Efficacy and safety of semaglutide by baseline BMI in SUSTAIN 1–5 and 7

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Aim

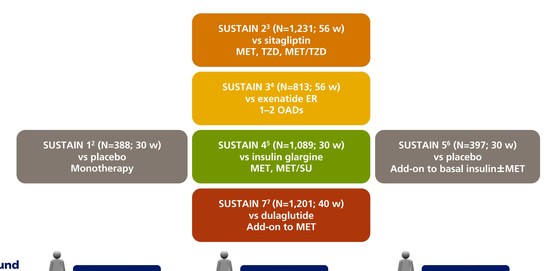
- Semaglutide (Novo Nordisk, Denmark) is a glucagon-like peptide-1 (GLP-1) analogue approved for the once-weekly subcutaneous treatment of type 2 diabetes (T2D).[1]
- The efficacy and safety of semaglutide were evaluated in the SUSTAIN clinical trial programme, which covered the continuum of care in T2D, including in drug-naïve subjects and those on background medication with oral antidiabetic drugs±insulin.[2–7]
- Across the SUSTAIN trials, semaglutide showed superior reductions in HbA_{1c} and body weight vs placebo and all active comparators (sitagliptin, exenatide extended release, insulin glargine, dulaglutide), and enabled a greater proportion of subjects to achieve clinically meaningful (≥5%) weight-loss responses.[2–7]
  - A higher body mass index (BMI) at baseline was generally associated with greater weight loss during semaglutide therapy.[8,9]
- As exposure to a drug may be affected by body weight,[10] the aim of this *post hoc* analysis was to assess if reductions in HbA_{1c} were affected by baseline BMI in the SUSTAIN trials.

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, or 7.0–10.5% for SUSTAIN 2, 3, and 7) were randomised to semaglutide 0.5 mg or 1.0 mg, placebo or active comparator (Figure 1).[2–7]

Figure 1: SUSTAIN 1–5 and 7 trials



SUSTAIN 6 was a cardiovascular outcomes trial in subjects at high risk of cardiovascular disease and, as such, was not included in the present analysis. Exenatide ER, exenatide extended release; MET, metformin; N, number of randomised subjects; OAD, oral antidiabetic drug; SU, sulphonylurea; TZD, thiazolidinedione; w, weeks.

- All semaglutide-treated subjects followed a fixed dose-escalation regimen:[2–7]
  - The semaglutide 0.5 mg maintenance dose was reached after 4 weeks of semaglutide 0.25 mg once weekly; the semaglutide 1.0 mg maintenance dose was reached after an additional 4 weeks of semaglutide 0.5 mg once weekly.
- Key endpoints were similar across trials:[2–7]
  - The primary endpoint was the change in HbA_{1c} from baseline to end of treatment.
  - The confirmatory secondary endpoint was the change in body weight from baseline to end of treatment.

Post hoc analysis

- For this *post hoc* analysis of data from the SUSTAIN 1–5 and 7 trials:
  - Subjects were grouped by baseline BMI (<25, 25 to <30, 30 to <35, and ≥35 kg/m²).
  - Change in HbA_{1c} was evaluated for semaglutide vs placebo or active comparator by trial for SUSTAIN 1–5 and 7 in a mixed model for repeated measurements, with treatment, BMI subgroup, and HbA_{1c} at baseline as covariates, and interaction between treatment and BMI subgroups at baseline.
  - Safety data were pooled and analysed by a Cochran–Mantel–Haenszel analysis stratified by trial.

Results

Baseline characteristics and demographics

- Baseline characteristics were broadly consistent across SUSTAIN 1–5 and 7, with mean baseline HbA_{1c} and body weight values ranging from 8.1% to 8.4% and 89.5 kg to 95.8 kg, respectively (Table 1).
- Diabetes duration at baseline ranged from 4.2 years to 13.3 years, reflecting the continuum of T2D care covered by the SUSTAIN trials (Table 1).

Table 1: Baseline characteristics and demographics by trial

		SUSTAIN 1[2] vs placebo	SUSTAIN 2[3] vs sitagliptin	SUSTAIN 3[4] vs exenatide ER	SUSTAIN 4[5] vs IGlar	SUSTAIN 5[6] vs placebo	SUSTAIN 7[7] vs dulaglutide
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)
	mmol/mol	64.5 (9.3)	64.8 (10.1)	67.7 (10.4)	65.8 (9.7)	67.9 (9.2)	66.4 (10.0)
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)
BMI, kg/m²		32.9 (7.7)	32.5 (6.2)	33.8 (6.7)	33.0 (6.5)	32.2 (6.2)	33.5 (6.8)

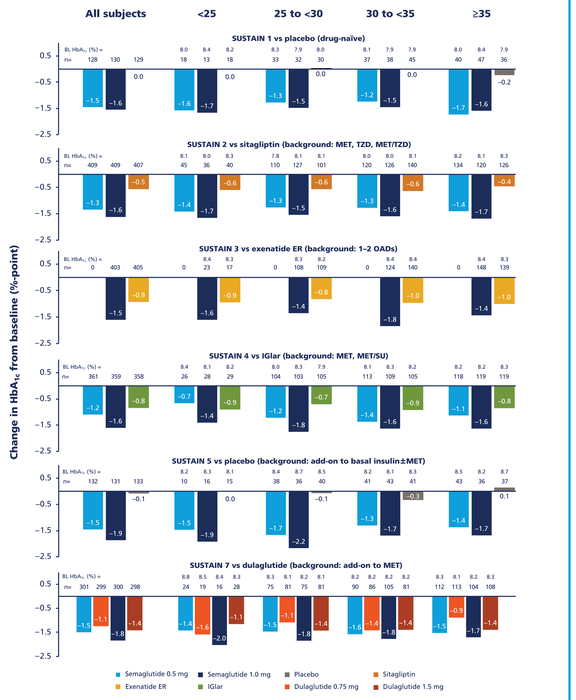
Values are mean (SD). BMI, body mass index; exenatide ER, exenatide extended release; IGlar, insulin glargine; SD, standard deviation.

Glycaemic control

- Reductions in mean HbA_{1c} (%) from baseline were generally greater with semaglutide vs placebo or active comparator in all BMI subgroups (Figure 2).
  - The only exception was in the <25 kg/m² BMI subgroup, for semaglutide 0.5 mg vs insulin glargine (–0.7% vs –0.9%, respectively) and for semaglutide 0.5 mg vs dulaglutide 0.75 mg (–1.4% vs –1.6%, respectively).
- There were no significant interactions between treatment and BMI, with the exception of semaglutide 0.5 mg in SUSTAIN 7.

Figure 2: Estimated change in HbA_{1c} by baseline BMI

Key result



Values shown are estimated mean changes from baseline for subjects on treatment without rescue medication. BL, baseline; BMI, body mass index; exenatide ER, exenatide extended release; IGlar, insulin glargine; MET, metformin; OAD, oral antidiabetic drug; SU, sulphonylurea; TZD, thiazolidinedione.

Safety

- In all treatment arms, adverse events (AEs) occurred in similar proportions of subjects across BMI subgroups (Table 2).
- The proportion of subjects with gastrointestinal AEs was higher with semaglutide vs placebo or active comparators; however, these events generally decreased with increasing baseline BMI.
- Premature treatment discontinuation due to AEs:
  - Decreased with increasing baseline BMI, potentially reflecting the trend in gastrointestinal AEs.
  - Was higher in all BMI subgroups with semaglutide vs placebo or active comparators.

Table 2: Adverse events by baseline BMI

	Semaglutide 0.5 mg				Semaglutide 1.0 mg				Comparator			
Baseline BMI subgroup, kg/m²	**<25**	**25 to <30**	**30 to <35**	**≥35**	**<25**	**25 to <30**	**30 to <35**	**≥35**	**<25**	**25 to <30**	**30 to <35**	**≥35**
All AEs	89 (71.8)	249 (69.0)	284 (70.6)	313 (70.0)	96 (72.2)	337 (69.9)	375 (68.9)	413 (72.1)	111 (66.0)	365 (67.0)	448 (69.9)	462 (68.6)
Serious AEs	5 (3.9)	19 (5.2)	31 (7.7)	29 (6.4)	4 (3.6)	29 (6.0)	36 (6.6)	58 (10.2)	6 (3.4)	26 (5.2)	46 (6.9)	53 (7.6)
AEs leading to premature treatment discontinuation	16 (13.5)	38 (10.5)	22 (5.7)	15 (3.4)	23 (18.0)	44 (9.2)	42 (7.7)	39 (6.9)	15 (8.3)	29 (4.6)	24 (3.7)	15 (2.3)
GI AEs	59 (47.8)	155 (43.2)	155 (38.8)	171 (38.4)	65 (50.5)	210 (43.7)	212 (39.0)	228 (39.9)	40 (21.2)	152 (25.8)	191 (28.9)	184 (25.5)

On-treatment data for number of subjects in the safety analysis set (% of total subjects) experiencing >1 event. Comparators were: placebo (SUSTAIN 1 and 5), sitagliptin (SUSTAIN 2), exenatide extended release (SUSTAIN 3), insulin glargine (SUSTAIN 4), and dulaglutide (SUSTAIN 7). AE, adverse event; BMI, body mass index; GI, gastrointestinal.

Discussion

- Achieving glycaemic control in T2D is challenging, and responsiveness to therapy is important.[11]
- In this *post hoc* analysis of the SUSTAIN 1–5 and 7 trials, the estimated treatment differences in mean HbA_{1c} for semaglutide vs placebo or active comparators did not appear to be influenced by baseline BMI, indicating a consistent effect of semaglutide.
  - A previous analysis of SUSTAIN 1–5 data, showing change in HbA_{1c} against change in body weight with semaglutide, resulted in similar findings.[12]
- Reductions in mean HbA_{1c} from baseline were generally greater with semaglutide vs placebo or active comparators in all BMI subgroups.
- AEs occurred in a similar proportion of subjects in all treatment arms and across BMI subgroups.
- Gastrointestinal AEs generally decreased with increasing BMI in subjects receiving semaglutide.

Conclusion

- Semaglutide consistently reduced HbA_{1c} vs placebo or active comparators in subjects with T2D regardless of their baseline BMI.
- Semaglutide had an acceptable safety profile in all BMI subgroups.

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References: (**1**) Lau J et al. J Med Chem 2015;58:7370–80; (**2**) Sorli C et al. Lancet Diabetes Endocrinol 2017;5:251–60; (**3**) Ahrén B et al. Lancet Diabetes Endocrinol 2017;5:341–54; (**4**) Ahmann AJ et al. Diabetes Care 2018;41:258–66; (**5**) Aroda VR et al. Lancet Diabetes Endocrinol 2017;5:355–66; (**6**) Rodbard HW et al. J Clin Endocrinol Metab 2018;103:2291–301; (**7**) Pratley RE et al. Lancet Diabetes Endocrinol 2018;6:275–86; (**8**) Leiter LA et al. Presented at the 77th Scientific Sessions of the American Diabetes Association, 9–13 June 2017, San Diego, CA, USA. Poster 1105-P; (**9**) Viljoen A et al. Presented at the 78th Scientific Sessions of the American Diabetes Association, 22–26 June 2018, Orlando, FL, USA. Poster 1083-P; (**10**) Carlsson Petri KC et al. Diabetes Ther 2018;9:1533–47; (**11**) Fonseca VA et al. Diabetes Care 2009;32:S151–6; (**12**) Rodbard HW et al. Presented at the 77th Scientific Sessions of the American Diabetes Association, 9–13 June 2017, San Diego, CA, USA. Poster 1124-P.