

Oral safiglipron (HRS-7535) versus dapagliflozin in adults with type 2 diabetes inadequately controlled with metformin

OUTSTAND-2 phase 3 trial

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Disclosures and study support

PRESENTER

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No conflicts of interest to disclose.

PRINCIPAL INVESTIGATOR

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STUDY SUPPORT

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Why compare oral small-molecule GLP-1RA and SGLT2 therapy?

CLINICAL CONTEXT

GLP-1 receptor agonists and SGLT2 inhibitors are established glucose-lowering options with complementary mechanisms^{1,2}.

Most GLP-1 receptor agonists require injection, while oral peptide GLP-1 receptor agonist therapy requires fasting and limits water intake³.

A nonpeptide oral GLP-1RA may reduce these administration constraints.

OUTSTAND-2 OBJECTIVE

Evaluate once-daily oral safiglipton (proposed INN; HRS-7535) 30, 60 and 90 mg versus dapagliflozin 10 mg in adults with type 2 diabetes inadequately controlled with metformin.

Primary question: Is safiglipton non-inferior to dapagliflozin for HbA1c reduction at Week 32?

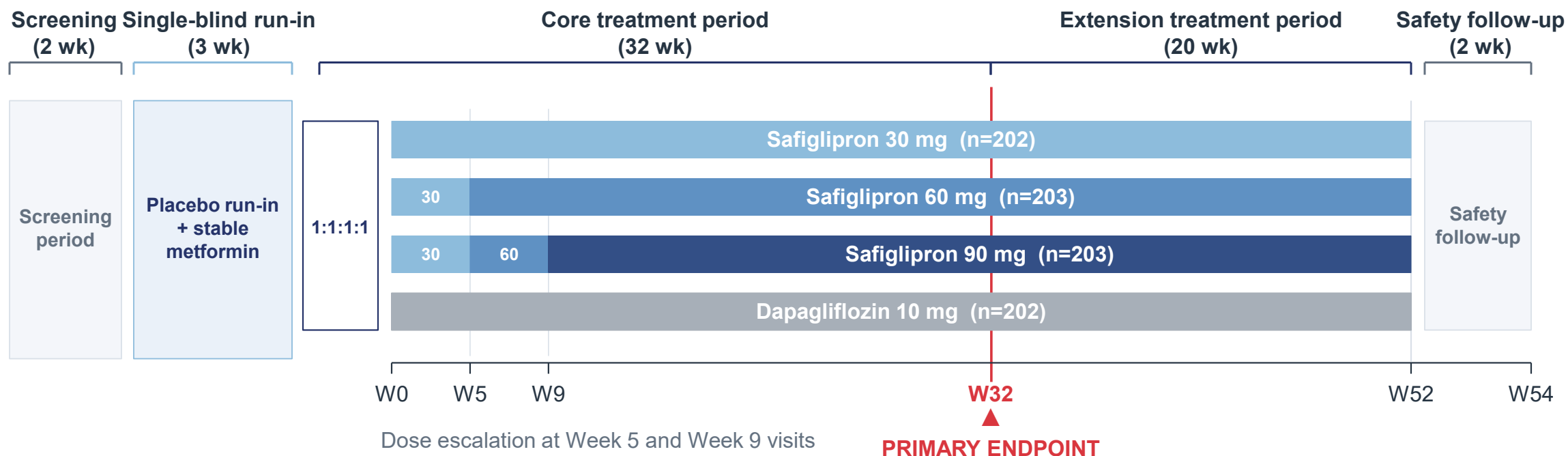
References

1. Bajaj M, et al. Diabetes Care. 2026;49:S183–S215.
2. Brown E, et al. Lancet. 2021;398:262–276.
3. Andersen A, et al. Drugs. 2021;81:1003–1030.



OUTSTAND-2: three safiglipron doses versus dapagliflozin

- ▶ Phase 3 trial at 98 sites in China: adults aged 18–75 years with type 2 diabetes inadequately controlled with stable metformin (HbA1c 7.5–11.0%; BMI 19.0–40.0 kg/m²).
- ▶ Participants were randomized 1:1:1:1 (double-blind, double-dummy) to once-daily safiglipron 30, 60 or 90 mg or dapagliflozin 10 mg, with stable metformin continued.



- ▶ **Primary endpoint: change from baseline in HbA1c at Week 32 (non-inferiority margin: 0.4 percentage points).**
- ▶ Key secondary endpoints: HbA1c target achievement, fasting plasma glucose and percentage change in body weight at Week 32.

How to interpret the efficacy analyses

1 PRIMARY ANALYSIS

Non-inferiority	Efficacy estimand
Superiority	Treatment-policy estimand

2 FIXED-SEQUENCE TESTING

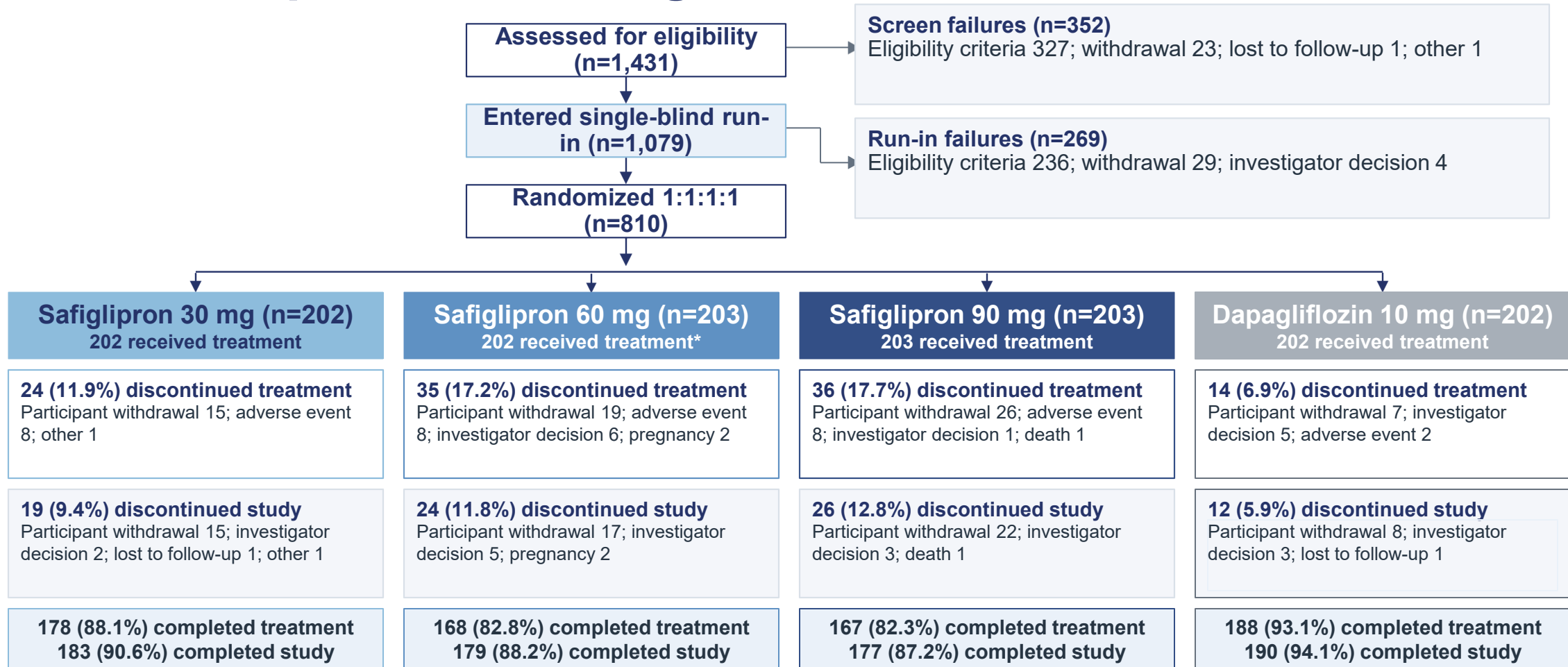
90 / 60 / 30 mg non-inferiority → 90 / 60 / 30 mg superiority → Key secondary endpoints

Sequence stopped at 60 mg superiority ($P=0.0789$); subsequent findings were non-confirmatory.

INTERPRETATION

- ✓ All three doses met the non-inferiority criterion.
- ✓ Safiglipron 90 mg demonstrated superior glycaemic control compared with dapagliflozin.
- ✓ Supportive, non-confirmatory improvements were observed in HbA1c target attainment, FPG, body weight, LDL-C, TG and TC.

Patient disposition through Week 52



* One participant in the safiglipton 60 mg group did not receive study treatment after post-randomization ineligibility was identified.

Baseline characteristics were balanced

DEMOGRAPHICS AND GLYCAEMIC PROFILE

Characteristic	Safiglipton 30 mg (n=202)	Safiglipton 60 mg (n=203)	Safiglipton 90 mg (n=203)	Dapagliflozin 10 mg (n=202)
Age, years	52.8 (10.81)	52.1 (10.46)	52.0 (10.80)	52.0 (10.75)
Age ≥65 years, n (%)	28 (13.9)	22 (10.8)	26 (12.8)	27 (13.4)
Male, n (%)	135 (66.8)	130 (64.0)	126 (62.1)	130 (64.4)
Bodyweight, kg	74.11 (12.73)	74.74 (14.02)	75.28 (13.83)	74.61 (15.49)
BMI, kg/m ²	26.97 (3.59)	27.07 (3.74)	27.27 (3.43)	27.18 (4.04)
T2D duration, years	5.54 (2.9–8.1)	4.21 (2.0–8.7)	4.47 (2.4–9.0)	4.97 (2.7–8.1)
HbA1c, %	8.57 (0.78)	8.58 (0.71)	8.62 (0.78)	8.61 (0.78)
HbA1c >8.5%, n (%)	94 (46.5)	94 (46.3)	94 (46.3)	94 (46.5)
FPG, mmol/L	9.98 (1.73)	10.13 (1.98)	10.08 (1.80)	9.93 (1.75)

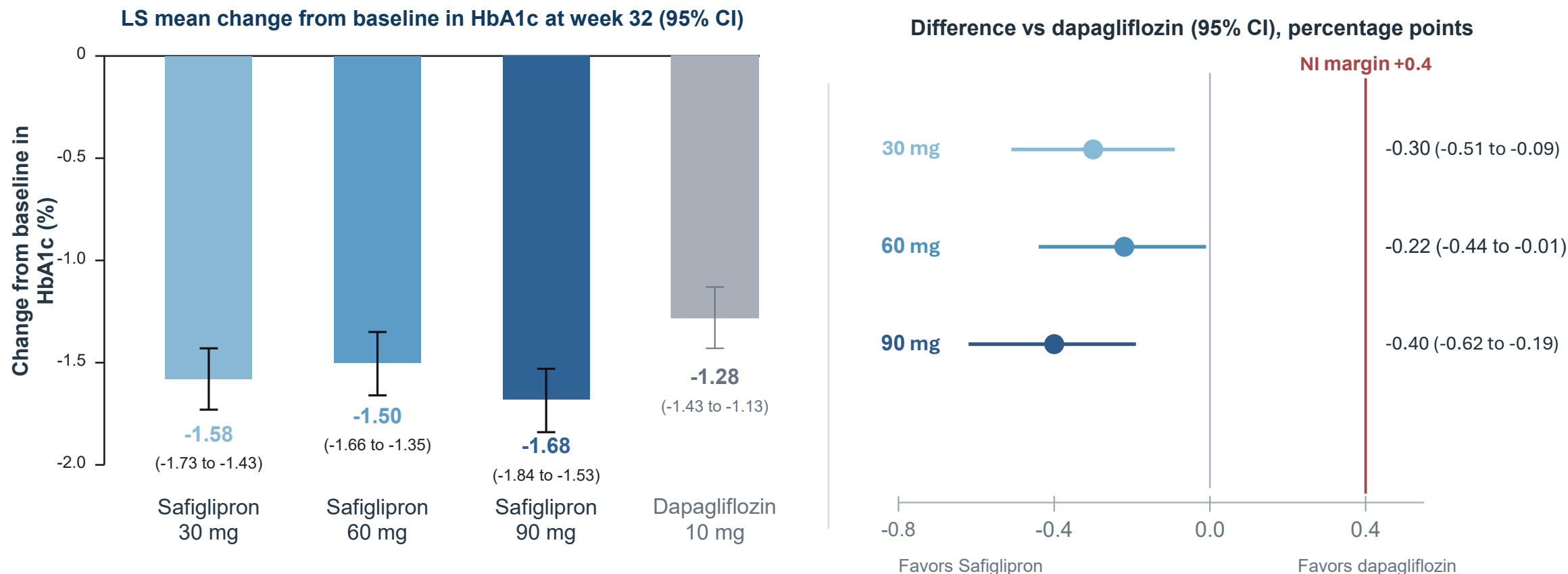
METABOLIC, RENAL AND CARDIOVASCULAR PROFILE

Characteristic	Safiglipton 30 mg (n=202)	Safiglipton 60 mg (n=203)	Safiglipton 90 mg (n=203)	Dapagliflozin 10 mg (n=202)
Fasting insulin, µIU/mL	11.73 (8.19)	11.52 (8.04)	12.58 (8.98)	11.94 (8.08)
C-peptide, ng/mL	2.02 (0.91)	2.12 (1.06)	2.18 (1.08)	2.14 (1.11)
HOMA-β, geometric mean*	31.22 (1.88)	30.42 (1.87)	32.90 (1.94)	31.88 (1.89)
HOMA-IR, geometric mean*	4.26 (1.91)	4.23 (1.93)	4.57 (1.93)	4.28 (2.00)
Triglycerides, mmol/L	2.17 (1.57)	2.11 (1.53)	2.14 (1.24)	2.32 (1.54)
Non-HDL cholesterol, mmol/L	3.60 (1.05)	3.69 (1.06)	3.54 (0.97)	3.61 (0.97)
UACR, mg/g	13.5 (4–47)	12.0 (4–46)	21.0 (5–67)	14.0 (4.5–44)
eGFR, mL/min/1.73 m ²	104.72 (14.42)	105.31 (12.99)	104.92 (15.78)	105.73 (14.57)
Systolic blood pressure, mmHg	124.6 (11.9)	125.3 (12.3)	125.5 (12.0)	123.1 (11.6)
Diastolic blood pressure, mmHg	81.1 (7.1)	81.5 (7.3)	81.7 (8.3)	81.2 (7.6)

Data are mean (SD) or n (%), unless otherwise indicated. T2D duration and UACR are median (Q1–Q3). *Geometric mean (geometric SD).

All doses met non-inferiority; 90 mg was superior to dapagliflozin

Bars and forest plot show the efficacy estimand. The bottom callout shows the treatment-policy estimand.



Treatment-policy estimand: safiglipton 90 mg met the prespecified superiority criterion versus dapagliflozin (difference -0.25%; 95% CI -0.45 to -0.05; one-sided P=0.0067).

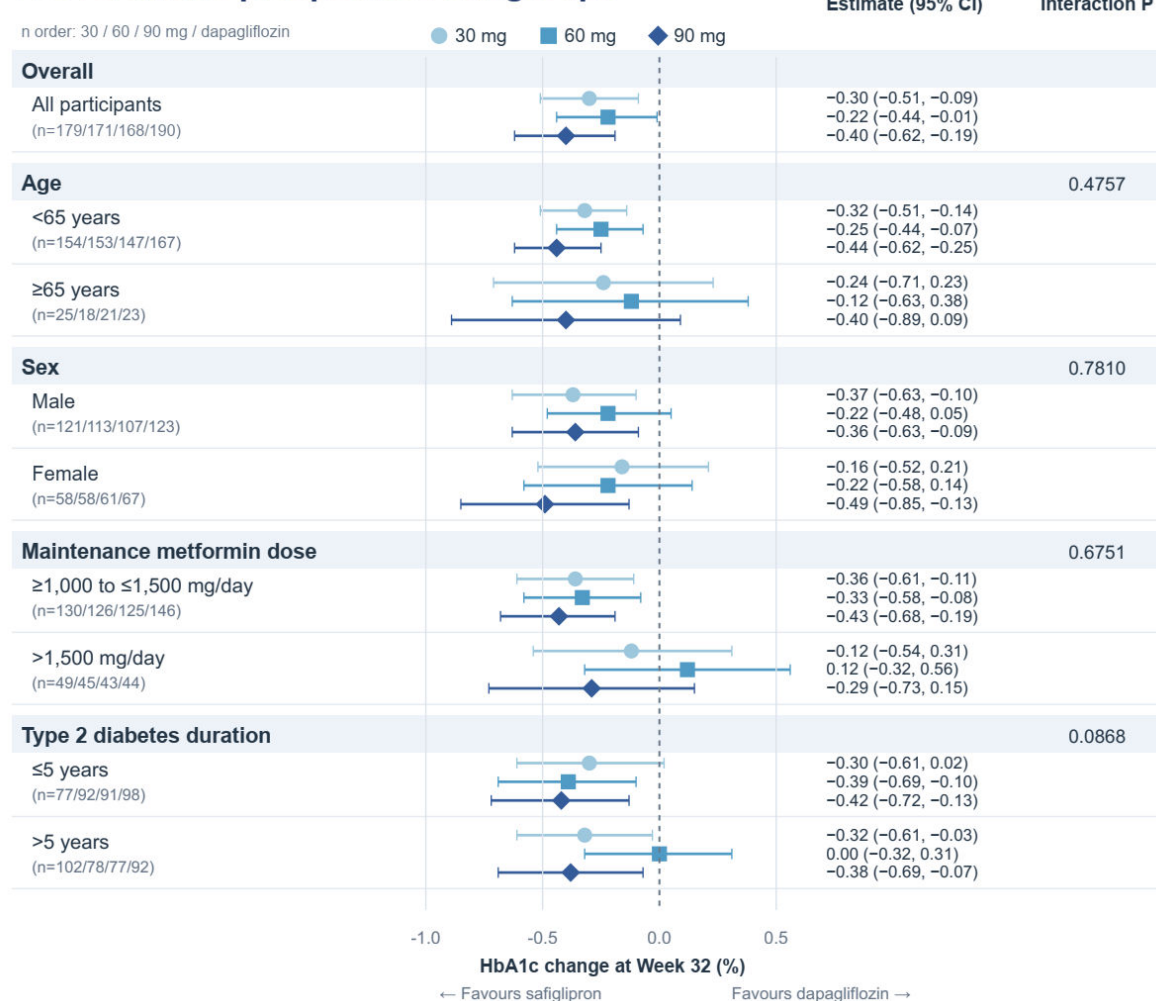
Efficacy estimand: hypothetical strategy for permanent treatment discontinuation and additional glucose-lowering therapy.

NI margin: 0.4 percentage points.

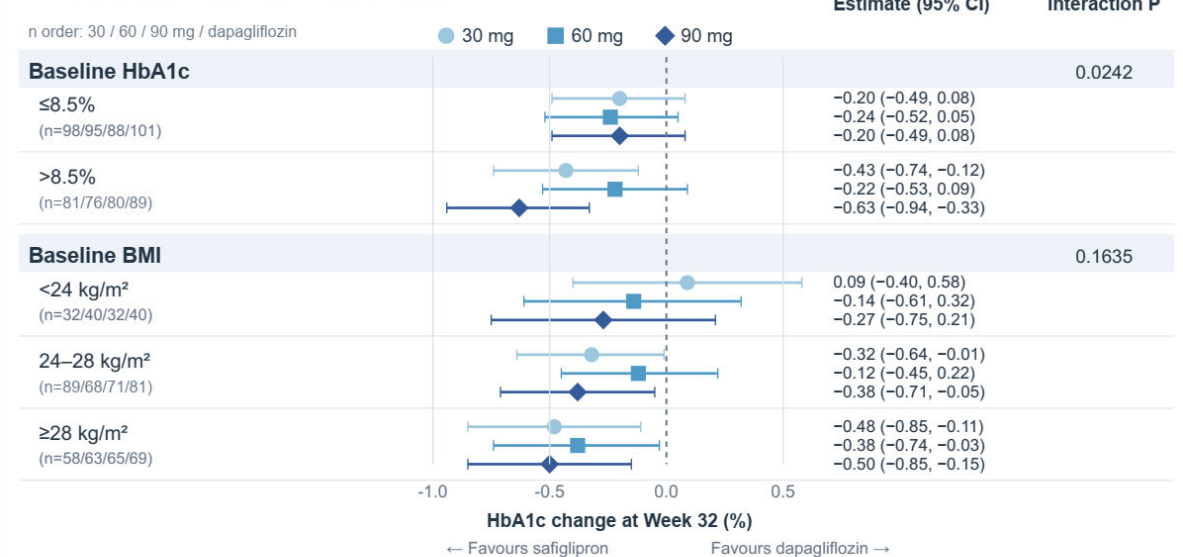
Treatment policy estimand: treatment policy for permanent treatment discontinuation and additional glucose-lowering therapy.

Week-32 HbA1c effects were consistent across subgroups

A Overall and prespecified subgroups



B Baseline HbA1c and BMI



KEY INTERPRETATION

- Effects were generally consistent across the prespecified subgroups.
- Baseline HbA1c showed a nominal interaction (P=0.0242).

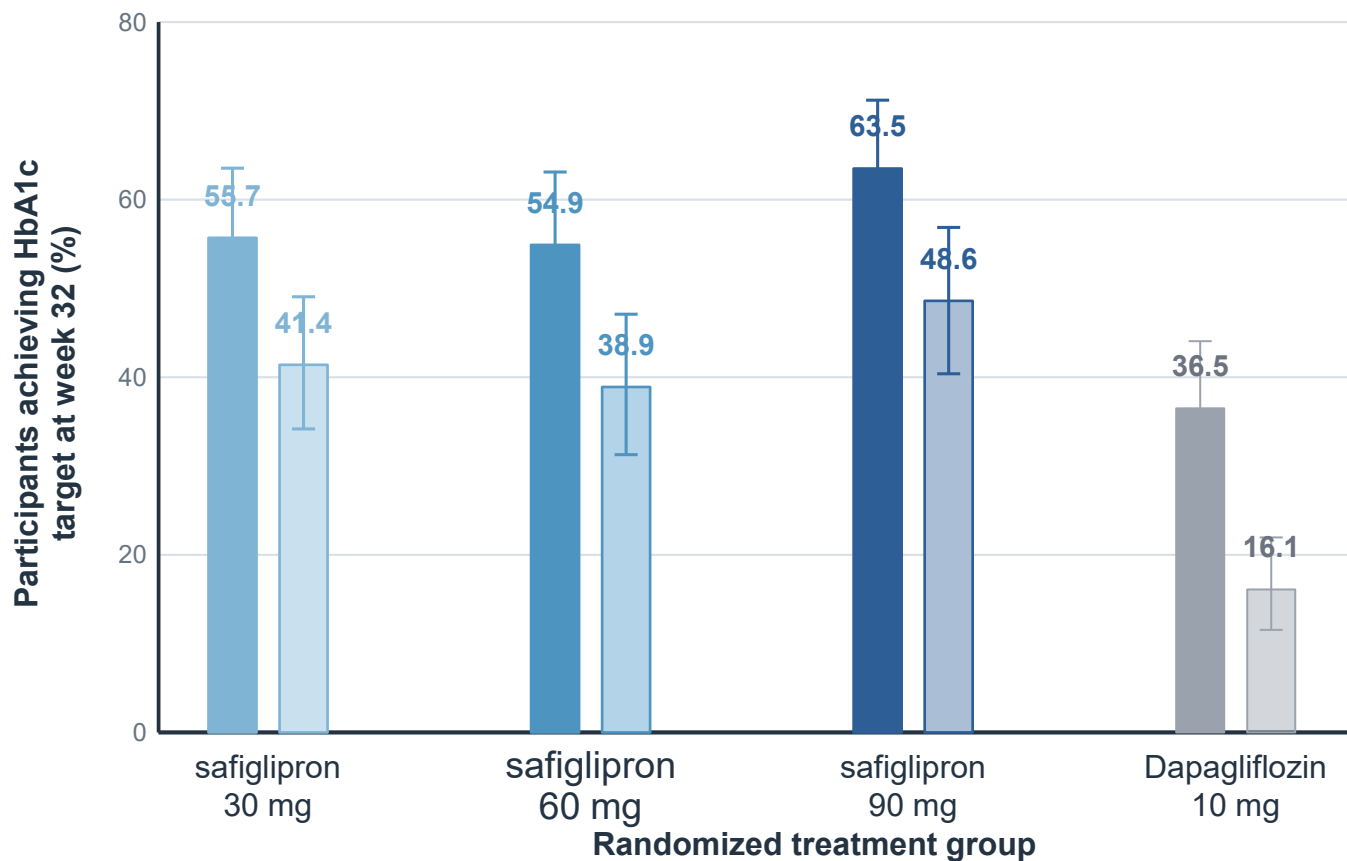
Exploratory analyses; interaction P values were nominal and were not adjusted for multiplicity.

HbA1c target attainment and fasting plasma glucose at Week 32

Prespecified key secondary findings; non-confirmatory since testing stopped

Estimated HbA1c target attainment at week 32

Model-estimated proportions under the efficacy estimand



Bars show model-estimated proportions; error bars show 95% CIs.

Darker bars: HbA1c <7.0% | Lighter bars: HbA1c ≤6.5%

Fasting plasma glucose

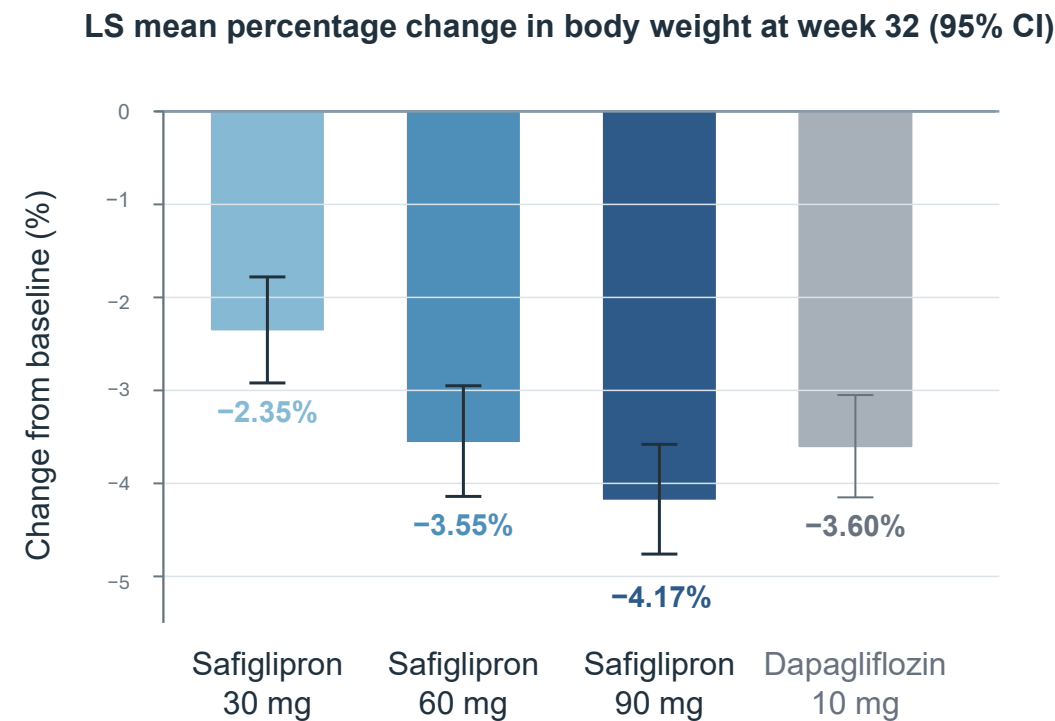
LS mean change from baseline at week 32 (mmol/L)



Difference vs dapagliflozin for 90 mg: -0.60 mmol/L
(95% CI -0.96 to -0.23).

Body weight change at Week 32

Prespecified key secondary endpoint; non-confirmatory since testing stopped

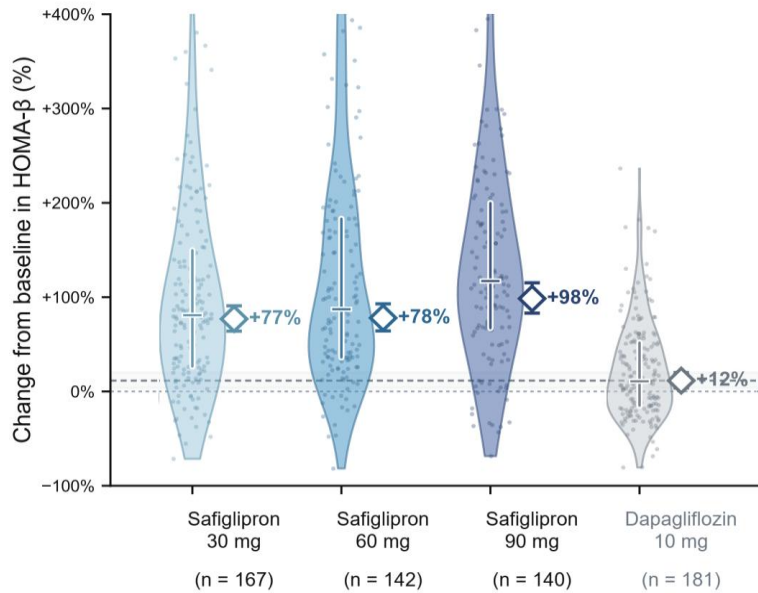


Difference vs dapagliflozin (95% CI)	
30 mg	+1.25 (0.46 to 2.04)
60 mg	+0.06 (-0.75 to 0.86)
90 mg	-0.56 (-1.37 to 0.24)

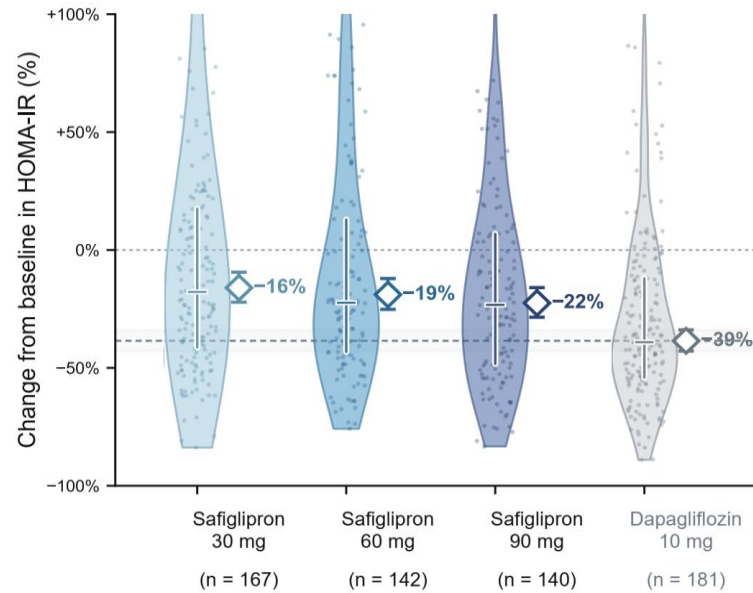
Percentage points (95% CI)

Changes in HOMA- β and HOMA-IR

Prespecified supportive endpoints at week 32



HOMA- β increased more with safiglipton



HOMA-IR decreased more with dapagliflozin

Week-32 geometric mean change

HOMA- β

+76.9% +78.0% +98.5%

safiglipton 30 / 60 / 90 mg

vs +11.5% with dapagliflozin

HOMA-IR

-16.0% -18.9% -22.5%

vs -38.5% with dapagliflozin

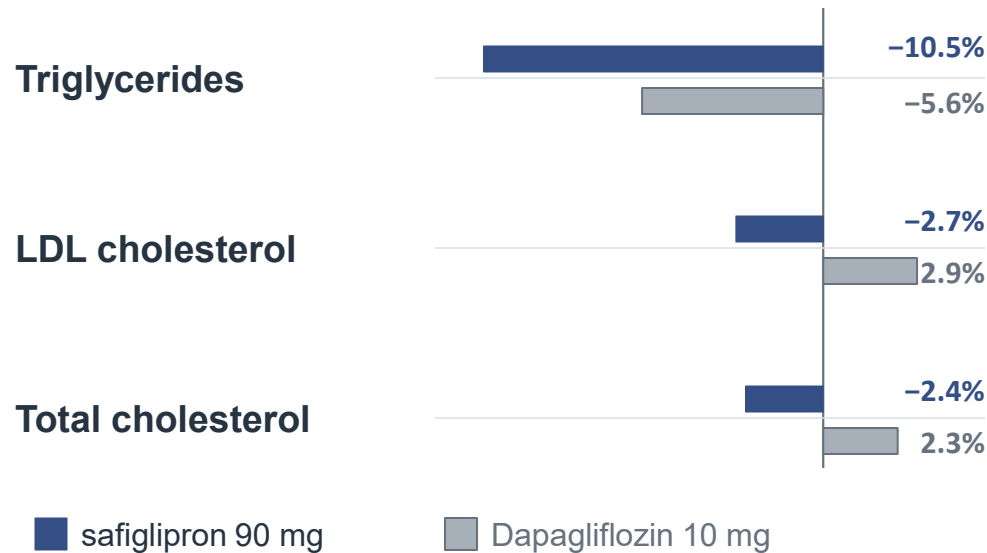
Supportive endpoints were analyzed under the efficacy estimand; no multiplicity adjustment.

Cardiometabolic and renal markers at Week 32

Prespecified exploratory analyses; no adjustment for multiplicity

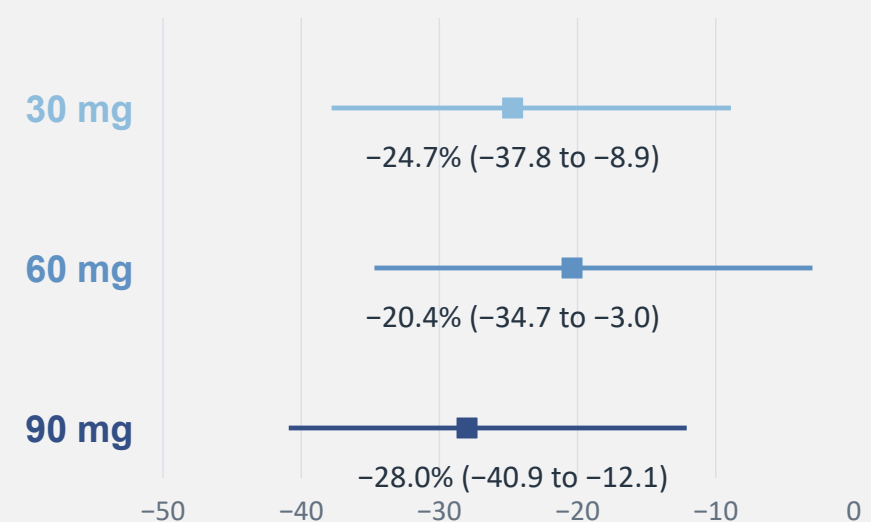
LIPIDS: Percentage change from baseline

safiglipron 90 mg compared with dapagliflozin



UACR: Difference vs dapagliflozin

Dapagliflozin-adjusted percentage difference (95% CI)



Exploratory biomarker findings only; no cardiovascular or renal outcome-benefit claim.

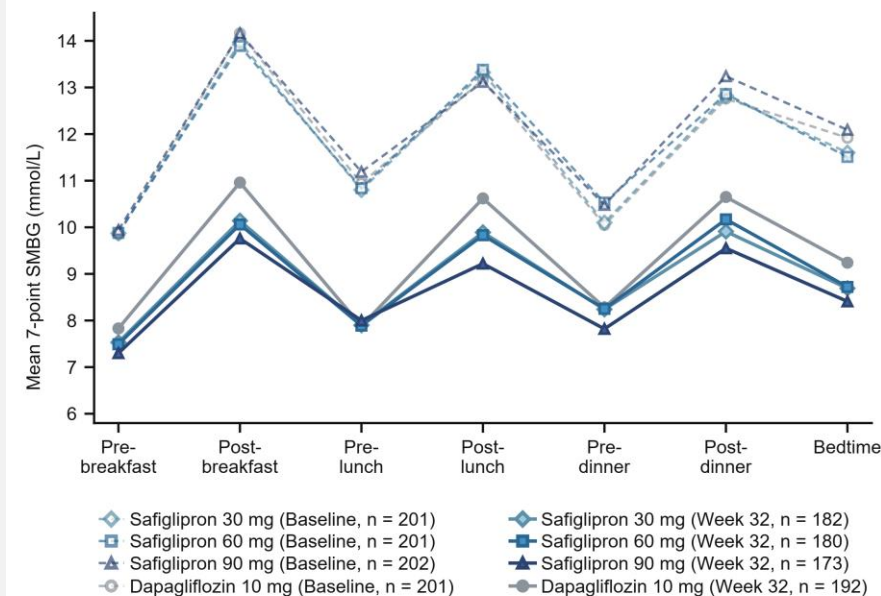
Supportive outcomes: secondary and exploratory endpoints

Outcome	Safiglipton 30 mg (N=202)	Safiglipton 60 mg (N=203)	Safiglipton 90 mg (N=203)	Dapagliflozin 10 mg (N=202)
WEEK 52 — SUPPORTIVE EFFICACY				
HbA1c change, %	-1.35	-1.20	-1.43	-1.11
FPG change, mmol/L	-1.94	-1.87	-2.42	-1.98
Body weight change, %	-1.85	-3.03	-3.07	-3.35
HbA1c <7.0%, %	45.0	40.9	47.3	31.2
HbA1c ≤6.5%, %	30.7	30.5	33.5	11.9
WEEK 32 — OTHER SUPPORTIVE OUTCOMES				
Rescue therapy, n (%)	3 (1.5)	2 (1.0)	1 (0.5)	0
DTSQ status score change	+2.0	+1.9	+2.2	+1.6

N denotes randomized participants. Week 32/52 results were not multiplicity-controlled; HbA1c and body weight were analyzed under the efficacy estimand. FPG, DTSQ, HbA1c target attainment, and SMBG were summarized descriptively.

7-POINT SMBG AT WEEK 32

Baseline (dashed) versus Week 32 (solid)



Profiles decreased in all groups; safiglipton showed numerically greater improvements in mean daily and postprandial glucose than dapagliflozin.

Overall safety summary through Week 52

SAFETY POPULATION | 52-WEEK TREATMENT PERIOD

Event, n (%)	Safiglipron 30 mg (N=202)	Safiglipron 60 mg (N=202)	Safiglipron 90 mg (N=203)	Dapagliflozin 10 mg (N=202)
Any TEAE	188 (93.1)	195 (96.5)	199 (98.0)	188 (93.1)
TEAE considered related to study treatment	149 (73.8)	175 (86.6)	174 (85.7)	112 (55.4)
Serious TEAE	21 (10.4)	12 (5.9)	10 (4.9)	18 (8.9)
Severe TEAE	7 (3.5)	6 (3.0)	5 (2.5)	8 (4.0)
Death	0	0	1 (0.5)	0
TEAE leading to permanent treatment discontinuation	8 (4.0)	8 (4.0)	8 (3.9)	3 (1.5)
Gastrointestinal TEAE leading to permanent treatment discontinuation	6 (3.0)	7 (3.5)	7 (3.4)	0
Any prespecified adverse event of special interest	0	1 (0.5)	0	0
Severe hypoglycaemia	0	0	0	0
Acute pancreatitis	0	1 (0.5)	0	0

HEPATIC SAFETY | No clinically significant hepatic enzyme abnormalities were reported; transaminases generally decreased and no cases met Hy's law criteria.

Data are n (%).
TEAE, treatment-emergent adverse event. The single death (acute myocardial infarction) was considered unrelated to study treatment by the investigator.



Common treatment-emergent adverse events through Week 52

SAFETY POPULATION | 52-WEEK TREATMENT PERIOD

Preferred terms reported in ≥10% of participants in any treatment group

Preferred term, n (%)	Safiglipton 30 mg (N=202)	Safiglipton 60 mg (N=202)	Safiglipton 90 mg (N=203)	Dapagliflozin 10 mg (N=202)
Nausea	46 (22.8)	77 (38.1)	95 (46.8)	14 (6.9)
Vomiting	27 (13.4)	60 (29.7)	69 (34.0)	4 (2.0)
Diarrhea	27 (13.4)	39 (19.3)	47 (23.2)	13 (6.4)
Abdominal distension	16 (7.9)	28 (13.9)	25 (12.3)	7 (3.5)
Lipase increased	37 (18.3)	36 (17.8)	32 (15.8)	9 (4.5)
Alanine aminotransferase increased	17 (8.4)	24 (11.9)	17 (8.4)	18 (8.9)
Ketone body urine present	4 (2.0)	5 (2.5)	7 (3.4)	21 (10.4)
Decreased appetite	43 (21.3)	50 (24.8)	63 (31.0)	18 (8.9)
Hyperuricemia	24 (11.9)	35 (17.3)	35 (17.2)	23 (11.4)
Hyperlipidemia	19 (9.4)	15 (7.4)	21 (10.3)	26 (12.9)
Upper respiratory tract infection	30 (14.9)	24 (11.9)	26 (12.8)	22 (10.9)
Diabetic retinopathy	19 (9.4)	22 (10.9)	17 (8.4)	26 (12.9)

Data are n (%).

Gastrointestinal events were the most common TEAEs and were mostly mild to moderate; occurrence was concentrated during dose titration and diminished over time.

Conclusions

PRIMARY ENDPOINT

Primary endpoint met

- Safiglipton 30, 60, and 90 mg met the prespecified non-inferiority criterion for HbA1c change at Week 32 under the efficacy estimand.
- The 90-mg dose also demonstrated statistical superiority under the treatment-policy estimand.

OTHER OUTCOMES

Supportive findings

- Benefits were observed for HbA1c target attainment, FPG, body weight, HOMA, and cardiometabolic and renal markers.

SAFETY

Safety through Week 52

- GI events and AE-related discontinuations were more frequent with safiglipton, although most GI events were mild or moderate.
- No severe hypoglycaemia or hepatic safety signal was identified; no cases met Hy's law criteria.

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Thank you

Questions & discussion
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