More patients achieved composite reductions of ≥1% HbA_{1c}, ≥5% body weight and ≥5 mmHg systolic blood pressure with semaglutide versus comparators (SUSTAIN 1–5, 7)

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Aim

- Cardiovascular (CV) disease is the leading cause of death among people with type 2 diabetes (T2D),[1] and treatments that reduce the risk of CV events in patients with T2D are warranted.
- Modification of CV risk factors is important for long-term CV risk management in patients with T2D.[2]
- Semaglutide (Novo Nordisk, Denmark) is a glucagon-like peptide-1 (GLP-1) analogue for the treatment of T2D.[3,4]
- SUSTAIN (Semaglutide Unabated Sustainability in Treatment of Type 2 Diabetes) is a global, phase 3 clinical trial programme designed to evaluate the efficacy and safety of once-weekly subcutaneous semaglutide.[5–11]
- Across the SUSTAIN trial programme, subjects with T2D achieved greater reductions in two or three of the CV risk factors: HbA_{1c}, body weight (BW) and systolic blood pressure (SBP), with semaglutide vs placebo or active comparators.[5–11]
- Decreases of HbA_{1c} ≥1%, BW ≥5% and SBP ≥5 mmHg are generally considered to be clinically meaningful.[12–14]
- This *post hoc* analysis evaluated to what extent subjects across the SUSTAIN trials 1–5 and 7 achieved clinically meaningful reductions in the composite of these three CV risk factors with semaglutide vs placebo or active comparators.

Methods

SUSTAIN 1–5 and 7 trial designs

- In SUSTAIN 1–5 and 7, adults with T2D (HbA_{1c} 7.0–10.0% for SUSTAIN 1, 4 and 5, and 7.0–10.5% for SUSTAIN 2, 3 and 7) were randomised to receive semaglutide 0.5 mg, semaglutide 1.0 mg or comparators (placebo, sitagliptin, exenatide extended release [ER], insulin glargine and dulaglutide) for 30, 40 or 56 weeks.[5–9,11]

Statistical analysis

- In this *post hoc* analysis, the composite endpoint (≥1% decrease in HbA_{1c}, ≥5% BW loss and ≥5 mmHg SBP reduction) was analysed using a logistic regression model with:
  - » Treatment, trial-specific stratification and country as fixed factors.
  - » Baseline values for individual components as covariates.
- Missing values for each component were imputed using a mixed model for repeated measurements.

Results

Baseline characteristics and demographics

- Baseline measurements were broadly consistent across SUSTAIN 1–5 and 7, with mean baseline HbA_{1c}, BW and SBP values ranging from 8.1–8.4%, 89.5–95.8 kg and 128.8–134.8 mmHg, respectively (Table 1).

Composite endpoint analyses

- Significantly more subjects achieved the composite endpoint with semaglutide (0.5 mg: 14–20%; 1.0 mg: 15–37%) than with placebo (2%) or active comparators (1–12%); p<0.001 for all comparisons (Figure 1).
- Evaluation of the two trials with GLP-1 receptor agonists (GLP-1RAs) as comparators showed that the composite endpoint was achieved by a significantly greater proportion of subjects treated with semaglutide (0.5 mg: 19%; 1.0 mg: 22–33%) vs exenatide ER (2.0 mg: 6%; SUSTAIN 3) or dulaglutide (0.75 mg: 7%; 1.5 mg: 12%; SUSTAIN 7); p<0.001 for all comparisons (Figure 1).
- A greater proportion of subjects achieved the composite endpoint at an early timepoint in the trials with semaglutide than with placebo or the active comparators, with differences being observed as early as week 8 (semaglutide vs placebo or insulin glargine) and week 12 (semaglutide vs sitagliptin, exenatide ER or dulaglutide) (Figure 2).

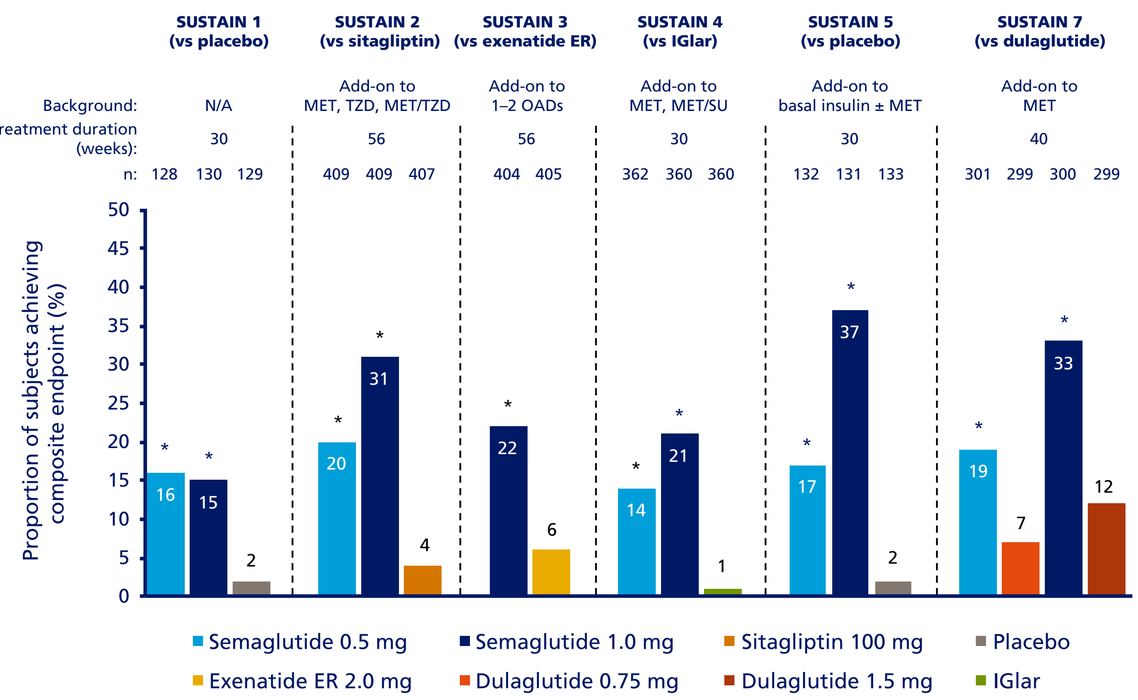
Table 1: Baseline characteristics and demographics

	SUSTAIN 1[5] (vs placebo)	SUSTAIN 2[6] (vs sitagliptin)	SUSTAIN 3[7] (vs exenatide ER)	SUSTAIN 4[8] (vs IGlar)	SUSTAIN 5[9] (vs placebo)	SUSTAIN 7[11] (vs dulaglutide)
	Mono-therapy	Add-on to MET, TZD, MET/TZD	Add-on to 1–2 OADs	Add-on to MET, MET/SU	Add-on to basal insulin ± MET	Add-on to MET
	30 weeks	56 weeks	56 weeks	30 weeks	30 weeks	40 weeks
Subject disposition, N (%)						
Randomised	388	1,231	813	1,089	397	1,201
Exposed	387 (99.7)	1,225 (99.5)	809 (99.5)	1,082 (99.4)	396 (99.7)	1,199 (99.8)
Baseline characteristics, mean (SD)						
Age, years	53.7 (11.3)	55.1 (10.0)	56.6 (10.7)	56.5 (10.4)	58.8 (10.1)	56.0 (10.6)
Diabetes duration, years	4.2 (5.5)	6.6 (5.1)	9.2 (6.3)	8.6 (6.3)	13.3 (7.8)	7.4 (5.7)
HbA_{1c}, %	8.1 (0.9)	8.1 (0.9)	8.3 (1.0)	8.2 (0.9)	8.4 (0.8)	8.2 (0.9)
Body weight, kg	91.9 (23.8)	89.5 (20.3)	95.8 (21.5)	93.5 (21.8)	91.7 (21.0)	95.2 (22.6)
SBP, mmHg	128.8 (13.2)	132.6 (14.9)	133.5 (14.5)	132.1 (15.3)	134.8 (16.0)	133.0 (14.3)

Exenatide ER, exenatide extended release; IGlar, insulin glargine; MET, metformin; N, number of subjects; OAD, oral antidiabetic drug; SBP, systolic blood pressure; SD, standard deviation; SU, sulphonylurea; TZD, thiazolidinedione

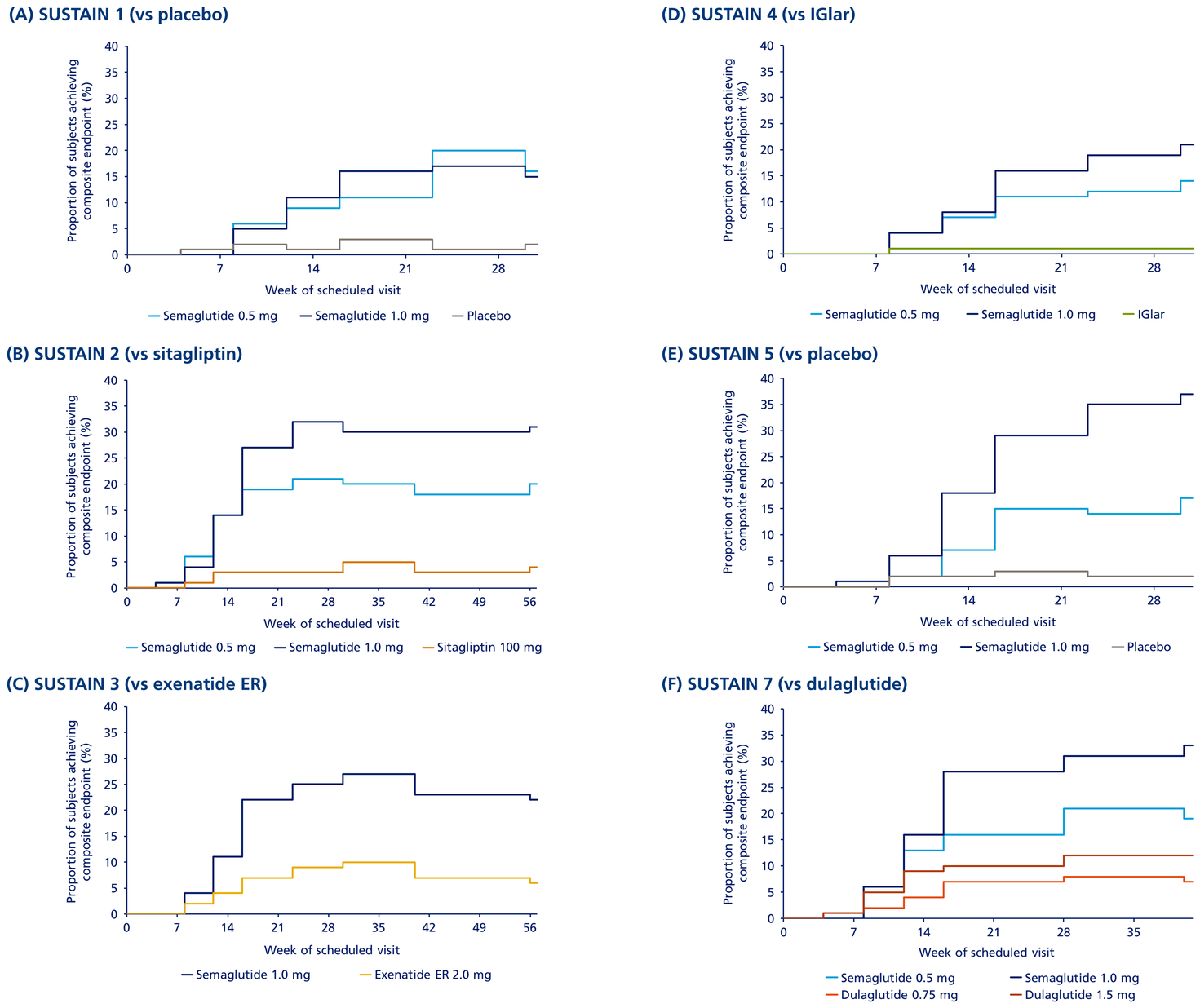
Key result

Figure 1: Proportion of subjects achieving the composite endpoint of ≥1% decrease in HbA_{1c}, ≥5% BW loss and ≥5 mmHg SBP reduction in the SUSTAIN 1–5 and 7 trials



*p<0.001 for semaglutide (0.5 mg or 1.0 mg) vs comparator. Comparison for SUSTAIN 7 is semaglutide 0.5 mg vs dulaglutide 0.75 mg and semaglutide 1.0 mg vs dulaglutide 1.5 mg. 'On-treatment without rescue medication' data are presented. Logistic regression with treatment, trial-specific stratification and country as fixed factors, and baseline HbA_{1c}, BW and SBP as covariate. Missing values for each component were imputed using a mixed model for repeated measurements with trial-specific stratification and country as fixed factors, and baseline value as covariate, all nested within visit. BW, body weight; exenatide ER, exenatide extended release; IGlar, insulin glargine; MET, metformin; N/A, not applicable; OAD, oral antidiabetic drug; SBP, systolic blood pressure; SU, sulphonylurea; TZD, thiazolidinedione

Figure 2: Proportion of subjects achieving the composite endpoint (≥1% decrease in HbA_{1c}, ≥5% BW loss and ≥5 mmHg SBP reduction) at each scheduled visit over the duration of each trial: (A) SUSTAIN 1, (B) SUSTAIN 2, (C) SUSTAIN 3, (D) SUSTAIN 4, (E) SUSTAIN 5 and (F) SUSTAIN 7



'On-treatment without rescue medication' data are presented. A mixed model for repeated measurements imputation was used for missing data. BW, body weight; exenatide ER, exenatide extended release; IGlar, insulin glargine; SBP, systolic blood pressure

- The biggest treatment difference for the individual components with the specified cutoffs (≥1% decrease in HbA_{1c}, ≥5% BW loss and ≥5 mmHg SBP reduction) was seen for HbA_{1c} and BW (data not shown).
- Similar results were observed when altering the cutoffs in the triple composite endpoints (data not shown):
  - » HbA_{1c} <7% (absolute value), ≥5% BW loss and ≥5 mmHg SBP reduction.
  - » ≥1% decrease in HbA_{1c}, ≥3% BW loss and ≥3 mmHg SBP reduction.

Discussion

- In this *post hoc* analysis across the SUSTAIN 1–5 and 7 trials, more subjects achieved the composite endpoint (≥1% decrease in HbA_{1c}, ≥5% weight loss and ≥5 mmHg SBP reduction) with semaglutide than with placebo or active comparators (p<0.001 for all).
- For the GLP-1RAs exenatide ER and dulaglutide, the difference between the treatments observed at the last visit was established from week 16 onwards (Figure 2: C and F).
- Semaglutide was associated with CV benefits in the SUSTAIN 6 trial, in which subjects with T2D and at high CV risk were treated with semaglutide or placebo.[10]
  - » The rate of CV death, non-fatal myocardial infarction or non-fatal stroke was significantly lower among subjects receiving semaglutide than among those receiving placebo (hazard ratio, 0.74, 95% confidence interval, 0.58–0.95; p<0.001 for non-inferiority, p=0.02 for superiority).[10]

Conclusion

- A higher proportion of subjects receiving semaglutide achieved the composite endpoint compared with placebo and comparators used in clinical practice (insulin glargine, dipeptidyl peptidase-4 inhibitors, GLP-1RAs).
- These clinically meaningful improvements in CV risk factors, including improvements in glycaemia, BW loss and SBP reduction, may contribute to a decrease in long-term CV complications in patients with T2D.

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