Semaglutide reduces HbA_{1c} and body weight across baseline HbA_{1c} subgroups in the SUSTAIN 1–5 clinical trials

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Background

- In spite of a variety of available treatment options, achieving HbA_{1c} targets remains a challenge for many patients with type 2 diabetes (T2D).[1] Furthermore, obesity is a common concomitant complication in subjects with T2D.[2]
- Semaglutide (Novo Nordisk, Denmark), a glucagon-like peptide-1 (GLP-1) analogue with 94% homology to native GLP-1, is currently in development for once-weekly subcutaneous (s.c.) treatment of T2D.[3]
- 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 semaglutide s.c. in patients with T2D, including drug-naïve patients and those on a background of oral antidiabetic drugs (OADs) and/or insulin.
- In SUSTAIN 1–5, the efficacy and safety of semaglutide were studied vs comparators.
  - Semaglutide 0.5 or 1.0 mg vs placebo (SUSTAIN 1).[4]
  - Semaglutide 0.5 or 1.0 mg vs once-daily sitagliptin 100 mg (SUSTAIN 2).[5]
  - Semaglutide 1.0 mg vs once-weekly exenatide extended release (ER) 2.0 mg (SUSTAIN 3).[6]
  - Semaglutide 0.5 or 1.0 mg vs once-daily insulin glargine (IGlar) (SUSTAIN 4).[7]
  - Semaglutide 0.5 or 1.0 mg vs placebo (add-on to insulin) (SUSTAIN 5).[8]
- Semaglutide demonstrated superior reductions in HbA_{1c} and body weight vs placebo and active comparators across the SUSTAIN 1–5 clinical trials.[4-8]
- This poster reports on a *post hoc* analysis of the SUSTAIN 1–5 trials, with regards to change in HbA_{1c}, body weight and episodes of severe or blood glucose (BG)-confirmed (<3.1 mmol/L) symptomatic hypoglycaemia by baseline HbA_{1c} subgroup.

Methods

SUSTAIN 1–5 study design

- In the SUSTAIN 1–5 phase 3a trials, adults with T2D (HbA_{1c} 7.0–10.0/10.5%) were randomised to once-weekly s.c. semaglutide or comparator.
- Background medication consisted of 1–2 OADs (metformin, sulphonylurea, thiazolidinediones) in SUSTAIN 2–4 and basal insulin ± metformin in SUSTAIN 5.
- All semaglutide-treated subjects followed a fixed dose-escalation regimen from a starting dose of semaglutide 0.25 mg, with dose doubling every 4 weeks until the trial dose was achieved.
- Key endpoints were similar across all trials.[4-8]
  - Primary endpoint was change in HbA_{1c} from baseline to end of treatment.
  - Secondary endpoints presented here included change from baseline in body weight, proportions of subjects achieving <7.0% or ≤6.5% HbA_{1c} targets, and rates of hypoglycaemia.

Post hoc analysis

- The changes in HbA_{1c}, body weight and episodes of severe or BG-confirmed symptomatic hypoglycaemia were analysed by baseline HbA_{1c} (≤7.5%, >7.5 to 8.0%, >8.0 to 8.5%, >8.5 to 9.0%, and >9.0%) based on randomised and exposed subjects using on-treatment without rescue medication data.

Results

Baseline characteristics and demographics

- In total, 3,918 subjects with T2D were randomised to once-weekly semaglutide s.c. 0.5 mg or 1.0 mg vs comparators.
  - Subject disposition and baseline characteristics are shown in Table 1.

Glycaemic control

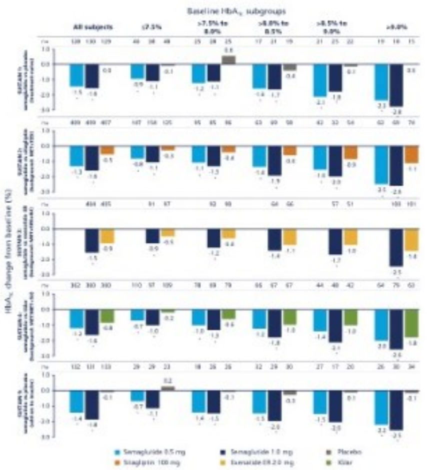
- Semaglutide reduced mean HbA_{1c} from baseline to end of treatment in all subgroups vs all comparators (Figure 1).
  - Mean HbA_{1c} decreased by 0.7–2.5% with semaglutide 0.5 mg and 0.9–2.8% with semaglutide 1.0 mg. With comparators, change from baseline in mean HbA_{1c} ranged from a decrease of 1.8% to an increase of 0.6%.
  - Across trials, the reduction in HbA_{1c} was consistently greater with higher baseline HbA_{1c} (Figure 1).
- A higher proportion of subjects achieved an HbA_{1c} target of <7.0% with semaglutide vs comparators (Table 2).
  - Furthermore, a greater proportion of semaglutide-treated subjects with the highest baseline HbA_{1c} (>9.0%) achieved an HbA_{1c} target of <7.0% or HbA_{1c} <8.0%, than comparators (Figure 2).

Table 1. Subject disposition and baseline characteristics in the SUSTAIN 1–5 trials.

	SUSTAIN 1: Semaglutide vs placebo 30 weeks	SUSTAIN 2: Semaglutide vs sitagliptin 100 mg 56 weeks	SUSTAIN 3: Semaglutide vs exenatide ER 2.0 mg 56 weeks	SUSTAIN 4: Semaglutide vs IGlar 30 weeks	SUSTAIN 5: Semaglutide add-on to insulin vs placebo 30 weeks
Subject disposition, N (%)					
Randomised	388	1,231	813	1,089	397
Exposed	387 (99.7)	1,225 (99.5)	809 (99.5)	1,082 (99.4)	396 (99.7)
Trial completers	359 (92.5)	1,163 (94.5)	743 (91.4)	1,020 (93.7)	380 (95.7)
Premature treatment discontinuation	47 (12.1)	146 (11.9)	167 (20.6)	130 (12.0)	43 (10.8)
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)
Male (%)	54.3	50.6	55.3	53.0	56.1
Diabetes duration (years)	4.2 (5.5)	6.6 (5.1)	9.2 (6.3)	8.6 (6.3)	13.3 (7.8)
Body weight (kg)	91.9 (23.8)	89.5 (20.3)	95.8 (21.5)	93.5 (21.8)	91.7 (21.0)
HbA_{1c} (%)	8.1 (0.9)	8.1 (0.9)	8.3 (1.0)	8.2 (0.9)	8.4 (0.8)
FPG (mmol/L)	9.7 (2.7)	9.4 (2.3)	10.5 (2.7)	9.7 (2.8)	8.6 (3.0)
BMI (kg/m²)	32.9 (7.7)	32.5 (6.2)	33.8 (6.7)	33.0 (6.5)	32.2 (6.2)

BMI, body mass index; exenatide ER, exenatide extended release; FPG, fasting plasma glucose; IGlar, insulin glargine; SD, standard deviation.

Figure 1. Change in HbA_{1c} from baseline to end of treatment in the SUSTAIN 1–5 trials.



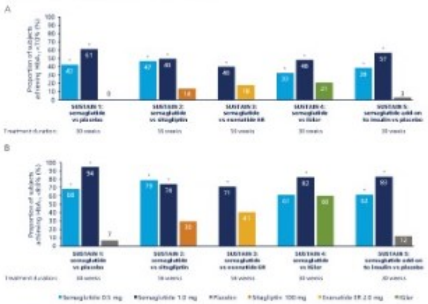
*p<0.05 vs comparator. Values are estimated means from a mixed model for repeated measurements analysis, with an interaction between treatment and subgroup variables as fixed factors and baseline value as covariate, all nested within visit. Exenatide ER, exenatide extended release; IGlar, insulin glargine; MET, metformin; SU, sulphonylurea; TZD, thiazolidinedione.

Table 2. Proportion of subjects (%) achieving an HbA_{1c} target of <7.0% in the SUSTAIN 1–5 trials.

Baseline HbA_{1c}	Number of subjects	Semaglutide 0.5 mg	Semaglutide 1.0 mg	Comparator
SUSTAIN 1: semaglutide vs placebo (30 weeks)				
All subjects	**387**	**74**	**72**	**25**
≤7.5%	132	67	76	40
>7.5% to 8.0%	78	68	61	12
>8.0% to 8.5%	57	76	48	11
>8.5% to 9.0%	68	62	48	9
>9.0%	52	42	61	0
SUSTAIN 2: semaglutide vs sitagliptin (56 weeks)				
All subjects	**1,225**	**69**	**78**	**36**
≤7.5%	426	73	77	55
>7.5% to 8.0%	276	58	80	39
>8.0% to 8.5%	190	52	75	17
>8.5% to 9.0%	128	38	44	24
>9.0%	205	47	49	14
SUSTAIN 3: semaglutide vs exenatide ER (56 weeks)				
All subjects	**809**	N/A	**67**	**40**
≤7.5%	188		65	54
>7.5% to 8.0%	182		65	39
>8.0% to 8.5%	130		53	32
>8.5% to 9.0%	108		49	18
>9.0%	201		40	18
SUSTAIN 4: semaglutide vs IGlar (30 weeks)				
All subjects	**1,082**	**57**	**73**	**38**
≤7.5%	318	65	72	50
>7.5% to 8.0%	226	59	61	35
>8.0% to 8.5%	200	39	55	33
>8.5% to 9.0%	134	32	54	19
>9.0%	206	33	48	21
SUSTAIN 5: semaglutide add-on to insulin vs placebo (30 weeks)				
All subjects	**396**	**61**	**79**	**11**
≤7.5%	81	69	76	9
>7.5% to 8.0%	70	67	58	12
>8.0% to 8.5%	91	50	83	17
>8.5% to 9.0%	63	37	41	10
>9.0%	90	38	57	3

Exenatide ER, exenatide extended release; IGlar, insulin glargine; N/A, not applicable (semaglutide 0.5 mg was not investigated in the SUSTAIN 3 trial).

Figure 2. Proportion of subjects with baseline HbA_{1c} >9.0% achieving an HbA_{1c} target of <7.0% (A) or HbA_{1c} <8.0% (B) in the SUSTAIN 1–5 trials.

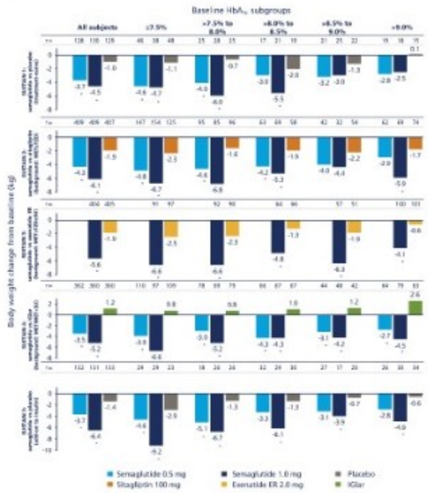


*p<0.05 vs comparator. The binary endpoint was analysed using a logistic regression model with treatment subgroup interaction and baseline HbA_{1c} value as covariate. Before analysis, missing data for change from baseline were imputed from the corresponding mixed model for repeated measurements analysis. Exenatide ER, exenatide extended release; IGlar, insulin glargine.

Body weight

- Greater weight reduction with semaglutide vs comparators was observed across all baseline HbA_{1c} subgroups: mean body weight decreased by 2.7–5.1 kg with semaglutide 0.5 mg, 2.5–9.2 kg with semaglutide 1.0 mg, and by 2.9 kg to an increase of 2.6 kg with comparators (Figure 3).
- There was no apparent relationship between the magnitude of weight reduction and baseline HbA_{1c} level.

Figure 3. Change in body weight from baseline to end of treatment in the SUSTAIN 1–5 trials.



*p<0.05 vs comparator. Values are estimated means from a mixed model for repeated measurements analysis, with an interaction between treatment and subgroup variables as fixed factors and baseline value as covariate, all nested within visit. Exenatide ER, exenatide extended release; IGlar, insulin glargine; MET, metformin; SU, sulphonylurea; TZD, thiazolidinedione.

Safety

- The overall incidence of adverse events (AEs) or serious AEs, pooled across trials, was higher with semaglutide (0.5 and 1.0 mg) than with comparators, mainly due to a higher proportion of subjects experiencing gastrointestinal disorders with semaglutide.[4-8]
- Rates of hypoglycaemia were generally low across baseline HbA_{1c} groups (Table 3).
  - In SUSTAIN 1–4, severe or BG-confirmed symptomatic hypoglycaemic episodes were fewer or similar with semaglutide than with comparators.
  - In SUSTAIN 5, on a background of basal insulin, more hypoglycaemic episodes were reported with semaglutide than with placebo (Table 3).
- No new safety or tolerability issues were identified with semaglutide in the SUSTAIN 1–5 trials.[4-8]

Table 3. Severe or BG-confirmed* symptomatic hypoglycaemia in the SUSTAIN 1–5 trials.

Baseline HbA_{1c}	Number of subjects	Semaglutide 0.5 mg N	%	E	R	Semaglutide 1.0 mg N	%	E	R	Comparator N	%	E	R
SUSTAIN 1: semaglutide vs placebo (30 weeks)													
All subjects	**387**	0				0				**2**	**1.6**	**3**	**3.7**
≤7.5%	132									1	2.1	1	3.3
>7.5% to 8.0%	78									0			
>8.0% to 8.5%	57									1	5.3	2	18.3
>8.5% to 9.0%	68									0			
>9.0%	52									0			
SUSTAIN 2: semaglutide vs sitagliptin (56 weeks)													
All subjects	**1,225**	**7**	**1.7**	**7**	**1.6**	**2**	**0.5**	**2**	**0.5**	**5**	**1.2**	**5**	**1.1**
≤7.5%	426	1	0.7	1	0.6	1	0.6	1	0.6	4	2.4	4	2.2
>7.5% to 8.0%	276	1	1.1	1	1.0	0				1	1.0	1	6.9
>8.0% to 8.5%	190	0				1	1.4	1	1.3	1	1.7	1	1.5
>8.5% to 9.0%	128	1	2.4	1	2.3	0				0			
>9.0%	205	4	6.5	4	8.1	0				0			
SUSTAIN 3: semaglutide vs exenatide ER (56 weeks)													
All subjects	**809**	N/A				**29**	**7.2**	**41**	**9.9**	**28**	**6.9**	**46**	**11.3**
≤7.5%	188					7	7.7	9	16.1	8	8.2	15	15.4
>7.5% to 8.0%	182					8	8.7	12	12.2	6	6.7	7	7.5
>8.0% to 8.5%	130					2	3.1	2	3.0	5	7.6	13	19.2
>8.5% to 9.0%	108					4	7.0	4	8.6	5	9.8	7	14.3
>9.0%	201					8	8.0	14	14.0	4	4.0	4	4.0
SUSTAIN 4: semaglutide vs IGlar (30 weeks)													
All subjects	**1,082**	**16**	**4.4**	**32**	**14.2**	**20**	**5.6**	**39**	**17.8**	**38**	**10.6**	**69**	**29.4**
≤7.5%	318	5	4.5	8	11.8	5	5.2	7	12.0	14	12.8	30	42.1
>7.5% to 8.0%	226	3	3.8	9	18.4	3	4.3	6	14.4	13	16.5	21	41.8
>8.0% to 8.5%	200	3	4.5	4	9.6	2	3.0	2	5.1	3	4.5	6	13.5
>8.5% to 9.0%	134	3	6.8	7	26.5	5	10.4	11	36.8	2	4.8	2	7.3
>9.0%	206	2	4.1	4	10.0	5	6.3	13	26.1	4	9.5	10	23.9
SUSTAIN 5: semaglutide add-on to insulin vs placebo (30 weeks)													
All subjects	**396**	**11**	**8.3**	**17**	**20.2**	**14**	**10.7**	**25**	**28.5**	**7**	**5.3**	**13**	**15.5**
≤7.5%	81	2	6.9	2	10.7	7	24.1	12	64.0	0			
>7.5% to 8.0%	70	2	11.1	4	25.2	2	7.7	5	32.3	2	7.7	3	17.1
>8.0% to 8.5%	91	3	9.4	4	20.4	3	10.3	4	21.5	1	3.3	2	10.8
>8.5% to 9.0%	63	3	11.1	7	39.9	1	5.9	1	10.9	0			
>9.0%	90	1	3.8	1	6.0	1	3.3	3	14.8	4	11.8	8	38.7

*<3.1 mmol/L. BG, blood glucose; E, number of events; exenatide ER, exenatide extended release; IGlar, insulin glargine; N/A, not applicable (semaglutide 0.5 mg was not investigated in the SUSTAIN 3 trial); R, rate of events per 100 observation years.

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Conclusions

- Semaglutide treatment consistently showed greater efficacy in lowering HbA_{1c} and body weight vs comparators, regardless of baseline HbA_{1c}.
- The reduction in HbA_{1c} was consistently greater with higher baseline HbA_{1c}.
- There was no apparent relationship between the magnitude of weight reduction and baseline HbA_{1c}.
- Rates of severe or BG-confirmed hypoglycaemia with semaglutide were generally low across baseline HbA_{1c} subgroups; higher rates were reported only with SU and/or insulin as baseline background therapy.
- Semaglutide was well tolerated, with a similar safety profile to that of other GLP-1 receptor agonists.[9,10]

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