;
- HbA1c 7.0–10.0%.



Completed trial follow-up: 261/284 (91.9%)

▲ Primary endpoint
Change from baseline in HbA1c at Week 32

Baseline population



49.4 years
Mean age



33.1%
Women



8.0%
Mean HbA1c



1.6 years
Median T2D duration



27.8 kg/m²
Mean BMI

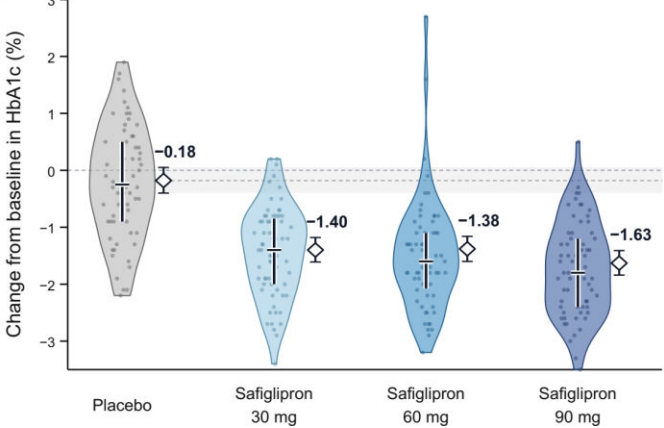
Efficacy outcomes

Placebo safiglipron 30 mg safiglipron 60 mg safiglipron 90 mg

A HbA1c change at Week 32

Treatment-policy estimand

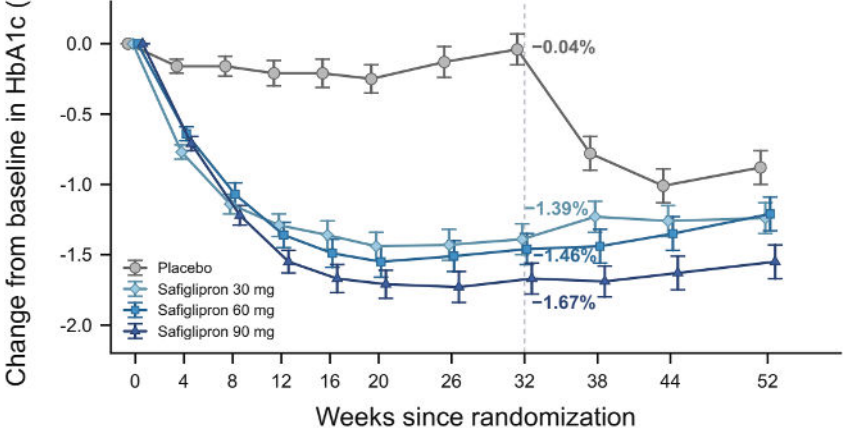
Mean baseline HbA1c: 8.0%



B HbA1c change through Week 52

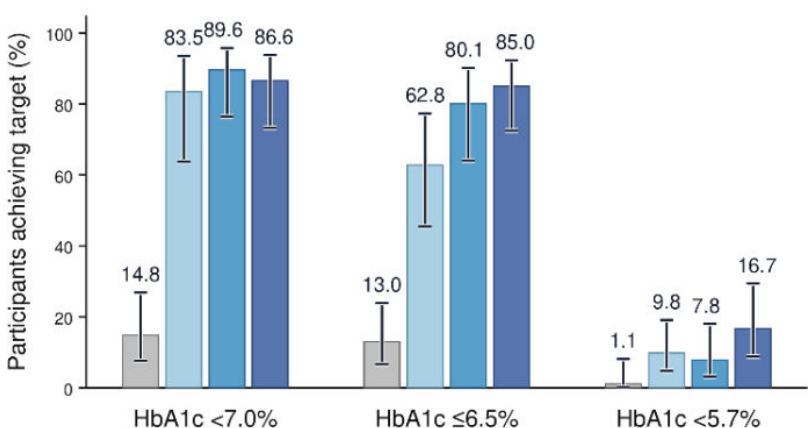
Efficacy estimand

Mean baseline HbA1c: 8.0%



C HbA1c target attainment at Week 32

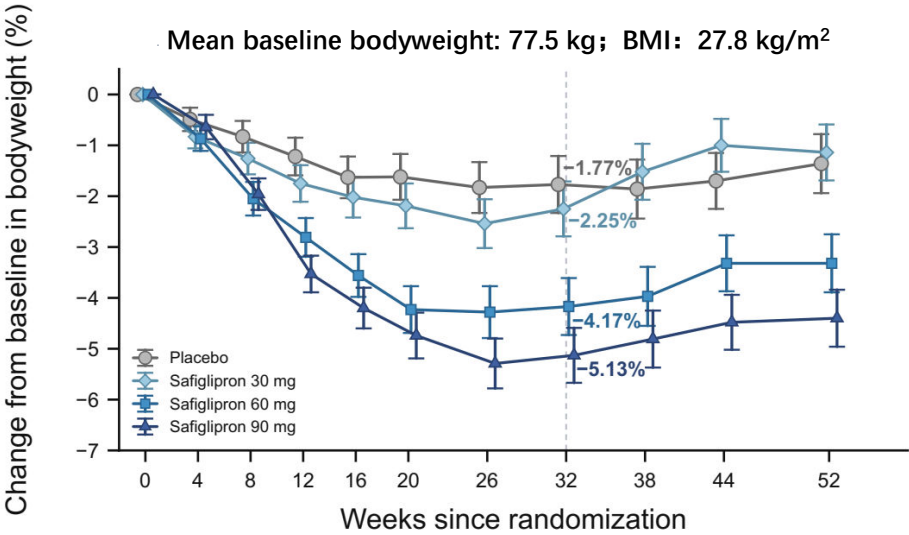
Efficacy estimand



D Bodyweight change through Week 52

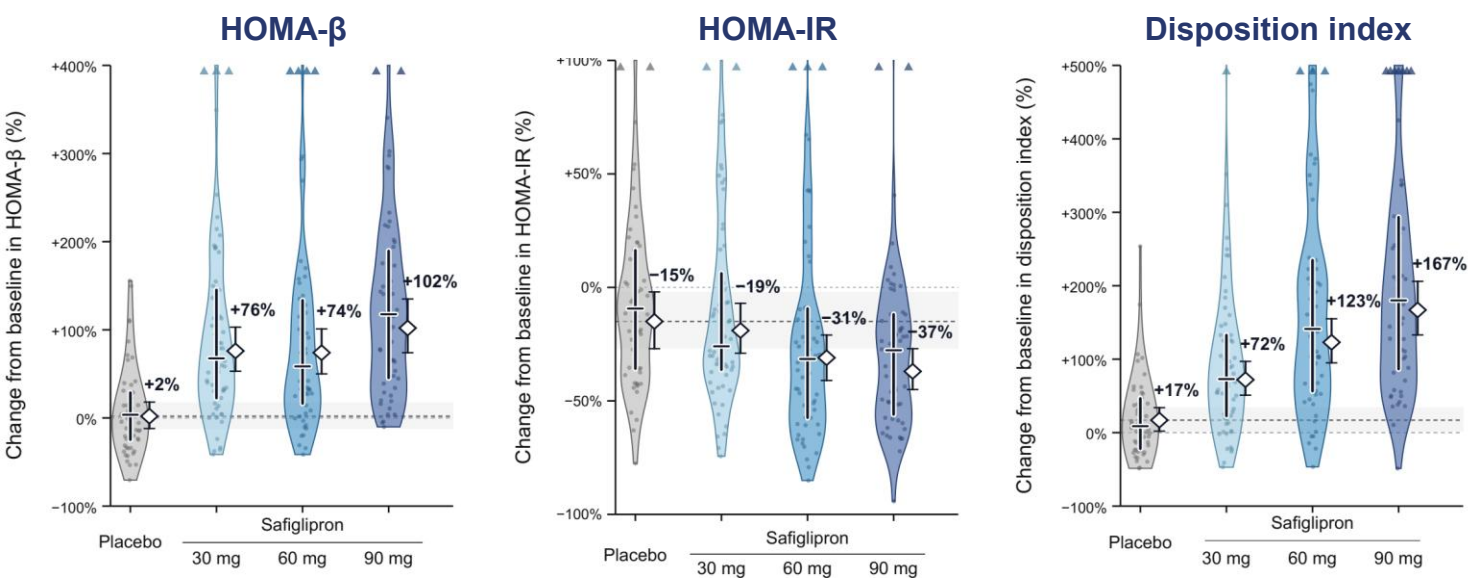
Efficacy estimand

Mean baseline bodyweight: 77.5 kg; BMI: 27.8 kg/m²



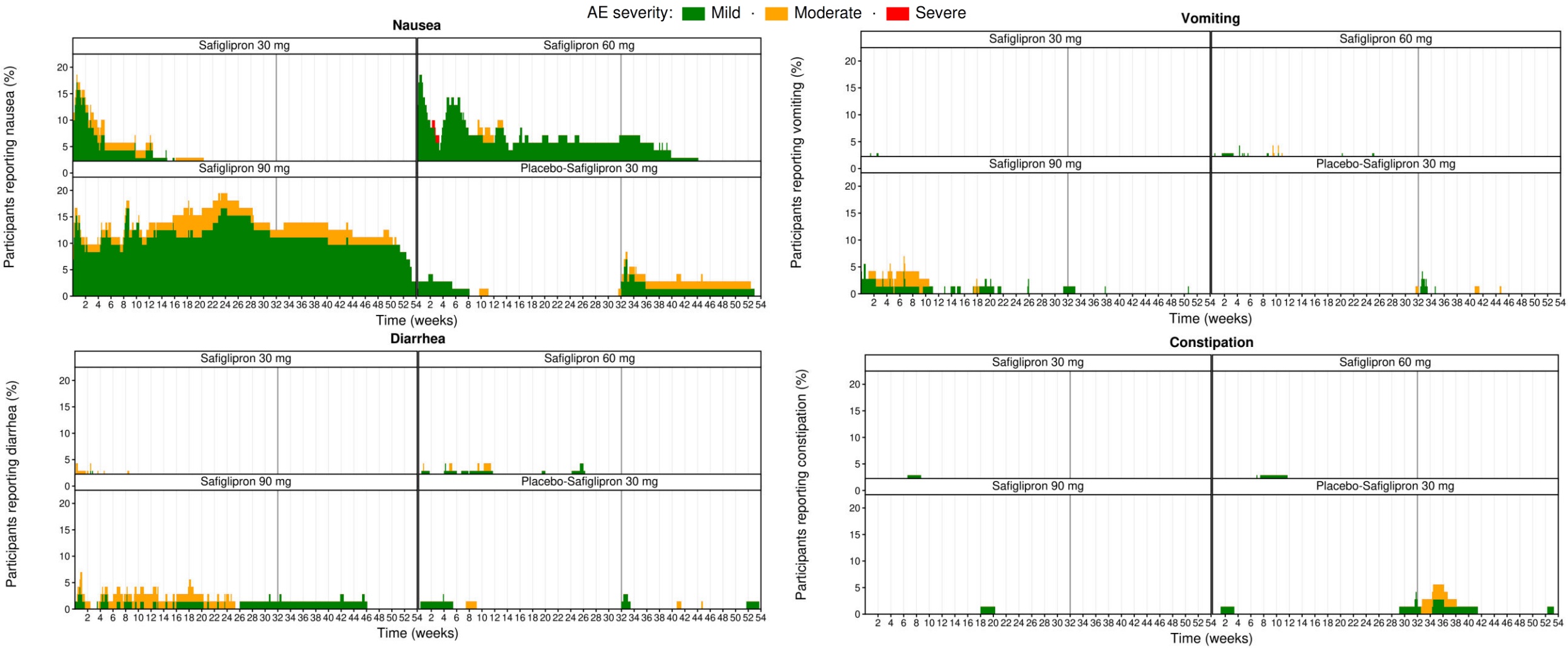
E β -cell function and insulin sensitivity at Week 32

Efficacy estimand



Safety and Tolerability Profile

- Gastrointestinal events were the most common AEs, increased with dose, and were mostly mild or moderate.
- No deaths, severe hypoglycemia, or Hy's law cases occurred.



Conclusions

- Once-daily oral safiglipron provided clinically meaningful glycemic control and bodyweight reductions, with improvements in indices of β -cell function and insulin sensitivity in adults with early type 2 diabetes.
- Safiglipron was generally well tolerated, with a gastrointestinal tolerability profile broadly similar to that reported with other oral small-molecule GLP-1 receptor agonists
- These findings support safiglipron as a promising, convenient oral treatment option for early type 2 diabetes, without fasting or dietary restrictions.

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Rationale, Study Design and Baseline Characteristics

- ◆ **Background:** Safiglipron (HRS-7535) is a once-daily oral small-molecule GLP-1 receptor agonist administered without fasting or dietary restrictions.
- ◆ **Design:** Phase 3, multicenter, randomized, double-blind, placebo-controlled trial at 46 sites in China.

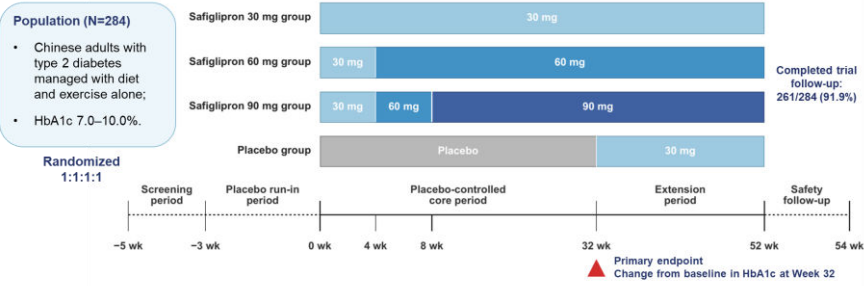
- ◆ Baseline characteristics were generally balanced across treatment groups (Table 1).
- ◆ Median T2D duration: 1.6 years | No previous glucose-lowering medication: 66.5%

Table 1. Baseline characteristics

Characteristic	Placebo N=72	Safiglipron 30 mg N=70	Safiglipron 60 mg N=70	Safiglipron 90 mg N=72
Age, years	49.7 (10.2)	48.7 (8.9)	48.9 (10.2)	50.3 (10.2)
Female, n (%)	24 (33.3)	29 (41.4)	21 (30.0)	20 (27.8)
HbA1c, %	7.99 (0.79)	7.87 (0.73)	7.97 (0.68)	7.98 (0.63)
Bodyweight, kg	78.0 (13.5)	76.3 (11.2)	77.9 (14.8)	77.6 (16.2)
BMI, kg/m ²	28.3 (3.9)	27.7 (3.4)	27.9 (3.6)	27.4 (3.9)

Data are mean (SD) or n (%).

Figure 1. OUTSTAND-1 study design



Efficacy outcomes

- ◆ All doses reduced HbA1c versus placebo (Figure 2A). Placebo-adjusted differences were -1.22%, -1.20%, and -1.45% for 30, 60, and 90 mg (all P<0.0001).
- ◆ FPG also fell by 1.58-2.08 mmol/L versus placebo.
- ◆ At Week 32, efficacy-estimand changes were -1.39%, -1.46%, and -1.67% with safiglipron 30, 60, and 90 mg (Figure 2B).

Figure 2A. HbA1c change at Week 32 (treatment-policy estimand)

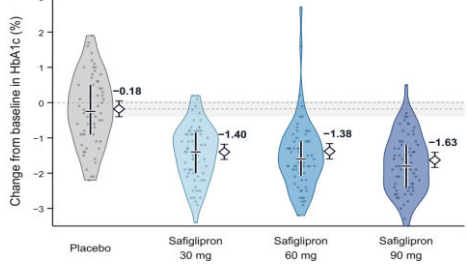
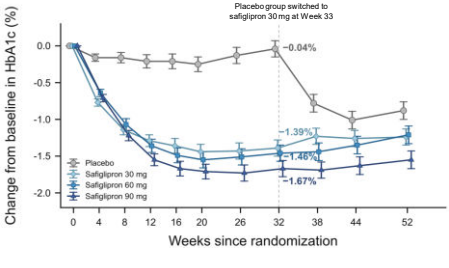


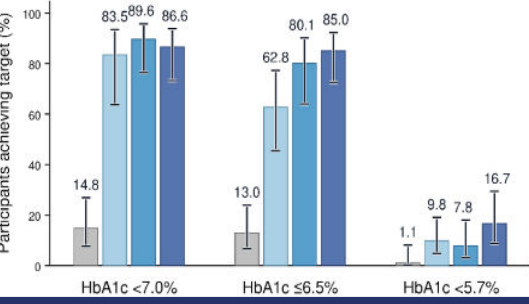
Figure 2B. HbA1c change through Week 52 (efficacy estimand)



Efficacy outcomes

- ◆ Under the efficacy estimand, 83.5-89.6% achieved HbA1c <7.0% versus 14.8% with placebo (Figure 2C). All safiglipron groups showed higher target attainment.

Figure 2C. HbA1c target attainment at Week 32 (efficacy estimand)

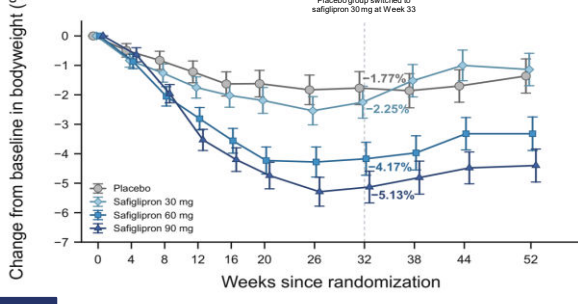


Safety through Week 32

Table 2. Summary of TEAEs

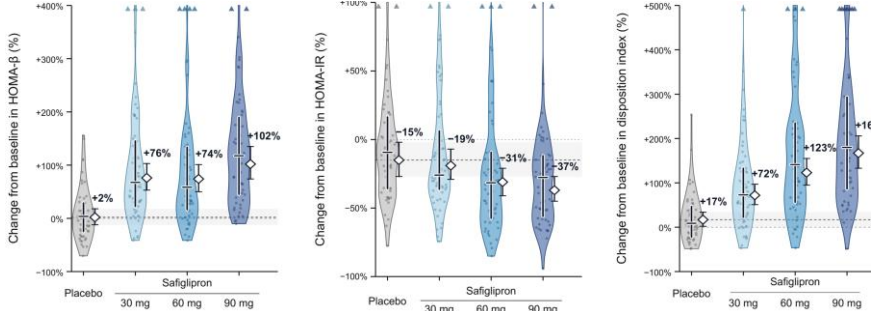
Event, n (%)	Placebo N=72	Safiglipron 30 mg N=70	Safiglipron 60 mg N=70	Safiglipron 90 mg N=72
Any TEAE	56 (77.8)	59 (84.3)	60 (85.7)	65 (90.3)
Gastrointestinal TEAE	11 (15.3)	31 (44.3)	42 (60.0)	53 (73.6)
Nausea	5 (6.9)	18 (25.7)	25 (35.7)	33 (45.8)
Diarrhea	3 (4.2)	15 (21.4)	14 (20.0)	21 (29.2)
Vomiting	0	9 (12.9)	13 (18.6)	16 (22.2)
Serious TEAE	1 (1.4)	7 (10.0)	2 (2.9)	5 (6.9)
TEAE leading to discontinuation	0	1 (1.4)	2 (2.9)	5 (6.9)

Figure 2D. Bodyweight change through Week 52 (efficacy estimand)



- ◆ Bodyweight reduction increased with dose (Figure 2D).
- ◆ Superiority was confirmed for 60 and 90 mg; 30 mg was not significant (P=0.21).
- ◆ HOMA-β increased by 74-102%, HOMA-IR decreased by 19-37%, and disposition index increased by 72-167% across safiglipron doses (Figure 2E).
- ◆ These supportive findings indicated improved β-cell function and insulin sensitivity.

Figure 2E. β-cell function and insulin sensitivity at Week 32



- ◆ Gastrointestinal events were the most common AEs, increased with dose, and were mostly mild or moderate.
- ◆ No deaths, severe hypoglycemia, or Hy's law cases occurred.

CONCLUSIONS

- ◆ Once-daily oral safiglipron provided clinically meaningful glycemic control and bodyweight reductions, with improvements in indices of β-cell function and insulin sensitivity in adults with early type 2 diabetes.
- ◆ Safiglipron was generally well tolerated, with a gastrointestinal tolerability profile broadly similar to that reported with other oral small-molecule GLP-1 receptor agonists.
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