Efficacy and safety of semaglutide by background sodium–glucose co-transporter-2 inhibitor: a *post hoc* analysis of SUSTAIN 9

Bernhard Ludvik[1]; Vaishali Bhosekar[2]; Robert S. Busch[3]; Ingrid Holst[4]; Athena Philis-Tsimikas[5]; James Thrasher[6]; Vincent C. Woo[7]; Emre Yildirim[4]; Bernard Zinman[8]

[1]1st Medical Department and Karl Landsteiner Institute for Obesity and Metabolic Disorders, Rudolfstiftung Hospital, Vienna, Austria; [2]Novo Nordisk, Bengaluru, India; [3]Albany Medical Center Division of Community Endocrinology, Albany, NY, USA; [4]Novo Nordisk A/S, Søborg, Denmark; [5]Scripps Whittier Diabetes Institute, San Diego, CA, USA; [6]Medical Investigations, Inc., Little Rock, AR, USA; [7]University of Manitoba, Winnipeg, MB, Canada; [8]Lunenfeld-Tanenbaum Research Institute, Mount Sinai Hospital, University of Toronto, Toronto, ON, Canada.

(qrs.ly/e5abn8z)

Aim

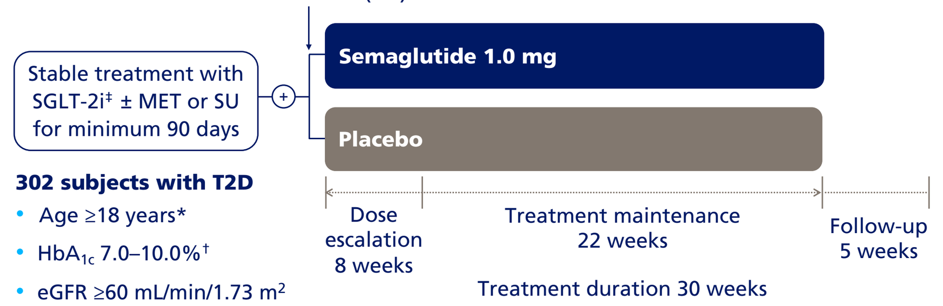
- Treatment guidelines recommend glucagon-like peptide-1 receptor agonists (GLP-1RAs) and sodium–glucose co-transporter-2 inhibitors (SGLT-2is) for use after metformin in patients with type 2 diabetes (T2D) and established cardiovascular disease.[1,2]
- However, clinical trial data on the efficacy and safety of the concomitant use of GLP-1RAs and SGLT-2is in the management of T2D are scarce.
- The SUSTAIN 9 trial showed that, in subjects with T2D inadequately controlled with SGLT-2i therapy with or without metformin or a sulphonylurea, the addition of the GLP-1RA semaglutide once weekly (Novo Nordisk, Denmark) improved glycaemic control, lowered body weight, and was generally well tolerated.[3]
- The aim of this *post hoc* analysis of SUSTAIN 9 was to assess whether the efficacy and safety of semaglutide vs placebo were consistent in subjects on different background SGLT-2is.

Methods

SUSTAIN 9 trial design

- SUSTAIN 9 was a randomised, double-blind, placebo-controlled, multinational trial (Figure 1).[3]
- Subjects were randomised to semaglutide 1.0 mg or placebo, both subcutaneous once weekly, as an add-on to SGLT-2i therapy, with or without metformin or a sulphonylurea.[3]
- Semaglutide dosing began at 0.25 mg, doubling every 4 weeks until the maintenance dose was reached.[3]
- The primary and confirmatory secondary endpoints were change in HbA_{1c} and body weight, respectively, from baseline to week 30.[3]

Figure 1: SUSTAIN 9 trial design[3]



*Japan: minimum age for enrolment ≥20 years. †53–86 mmol/mol. ‡Stable treatment with SGLT-2i was defined as having started SGLT-2i treatment ≥90 days before screening. eGFR, estimated glomerular filtration rate; MET, metformin; SGLT-2i, sodium–glucose co-transporter-2 inhibitor; SU, sulphonylurea.

Statistical analysis

- In this *post hoc* analysis of SUSTAIN 9, changes in HbA_{1c} and body weight from baseline to week 30 were analysed by background SGLT-2i: canagliflozin; dapagliflozin (includes dapagliflozin and dapagliflozin propanediol monohydrate); empagliflozin; or other (ipragliflozin L-proline, luseogliflozin, and tofogliflozin; drugs available only in Japan) using an analysis of covariance.
- Proportions of subjects achieving HbA_{1c} targets (<7.0% and ≤6.5%), weight-loss responses (≥5% and ≥10%), and the triple composite endpoint of HbA_{1c} <7.0%, no weight gain, and no severe or blood glucose-confirmed hypoglycaemia were analysed by background SGLT-2i using a logistic regression model.
- A test for interaction was used to evaluate any impact of background SGLT-2i on treatment effect.

Results

Baseline characteristics and demographics

- A total of 302 subjects with T2D, on stable treatment with SGLT-2i with or without metformin or a sulphonylurea, were randomised to receive either semaglutide or placebo; one subject was assigned to treatment but did not receive treatment.[3]
- Baseline characteristics for subjects enrolled in SUSTAIN 9 were similar across SGLT-2i subgroups (Table 1).[3]

Table 1: Baseline characteristics and demographics by background SGLT-2i

	All subjects*		Canagliflozin		Dapagliflozin†		Empagliflozin	
	Semaglutide 1.0 mg (n=150)	Placebo (n=151)	Semaglutide 1.0 mg (n=39)	Placebo (n=29)	Semaglutide 1.0 mg (n=44)	Placebo (n=62)	Semaglutide 1.0 mg (n=52)	Placebo (n=50)
Age, years	57.5 (8.9)	56.6 (10.1)	55.2 (10.1)	54.3 (8.7)	56.5 (9.2)	56.1 (10.7)	59.6 (7.5)	57.7 (10.9)
Diabetes duration, years	9.8 (6.3)	9.6 (5.9)	11.1 (8.0)	7.1 (3.8)	8.0 (4.6)	10.2 (6.2)	9.4 (5.0)	9.7 (6.1)
HbA_{1c}, %	8.0 (0.8)	8.1 (0.8)	7.8 (0.8)	7.8 (0.8)	8.1 (0.9)	8.2 (0.9)	8.0 (0.7)	7.9 (0.8)
FPG, mmol/L	9.1 (2.1)	8.9 (2.2)	8.5 (1.9)	8.8 (2.6)	9.3 (2.1)	9.3 (2.4)	9.5 (2.4)	8.7 (1.7)
BMI, kg/m^2	31.1 (6.2)	32.7 (6.9)	33.9 (7.2)	35.4 (7.0)	32.1 (5.6)	32.9 (6.0)	30.2 (4.6)	32.3 (7.3)
eGFR, mL/min/1.73 m^2	94.5 (15.3)	96.0 (15.1)	96.0 (13.3)	98.4 (14.5)	95.0 (15.7)	95.9 (15.7)	92.1 (16.0)	94.2 (15.8)

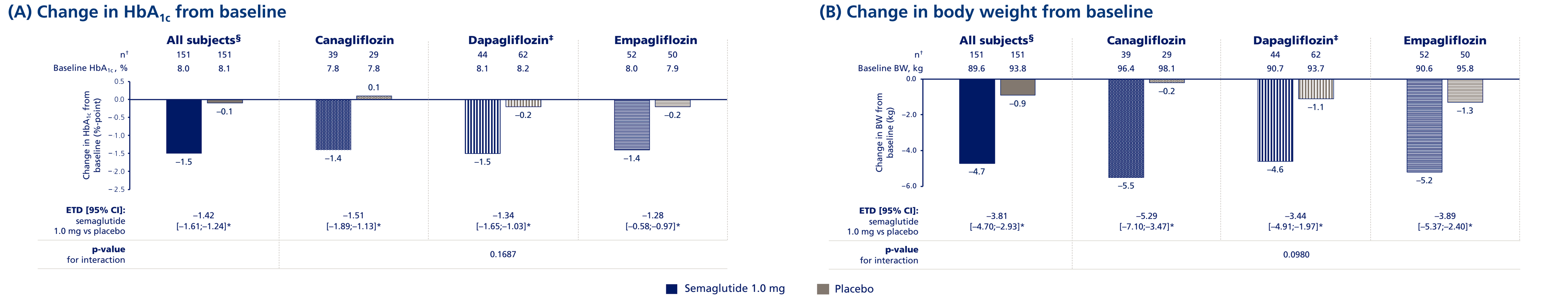
*25 subjects who received other SGLT-2is were randomised to receive semaglutide 1.0 mg (n=15) or placebo (n=10); data not presented owing to small number of subjects. †Includes subjects receiving dapagliflozin or dapagliflozin propanediol monohydrate. Values are mean (SD). BMI, body mass index; eGFR, estimated glomerular filtration rate; FPG, fasting plasma glucose; SD, standard deviation; SGLT-2i, sodium–glucose co-transporter-2 inhibitor.

Glycaemic control and body weight

- At 30 weeks, there was no significant interaction between background SGLT-2i and treatment effect for any of the endpoints (interaction p>0.05 for all; Figures 2 and 3).
- Across background SGLT-2i groups, reductions in HbA_{1c} (Figure 2A) and body weight (Figure 2B) were significantly greater with semaglutide vs placebo.
- The proportions of subjects achieving American Diabetes Association and American Association of Clinical Endocrinologists HbA_{1c} targets of <7.0% and ≤6.5%, respectively, weight-loss responses of ≥5%, and the composite endpoint of HbA_{1c} <7.0% without weight gain and no severe or blood glucose-confirmed symptomatic hypoglycaemia, were also significantly greater for semaglutide vs placebo, with a similar pattern for all SGLT-2is (Figure 3A–C, E).

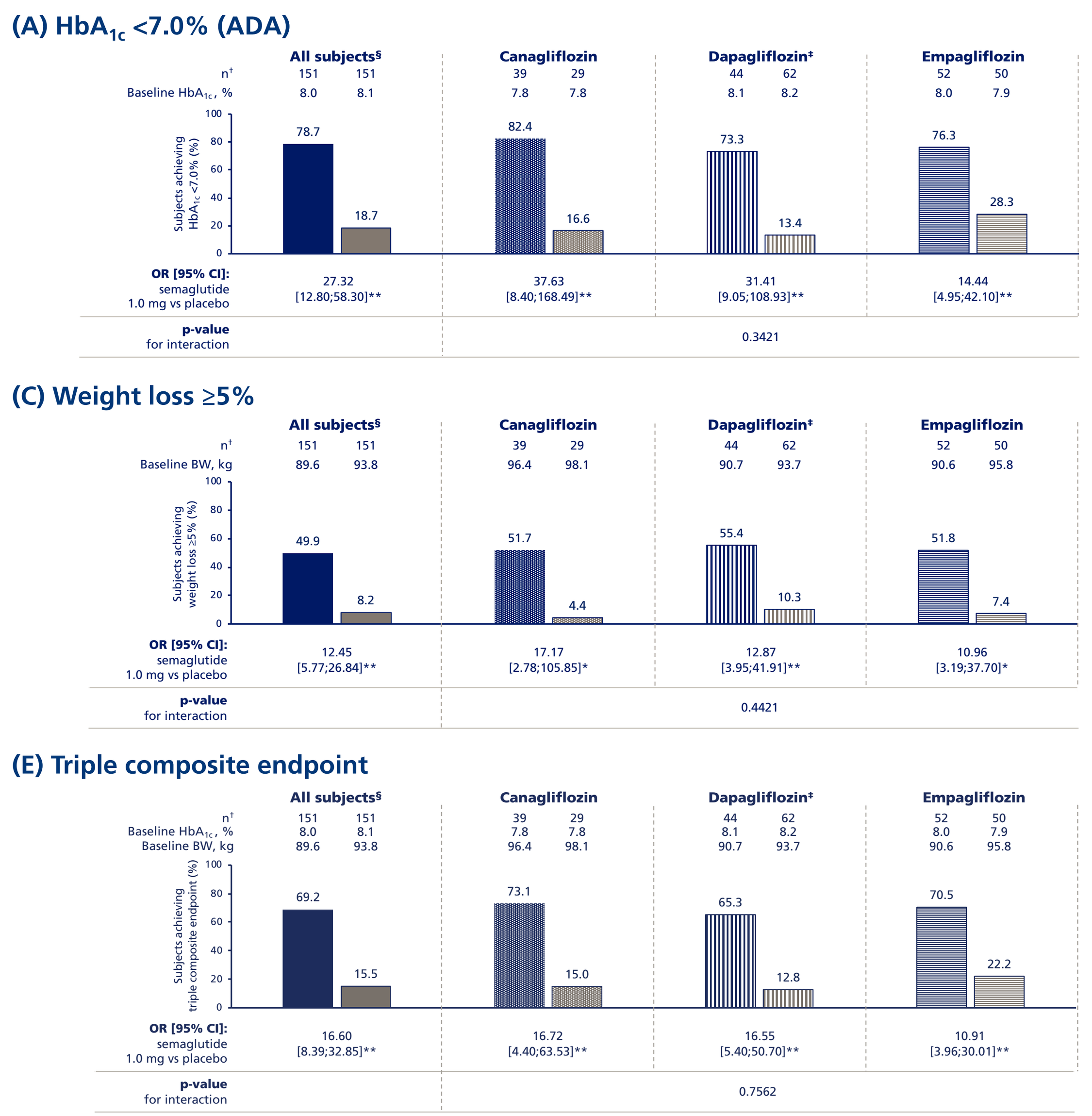
Key results

Figure 2: Change in (A) HbA_{1c} and (B) body weight from baseline at 30 weeks by SGLT-2i therapy



*p<0.0001 vs placebo. p-value for interaction of background SGLT-2i on treatment effect. †302 subjects were randomised and 301 received trial medication; one subject was randomised but not included in this analysis due to not receiving SGLT-2i at screening. ‡Includes subjects receiving dapagliflozin or dapagliflozin propanediol monohydrate. §25 subjects received other SGLT-2is and were randomised to receive semaglutide 1.0 mg (n=15) or placebo (n=10); data not presented owing to small number of subjects. 'On-treatment without rescue medication' data analysed using an analysis of covariance with treatment, subgroup and treatment by subgroup interaction, stratification factor, and region as fixed factors, and baseline value as covariate. Mean baseline values and mean changes from baseline are shown. BW, body weight; CI, confidence interval; ETD, estimated treatment difference; SGLT-2i, sodium–glucose co-transporter-2 inhibitor.

Figure 3: Proportion of subjects achieving, at 30 weeks, (A) HbA_{1c} <7.0%, (B) HbA_{1c} ≤6.5%, (C) weight loss ≥5%, (D) weight loss ≥10%, (E) triple composite of HbA_{1c} <7.0% without weight gain and no severe or blood glucose-confirmed symptomatic hypoglycaemia



*p<0.01 vs placebo; **p<0.0001 vs placebo. p-value for interaction of background SGLT-2i on treatment effect. †302 subjects were randomised and 301 received trial medication; one subject was randomised but not included in this analysis due to not receiving SGLT-2i at screening. ‡Includes subjects receiving dapagliflozin or dapagliflozin propanediol monohydrate. §25 subjects received other SGLT-2is and were randomised to receive semaglutide 1.0 mg (n=15) or placebo (n=10); data not presented owing to small number of subjects. 'On-treatment without rescue medication' data analysed using an analysis of covariance with treatment, subgroup and treatment by subgroup interaction, stratification factor, and region as fixed factors, and baseline value as covariate. AACE, American Association of Clinical Endocrinologists; ADA, American Diabetes Association; BW, body weight, CI, confidence interval; NE, not estimable; OR, odds ratio; SGLT-2i, sodium–glucose co-transporter-2 inhibitor.

- The proportion of subjects achieving a weight-loss response of ≥10% was significantly greater for semaglutide vs placebo for all subjects, but there was no significant difference between the treatment arms when analysed by individual SGLT-2i group (Figure 3D).
- Results for subjects who received other SGLT-2is (n=25; data not shown) were similar to those for subjects receiving canagliflozin, dapagliflozin, or empagliflozin.

Safety

- No new safety concerns were identified when adding semaglutide to SGLT-2i therapy.
- Reported adverse events by treatment arm were similar between the SGLT-2i subgroups (Table 2). Results for subjects who received other SGLT-2is (n=25; data not shown) were similar to those for subjects receiving canagliflozin, dapagliflozin, or empagliflozin.

Table 2: Adverse events by background SGLT-2i

	All subjects*		Canagliflozin		Dapagliflozin†		Empagliflozin	
	Semaglutide 1.0 mg (n=150)	Placebo (n=151)	Semaglutide 1.0 mg (n=39)	Placebo (n=29)	Semaglutide 1.0 mg (n=43)	Placebo (n=62)	Semaglutide 1.0 mg (n=52)	Placebo (n=50)
All AEs	104 (69.3)	91 (60.3)	34 (87.2)	21 (72.4)	29 (67.4)	33 (53.2)	35 (67.3)	32 (64.0)
Serious AEs	7 (4.7)	6 (4.0)	3 (7.7)	1 (3.4)	1 (2.3)	1 (1.6)	3 (5.8)	4 (8.0)
AEs leading to premature treatment discontinuation	13 (8.7)	3 (2.0)	4 (10.3)	1 (3.4)	3 (7.0)	2 (3.2)	5 (9.6)	0
GI AEs	56 (37.3)	20 (13.2)	14 (35.9)	4 (13.8)	18 (41.9)	8 (12.9)	21 (40.4)	6 (12.0)
Severe or BG-confirmed‡ symptomatic hypoglycaemia	4 (2.7)	0	2 (5.1)	0	1 (2.3)	0	1 (1.9)	0
Infections and infestations	34 (22.7)	31 (20.5)	13 (33.3)	5 (17.2)	11 (25.6)	16 (25.8)	10 (19.2)	10 (20.0)

*25 subjects who received other SGLT-2is were randomised to receive semaglutide 1.0 mg (n=15) or placebo (n=10); data not presented owing to small number of subjects. †Includes subjects receiving dapagliflozin or dapagliflozin propanediol monohydrate. ‡ADA classified, including hypoglycaemia episodes classified as severe, documented symptomatic, asymptomatic, probable symptomatic, and pseudo-hypoglycaemia. Severe or BG-confirmed hypoglycaemia defined as a plasma glucose value below 3.1 mmol/L (55.8 mg/dL) with symptoms consistent with hypoglycaemia. AEs include events that had onset, or increase in severity, from first exposure to the planned follow-up visit scheduled 5 weeks (with a 7-day visit window) after end-of-treatment visit at 30 weeks (on-treatment data). All AEs coded using version 21.0 of the Medical Dictionary for Regulatory Activities. Values are number (percentage) of subjects experiencing ≥1 event. ADA, American Diabetes Association; AE, adverse event; BG, blood glucose; GI, gastrointestinal; SGLT-2i, sodium–glucose co-transporter-2 inhibitor.

Discussion

- This *post hoc* analysis of the SUSTAIN 9 trial shows that, when once-weekly semaglutide is used as an add-on to SGLT-2i therapy, no interaction is observed between the individual SGLT-2is and treatment effect. This indicates that the same efficacy can be expected with semaglutide, regardless of background SGLT-2i.
- Reductions in HbA_{1c} and body weight with semaglutide, compared with placebo, were significant and clinically relevant. These findings are consistent with those of previous SUSTAIN trials.[4–10]

Conclusion

- In this *post hoc* analysis of SUSTAIN 9, in subjects with T2D already receiving an SGLT-2i, semaglutide once weekly resulted in superior HbA_{1c} and body weight reductions vs placebo; effects were consistent across SGLT-2i subgroups.
- No new safety concerns were identified.

This study was sponsored by Novo Nordisk and is registered with ClinicalTrials.gov (NCT03086330).
Presenter Bernhard Ludvik has received grants from Novo Nordisk.
The authors are grateful to Gabriel Hoppen and Fraser Harris, AXON Communications (supported by Novo Nordisk), for writing assistance.
Presented at the 55th Annual Meeting of the European Association for the Study of Diabetes, 16–20 September 2019, Barcelona, Spain.

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