BMJ Open

Impact of patient characteristics on efficacy and safety of OW semaglutide vs dulaglutide: SUSTAIN 7 *post hoc* analyses

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2020-037883
Article Type:	Original research
Date Submitted by the Author:	05-Mar-2020
Complete List of Authors:	Pratley, Richard; AdventHealth Translational Research Institute for Metabolism and Diabetes Aroda, Vanita ; Brigham and Women's Hospital Catarig, Andrei-Mircea; Novo Nordisk A/S Lingvay, Ildiko; University of Texas Southwestern Medical Center Lüdemann, Jörg; diabetes-falkensee, Diabetes Centre and Centre for Clinical Studies Yildirim, Emre; Novo Nordisk A/S Viljoen, Adie; Borthwick Diabetes Research Centre, Lister Hospital
Keywords:	General diabetes < DIABETES & ENDOCRINOLOGY, Diabetes & endocrinology < INTERNAL MEDICINE, Clinical trials < THERAPEUTICS

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

Title page

Full title: Impact of patient characteristics on efficacy and safety of OW semaglutide vs dulaglutide: SUSTAIN 7 *post hoc* analyses

Authors: Pratley Richard E[1], Aroda Vanita R[2], Catarig Andrei M[3], Lingvay Ildiko[4], Lüdemann Jörg[5], Yildirim Emre[3], Viljoen Adie[6]

Author affiliations:

[1]AdventHealth Translational Research Institute for Metabolism and Diabetes, Orlando, FL, USA; [2]Brigham and Women's Hospital, Boston, MA, USA; [3]Novo Nordisk A/S, Søborg, Denmark; [4]University of Texas Southwestern Medical Center, Dallas, TX, USA; [5]diabetes-falkensee, Diabetes Centre and Centre for Clinical Studies, Falkensee, Germany; [6]Borthwick Diabetes Research Centre, Lister Hospital, Stevenage, UK

Keywords: type 2 diabetes, GLP-1, semaglutide, SUSTAIN, age, body mass index

Contact details for corresponding author:

Dr Richard E. Pratley

AdventHealth Translational Research Institute for Metabolism and Diabetes

301 E. Princeton Street, Orlando, FL 32804, USA

Phone: +1-407-303-2519

E-mail: Richard.Pratley.MD@AdventHealth.com

ABSTRACT

OBJECTIVE: In SUSTAIN 7, once-weekly semaglutide demonstrated superior glycated haemoglobin (HbA_{1c}) and body weight (BW) reductions vs once-weekly dulaglutide in subjects with type 2 diabetes (T2D). The aim of this *post hoc* analysis was to investigate the impact of clinically relevant subject characteristics on the treatment effects of semaglutide vs dulaglutide.

DESIGN: *Post hoc* analyses by baseline age (<65, ≥65 years), sex (male, female), diabetes duration (≤5, >5–10, >10 years), HbA_{1c} (≤7.5, >7.5–8.5, >8.5% [≤58, >58–69, >69 mmol/mol]) and body mass index (BMI) (<30, 30–<35, ≥35 kg/m^2).

SETTING: Conducted in 194 sites, across 16 countries.

PARTICIPANTS: Overall, 1,199 subjects with T2D were exposed to treatment and included in the analyses.

INTERVENTIONS: Semaglutide 0.5 mg vs dulaglutide 0.75 mg (low-dose comparison); semaglutide 1.0 mg vs dulaglutide 1.5 mg (high-dose comparison), all administered subcutaneously once weekly.

PRIMARY AND SECONDARY OUTCOME MEASURES: Change in HbA_{1c} (primary endpoint) and BW (confirmatory secondary endpoint) from baseline to week 40; proportion of subjects achieving HbA_{1c} targets (<7, ≤6.5% [<53, ≤48 mmol/mol]) and weight-loss responses (≥5%, ≥10%) at week 40; and safety were assessed.

RESULTS: HbA_{1c} and BW reductions and proportion of subjects achieving HbA_{1c} targets and weight-loss responses were greater with semaglutide vs dulaglutide and, excepting glycaemic control within the low-dose comparison in HbA_{1c} subgroups, this was irrespective of subgroup or dose comparison analysed. Gastrointestinal adverse events, the most common with both treatments, were reported by more females than males and, with semaglutide, decreased with increasing BMI.

CONCLUSIONS: Consistently greater improvements in HbA_{1c} and BW with semaglutide vs dulaglutide were observed, regardless of age, sex, diabetes duration, glycaemic control

and BMI; supporting the efficacy of semaglutide across the continuum of care in a heterogeneous T2D population.

Clinical Trial Registration: NCT02648204 [ClinicalTrials.gov]

STRENGTHS AND LIMITATIONS OF THIS STUDY

- The analysis was designed to provide insight on the influence of five of the most common and relevant patient-level factors from a clinical perspective
- The inclusion of comparator data allows for a more robust analysis and direct comparison of the differences in efficacy and safety of semaglutide vs dulaglutide across the subgroups and subgroup categories
- As the analysis is based on SUSTAIN 7 data alone, it may only be representative of the trial-specific patient population
- The relatively small number of subjects in each subgroup category is a limitation
- As this is a *post hoc* analysis of a randomised clinical trial, there are inherent limitations and, as such, the data should be interpreted with caution

INTRODUCTION

The population of adults with type 2 diabetes (T2D) is heterogeneous, with varying clinical characteristics and comorbidities.(1) The importance of considering this heterogeneity when making treatment decisions is emphasised in guidelines on the management of T2D,(1-2) which recommend individualised patient-centred care considering the presence of comorbidities, including obesity, chronic kidney disease and cardiovascular disease.(2) Some studies have attempted to identify clusters of patients according to their clinical characteristics and risk of complications, in the hope this might enable treatment to be more precisely targeted to those who are likely to benefit most.(3) However, there is an ongoing debate about whether clustering or stratifying patients based on simple clinical characteristics is the most useful approach.(4,5)

Glucagon-like peptide-1 receptor agonists (GLP-1RAs) are an established treatment for T2D, recommended in current management guidelines.(1-2) The efficacy and safety of two once-weekly (OW) subcutaneous medications from the GLP-1RA class, semaglutide and dulaglutide, were respectively investigated in the global phase 3a SUSTAIN (Semaglutide Unabated Sustainability in Treatment of Type 2 Diabetes) (6-10) and AWARD (Assessment of Weekly AdministRation of LY2189265 in Diabetes) (11-20) clinical trial programmes. Both drugs have also been investigated in large-scale cardiovascular outcomes trials.(21,22) *Post hoc* analyses of the SUSTAIN and the AWARD trials have analysed patient subgroups across the continuum of T2D care.(23-35) Such analyses showed consistent, clinically relevant reductions in glycated haemoglobin (HbA_{1c}) and body weight (BW) with semaglutide across patient subgroups based on characteristics including age, baseline body mass index (BMI), baseline HbA_{1c}, diabetes duration, race and ethnicity.(23-26,28) Dulaglutide has also been shown to be efficacious across subgroups based on sex, age, duration of diabetes, beta-cell function, HbA_{1c}, BW and BMI.(29-35)

In the phase 3b SUSTAIN 7 clinical trial, semaglutide and dulaglutide were compared head-to-head in subjects with T2D on background treatment with metformin.(36) The

trial showed superior reductions in HbA_{1c} and BW with semaglutide vs dulaglutide, for both low-dose (semaglutide 0.5 mg vs dulaglutide 0.75 mg) and high-dose (semaglutide 1.0 mg vs dulaglutide 1.5 mg) comparisons.(36) Although both semaglutide and dulaglutide have individually demonstrated efficacy across multiple patient subpopulations,(23-27,29-35) it is as yet unknown whether the treatment differences observed in the SUSTAIN 7 trial are influenced by heterogeneity in the characteristics of the patients with T2D.

To evaluate whether clinically relevant patient characteristics (age, sex, diabetes duration, HbA_{1c} and BMI at baseline) affected the efficacy and safety of semaglutide vs dulaglutide, *post hoc* analyses of data from the SUSTAIN 7 trial were performed.

MATERIALS AND METHODS

Trial design

The design of the SUSTAIN 7 trial has been previously reported.(36) Briefly, this was an open-label trial in which subjects with uncontrolled T2D were randomised to receive semaglutide OW 0.5 mg or 1.0 mg, or dulaglutide OW 0.75 mg or 1.5 mg, as add-on to background treatment with metformin, and were followed throughout a 40-week treatment period. Semaglutide was administered subcutaneously via a prefilled injection device at one of two maintenance dose levels (0.5 mg or 1.0 mg OW), after following a fixed-dose escalation regimen, as previously reported.(36) Dulaglutide was administered subcutaneously in accordance with the regimen used in the phase 3 clinical trial programme (0.75 mg or 1.5 mg OW), without dose escalation.(37)

The trial was registered with ClinicalTrials.gov (NCT02648204) and conducted in accordance with the International Conference on Harmonisation Good Clinical Practice guidelines and the Declaration of Helsinki. The trial protocol (see Supplement) was approved by the institutional review boards and ethics committees at each participating

centre and subjects provided written informed consent before trial-related activities commenced.

Patient and public involvement

The research question and endpoints, such as efficacy and safety, were informed indirectly by patients' priorities, experiences and preferences, via input from clinicians during advisory board meetings. No patients were involved directly in the design, recruitment and conduct of the trial. Furthermore, the trial results were not directly disseminated to trial patients, but were publicly communicated and available via press release, trial portal and journal publication. In the trial, the burden of intervention was not assessed by the patients, nor were there any patient advisers involved.

Patient population

The inclusion and exclusion criteria for the SUSTAIN 7 trial are described in detail elsewhere.(36) Key inclusion criteria were: diagnosis of T2D; age ≥18 years; HbA_{1c} ≥7.0–10.5% (53–91 mmol/mol). Key exclusion criteria were: estimated glomerular filtration rate <60 mL/min/1.73 m^2; history of chronic or idiopathic acute pancreatitis; known proliferative retinopathy or maculopathy requiring acute treatment (determined by fundoscopy/fundus photography performed within 90 days before randomisation according to local practice); screening calcitonin value ≥50 ng/L; personal/family history of medullary thyroid carcinoma or multiple endocrine neoplasia syndrome type 2; acute coronary or cerebrovascular event within 90 days before randomisation; heart failure (New York Heart Association Class IV); and any of the following: myocardial infarction, stroke, or hospitalisation for unstable angina and/or transient ischaemic attack within the past 180 days prior to screening.(36)

Endpoints

The primary endpoint was change in HbA_{1c} (%-point) from baseline to end of treatment at week 40 and the secondary confirmatory endpoint was change in BW (kg) over the same period. Predefined clinical treatment targets were assessed; proportion of subjects

achieving HbA_{1c} targets of <7% (53 mmol/mol) and ≤6.5% (48 mmol/mol). The proportion of subjects achieving weight-loss responses of ≥5% and ≥10% was also assessed.

The numbers of adverse events (AEs), serious AEs and AEs leading to premature treatment discontinuation were reported. Specific AEs of clinical interest, such as gastrointestinal (GI) disorders and hypoglycaemic events, were also evaluated.

Subgroup analyses

For this *post hoc* analysis, subjects were stratified into subgroups selected for potential clinical relevance: age at baseline (<65 years, ≥65 years), sex (male, female), diabetes duration at baseline (≤5 years, >5–10 years, >10 years), baseline HbA_{1c} (≤7.5%, >7.5–8.5%, >8.5% [≤58, >58–69, >69 mmol/mol]) and baseline BMI (<30 kg/m^2, 30–<35 kg/m^2, ≥35 kg/m^2). The baseline BMI <25 kg/m^2 subgroup category was also evaluated; however, due to the small number of subjects (representing less than 10% of the total trial population), these data are not included in the Results, but are provided in the Supplement.

Statistical analyses

The efficacy analyses were based on the full analysis set, comprising all subjects randomised and exposed to at least one dose of the trial product, using 'on-treatment without rescue medication' data (as randomised). Analysis of covariance was performed for each endpoint, including the interaction between treatment and subgroup as a factor. Multiple imputation was used to account for missing data. Specifically, using a sequential multiple-imputation approach, missing values for the underlying continuous assessments were imputed by treatment group, assuming missing data were missing at random, and based on a linear-regression model. A sequential conditional-regression approach was applied whereby missing observations at any post-baseline visits were imputed based on a linear-regression model and incorporating observations from previous visits including

baseline. Binary endpoints were created and logistic-regression models run on the complete data set; inference was drawn using Rubin's rule.

Values for the mean change from baseline for HbA_{1c} and BW were calculated, and the data are presented as mean and standard error. Estimated treatment differences (ETDs) for the change from baseline in HbA_{1c} and BW, and odds ratios (ORs) for the proportions of subjects achieving HbA_{1c} targets or weight-loss responses, both with 95% confidence intervals, were also calculated for the low-dose (semaglutide 0.5 mg vs dulaglutide 0.75 mg) and high-dose (semaglutide 1.0 mg vs dulaglutide 1.5 mg) comparisons. To evaluate the evidence of heterogeneity of treatment effects across the clinical characteristics, a p-value for interaction between treatment effect and subgroup categories was calculated for both dose comparisons in all subgroup analyses, without adjustment for multiplicity.

Safety analyses were based on the safety analysis set, which included all randomised subjects who were exposed to at least one dose of trial product, based on 'as-treated' data and summarised descriptively. Safety was assessed within each treatment arm (semaglutide 0.5 mg, dulaglutide 0.75 mg, semaglutide 1.0 mg, dulaglutide 1.5 mg) in each of the subgroup categories.

Baseline characteristics and AEs are provided as descriptive data only.

RESULTS

Subject disposition and baseline characteristics

Baseline characteristics are summarised by treatment arm within each subgroup category (**Tables 1 and 2; Supplementary Section I, Tables 1–3**). Subject characteristics were generally comparable across subgroup categories with some exceptions. In all treatment arms, diabetes duration was longer, and BW and BMI were lower in the elderly (≥65 years) subgroup compared with the non-elderly (<65 years) subgroup (**Table 1**). Males were generally heavier but with a lower BMI, and had a

longer diabetes duration than females (**Supplementary Table 1**). In the diabetes duration subgroup categories (≤5 years, >5–10 years, >10 years), age increased with increasing diabetes duration and, in the semaglutide 1.0 mg treatment arm, BW and BMI decreased with increasing diabetes duration (**Supplementary Table 2**). Across the baseline HbA_{1c} subgroups (≤7.5%, >7.5–8.5, >8.5% [≤58, >58–69, >69 mmol/mol]), subjects in the semaglutide 0.5 mg treatment arm exhibited decreasing BW and BMI with increasing HbA_{1c} (**Supplementary Table 3**). In keeping with the distribution of subjects in the sex subgroup categories, there was a greater proportion of females vs males in the two highest BMI subgroups, and the proportion of Asian subjects was higher in the subgroup with the lowest BMI vs the subgroup with the highest BMI (**Table 2**). When compared with the other BMI subgroup categories, subjects with BMI <25 kg/m^2 had the highest HbA_{1c} levels, the highest proportions of male and Asian subjects and, as expected, the lowest BW (**Supplementary Table 4**).

Table 1. Subject demographics and baseline characteristics by age

		<65 years				≥65 years			
	All subjects	Sema 0.5 mg	Dula 0.75 mg	Sema 1.0 mg	Dula 1.5 mg	Sema 0.5 mg	Dula 0.75 mg	Sema 1.0 mg	Dula 1.5 mg
n	**1,199**	**222**	**238**	**247**	**232**	**79**	**61**	**53**	**67**
Age, years	56 (10.6)	51.6 (8.4)	51.7 (8.3)	52.4 (9.0)	52.0 (8.5)	69.4 (4.4)	69.1 (3.9)	69.3 (4.2)	69.4 (3.9)
Sex, n (%)									
Male	662 (55.2)	119 (53.6)	131 (55.0)	132 (53.4)	130 (56.0)	50 (63.3)	29 (47.5)	30 (56.6)	41 (61.2)
Female	537 (44.8)	103 (46.4)	107 (45.0)	115 (46.6)	102 (44.0)	29 (36.7)	32 (52.5)	23 (43.4)	26 (38.8)
Diabetes duration, years	7.4 (5.7)	6.8 (5.4)	6.3 (5.2)	6.6 (5.3)	6.9 (5.2)	10.2 (6.7)	9.8 (5.9)	10.2 (6.6)	10.3 (6.3)
HbA_{1c}, %	8.2 (0.9)	8.4 (1.0)	8.2 (0.9)	8.3 (0.9)	8.3 (0.9)	8.1 (0.9)	8.0 (0.8)	7.9 (0.8)	8.0 (0.8)
HbA_{1c}, mmol/mol	66.4 (10.0)	68.2 (10.7)	66.2 (10.1)	66.9 (10.1)	66.7 (9.9)	65.4 (9.7)	63.6 (9.0)	62.8 (9.2)	64.1 (8.7)
Body weight, kg	95.2(22.6)	97.8 (25.6)	96.5 (23.6)	97.2 (20.7)	94.3 (23.2)	92.4 (20.1)	92.1 (20.4)	87.4 (20.2)	90.2 (15.8)
BMI, kg/m^2	33.5 (6.8)	34.4 (7.7)	34.0 (7.1)	34.2 (6.6)	33.4 (6.9)	31.7 (4.5)	32.4 (5.9)	30.9 (5.1)	32.1 (5.4)
Race, n (%)									
Asian	191 (15.9)	44 (19.8)	45 (18.9)	34 (13.8)	52 (22.4)	6 (7.6)	3 (4.9)	4 (7.5)	3 (4.5)
Black/African American	70 (5.8)	13 (5.9)	13 (5.5)	14 (5.7)	16 (6.9)	4 (5.1)	4 (6.6)	4 (7.5)	2 (3.0)
White	928 (77.4)	164 (73.9)	178 (74.8)	198 (80.2)	158 (68.1)	69 (87.3)	54 (88.5)	45 (84.9)	62 (92.5)
Other	10 (0.8)	1 (0.5)	2 (0.8)	1 (0.4)	6 (2.6)	0	0	0	0
Ethnic group, n (%)									
Hispanic/Latino	138 (11.5)	23 (10.4)	30 (12.6)	30 (12.1)	38 (16.4)	6 (7.6)	1 (1.6)	5 (9.4)	5 (7.5)
Non-Hispanic/Latino	1,061 (88.5)	199 (89.6)	208 (87.4)	217 (87.9)	194 (83.6)	73 (92.4)	60 (98.4)	48 (90.6)	62 (92.5)

'On-treatment without rescue medication' data. Subgroup data are presented as mean (standard deviation) unless otherwise indicated. BMI, body mass index; Dula, dulaglutide; HbA_{1c}, glycated haemoglobin; n, number of subjects randomised and exposed to at least one dose of trial product as randomised (full analysis set); Sema, semaglutide.

Table 2. Subject demographics and baseline characteristics by baseline BMI

		<30 kg/m²				30–<35 kg/m²				≥35 kg/m²			
	All subjects	Sema 0.5 mg	Dula 0.75 mg	Sema 1.0 mg	Dula 1.5 mg	Sema 0.5 mg	Dula 0.75 mg	Sema 1.0 mg	Dula 1.5 mg	Sema 0.5 mg	Dula 0.75 mg	Sema 1.0 mg	Dula 1.5 mg
n	**1,199**	**99**	**100**	**91**	**109**	**90**	**86**	**105**	**81**	**112**	**113**	**104**	**108**
Age, years	56 (10.6)	57.4 (11.2)	56.0 (11.4)	57.5 (10.4)	56.9 (10.5)	58.7 (10.1)	55.3 (9.6)	54.4 (11.8)	57.9 (10.7)	53.3 (10.7)	54.5 (10.0)	54.6 (9.3)	53.5 (10.4)
Sex, n (%)													
Male	662 (55.2)	57 (57.6)	60 (60.0)	56 (61.5)	71 (65.1)	53 (58.9)	44 (51.2)	62 (59.0)	47 (58.0)	59 (52.7)	56 (49.6)	44 (42.3)	52 (48.1)
Female	537 (44.8)	42 (42.4)	40 (40.0)	35 (38.5)	38 (34.9)	37 (41.1)	42 (48.8)	43 (41.0)	34 (42.0)	53 (47.3)	57 (50.4)	60 (57.7)	56 (51.9)
Diabetes duration, years	7.4 (5.7)	8.0 (6.9)	8.0 (6.3)	9.0 (6.9)	7.3 (5.8)	7.5 (5.1)	6.2 (4.6)	7.0 (4.9)	7.9 (5.7)	7.7 (5.6)	6.7 (5.3)	6.0 (4.8)	7.8 (5.5)
HbA_{1c}, %	8.2 (0.9)	8.4 (1.0)	8.2 (0.9)	8.3 (1.0)	8.1 (0.9)	8.2 (1.0)	8.2 (1.0)	8.1 (0.8)	8.2 (0.8)	8.3 (0.9)	8.1 (0.9)	8.2 (0.9)	8.3 (0.9)
HbA_{1c}, mmol/mol	66.4 (10.0)	68.6 (10.9)	65.7 (9.6)	66.9 (10.8)	65.5 (9.8)	66.2 (10.6)	66.4 (10.8)	65.5 (9.1)	65.9 (8.7)	67.4 (9.9)	65.1 (9.6)	66.3 (10.3)	66.9 (10.3)
Body weight, kg	95.2 (22.6)	73.8 (12.4)	75.1 (12.4)	78.4 (13.0)	74.7 (12.6)	94.1 (12.6)	91.8 (11.6)	92.8 (12.3)	93.5 (11.3)	118.2 (20.1)	116.8 (18.2)	113.2 (19.7)	112.3 (18.5)
BMI, kg/m²	33.5 (6.8)	26.5 (2.5)	26.8 (2.3)	27.2 (2.2)	26.7 (2.5)	32.6 (1.4)	32.3 (1.4)	32.4 (1.5)	32.7 (1.5)	40.9 (5.5)	40.7 (5.1)	40.5 (5.5)	39.8 (4.9)
Race, n (%)													
Asian	191 (15.9)	37 (37.4)	31 (31.0)	23 (25.3)	41 (37.6)	9 (10.0)	14 (16.3)	13 (12.4)	7 (8.6)	4 (3.6)	3 (2.7)	2 (1.9)	6 (5.6)
Black/African American	70 (5.8)	2 (2.0)	7 (7.0)	9 (9.9)	4 (3.7)	5 (5.6)	3 (3.5)	5 (4.8)	6 (7.4)	10 (8.9)	7 (6.2)	4 (3.8)	8 (7.4)
White	928 (77.4)	60 (60.6)	62 (62.0)	59 (64.8)	63 (57.8)	76 (84.4)	69 (80.2)	87 (82.9)	67 (82.7)	97 (86.6)	101 (89.4)	97 (93.3)	90 (83.3)

Other	10 (0.8)	0	0	0	1 (0.9)	0	0	0	1 (1.2)	1 (0.9)	2 (1.8)	1 (1.0)	4 (3.7)
Ethnic group, n (%)													
Hispanic/Latino	138 (11.5)	8 (8.1)	15 (15.0)	13 (14.3)	18 (16.5)	10 (11.1)	7 (8.1)	13 (12.4)	11 (13.6)	11 (9.8)	9 (8.0)	9 (8.7)	14 (13.0)
Non-Hispanic/Latino	1,061 (88.5)	91 (91.9)	85 (85.0)	78 (85.7)	91 (83.5)	80 (88.9)	79 (91.9)	92 (87.6)	70 (86.4)	101 (90.2)	104 (92.0)	95 (91.3)	94 (87.0)

'On-treatment without rescue medication' data. Subgroup data are presented as mean (standard deviation) unless otherwise indicated. BMI, body mass index; Dula, dulaglutide; HbA_{1c}, glycated haemoglobin; n, number of subjects randomised and exposed to at least one dose of trial product as randomised (full analysis set); Sema, semaglutide.

Glycaemic control and body weight changes

Overall, the mean changes from baseline in HbA_{1c} and BW (**Supplementary Section II, Figure 1**) and the proportions of subjects achieving HbA_{1c} targets of <7% (53 mmol/mol) and ≤6.5% (48 mmol/mol) and weight-loss responses of ≥5% and ≥10% (**Supplementary Section II, Figures 2 and 3**) were of greater magnitude with semaglutide vs dulaglutide treatment. This observation was confirmed by the ETDs for change from baseline (**Figure 1**) and the ORs for proportions of subjects (**Supplementary Section II, Figures 4 and 5**) which significantly favoured semaglutide in the majority of both the low-dose and high-dose comparisons within each subgroup category.

For the individual analyses by subgroup, the findings were as follows:

Age at baseline (<65 years, ≥65 years): the proportion of elderly vs non-elderly subjects achieving glycaemic targets and weight-loss response of ≥5% was consistently higher with both semaglutide and dulaglutide (**Supplementary Figure 2A and B, and 3A**), despite elderly subjects having a lower baseline HbA_{1c} and BMI than non-elderly subjects (**Table 1**). Proportions of subjects achieving ≥10% weight loss were comparable between the two age subgroups for both treatment arms (**Supplementary Figure 3B**).

Sex (male, female): Reductions in HbA_{1c} and BW were generally greater in female than in male subjects (**Supplementary Figure 1C and D**), as was baseline BMI (**Supplementary Table 1**). This was reflected in the correspondingly greater proportions of female vs male subjects achieving the glycaemic targets and weight-loss responses (**Supplementary Figure 2C and D, and 3C and D**).

Diabetes duration at baseline (≤5 years, >5–10 years, >10 years): comparatively smaller reductions in HbA_{1c} and BW were observed with semaglutide 1.0 mg in subjects with diabetes duration of >10 years vs ≤10 years, with no apparent differences observed in the other treatment arms (**Supplementary Figure 1E and F**). A similar pattern was observed for the proportions of subjects achieving glycaemic targets and weight-loss

responses in the semaglutide 1.0 mg treatment group (**Supplementary Figure 2E and F, and 3E and F**).

Baseline HbA_{1c} (≤7.5%, >7.5–8.5%, >8.5% [≤58, >58–69, >69 mmol/mol]): with semaglutide 0.5 mg, and to a greater degree with semaglutide 1.0 mg, the magnitude of the mean reduction in HbA_{1c} from baseline increased with increasing baseline HbA_{1c}; the converse was apparent for BW, whereby the amount of weight lost was less with increasing baseline HbA_{1c} (**Supplementary Figure 1G and H**). A similar though less apparent pattern was observed with dulaglutide, (**Supplementary Figure 1G and H**), and this was reflected in the proportions of subjects achieving glycaemic targets (**Supplementary Figure 2G and H**). Across baseline HbA_{1c} subgroups, the greatest proportion of subjects achieving ≥5% weight loss was observed in those subjects receiving semaglutide 1.0 mg, particularly in the HbA_{1c} subgroup categories of ≤7.5% (58 mmol/mol) and >7.5–8.5% (58–69 mmol/mol) (**Supplementary Figure 3G**). There were no other apparent differences across the subgroup categories regarding the proportions of subjects achieving weight-loss responses (**Supplementary Figure 3G and H**).

Baseline BMI (<30 kg/m², 30–<35 kg/m², ≥35 kg/m²): mean reductions in BW for both semaglutide and dulaglutide increased with increasing baseline BMI, with the greatest reductions in the ≥35 kg/m² BMI subgroup category for all treatment arms (**Supplementary Figure 1J**). There were no apparent trends in other BW or glycaemic outcomes across the BMI categories for either dose comparison (**Supplementary Figure 1I**; **Supplementary Figure 2I and J; Supplementary Figure 3I and J; Supplementary Figure 6**), or when BW reduction was expressed as percentage change (**Supplementary Figure 6)**. Changes in the <25 kg/m² BMI subgroup were largely consistent with those observed in the broader population (**Supplementary Section IV, Figures 7 and 8**).

Treatment–subgroup interaction effects

For each of the subgroups, analysis of the ETDs for the change from baseline in HbA_{1c} in the age, sex, diabetes duration, baseline HbA_{1c} and baseline BMI subgroups, the p-values for the low-dose and high-dose comparisons were nonsignificant, except in the analysis of the HbA_{1c} subgroups within the low-dose comparison ($p<0.05$ for the treatment–subgroup interaction effect) (**Figure 1A**). The change from baseline in BW in the age, sex, diabetes duration, baseline HbA_{1c} and baseline BMI subgroups was similar, with nonsignificant treatment–subgroup interactions for both dose comparisons (**Figure 1B**). Similarly, treatment–subgroup interactions were nonsignificant for the analysis of the ORs for the proportions of subjects achieving glycaemic targets and weight-loss responses (**Supplementary Section II, Figures 4 and 5**).

Safety outcomes

Overall, AEs were reported in more than half of subjects irrespective of the subgroup category (ranging from 55.3% [dulaglutide 0.75 mg; diabetes duration >5–10 years] to 80.6% [dulaglutide 1.5 mg; elderly]) and were generally more common with semaglutide 0.5 mg than with dulaglutide 0.75 mg, and less common with semaglutide 1.0 mg than with dulaglutide 1.5 mg. Premature treatment discontinuations due to AEs were higher with semaglutide than with dulaglutide, and were primarily due to GI AEs (**Tables 3 and 4**; **Supplementary Section III, Tables 5–7**).

Table 3. Adverse events by age

n (%)	All subjects	<65 years				≥65 years			
		Sema 0.5 mg	Dula 0.75 mg	Sema 1.0 mg	Dula 1.5 mg	Sema 0.5 mg	Dula 0.75 mg	Sema 1.0 mg	Dula 1.5 mg
	1,199	222	238	247	232	79	61	53	67
AEs	818 (68.2)	152 (68.5)	150 (63.0)	166 (67.2)	167 (72.0)	52 (65.8)	36 (59.0)	41 (77.4)	54 (80.6)
Serious AEs	86 (7.2)	10 (4.5)	18 (7.6)	20 (8.1)	16 (6.9)	7 (8.9)	6 (9.8)	3 (5.7)	6 (9.0)
AEs leading to premature treatment discontinuation	87 (7.3)	17 (7.7)	12 (5.0)	19 (7.7)	16 (6.9)	7 (8.9)	2 (3.3)	10 (18.9)	4 (6.0)
Gastrointestinal AEs leading to premature treatment discontinuation	54 (4.5)	12 (5.4)	5 (2.1)	13 (5.2)	13 (5.6)	4 (5.1)	1 (1.6)	5 (9.4)	1 (1.5)
Gastrointestinal AEs	505 (42.1)	99 (44.6)	80 (33.6)	105 (42.5)	108 (46.6)	30 (38.0)	20 (32.8)	28 (52.8)	35 (52.2)
Vomiting	103 (8.6)	23 (10.4)	7 (2.9)	27 (10.9)	21 (9.1)	8 (10.1)	5 (8.2)	4 (7.5)	8 (11.9)
Nausea	230 (19.2)	49 (22.1)	33 (13.9)	52 (21.1)	43 (18.5)	19 (24.1)	6 (9.8)	11 (20.8)	17 (25.4)
Diarrhoea	160 (13.3)	32 (14.4)	21 (8.8)	32 (13.0)	42 (18.1)	11 (13.9)	2 (3.3)	9 (17.0)	11 (16.4)
Hypoglycaemia (severe/BG-confirmed)	15 (1.3)	2 (0.9)	1 (0.4)	4 (1.6)	5 (2.2)	0	2 (3.3)	1 (1.9)	0

Data are presented as number and proportion (%) of subjects with adverse events. Hypoglycaemia was defined as an episode that was severe (according to the American Diabetes Association classification) or BG-confirmed (plasma glucose value <56 mg/dL [3.1 mmol/L]) with symptoms consistent with hypoglycaemia. AE, adverse event; BG, blood glucose; Dula, dulaglutide; n, number of subjects randomised and exposed to at least one dose of trial product as treated (safety analysis set); Sema, semaglutide.

Table 4. Adverse events by baseline BMI

n (%)	All subjects	<30 kg/m²				30–<35 kg/m²				≥35 kg/m²			
		Sema 0.5 mg	Dula 0.75 mg	Sema 1.0 mg	Dula 1.5 mg	Sema 0.5 mg	Dula 0.75 mg	Sema 1.0 mg	Dula 1.5 mg	Sema 0.5 mg	Dula 0.75 mg	Sema 1.0 mg	Dula 1.5 mg
	1,199	**99**	**100**	**91**	**109**	**90**	**86**	**105**	**81**	**112**	**113**	**104**	**108**
AEs	818 (68.2)	65 (65.7)	60 (60.0)	65 (71.4)	84 (77.1)	60 (66.7)	54 (62.8)	66 (62.9)	65 (80.2)	79 (70.5)	72 (63.7)	76 (73.1)	71 (65.7)
Serious AEs	86 (7.2)	4 (4.0)	4 (4.0)	5 (5.5)	4 (3.7)	6 (6.7)	6 (7.0)	5 (4.8)	12 (14.8)	7 (6.3)	14 (12.4)	13 (12.5)	6 (5.6)
AEs leading to premature treatment discontinuation	87 (7.3)	12 (12.1)	8 (8.0)	12 (13.2)	16 (14.7)	8 (8.9)	5 (5.8)	8 (7.6)	2 (2.5)	4 (3.6)	1 (0.9)	9 (8.7)	2 (1.9)
Gastrointestinal AEs leading to premature treatment discontinuation	54 (4.5)	9 (9.1)	4 (4.0)	9 (9.9)	11 (10.1)	5 (5.6)	2 (2.3)	5 (4.8)	2 (2.5)	2 (1.8)	0	4 (3.8)	1 (0.9)
Gastrointestinal AEs	505 (42.1)	48 (48.5)	32 (32.0)	44 (48.4)	59 (54.1)	39 (43.3)	27 (31.4)	44 (41.9)	41 (50.6)	42 (37.5)	41 (36.3)	45 (43.3)	42 (38.9)
Vomiting	103 (8.6)	16 (16.2)	5 (5.0)	11 (12.1)	15 (13.8)	6 (6.7)	3 (3.5)	12 (11.4)	4 (4.9)	9 (8.0)	4 (3.5)	8 (7.7)	10 (9.3)
Nausea	230 (19.2)	25 (25.3)	9 (9.0)	19 (20.9)	24 (22.0)	21 (23.3)	11 (12.8)	24 (22.9)	19 (23.5)	22 (19.6)	19 (16.8)	20 (19.2)	17 (15.7)
Diarrhoea	160 (13.3)	18 (18.2)	6 (6.0)	14 (15.4)	28 (25.7)	13 (14.4)	9 (10.5)	14 (13.3)	14 (17.3)	12 (10.7)	8 (7.1)	13 (12.5)	10 (9.3)
Hypoglycaemia (severe/BG-confirmed)	15 (1.3)	0	1 (1.0)	0	3 (2.8)	0	1 (1.2)	2 (1.9)	0	2 (1.8)	1 (0.9)	3 (2.9)	2 (1.9)

Data are presented as number and proportion (%) in percent of subjects with adverse events. Hypoglycaemia was defined as an episode that was severe (according to the American Diabetes Association classification) or BG-confirmed (plasma glucose value <56 mg/dL [3.1 mmol/L]) with symptoms consistent with hypoglycaemia. AE, adverse event; BG, blood glucose; BMI, body mass index; Dula, dulaglutide; n, number of subjects randomised and exposed to at least one dose of trial product as treated (safety analysis set); Sema, semaglutide.

GI AEs were the most frequently reported events, with generally higher rates with semaglutide 0.5 mg vs dulaglutide 0.75 mg, and dulaglutide 1.5 mg vs semaglutide 1.0 mg, across the subgroups and subgroup categories (ranging from 27.7% [dulaglutide 0.75 mg; diabetes duration >5–10 years] to 59.5% [dulaglutide 1.5 mg; HbA_{1c} ≤7.5% [58 mmol/mol]), with nausea being the most common (ranging from 8.1% [dulaglutide 0.75 mg; male] to 29.5% [semaglutide 0.5 mg; female]) (**Tables 3 and 4**; **Supplementary Section III, Tables 5–7**). Across the subgroup categories, more female than male subjects reported GI AEs overall, with GI AEs generally decreasing with increasing BMI in subjects treated with semaglutide (**Table 4 and Supplementary Section III, Table 4**). The highest proportion of GI AEs were reported by subjects with BMI <25 kg/m^2 (**Supplementary Section V, Table 8**).

DISCUSSION

Given the heterogeneous profile of patients with T2D and the guidance for such differences to be considered when making treatment choices,(2-3) this *post hoc* analysis of SUSTAIN 7 data assessed the impact of individual clinical characteristics on the effect of semaglutide vs dulaglutide treatment. The analyses indicate that the effect of semaglutide vs dulaglutide was not influenced by age, sex, diabetes duration, HbA_{1c} or BMI at baseline, with the exception of the low-dose comparison for HbA_{1c} in the baseline HbA_{1c} subgroup, which showed increasing efficacy for semaglutide 0.5 mg vs dulaglutide 0.75 mg in subjects with increasing HbA_{1c} at baseline.

This *post hoc* analysis supports the finding from the overall SUSTAIN 7 trial that semaglutide was superior to dulaglutide in reducing HbA_{1c} and BW;(36) the same was observed across each of the subgroups and within the various subgroup categories presented here.

This *post hoc* analysis also supports findings from similar subgroup analyses of SUSTAIN trials. An analysis of SUSTAIN 1–5 data showed greater reductions in HbA_{1c} and BW with

semaglutide vs comparators, and comparable efficacy in elderly subjects (a population often presenting with comorbidities) and non-elderly subjects, without an increased risk of hypoglycaemia.(25) Similarly, analyses of pooled SUSTAIN data showed clinically relevant reductions in HbA_{1c} and BW with semaglutide, regardless of baseline BW, HbA_{1c}, diabetes duration, race and ethnicity.(23-26,28)

HbA_{1c} reductions were greater with increasing baseline HbA_{1c} for both semaglutide and dulaglutide in the present analyses, which has been observed with dulaglutide previously,(29,31-33) as well as with liraglutide,(38) lixisenatide (39) and other antihyperglycaemic agents. Furthermore, a converse relationship between weight loss and baseline HbA_{1c} levels was observed, whereby increasing baseline HbA_{1c} was associated with greater reductions in HbA_{1c} but a decreasing magnitude of weight loss. A similar pattern has been observed with liraglutide as an add-on to insulin treatment,(40) with exenatide alone (41) and with dulaglutide.(31,32) These findings have relevance for clinical practice, indicating that there may be an effect with GLP-1RAs (and potentially other antihyperglycaemic therapies) in predicting treatment responses based on HbA_{1c} levels.(40) Conversely, a recent analysis of the AWARD trials found a weak positive correlation between HbA_{1c} reduction and weight loss with dulaglutide.(42) Several mechanisms, also associated with other antihyperglycaemic agents, may contribute to these results.(43) Improved treatment-related glycaemic control is associated with decreased glycosuria,(40,43) normalised protein turnover and a decreased catabolic effect,(43) in addition to decreased energy expenditure and resting metabolic rate.(43) As GLP-1RAs exhibit a glucose-dependent mechanism of action, the greater post-treatment reductions in HbA_{1c} from a higher initial baseline HbA_{1c} may contribute to the retention of glucose calories and, thereby, moderation of the achievable weight loss. In these analyses, greater weight loss was observed with increasing baseline BMI for both semaglutide and dulaglutide, aligning with what has been previously reported for semaglutide (23) and dulaglutide.(35) While percentage weight loss was also greater with semaglutide vs dulaglutide, the percentage change in weight loss was generally of a

similar magnitude across BMI categories, indicating that the weight-loss pattern observed across the HbA_{1c} subgroup categories may be associated with subjects' baseline BMI. High BMI is associated with an insulin resistant-phenotype in some patients,(3) and less weight loss is observed in patients with diabetes who are insulin resistant than in those with insulin sensitivity.(44) However, clinically relevant reductions in BW were achieved for all BMI subgroup categories, and the magnitude of weight loss was comparatively greater for semaglutide than for dulaglutide. This is an important consideration for clinical practice, given the increasing interest in weight management as a key aspect of treatment for T2D.(1)

Analysis of the ETDs for change from baseline in HbA_{1c} and BW and ORs for the proportions of subjects achieving HbA_{1c} targets or weight-loss responses indicated a consistent effect of semaglutide vs dulaglutide across subgroup categories. These findings are aligned with previous analyses of subpopulations treated with GLP-1RAs, including semaglutide and dulaglutide, which also reported a nonsignificant impact of age, sex or diabetes duration on treatment effect,(23-27,29-35) although weight loss tended to be greater in women than in men with dulaglutide,(31) as was also observed in this analysis.

Consistent with the known class effect of GLP-1RAs,(45) both semaglutide and dulaglutide reported relatively high levels of GI AEs. The rate of GI AEs was higher with semaglutide vs dulaglutide in the low-dose comparison; in the high-dose comparison it was higher with dulaglutide vs semaglutide.(36) Premature treatment discontinuations due to AEs were higher with semaglutide than with dulaglutide, which may be due to the higher levels of moderate GI AEs observed in the overall SUSTAIN 7 trial.(36) The occurrence of some GIs AEs may be dose-dependent and nausea (and also vomiting for semaglutide) is usually transient with both semaglutide (46) and dulaglutide;(14) furthermore, the dose-escalation regimen approved for semaglutide has been shown to mitigate these AEs.(46) In the subgroups in the present analyses, GI AEs were higher with dulaglutide 1.5 mg vs semaglutide 1.0 mg in elderly subjects with longer diabetes

duration, and lower in subjects with HbA_{1c} >8.5% (69 mmol/mol) and higher BMI. There were no other associations between subjects' baseline characteristics with the incidence of GI AEs. Subjects who experience GI AEs, specifically nausea and vomiting, have greater weight loss compared with those who do not.(23,47) While this hypothesised association might be considered an explanation for the observed greater weight loss with semaglutide vs dulaglutide in the low-dose comparison, a mediation analysis has previously shown that the direct effects of semaglutide on BW are the main contributors to weight loss with very little effect attributable to GI AEs.(47,48). Our analyses support this finding as, overall, there were no clear trends between the incidence of GI AEs and the greater efficacy of semaglutide in terms of HbA_{1c} reduction and weight loss vs dulaglutide.(31) With semaglutide, there was a trend towards decreasing GI AEs with increasing baseline BMI, which has also been previously reported for the SUSTAIN 1–5 (23) and the AWARD 1–6 (49) trials, and may be due to differences in exposure–response levels associated with BW as has been demonstrated with semaglutide.(50) Similarly, an analysis has shown that elderly patients with a lower BMI are more likely to experience side effects (including GI AEs) with dulaglutide than younger patients with a higher BMI.(49) However, it is noted that this was a *post hoc* analysis in Japanese patients, with low event rates for some GI AEs, and so the results may not be generalizable to a wider diabetes population. In either case, a dose-escalation regimen may be beneficial.

A strength of the present analysis is the inclusion of comparator data, which allows for a more robust analysis and direct comparison of the differences in efficacy and safety of semaglutide vs dulaglutide across the subgroups and subgroup categories. However, the *post hoc* nature of this analysis means there are inherent limitations and, as such, the data should be interpreted with caution. Also, as the analysis is based on SUSTAIN 7 alone, it may only be representative of the trial-specific patient population. A further limitation is the relatively small number of subjects in each subgroup category. Additionally, in the age subgroups, there was an imbalance in subject numbers (elderly

vs non-elderly), with relatively few patients in the elderly subgroup (260; 22% of the analysis population). However, given the overall consistency of the age-subgroup analyses, as well as the general limitations of these *post hoc* analyses, the difference in subject numbers between the age subgroup categories seemed to have had little or no impact. Furthermore, elderly subjects in previous pooled analyses of the SUSTAIN 1–5 (26) and AWARD (30,32) trials have demonstrated similar efficacy and safety, supporting the results obtained here.

This analysis provides insight on the influence of five of the most common and relevant patient-level factors from a clinical perspective and highlights semaglutide as an effective choice across these patient subgroups that are commonly encountered in clinical practice. Understanding the impact of heterogeneity in clinical characteristics on the treatment differences between GLP-1RAs further supports patient-centred decision-making in clinical practice.

CONCLUSIONS

Semaglutide was associated with superior efficacy to dulaglutide across various clinically relevant patient subgroups that are commonly encountered in clinical practice, with a safety profile similar to other GLP-1RAs and in line with previously published data for semaglutide. The treatment effect for semaglutide vs dulaglutide did not appear to be influenced by age, sex, diabetes duration, HbA_{1c} or BMI at baseline. This indicates that the efficacy of semaglutide vs dulaglutide is retained across a range of diverse clinical characteristics, thereby increasing the evidence base available to clinicians to guide care.

ACKNOWLEDGEMENTS

We thank all the trial subjects, investigators and trial-site staff members who were involved in the SUSTAIN trials; Charlotte Hindsberger and Thomas Hansen (both Novo Nordisk) for review and suggestions for revising the manuscript; and

Stacy Carl-McGrath (AXON Communications) for medical writing and editorial assistance. This study and the associated trials were supported by Novo Nordisk A/S, Denmark. The funding sources contributed to the design and conduct of the trials, the analysis and interpretation of the data and the preparation, review and approval of the manuscript.

COMPETING INTERESTS

The authors received no grants or funding for the writing of this article. In relation to the submitted work, RP reports grants from Novo Nordisk to his institution, AdventHealth, a nonprofit organisation, and VA also reports grants from Novo Nordisk to her institution.

Outside of this work, RP reports speaker and consulting fees from AstraZeneca; consulting fees from Boehringer Ingelheim; consulting fees from Eisai, Inc.; consulting fees from GlaxoSmithKline; consulting fees from Glytec, LLC; consulting fees from Janssen; grants from Lexicon Pharmaceuticals; grants and consulting fees from Ligand Pharmaceuticals, Inc;, grants and consulting fees from Lilly; grants and consulting fees from Merck; consulting fees from Mundipharma; grants, speaker fees and consulting fees from Novo Nordisk; consulting fees from Pfizer; grants and consulting fees from Sanofi; grants, speaker fees and consulting fees from Takeda; and personal consulting fees from Sanofi US Services, Inc. Except for consulting fees in February 2018 and June 2018 from Sanofi US Services, Inc., RP's services were paid for directly to AdventHealth. VA has received consulting fees (to her institution) from Adocia; grants (to her institution) and consulting fees (to her institution) from AstraZeneca/BMS; consulting fees from Becton-Dickinson; grants (to her institution) from Boehringer Ingelheim; grants (to her institution) from Calibra; consulting fees from Duke University; grants (to her institution) from Eisai; grants (to her institution) from Fractyl; grants (to her institution) from Janssen; grants (to her institution) and consulting fees from Novo Nordisk; grants (to her institution) and consulting fees from Sanofi; grants (to her institution) from Theracos; and consulting fees from Zafgen, all outside of the submitted work; and is the spouse of an employee of Merck Research Laboratories. AMC is an employee of

Novo Nordisk. In relation to the submitted work, IL reports grants to her institution from Novo Nordisk. Outside of the submitted work, IL has received consulting fees from AstraZeneca; consulting fees from Boehringer Ingelheim; grants from GI Dynamics; consulting fees from Intarcia; consulting fees from Janssen; consulting fees from Lilly; consulting fees from Mannkind; grants from Merck; grants from Mylan; grants from Novartis; grants and consulting fees from Novo Nordisk; grants from Pfizer; consulting fees from Sanofi; consultant fees from TARGETPharma; and consulting fees from Valeritas, all outside of the submitted work. JL reports being an investigator in clinical studies for Eli Lilly and Novo Nordisk outside of the submitted work. EY is an employee and minor shareholder of Novo Nordisk. AV has received lecture/other fees and non-financial (clinical research) support from AstraZeneca; non-financial (clinical research) support from Amgen; lecture/other fees from Boehringer Ingelheim; lecture/other fees and non-financial (clinical research) support from Eli Lilly; lecture/other fees from Merck Sharp & Dohme; lecture/other fees from Napp, lecture/other fees and non-financial (clinical research) support from Novo Nordisk; non-financial (clinical research) support from Novartis; and lecture/other fees and non-financial (clinical research) support from Sanofi, all outside of the submitted work.

FUNDING

This work was supported by Novo Nordisk A/S. Editorial support was provided by Stacy Carl-McGrath PhD (AXON Communications), funded by Novo Nordisk A/S.

DATA SHARING STATEMENT

Individual participant data will be shared in datasets in a deidentified format, including datasets from Novo Nordisk-sponsored clinical research completed after 2001 for product indications approved in both the European Union and USA. The study protocol and redacted clinical study report will be available according to Novo Nordisk data sharing

commitments. Data will be available permanently after research completion and approval of product and product use in the European Union and USA. Data will only be shared with *bona fide* researchers submitting a research proposal and requesting access to data, for use as approved by the independent review board and according to its charter. The access request proposal form and the access criteria can be found online. Data will be made available on a specialised Statistical Analysis System data platform.

AUTHOR CONTRIBUTIONS

RP: conduct of trial, data collection, data analysis, data interpretation, manuscript preparation, approval of submitted version; VA: conduct of trial, data collection, data interpretation, manuscript preparation, approval of submitted version; AMC: data interpretation, manuscript preparation, approval of submitted version; IL: conduct of trial, data collection, data interpretation, manuscript preparation, approval of submitted version; JL: conduct of the trial, data collection, data interpretation, manuscript preparation, approval of submitted version; EY: data interpretation, manuscript preparation, approval of submitted version; AV: data interpretation, manuscript preparation, approval of submitted version.

REFERENCES

1. American Diabetes Association. Standards of Medical Care in Diabetes–2019. Diabetes Care. 2019;42(Suppl 1).
2. Cosentino F, Grant PJ, Aboyans V, et al. 2019 ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD. *Eur Heart J* 2019; doi: 10.1093/eurheartj/ehz486. [Epub ahead of print].
3. Ahlqvist E, Storm P, Käräjämäki A, et al. Novel subgroups of adult-onset diabetes and their association with outcomes: a data-driven cluster analysis of six variables. Lancet *Diabetes Endocrinol* 2018;6(5):361–9.
4. Pearson ER. Type 2 diabetes: a multifaceted disease. *Diabetologia* 2019;62(7):1107–12.
5. Dennis JM, Shields BM, Henley WE, et al. Disease progression and treatment response in data-driven subgroups of type 2 diabetes compared with models based on simple clinical features: an analysis using clinical trial data. *Lancet Diabetes Endocrinol* 2019;7(6):442–51.
6. Rodbard HW, Lingvay I, Reed J,et al. Semaglutide added to basal insulin in type 2 diabetes (SUSTAIN 5): a randomized, controlled trial. *J Clin Endocrinol Metab* 2018;103(6):2291–301.
7. Sorli C, Harashima SI, Tsoukas GM, et al. Efficacy and safety of once-weekly semaglutide monotherapy versus placebo in patients with type 2 diabetes (SUSTAIN 1): a double-blind, randomised, placebo-controlled, parallel-group, multinational, multicentre phase 3a trial. *Lancet Diabetes Endocrinol* 2017;5(4):251–60.
8. Ahmann AJ, Capehorn M, Charpentier G, et al. Efficacy and safety of once-weekly semaglutide versus exenatide ER in subjects with type 2 diabetes (SUSTAIN 3): a 56-week, open-label, randomized clinical trial. *Diabetes Care* 2018;41(2):258–66.
9. Ahrén B, Masmiquel L, Kumar H, et al. Efficacy and safety of once-weekly semaglutide versus once-daily sitagliptin as an add-on to metformin, thiazolidinediones, or both, in patients with type 2 diabetes (SUSTAIN 2): a 56-week, double-blind, phase 3a, randomised trial. *Lancet Diabetes Endocrinol* 2017;5(5):341–54.
10. Aroda VR, Bain SC, Cariou B, et al. Efficacy and safety of once-weekly semaglutide versus once-daily insulin glargine as add-on to metformin (with or without sulfonylureas) in insulin-naive patients with type 2 diabetes (SUSTAIN 4): a

randomised, open-label, parallel-group, multicentre, multinational, phase 3a trial. *Lancet Diabetes Endocrinol* 2017;5(5):355–66.

11. Dungan KM, Weitgasser R, Perez Manghi F, et al. A 24-week study to evaluate the efficacy and safety of once-weekly dulaglutide added on to glimepiride in type 2 diabetes (AWARD-8). *Diabetes Obes Metab* 2016;18(5):475–82.
12. Ludvik B, Frías JP, Tinahones FJ, et al. Dulaglutide as add-on therapy to SGLT2 inhibitors in patients with inadequately controlled type 2 diabetes (AWARD-10): a 24-week, randomised, double-blind, placebo-controlled trial. *Lancet Diabetes Endocrinol* 2018;6(5):370–81.
13. Tuttle KR, Lakshmanan MC, Rayner B, et al. Dulaglutide versus insulin glargine in patients with type 2 diabetes and moderate-to-severe chronic kidney disease (AWARD-7): a multicentre, open-label, randomised trial. *Lancet Diabetes Endocrinol* 2018;6(8):605–17.
14. Wysham C, Blevins T, Arakaki R, et al. Efficacy and safety of dulaglutide added onto pioglitazone and metformin versus exenatide in type 2 diabetes in a randomized controlled trial (AWARD-1). *Diabetes Care* 2014;37(8):2159–67.
15. Umpierrez G, Tofé Povedano S, Pérez Manghi F, et al. Efficacy and safety of dulaglutide monotherapy versus metformin in type 2 diabetes in a randomized controlled trial (AWARD-3). *Diabetes Care* 2014;37(8):2168–76.
16. Nauck M, Weinstock RS, Umpierrez GE, et al. Efficacy and safety of dulaglutide versus sitagliptin after 52 weeks in type 2 diabetes in a randomized controlled trial (AWARD-5). *Diabetes Care* 2014;37(8):2149–58.
17. Giorgino F, Benroubi M, Sun JH, et al. Efficacy and safety of once-weekly dulaglutide versus insulin glargine in patients with type 2 diabetes on metformin and glimepiride (AWARD-2). *Diabetes Care* 2015;38(12):2241–9.
18. Blonde L, Jendle J, Gross J, et al. Once-weekly dulaglutide versus bedtime insulin glargine, both in combination with prandial insulin lispro, in patients with type 2 diabetes (AWARD-4): a randomised, open-label, phase 3, non-inferiority study. *Lancet* 2015;385(9982):2057–66.
19. Dungan KM, Povedano ST, Forst T, et al. Once-weekly dulaglutide versus once-daily liraglutide in metformin-treated patients with type 2 diabetes (AWARD-6): a randomised, open-label, phase 3, non-inferiority trial. *Lancet* 2014;384(9951):1349–57.
20. Pozzilli P, Norwood P, Jódar E, et al. Placebo-controlled, randomized trial of the addition of once-weekly glucagon-like peptide-1 receptor agonist dulaglutide to

titrated daily insulin glargine in patients with type 2 diabetes (AWARD-9). *Diabetes Obes Metab* 2017;19(7):1024–31.

21. Marso SP, Bain SC, Consoli A, et al. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. *N Engl J Med* 2016;375(19):1834–44.
22. Gerstein HC, Colhoun HM, Dagenais GR, et al. Dulaglutide and cardiovascular outcomes in type 2 diabetes (REWIND): a double-blind, randomised placebo-controlled trial. *Lancet* 2019;394(10193):121–30.
23. Ahrén B, Atkin SL, Charpentier G, et al. Semaglutide induces weight loss in subjects with type 2 diabetes regardless of baseline BMI or gastrointestinal adverse events in the SUSTAIN 1 to 5 trials. *Diabetes Obes Metab* 2018;20(9):2210–9.
24. Bain SC, Araki E, Desouza C, et al. Semaglutide reduces HbA_{1c} across baseline HbA_{1c} subgroups in the SUSTAIN 1–5 clinical trials. 77th Scientific Sessions of the American Diabetes Association, San Diego, CA, USA, June 9–13, 2017 (Poster 1123P).
25. Warren M, Chaykin L, Trachtenbarg D, et al. Semaglutide as a therapeutic option for elderly patients with type 2 diabetes: pooled analysis of the SUSTAIN 1-5 trials. *Diabetes Obes Metab* 2018;20(9):2291–7.
26. Rosenstock J, Chaykin L, Lüdemann J, et al. Consistent HbA_{1c} and body weight reduction with semaglutide independent of diabetes duration: SUSTAIN 1–5 and 7 patient-level meta-analysis. 78th Scientific Sessions of the American Diabetes Association, Orlando, FL, USA, June 22–26, 2018 (Poster 1081-P).
27. Hramiak I, Desouza C, Seufert J, et al. Semaglutide consistently reduces cardiovascular events in both male and female subjects with type 2 diabetes. 78th Scientific Sessions of the American Diabetes Association, Orlando, FL, USA, June 22–26, 2018 (Poster 1085-P).
28. Desouza C, Garg SK, Cariou B, et al. Efficacy and safety of semaglutide in subjects with type 2 diabetes across race and ethnicity subgroups: a *post hoc* analysis of the SUSTAIN trials. 27th Annual Scientific & Clinical Congress of the American Association of Clinical Endocrinologists, Boston, MA, USA, May 16–20, 2018 (Poster 298).
29. Wysham C, Guerci B, D'Alessio D, et al. Baseline factors associated with glycaemic response to treatment with once-weekly dulaglutide in patients with type 2 diabetes. *Diabetes Obes Metab* 2016;18(11):1138–42.

30. Boustani MA, Pittman I 4th, Yu M, et al. Similar efficacy and safety of once-weekly dulaglutide in patients with type 2 diabetes aged ≥65 and <65 years. *Diabetes Obes Metab* 2016;18(8):820–8.

31. Gallwitz B, Dagogo-Jack S, et al. Effect of once-weekly dulaglutide on glycated haemoglobin (HbA1c) and fasting blood glucose in patient subpopulations by gender, duration of diabetes and baseline HbA1c. *Diabetes Obes Metab* 2018;20(2):409–18.

32. Pantalone KM, Patel H, Yu M, et al. Dulaglutide 1.5 mg as an add-on option for patients uncontrolled on insulin: subgroup analysis by age, duration of diabetes and baseline glycated haemoglobin concentration. *Diabetes Obes Metab* 2018;20(6):1461–9.

33. Gentilella R, Romera I, Nicolay C, et al. Change in HbA_{1c} across the baseline HbA_{1c} range in type 2 diabetes patients receiving once-weekly dulaglutide versus other incretin agents. *Diabetes Ther* 2019;10(3):1113–25.

34. Mathieu C, Del Prato S, Botros FT, et al. Effect of once weekly dulaglutide by baseline beta-cell function in people with type 2 diabetes in the AWARD programme. *Diabetes Obes Metab* 2018;20(8):2023–8.

35. Fuechtenbusch M, Aberle J, Heitmann E, et al. Weight loss in patients with type 2 diabetes receiving once-weekly dulaglutide plus insulin lispro or insulin glargine plus insulin lispro: a post-hoc analysis of the AWARD-4 study across baseline body mass index subgroups. *Diabetes Obes Metab* 2019;21(6):1340–8.

36. Pratley RE, Aroda VR, Lingvay I, et al. Semaglutide versus dulaglutide once weekly in patients with type 2 diabetes (SUSTAIN 7): a randomised, open-label, phase 3b trial. *Lancet Diabetes Endocrinol* 2018;6(4):275–86.

37. Jendle J, Grunberger G, Blevins T, et al. Efficacy and safety of dulaglutide in the treatment of type 2 diabetes: a comprehensive review of the dulaglutide clinical data focusing on the AWARD phase 3 clinical trial program. *Diabetes Metab Res Rev* 2016;32(8):776–90.

38. Henry RR, Buse JB, Sesti G, et al. Efficacy of antihyperglycemic therapies and the influence of baseline hemoglobin A(1C): a meta-analysis of the liraglutide development program. *Endocr Pract* 2011;17(6):906–13.

39. Blonde L, Chava P, Dex T, et al. Predictors of outcomes in patients with type 2 diabetes in the lixisenatide GetGoal clinical trials. *Diabetes Obes Metab* 2017;19(2):275–83.

40. Dahlqvist S, Ahlén E, Filipsson K, et al. Variables associated with HbA1c and weight reductions when adding liraglutide to multiple daily insulin injections in persons with

type 2 diabetes (MDI Liraglutide trial 3). *BMJ Open Diabetes Res Care* 2018;6(1):e000464.

41. Frías JP, Hardy E, Ahmed A, et al. Effects of exenatide once weekly plus dapagliflozin, exenatide once weekly alone, or dapagliflozin alone added to metformin monotherapy in subgroups of patients with type 2 diabetes in the DURATION-8 randomized controlled trial. *Diabetes Obes Metab* 2018;20(6):1520–5.
42. Umpierrez GE, Pantalone KM, Kwan AY, et al. Relationship between weight change and glycaemic control in patients with type 2 diabetes receiving once-weekly dulaglutide treatment. *Diabetes Obes Metab* 2016;18(6):615–22.
43. Pi-Sunyer FX. Weight loss in type 2 diabetic patients. *Diabetes Care* 2005;28(6):1526–27.
44. Fonseca VA, Capehorn MS, Garg SK, et al. Reductions in insulin resistance are mediated primarily via weight loss in subjects with type 2 diabetes on semaglutide. *J Clin Endocrinol Metab* 2019. doi: 10.1210/jc.2018-02685. [Epub ahead of print].
45. Bettge K, Kahle M, Abd El Aziz MS, et al. Occurrence of nausea, vomiting and diarrhoea reported as adverse events in clinical trials studying glucagon-like peptide-1 receptor agonists: a systematic analysis of published clinical trials. *Diabetes Obes Metab* 2017;19(3):336–47.
46. Nauck MA, Petrie JR, Sesti G, et al. A phase 2, randomized, dose-finding study of the novel once-weekly human GLP-1 analog, semaglutide, compared with placebo and open-label liraglutide in patients with type 2 diabetes. *Diabetes Care* 2016;39(2):231–41.
47. Atkin S, Woo V, de la Rosa R, et al. The impact of gastrointestinal adverse events on weight loss with semaglutide in subjects with type 2 diabetes. 53rd Annual Meeting of the European Association for the Study of Diabetes (EASD), Lisbon, Portugal, 11–15 September, 2017 (Poster 821).
48. Ahrén B, Atkin SL, Charpentier G, et al. Semaglutide induces weight loss in subjects with type 2 diabetes regardless of baseline BMI or gastrointestinal adverse events in the SUSTAIN 1 to 5 trials. *Diabetes Obes Metab* 2018;20(9):2210–9.
49. Hamano K, Nishiyama H, Matsui A, et al. Efficacy and safety analyses across 4 subgroups combining low and high age and body mass index groups in Japanese phase 3 studies of dulaglutide 0.75 mg after 26 weeks of treatment. *Endocr J* 2017;64(4):449-45.

50. Petri KCC, Ingwersen SH, Flint A, et al. Exposure-response analysis for evaluation of semaglutide dose levels in type 2 diabetes. *Diabetes Obes Metab* 2018;20(9): 2238–45.

Figure Legends

Figure 1. Estimated treatment differences for change from baseline in HbA_{1c} shown as %-points (A), HbA_{1c} shown as mmol/mol (B) and body weight (C) at week 40 by age, sex, diabetes duration, HbA_{1c} and BMI at baseline. *p<0.05, **p<0.001, ***p<0.0001; †p-values represent the test for treatment by subgroup interaction. Values are ETDs [95% CIs] for semaglutide vs dulaglutide (low-dose comparison [semaglutide 0.5 mg vs dulaglutide 0.75 mg] and high-dose comparison [semaglutide 1.0 mg vs dulaglutide 1.5 mg) from ANCOVAs with multiple imputations using data from all randomised subjects exposed to at least one dose of trial product and did not discontinue treatment or receive any non-investigational antihyperglycaemic treatment (full analysis set) obtained while on treatment and prior to onset of rescue medication. ANCOVA controlled for baseline HbA_{1c} (A) or body weight (B) and interaction between randomised treatment and subgroup. ANCOVA, analysis of covariance; BMI, body mass index; CI, confidence interval; ETD, estimated treatment difference; HbA_{1c}, glycated haemoglobin.

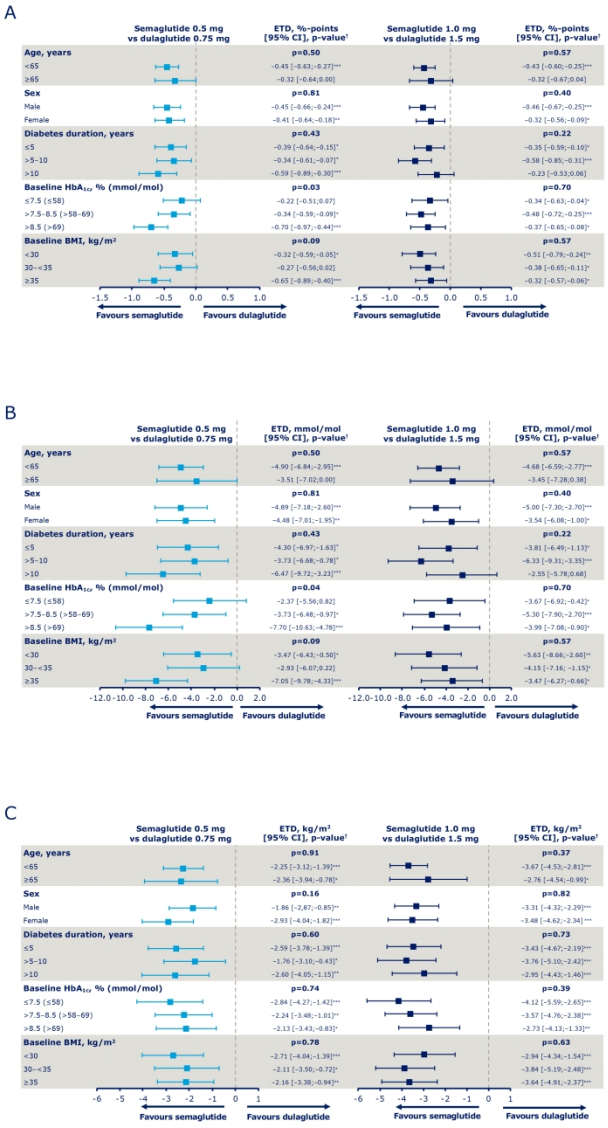


Figure 1. Estimated treatment differences for change from baseline in HbA_{1c} shown as %-points (A), HbA_{1c} shown as mmol/mol (B) and body weight (C) at week 40 by age, sex, diabetes duration, HbA_{1c} and BMI at baseline. *p<0.05, **p<0.001, ***p<0.0001; †p values represent the test for treatment by subgroup interaction. Values are ETDs [95% CIs] for semaglutide vs dulaglutide (low-dose comparison [semaglutide 0.5 mg vs dulaglutide 0.75 mg] and high-dose comparison [semaglutide 1.0 mg vs dulaglutide 1.5 mg) from ANCOVAs with multiple imputations using 'on-treatment without rescue medication' data from all randomised subjects exposed to at least one dose of trial product as randomised (full analysis set) obtained while on treatment and prior to onset of rescue medication. ANCOVA controlled for baseline HbA_{1c} (A, B) or body weight (C) and interaction between randomised treatment and subgroup. ANCOVA, analysis of covariance; BMI, body mass index; CI, confidence interval; ETD, estimated treatment difference; HbA_{1c}, glycated haemoglobin.

Supplementary Materials

Full title:

Impact of patient characteristics on efficacy and safety of OW semaglutide vs dulaglutide: SUSTAIN 7 *post hoc* analyses

Authors:

Pratley Richard E[1], Aroda Vanita R[2], Catarig Andrei M[3], Lingvay Ildiko[4], Lüdemann Jörg[5], Yildirim Emre[3], Viljoen Adie[6]

Author affiliations:

[1]AdventHealth Translational Research Institute for Metabolism and Diabetes, Orlando, FL, USA; [2]Brigham and Women's Hospital, Boston, MA, USA; [3]Novo Nordisk A/S, Søborg, Denmark; [4]University of Texas Southwestern Medical Center, Dallas, TX, USA; [5]diabetes-falkensee, Diabetes Centre and Centre for Clinical Studies, Falkensee, Germany; [6]Borthwick Diabetes Research Centre, Lister Hospital, Stevenage, UK

Contact details for corresponding author:

Dr Richard E. Pratley

AdventHealth Translational Research Institute for Metabolism and Diabetes

301 E. Princeton Street, Orlando, FL 32804, USA

Phone: +1-407-303-2519

E-mail: Richard.Pratley.MD@AdventHealth.com

Supplementary Section I: Baseline Characteristics

Supplementary Table 1. Baseline characteristics by sex subgroups

		Male				Female			
	All subjects	Sema 0.5 mg	Dula 0.75 mg	Sema 1.0 mg	Dula 1.5 mg	Sema 0.5 mg	Dula 0.75 mg	Sema 1.0 mg	Dula 1.5 mg
n	**1,199**	**169**	**160**	**162**	**171**	**132**	**139**	**138**	**128**
Age, years	56 (10.6)	57.0 (10.9)	55.6 (10.1)	55.6 (10.3)	56.8 (10.5)	55.3 (10.9)	54.9 (10.7)	55.1 (11.0)	54.7 (10.7)
Sex, n (%)									
Male	662 (55.2)	169 (100)	160 (100)	162 (100)	171 (100)	-	-	-	-
Female	537 (44.8)	-	-	-	-	132 (100)	139 (100)	138 (100)	128 (100)
Diabetes duration, years	7.4 (5.7)	7.8 (5.8)	7.1 (5.7)	7.4 (5.5)	8.0 (5.6)	7.7 (6.1)	6.9 (5.2)	7.1 (5.9)	7.2 (5.7)
HbA_{1c}, %	8.2 (0.9)	8.4 (1.0)	8.2 (0.9)	8.2 (0.9)	8.2 (0.8)	8.3 (1.0)	8.1 (0.9)	8.2 (0.9)	8.2 (1.0)
HbA_{1c}, mmol/mol	66.4 (10.0)	67.8 (10.5)	66.2 (10.0)	66.0 (10.2)	65.8 (9.0)	67.1 (10.4)	66.4 (9.9)	65.2 (9.9)	66.6 (10.6)
Body weight, kg	95.2 (22.6)	102.3 (23.9)	100.6 (23.4)	100.8 (21.0)	96.9 (21.5)	88.9 (23.0)	89.9 (21.3)	89.3 (19.0)	88.8 (21.3)
BMI, kg/m^2	33.5 (6.8)	33.3 (6.8)	32.8 (6.6)	32.7 (6.2)	32.0 (5.8)	34.2 (7.5)	34.6 (7.2)	34.7 (6.7)	34.5 (7.2)
Race, n (%)									
Asian	191 (15.9)	24 (14.2)	31 (19.4)	25 (15.4)	32 (18.7)	26 (19.7)	17 (12.2)	13 (9.4)	23 (18.0)
Black/African American	70 (5.8)	5 (3.0)	4 (2.5)	7 (4.3)	6 (3.5)	12 (9.1)	13 (9.4)	11 (8.0)	12 (9.4)
White	928 (77.4)	139 (82.2)	124 (77.5)	130 (80.2)	128 (74.9)	94 (71.2)	108 (77.7)	113 (81.9)	92 (71.9)
Other	10 (0.8)	1 (0.6)	1 (0.6)	0	5 (2.9)	0	1 (0.7)	1 (0.7)	1 (0.8)
Ethnic group, n (%)									
Hispanic/Latino	138 (11.5)	18 (10.7)	15 (9.4)	14 (8.6)	24 (14.0)	11 (8.3)	16 (11.5)	21 (15.2)	19 (14.8)
Non-Hispanic/ Latino	1,061 (88.5)	151 (89.3)	145 (90.6)	148 (91.4)	147 (86.0)	121 (91.7)	123 (88.5)	117 (84.8)	109 (85.2)

'On-treatment without rescue medication' data. Subgroup data are presented as mean (standard deviation) unless otherwise indicated. BMI, body mass index; Dula, dulaglutide; HbA_{1c}, glycated haemoglobin; n, number of subjects randomised and exposed to at least one dose of trial product as randomised (full analysis set); Sema, semaglutide.

Supplementary Table 2. Baseline characteristics by diabetes duration subgroups

		≤5 years				>5–10 years				>10 years			
	All subjects	Sema 0.5 mg	Dula 0.75 mg	Sema 1.0 mg	Dula 1.5 mg	Sema 0.5 mg	Dula 0.75 mg	Sema 1.0 mg	Dula 1.5 mg	Sema 0.5 mg	Dula 0.75 mg	Sema 1.0 mg	Dula 1.5 mg
n	**1,199**	**113**	**128**	**122**	**114**	**101**	**94**	**103**	**92**	**87**	**77**	**75**	**93**
Age, years	56 (10.6)	52.3 (11.0)	51.7 (10.1)	51.1 (11.6)	51.8 (10.2)	55.5 (9.8)	57.0 (8.5)	56.8 (7.9)	57.0 (10.3)	62.3 (9.3)	58.9 (11.0)	60.4 (9.4)	59.9 (9.7)
Sex, n (%)													
Male	662 (55.2)	62 (54.9)	71 (55.5)	61 (50.0)	53 (46.5)	55 (54.5)	46 (48.9)	58 (56.3)	64 (69.6)	52 (59.8)	43 (55.8)	43 (57.3)	54 (58.1)
Female	537 (44.8)	51 (45.1)	57 (44.5)	61 (50.0)	61 (53.5)	46 (45.5)	48 (51.1)	45 (43.7)	28 (30.4)	35 (40.2)	34 (44.2)	32 (42.7)	39 (41.9)
Diabetes duration, years	7.4 (5.7)	2.6 (1.3)	2.5 (1.3)	2.5 (1.4)	2.6 (1.4)	7.0 (1.4)	7.1 (1.3)	7.3 (1.3)	7.0 (1.4)	15.3 (4.9)	14.5 (4.5)	14.9 (5.3)	14.5 (4.4)
HbA_{1c}, %	8.2 (0.9)	8.2 (1.0)	8.1 (0.9)	8.2 (0.9)	8.2 (0.9)	8.3 (1.0)	8.2 (0.9)	8.2 (1.0)	8.2 (0.8)	8.4 (0.9)	8.2 (0.9)	8.2 (0.9)	8.2 (0.9)
HbA_{1c}, mmol/mol	66.4 (10.0)	66.6 (10.8)	65.3 (10.2)	66.6 (9.6)	65.9 (10.1)	67.5 (10.4)	66.1 (9.8)	65.9 (10.5)	66.4 (9.0)	68.6 (10.1)	66.0 (9.8)	65.9 (10.3)	66.2 (10.0)
Body weight, kg	95.2 (22.6)	97.2 (27.6)	96.8 (24.0)	100.4 (23.6)	92.0 (22.9)	95.1 (21.8)	96.6 (23.7)	94.7 (18.1)	95.1 (23.3)	96.8 (23.0)	92.4 (20.3)	88.6 (17.7)	93.5 (18.8)
BMI, kg/m^2	33.5 (6.8)	34.0 (7.9)	34.3 (7.3)	35.1 (7.8)	33.0 (6.7)	33.3 (6.3)	33.9 (7.2)	33.3 (5.4)	33.2 (6.9)	33.7 (7.1)	32.3 (5.7)	31.6 (4.7)	33.1 (6.1)
Race, n (%)													
Asian	191 (15.9)	25 (22.1)	30 (23.4)	19 (15.6)	35 (30.7)	18 (17.8)	11 (11.7)	9 (8.7)	13 (14.1)	7 (8.0)	7 (9.1)	10 (13.3)	7 (7.5)
Black/African American	70 (5.8)	2 (1.8)	8 (6.3)	5 (4.1)	6 (5.3)	6 (5.9)	4 (4.3)	7 (6.8)	1 (1.1)	9 (10.3)	5 (6.5)	6 (8.0)	11 (11.8)
White	928 (77.4)	86 (76.1)	89 (69.5)	97 (79.5)	72 (63.2)	76 (75.2)	79 (84.0)	87 (84.5)	77 (83.7)	71 (81.6)	64 (83.1)	59 (78.7)	71 (76.3)
Other	10 (0.8)	0	1 (0.8)	1 (0.8)	1 (0.9)	1 (1.0)	0	0	1 (1.1)	0	1 (1.3)	0	4 (4.3)

Ethnic group, n (%)													
Hispanic/Latino	138 (11.5)	11 (9.7)	9 (7.0)	13 (10.7)	17 (14.9)	5 (5.0)	7 (7.4)	12 (11.7)	15 (16.3)	13 (14.9)	15 (19.5)	10 (13.3)	11 (11.8)
Non-Hispanic/Latino	1,061 (88.5)	102 (90.3)	119 (93.0)	109 (89.3)	97 (85.1)	96 (95.0)	87 (92.6)	91 (88.3)	77 (83.7)	74 (85.1)	62 (80.5)	65 (86.7)	82 (88.2)

'On-treatment without rescue medication' data. Subgroup data are presented as mean (standard deviation) unless otherwise indicated. BMI, body mass index; Dula, dulaglutide; HbA_{1c}, glycated haemoglobin; n, number of subjects randomised and exposed to at least one dose of trial product as randomised (full analysis set); Sema, semaglutide.

Supplementary Table 3. Baseline characteristics by baseline HbA_{1c} subgroups

		≤7.5% (≤58 mmol/mol)				>7.5–8.5% (>58–69 mmol/mol)				>8.5% (>69 mmol/mol)			
	All subjects	Sema 0.5 mg	Dula 0.75 mg	Sema 1.0 mg	Dula 1.5 mg	Sema 0.5 mg	Dula 0.75 mg	Sema 1.0 mg	Dula 1.5 mg	Sema 0.5 mg	Dula 0.75 mg	Sema 1.0 mg	Dula 1.5 mg
n	**1,199**	**74**	**94**	**83**	**84**	**120**	**105**	**124**	**120**	**107**	**100**	**93**	**95**
Age, years	56 (10.6)	57.5 (12.2)	57.0 (10.4)	57.7 (11.1)	58.1 (10.2)	57.3 (10.1)	53.3 (10.6)	55.6 (9.7)	55.4 (10.5)	54.3 (10.7)	53.5 (9.9)	53.1 (10.9)	54.5 (10.9)
Sex, n (%)													
Male	662 (55.2)	39 (52.7)	50 (53.2)	48 (57.8)	45 (53.6)	69 (57.5)	53 (50.5)	67 (54.0)	69 (57.5)	61 (57.0)	57 (57.0)	47 (50.5)	57 (60.0)
Female	537 (44.8)	35 (47.3)	44 (46.8)	35 (42.2)	39 (46.4)	51 (42.5)	52 (49.5)	57 (46.0)	51 (42.5)	46 (43.0)	43 (43.0)	46 (49.5)	38 (40.0)
Diabetes duration, years	7.4 (5.7)	6.7 (4.6)	7.0 (6.2)	8.0 (5.9)	8.0 (6.5)	7.8 (6.1)	6.9 (4.8)	6.3 (5.0)	7.4 (5.5)	8.3 (6.5)	7.1 (5.5)	7.9 (6.1)	7.6 (5.0)
HbA_{1c}, %	8.2 (0.9)	7.3 (0.2)	7.2 (0.2)	7.2 (0.2)	7.2 (0.2)	8.0 (0.3)	8.0 (0.3)	8.0 (0.3)	8.0 (0.3)	9.4 (0.6)	9.3 (0.5)	9.4 (0.6)	9.3 (0.5)
HbA_{1c}, mmol/mol	66.4 (10.0)	55.8 (2.4)	55.4 (2.3)	55.6 (2.3)	55.7 (2.3)	64.0 (3.1)	63.5 (2.9)	63.9 (3.0)	64.1 (3.1)	79.4 (6.5)	77.7 (5.8)	78.7 (6.6)	78.0 (5.7)
Body weight, kg	95.2 (22.6)	99.1 (24.1)	96.9 (21.9)	97.9 (24.3)	93.0 (21.5)	97.4 (22.9)	94.8 (23.0)	94.8 (18.9)	93.8 (21.5)	93.4 (26.1)	95.3 (24.2)	94.3 (20.3)	93.3 (22.7)
BMI, kg/m^2	33.5 (6.8)	34.2 (6.9)	34.0 (6.3)	34.6 (8.3)	33.4 (6.7)	34.1 (6.7)	33.4 (7.4)	33.1 (4.9)	33.1 (6.7)	32.8 (7.7)	33.5 (7.0)	33.4 (6.5)	32.8 (6.3)
Race, n (%)													
Asian	191 (15.9)	5 (6.8)	12 (12.8)	12 (14.5)	17 (20.2)	18 (15.0)	15 (14.3)	13 (10.5)	23 (19.2)	27 (25.2)	21 (21.0)	13 (14.0)	15 (15.8)
Black/African American	70 (5.8)	8 (10.8)	6 (6.4)	8 (9.6)	6 (7.1)	5 (4.2)	6 (5.7)	6 (4.8)	9 (7.5)	4 (3.7)	5 (5.0)	4 (4.3)	3 (3.2)
White	928 (77.4)	61 (82.4)	76 (80.9)	63 (75.9)	60 (71.4)	96 (80.0)	84 (80.0)	105 (84.7)	87 (72.5)	76 (71.0)	72 (72.0)	75 (80.6)	73 (76.8)
Other	10 (0.8)	0	0	0	1 (1.2)	1 (0.8)	0	0	1 (0.8)	0	2 (2.0)	1 (1.1)	4 (4.2)

Ethnic group, n (%)													
Hispanic/Latino	138 (11.5)	6 (8.1)	8 (8.5)	8 (9.6)	7 (8.3)	8 (6.7)	8 (7.6)	15 (12.1)	15 (12.5)	15 (14.0)	15 (15.0)	12 (12.9)	21 (22.1)
Non-Hispanic/Latino	1,061 (88.5)	68 (91.9)	86 (91.5)	75 (90.4)	77 (91.7)	112 (93.3)	97 (92.4)	109 (87.9)	105 (87.5)	92 (86.0)	85 (85.0)	81 (87.1)	74 (77.9)

'On-treatment without rescue medication' data. Subgroup data are presented as mean (standard deviation) unless otherwise indicated. BMI, body mass index; Dula, dulaglutide; n, number of subjects randomised and exposed to at least one dose of trial product as randomised (full analysis set); Sema, semaglutide.

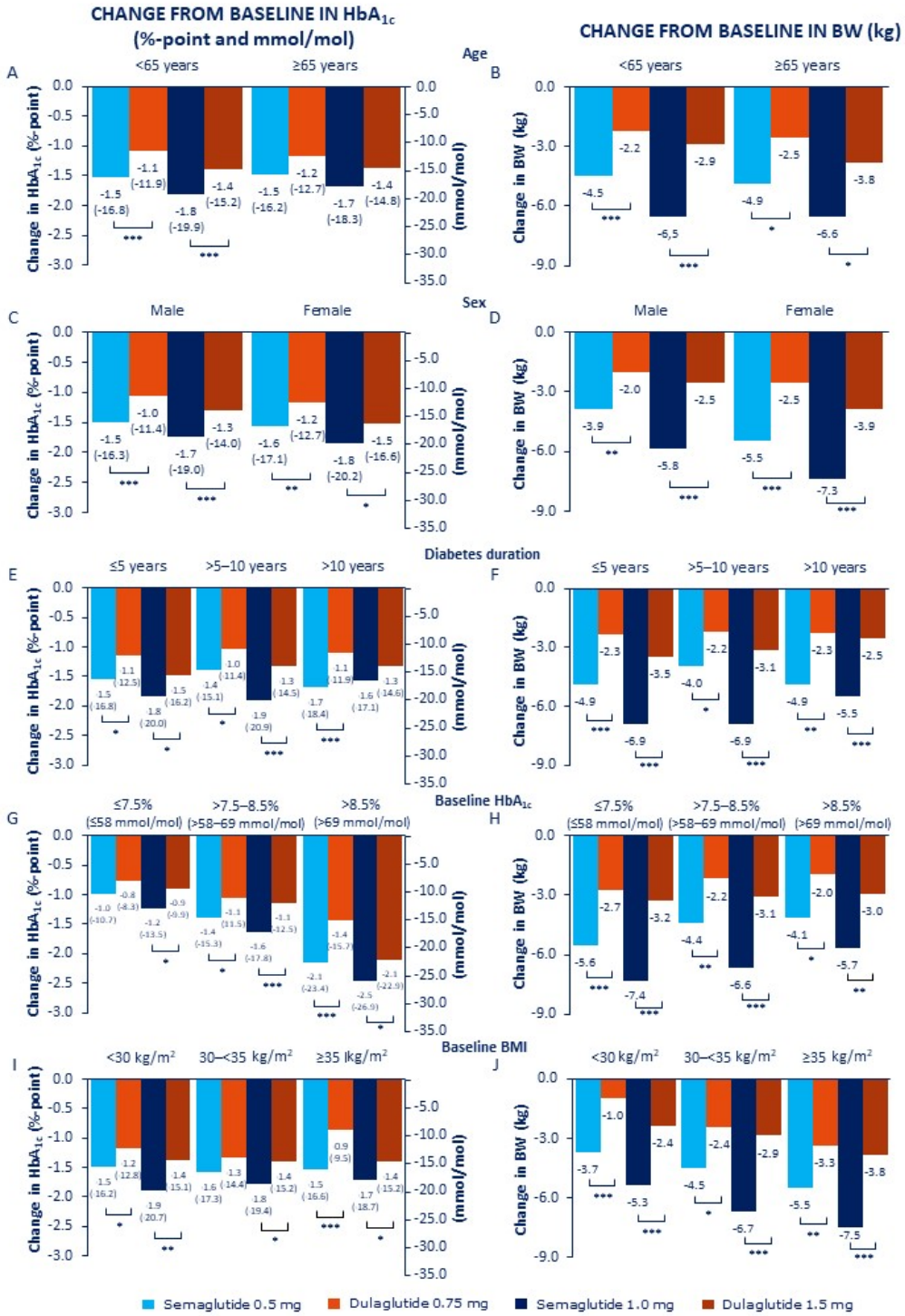
Supplementary Table 4. Baseline characteristics of subjects with BMI <25 kg/m² at baseline

	All subjects	Sema 0.5 mg	Dula 0.75 mg	Sema 1.0 mg	Dula 1.5 mg
n	**1,199**	**24**	**19**	**16**	**28**
Age, years	56 (10.6)	56.9 (10.0)	51.2 (12.1)	61.8 (11.5)	56.8 (11.8)
Sex, N (%)					
Male	662 (55.2)	15 (62.5)	13 (68.4)	8 (50.0)	18 (64.3)
Female	537 (44.8)	9 (37.5)	6 (31.6)	8 (50.0)	10 (35.7)
Diabetes duration, years	7.4 (5.7)	6.8 (6.4)	7.8 (6.6)	12.2 (9.2)	7.3 (5.7)
HbA_{1c}, %	8.2 (0.9)	8.8 (1.1)	8.5 (0.8)	8.4 (1.1)	8.3 (1.1)
HbA_{1c}, mmol/mol	66.4 (10.0)	72.4 (11.5)	69.6 (8.6)	68.2 (12.1)	67.6 (11.5)
Body weight, kg	95.2 (22.6)	62.9 (8.2)	61.8 (9.7)	64.5 (8.4)	62.4 (7.8)
BMI, kg/m²	33.5 (6.8)	23.0 (1.6)	23.1 (1.6)	23.4 (1.6)	23.1 (1.2)
Race, n (%)					
Asian	191 (15.9)	17 (70.8)	9 (47.4)	7 (43.8)	16 (57.1)
Black/African American	70 (5.8)	0	0	0 (0)	1 (3.6)
White	928 (77.4)	7 (29.2)	10 (52.6)	9 (56.3)	11 (39.3)
Other	10 (0.8)	0	0	0 (0)	0 (0)
Ethnic group, n (%)					
Hispanic/Latino	138 (11.5)	2 (8.3)	5 (26.3)	3 (18.8)	3 (10.7)
Non-Hispanic/Latino	1,061 (88.5)	22 (91.7)	14 (73.7)	13 (81.3)	25 (89.3)

'On-treatment without rescue medication' data. Subgroup data are presented as mean (standard deviation) unless otherwise indicated. BMI, body mass index; Dula, dulaglutide; HbA_{1c}, glycated haemoglobin; n, number of subjects randomised and exposed to at least one dose of trial product as randomised (full analysis set); Sema, semaglutide.

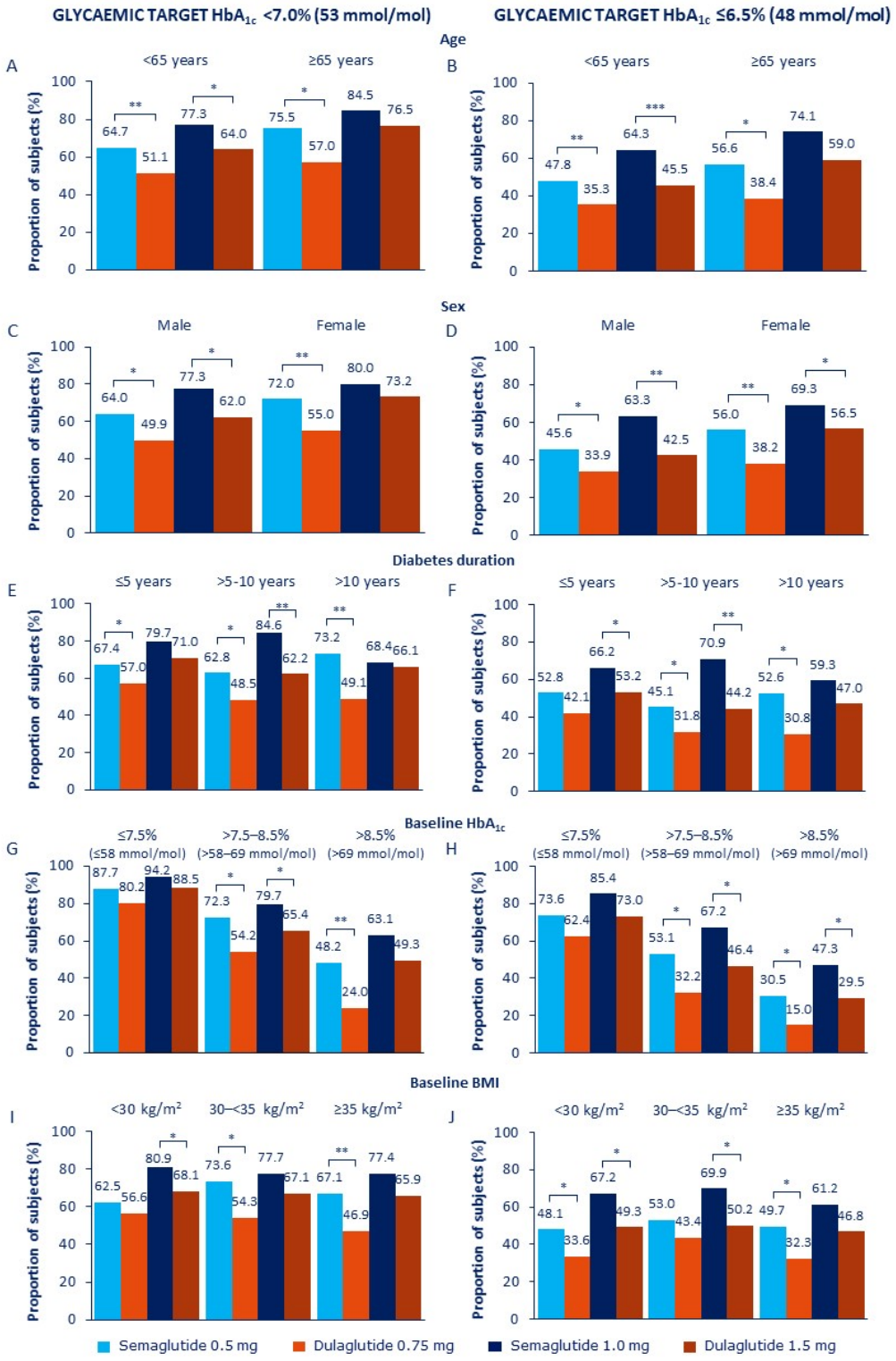
SUPPLEMENTARY SECTION II: GLYCAEMIC TARGETS & WEIGHT-LOSS RESPONSES

Supplementary Figure 1. Change from baseline in HbA_{1c} (A, C, E, G, I) and body weight (B, D, F, H, J) at week 40 by age (A, B), sex (C, D), diabetes duration (E, F), HbA1c (G, H) and BMI (I, J) at baseline.



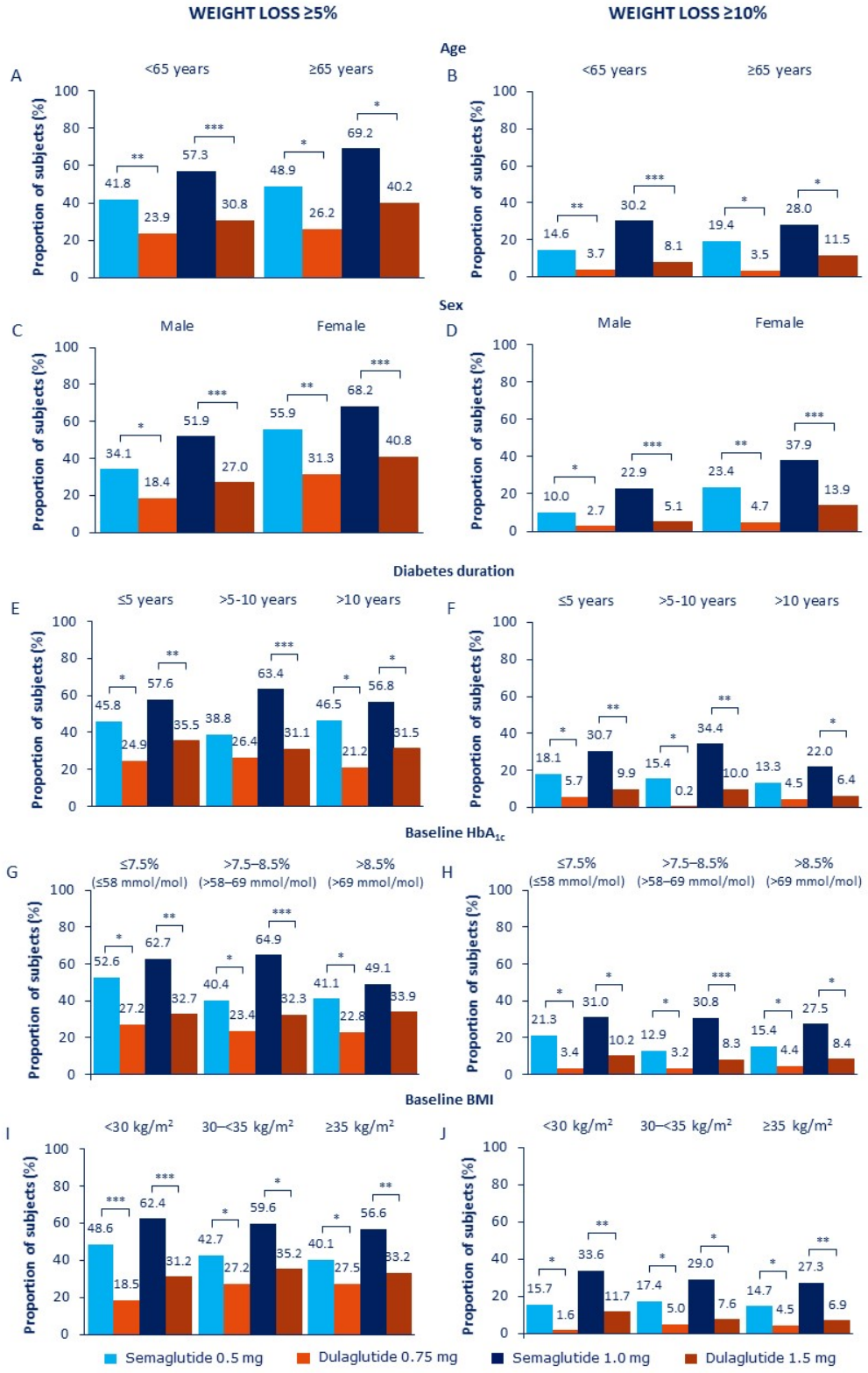
*p<0.05, **p<0.001, ***p<0.0001. Values are estimated means from ANCOVAs controlled for baseline HbA_{1c} (A, C, E, G, I) or BW (B, D, F, H, I) with multiple imputations using data from all randomised subjects exposed to at least one dose of trial product and did not discontinue treatment or receive any non-investigational antihyperglycaemic treatment (full analysis set) obtained while on treatment and prior to onset of rescue medication. P-values are based on ETDs; statistical analyses were not performed for change from baseline.
ANCOVA, analysis of covariance; BMI, body mass index; BW, body weight; ETD, estimated treatment difference; HbA_{1c}, glycated haemoglobin.

Supplementary Figure 2. Proportion of subjects achieving HbA_{1c} < 7.0% (53 mmol/mol; A, C, E, G and I) and HbA_{1c} ≤6.5% (48 mmol/mol; B, D, F, H and J) at 40 weeks



*p<0.05, **p<0.001, ***p<0.0001. Values are estimated proportions from ANCOVAs with multiple imputations using 'on-treatment without rescue medication' data from all randomised subjects exposed to at least one dose of trial product as randomised (full analysis set) obtained while on treatment and prior to onset of rescue medication. ANCOVA, analysis of covariance; BMI, body mass index; BW, body weight; HbA_{1c}, glycated haemoglobin.

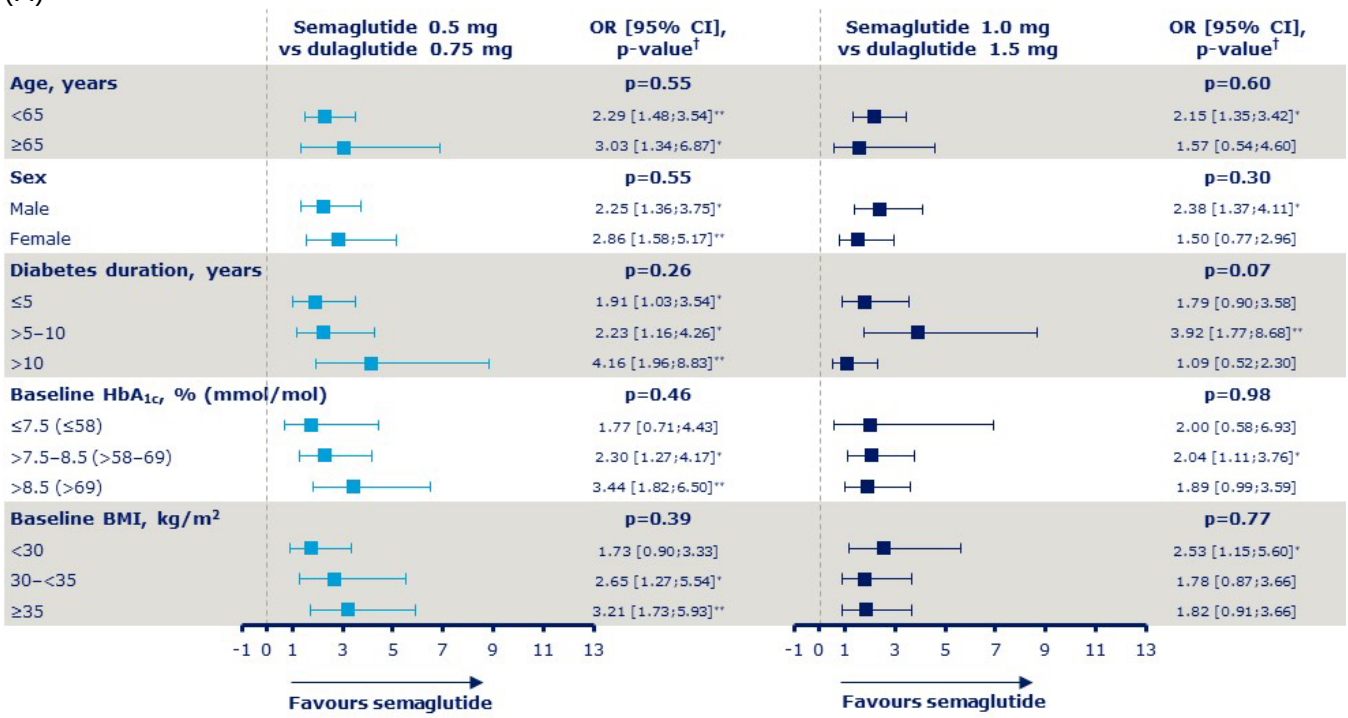
Supplementary Figure 3. Proportion of subjects achieving weight loss ⩾5% (A, C, E, G and I) and weight loss ⩾10% (B, D, F, H and J) at 40 weeks



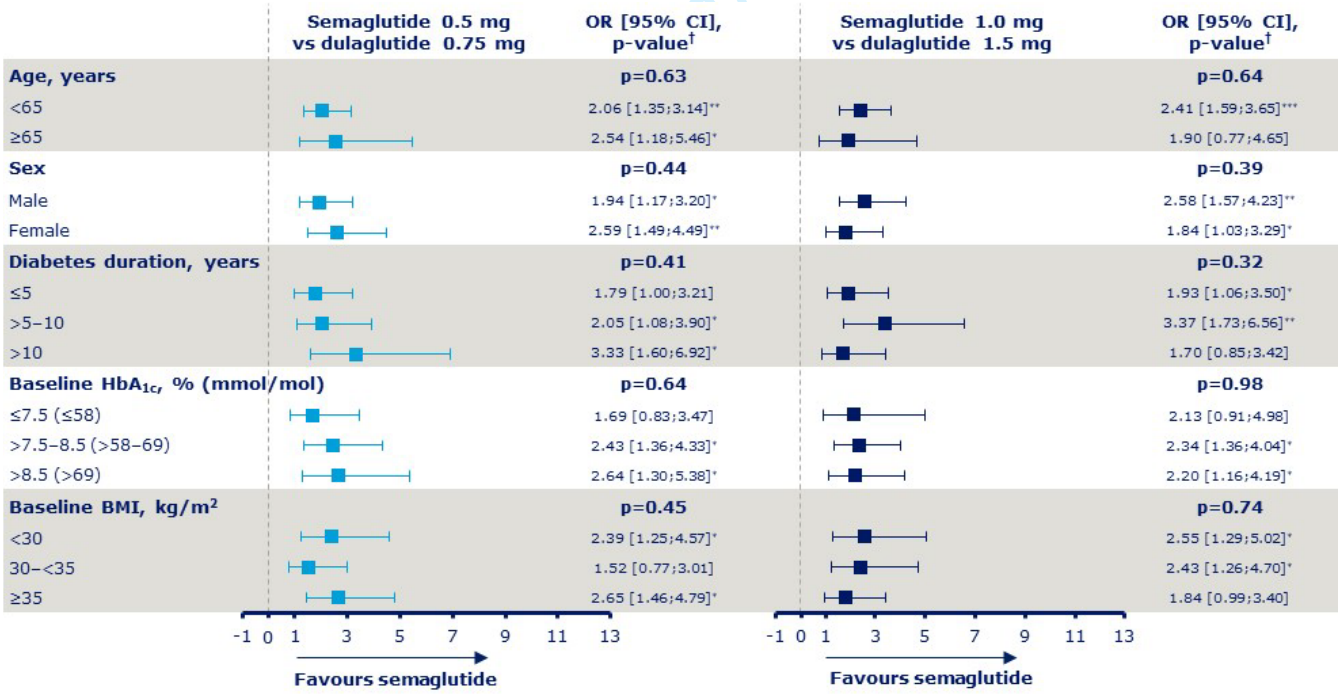
*p<0.05, **p<0.001, ***p<0.0001. Values are estimated proportions from ANCOVAs with multiple imputations using 'on-treatment without rescue medication' data from all randomised subjects exposed to at least one dose of trial product as randomised (full analysis set) obtained while on treatment and prior to onset of rescue medication. P-values are based on ETDs; statistical analyses were not performed for change from baseline. ANCOVA, analysis of covariance; BMI, body mass index; ETD, estimated treatment difference; BW, body weight.

Supplementary Figure 4. Odds ratios for the proportion of subjects achieving HbA_{1c} <7.0% (53 mmol/mol; A) and HbA_{1c} ⩽6.5% (48 mmol/mol; B) at 40 weeks by age, sex, diabetes duration, HbA_{1c} and BMI at baseline

(A)



(B)

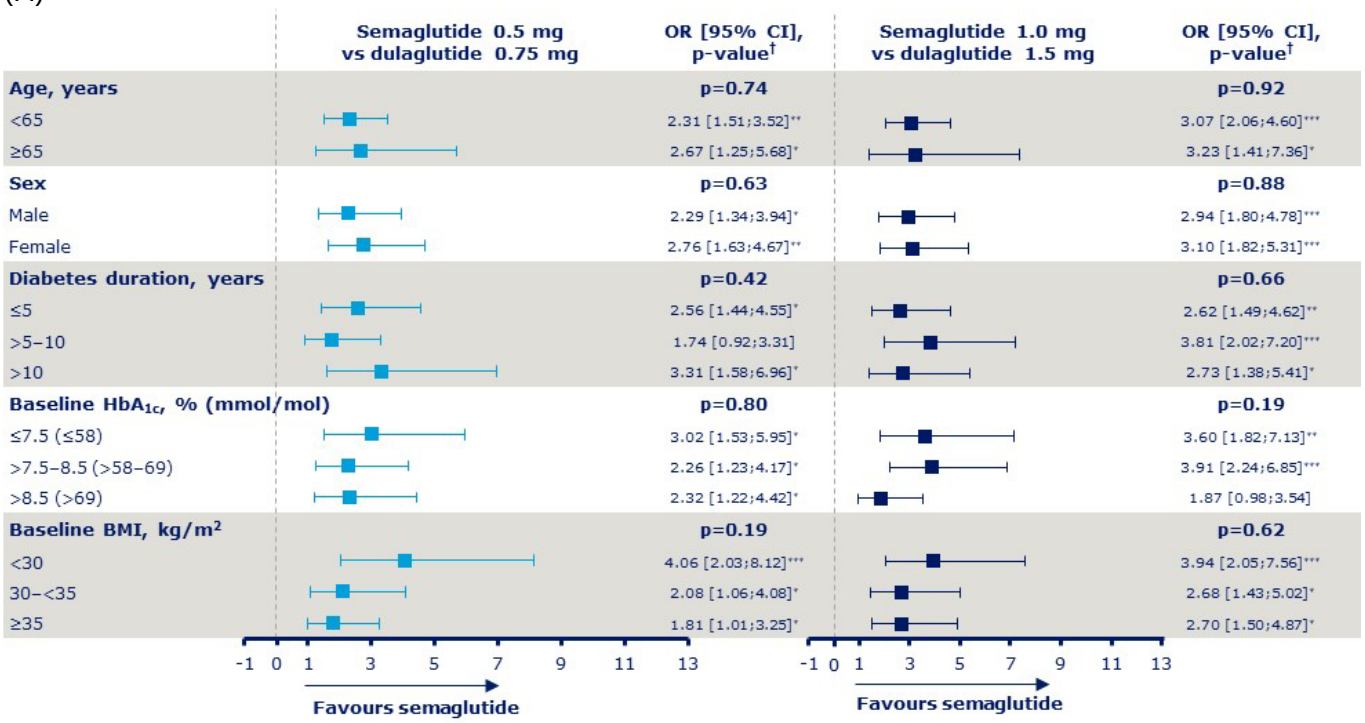


*p<0.05, **p<0.001, ***p<0.0001; †p-values represent the test for treatment by subgroup interaction. Values are ORs [95% CIs] from ANCOVAs with multiple imputations using 'on-treatment without rescue medication' data

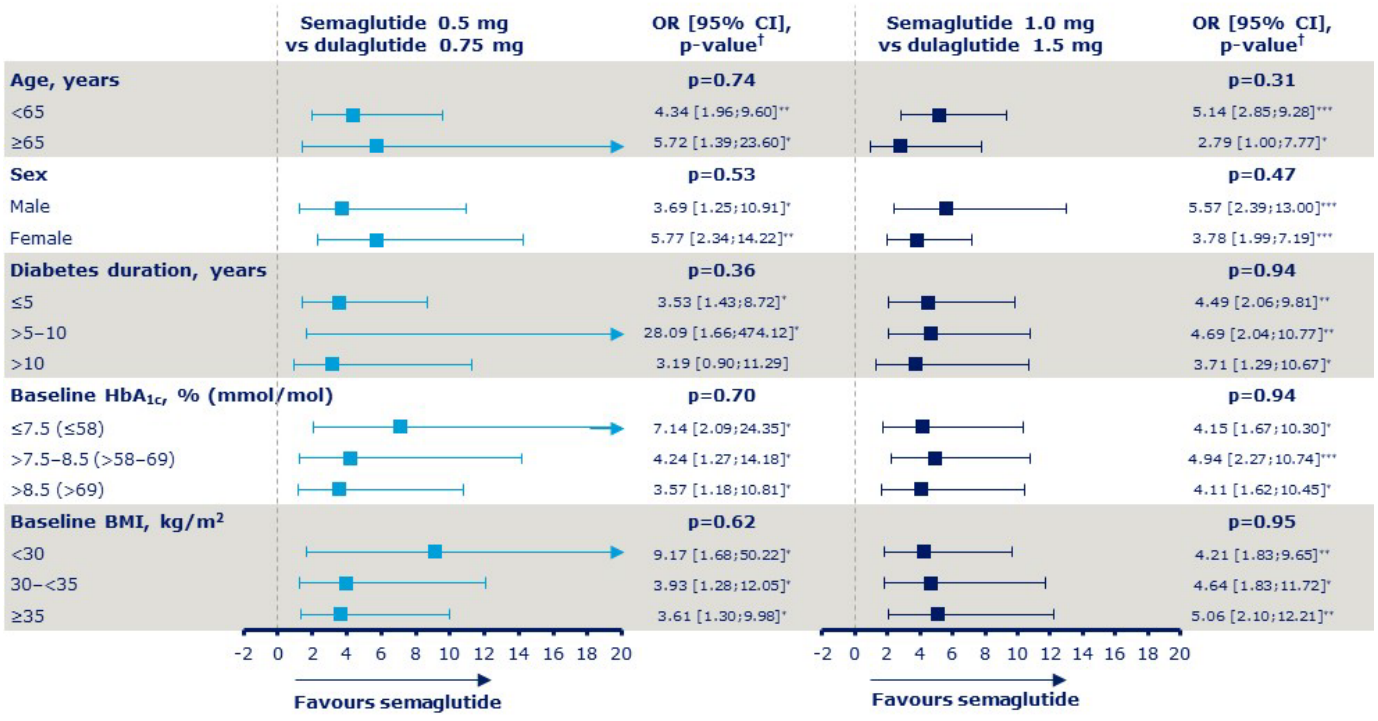
from all randomised subjects exposed to at least one dose of trial product as randomised (full analysis set) obtained while on treatment and prior to onset of rescue medication. ANCOVA controlled for baseline HbA_{1c} and interaction between randomised treatment and subgroup. ANCOVA, analysis of covariance; BMI, body mass index; CI, confidence interval; HbA_{1c}, glycated haemoglobin; OR, odds ratio.

Supplementary Figure 5. Odds ratios for the proportion of subjects achieving weight loss ⩾5% (A) and weight loss ⩾10% (B) at 40 weeks by age, sex, diabetes duration, HbA_{1c} and BMI at baseline

(A)

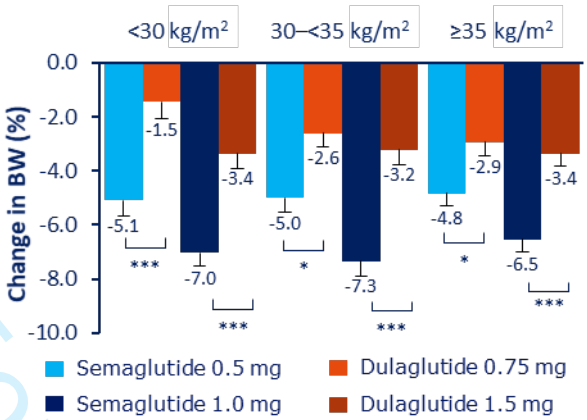


(B)



*p<0.05, **p<0.001, ***p<0.0001; †p-values represent the test for treatment by subgroup interaction. Values are ORs [95% CIs] from ANCOVA analyses with multiple imputations using 'on-treatment without rescue medication' data from all randomised subjects exposed to at least one dose of trial product as randomised (full analysis set) obtained while on treatment and prior to onset of rescue medication. ANCOVA controlled for baseline HbA_{1c} and interaction between randomised treatment and subgroup. ANCOVA, analysis of covariance; BMI, body mass index; CI, confidence interval; HbA_{1c}, glycated haemoglobin; OR, odds ratio.

Supplementary Figure 6: Change in body weight (%) from baseline to week 40 by baseline BMI category



*p<0.05, ***p<0.0001. Values are estimated means from ANCOVAs with multiple imputations using 'on-treatment without rescue medication' data from all randomised subjects exposed to at least one dose of trial product as randomised (full analysis set) obtained while on treatment and prior to onset of rescue medication. ANCOVA, analysis of covariance; BMI, body mass index; BW, body weight.

Supplementary Section III: Adverse Events

Supplementary Table 5. Adverse events by sex subgroups

n (%)	All subjects	Male				Female			
		Sema 0.5 mg	Dula 0.75 mg	Sema 1.0 mg	Dula 1.5 mg	Sema 0.5 mg	Dula 0.75 mg	Sema 1.0 mg	Dula 1.5 mg
	1,199	169	160	162	171	132	139	138	128
AEs	818 (68.2)	111 (65.7)	97 (60.6)	113 (69.8)	129 (75.4)	93 (70.5)	89 (64.0)	94 (68.1)	92 (71.9)
Serious AEs	86 (7.2)	11 (6.5)	15 (9.4)	10 (6.2)	12 (7.0)	6 (4.5)	9 (6.5)	13 (9.4)	10 (7.8)
AEs leading to premature treatment discontinuation	87 (7.3)	13 (7.7)	8 (5.0)	15 (9.3)	12 (7.0)	11 (8. 3)	6 (4.3)	14 (10.1)	8 (6.3)
Gastrointestinal AEs leading to premature treatment discontinuation	54 (4.5)	8 (4.7)	1 (0.6)	9 (5.6)	8 (4.7)	8 (6.1)	5 (3.6)	9 (6.5)	6 (4.8)
Gastrointestinal AEs	505 (42.1)	67 (39.6)	47 (29.4)	67 (41.4)	81 (47.4)	62 (47.0)	53 (38.1)	66 (47.8)	62 (48.4)
Vomiting	103 (8.6)	13 (7.7)	5 (3.1)	11 (6.8)	16 (9.4)	18 (13.6)	7 (5.0)	20 (14.5)	13 (10.2)
Nausea	230 (19.2)	29 (17.2)	13 (8.1)	25 (15.4)	33 (19.3)	39 (29.5)	26 (18.7)	38 (27.5)	27 (21.1)
Diarrhoea	160 (13.3)	21 (12.4)	10 (6.3)	19 (11.7)	33 (19.3)	22 (16.7)	13 (9.4)	22 (15.9)	20 (15.6)
Hypoglycaemia (severe/BG-confirmed)	15 (1.3)	1 (0.6)	3 (1.9)	3 (1.9)	3 (1.8)	1 (0.8)	0	2 (1.4)	2 (1.6)

Data are presented as number and proportion in percent of subjects with adverse events. Hypoglycaemia was defined as an episode that was severe (according to the American Diabetes Association classification) or BG-confirmed (plasma glucose value <56 mg/dL [3.1 mmol/L]) with symptoms consistent with hypoglycaemia. AE, adverse event; BG, blood glucose; Dula, dulaglutide; n, number of subjects randomised and exposed to at least one dose of trial product as treated (safety analysis set); Sema, semaglutide.

Supplementary Table 6. Adverse events by diabetes duration subgroups

n (%)	All subjects	≤5 years				>5–10 years				>10 years			
		Sema 0.5 mg	Dula 0.75 mg	Sema 1.0 mg	Dula 1.5 mg	Sema 0.5 mg	Dula 0.75 mg	Sema 1.0 mg	Dula 1.5 mg	Sema 0.5 mg	Dula 0.75 mg	Sema 1.0 mg	Dula 1.5 mg
	1,199	113	128	122	114	101	94	103	92	87	77	75	93
AEs	818 (68.2)	76 (67.3)	81 (63.3)	79 (64.8)	76 (66.7)	66 (65.3)	52 (55.3)	74 (71.8)	73 (79.3)	62 (71.3)	53 (68.8)	54 (72.0)	72 (77.4)
Serious AEs	86 (7.2)	5 (4.4)	9 (7.0)	10 (8.2)	9 (7.9)	4 (4.0)	6 (6.4)	7 (6.8)	6 (6.5)	8 (9.2)	9 (11.7)	6 (8.0)	7 (7.5)
AEs leading to premature treatment discontinuation	87 (7.3)	9 (8.0)	3 (2.3)	9 (7.4)	5 (4.4)	10 (9.9)	5 (5.3)	9 (8.7)	8 (8.7)	5 (5.7)	6 (7.8)	11 (14.7)	7 (7.5)
Gastrointestinal AEs leading to premature treatment discontinuation	54 (4.5)	7 (6.2)	1 (0.8)	6 (4.9)	3 (2.6)	6 (5.9)	1 (1.1)	5 (4.9)	5 (5.4)	3 (3.4)	4 (5.2)	7 (9.3)	6 (6.5)
Gastrointestinal AEs	505 (42.1)	52 (46.0)	44 (34.4)	57 (46.7)	52 (45.6)	44 (43.6)	26 (27.7)	42 (40.8)	48 (52.2)	33 (37.9)	30 (39.0)	34 (45.3)	43 (46.2)
Vomiting	103 (8.6)	14 (12.4)	5 (3.9)	18 (14.8)	8 (7.0)	10 (9.9)	4 (4.3)	6 (5.8)	9 (9.8)	7 (8.0)	3 (3.9)	7 (9.3)	12 (12.9)
Nausea	230 (19.2)	25 (22.1)	17 (13.3)	24 (19.7)	21 (18.4)	22 (21.8)	10 (10.6)	24 (23.3)	20 (21.7)	21 (24.1)	12 (15.6)	15 (20.0)	19 (20.4)
Diarrhoea	160 (13.3)	16 (14.2)	14 (10.9)	22 (18.0)	20 (17.5)	18 (17.8)	4 (4.3)	11 (10.7)	18 (19.6)	9 (10.3)	5 (6.5)	8 (10.7)	15 (16.1)
Hypoglycaemia (severe/BG-confirmed)	15 (1.3)	0	1 (0.8)	2 (1.6)	2 (1.8)	0	0	2 (1.9)	2 (2.2)	2 (2.3)	2 (2.6)	1 (1.3)	1 (1.1)

Data are presented as number and proportion in percent of subjects with adverse events. Hypoglycaemia was defined as an episode that was severe (according to the American Diabetes Association classification) or BG-confirmed (plasma glucose value <56 mg/dL [3.1 mmol/L]) with symptoms consistent with hypoglycaemia. AE, adverse event; BG, blood glucose; Dula, dulaglutide; n, number of subjects randomised and exposed to at least one dose of trial product as treated (safety analysis set); Sema, semaglutide.

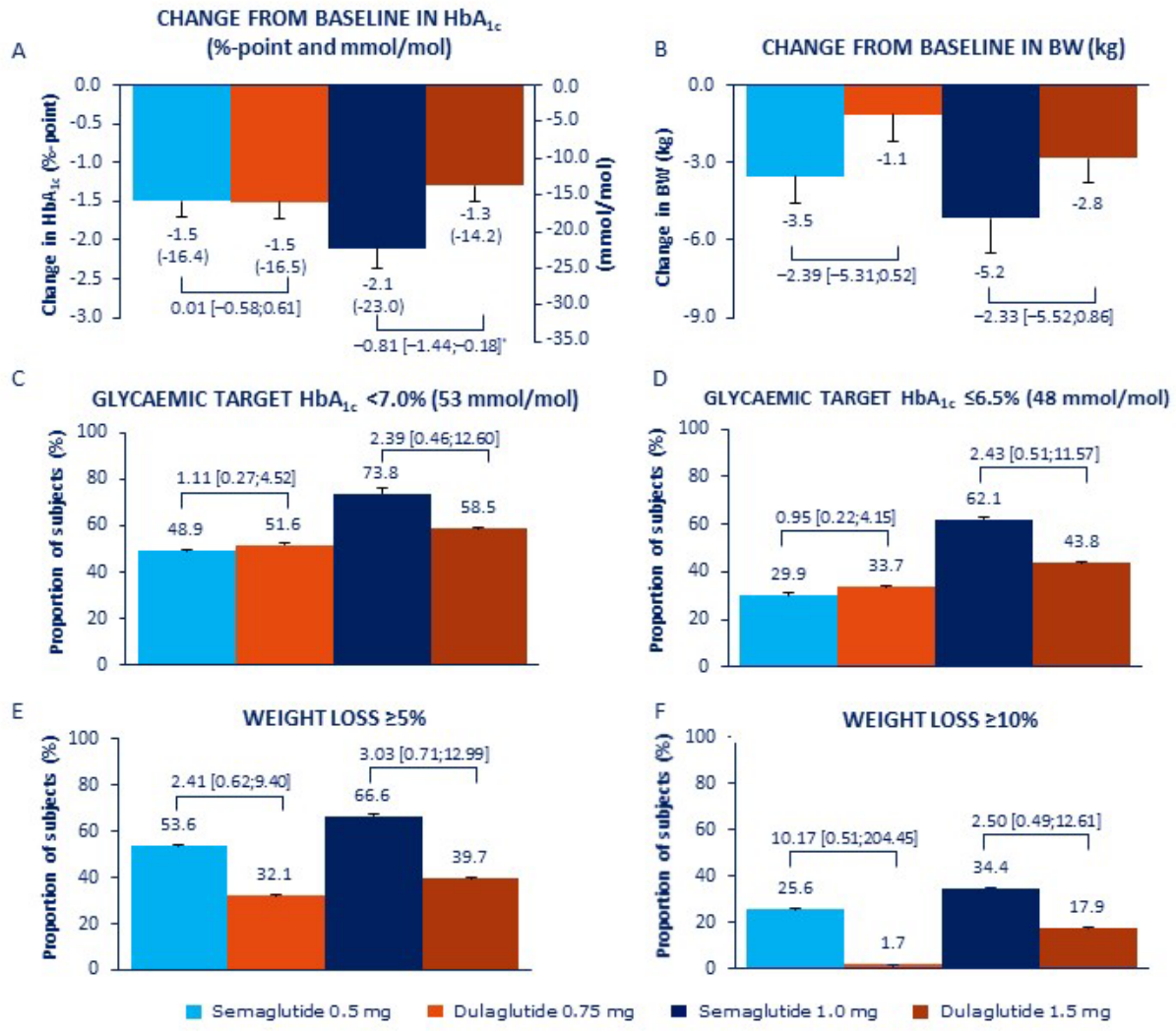
Supplementary Table 7. Adverse events by baseline HbA_{1c} subgroups

n (%)	All subjects	≤7.5% (≤58 mmol/mol)				>7.5–8.5% (>58–69 mmol/mol)				>8.5% (>69 mmol/mol)			
		Sema 0.5 mg	Dula 0.75 mg	Sema 1.0 mg	Dula 1.5 mg	Sema 0.5 mg	Dula 0.75 mg	Sema 1.0 mg	Dula 1.5 mg	Sema 0.5 mg	Dula 0.75 mg	Sema 1.0 mg	Dula 1.5 mg
	1,199	**74**	**94**	**83**	**84**	**120**	**105**	**124**	**120**	**107**	**100**	**93**	**95**
AEs	818 (68.2)	51 (68.9)	62 (66.0)	57 (68.7)	66 (78.6)	80 (66.7)	65 (61.9)	83 (66.9)	94 (78.3)	73 (68.2)	59 (59.0)	67 (72.0)	61 (64.2)
Serious AEs	86 (7.2)	3 (4.1)	9 (9.6)	6 (7.2)	3 (3.6)	7 (5.8)	8 (7.6)	9 (7.3)	7 (5.8)	7 (6.5)	7 (7.0)	8 (8.6)	12 (12.6)
AEs leading to premature treatment discontinuation	88 (7.3)	6 (8.1)	5 (5.3)	8 (9.6)	11 (13.1)	11 (9.2)	5 (4.8)	12 (9.7)	4 (3.3)	7 (6.5)	4 (4.0)	9 (9.7)	5 (5.3)
Gastrointestinal AEs leading to premature treatment discontinuation	54 (4.5)	5 (6.8)	2 (2.1)	6 (7.2)	9 (10.7)	6 (5.0)	2 (1.9)	8 (6.5)	1 (0.8)	5 (4.7)	2 (2.0)	4 (4.3)	4 (4.2)
Gastrointestinal AEs	505 (42.1)	33 (44.6)	32 (34.0)	38 (45.8)	50 (59.5)	52 (43.3)	40 (38.1)	53 (42.7)	55 (45.8)	44 (41.1)	28 (28.0)	42 (45.2)	38 (40.0)
Vomiting	103 (8.6)	7 (9.5)	5 (5.3)	8 (9.6)	7 (8.3)	14 (11.7)	2 (1.9)	14 (11.3)	11 (9.2)	10 (9.3)	5 (5.0)	9 (9.7)	11 (11.6)
Nausea	230 (19.2)	16 (21.6)	11 (11.7)	16 (19.3)	19 (22.6)	28 (23.3)	14 (13.3)	28 (22.6)	22 (18.3)	24 (22.4)	14 (14.0)	19 (20.4)	19 (20.0)
Diarrhoea	160 (13.3)	12 (16.2)	6 (6.4)	14 (16.9)	25 (29.8)	20 (16.7)	11 (10.5)	17 (13.7)	17 (14.2)	11 (10.3)	6 (6.0)	10 (10.8)	11 (11.6)
Hypoglycaemia (severe/BG-confirmed)	15 (1.3)	0	1 (1.1)	2 (2.4)	1 (1.2)	2 (1.7)	1 (1.0)	1 (0.8)	2 (1.7)	0	1 (1.0)	2 (2.2)	2 (2.1)

Data are presented as number and proportion in percent of subjects with adverse events. Hypoglycaemia was defined as an episode that was severe (according to the American Diabetes Association classification) or BG-confirmed (plasma glucose value <56 mg/dL [3.1 mmol/L]) with symptoms consistent with hypoglycaemia. AE, adverse event; BG, blood glucose; Dula, dulaglutide; n, number of subjects randomised and exposed to at least one dose of trial product as treated (safety analysis set); Sema, semaglutide.

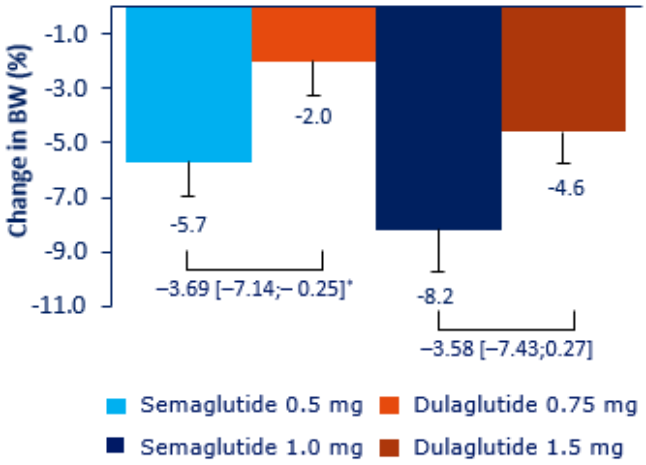
Supplementary Section IV: Results in subjects with BMI <25 kg/m^2

Supplementary Figure 7. Change in HbA_{1c} (A) and body weight (B) from baseline to week 40 and the proportion of subjects achieving HbA_{1c} <7.0% (53 mmol/mol; C), HbA_{1c} ⩽6.5% (48 mmol/mol; D), weight loss ⩾5% (E) and weight loss ⩾10% (F) in subjects with BMI <25 kg/m² at baseline



*p<0.05. Values are estimated means (A, B), estimated proportions (C–F), ETDs [95% CIs] (A, B) or ORs [95% CIs] (C–F) from ANCOVAs with multiple imputations using 'on-treatment without rescue medication' data from all randomised subjects exposed to at least one dose of trial product as randomised (full analysis set). ANCOVA analyses were controlled for baseline HbA_{1c} and interaction between randomised treatment and subgroup. ANCOVA, analysis of covariance; BMI, body mass index, BW, body weight; CI, confidence interval; ETD, estimated treatment difference; HbA_{1c}, glycated haemoglobin; OR, odds ratio.

Supplementary Figure 8. Change in body weight (%) from baseline to week 40 in subjects with BMI <25 kg/m² at baseline



*p<0.05. Values are estimated means from ANCOVAs with multiple imputations using 'on-treatment without rescue medication' data from all randomised subjects exposed to at least one dose of trial product as randomised (full analysis set). ANCOVAs were controlled for baseline HbA_{1c} and interaction between randomised treatment and subgroup. ANCOVA, analysis of covariance; BMI, body mass index; BW, body weight; CI, confidence interval; ETD, estimated treatment difference.

Supplementary Table 8. Adverse events in subjects with BMI <25 kg/m² at baseline

n (%)	All subjects	Sema 0.5 mg	Dula 0.75 mg	Sema 1.0 mg	Dula 1.5 mg
	1,199	**24**	**19**	**16**	**28**
AEs	818 (68.2)	18 (75.0)	14 (73.7)	12 (75.0)	23 (82.1)
Serious AEs	86 (7.2)	1 (4.2)	1 (5.3)	2 (12.5)	2 (7.1)
AEs leading to premature treatment discontinuation	87 (7.3)	5 (20.8)	2 (10.5)	4 (25.0)	6 (21.4)
Gastrointestinal AEs leading to premature treatment discontinuation	54 (4.5)	4 (16.7)	0	2 (12.5)	2 (7.1)
Gastrointestinal AEs	505 (42.1)	14 (58.3)	6 (31.6)	10 (62.5)	17 (60.7)
Vomiting	103 (8.6)	6 (25.0)	1 (5.3)	2 (12.5)	3 (10.7)
Nausea	230 (19.2)	6 (25.0)	1 (5.3)	4 (25.0)	6 (21.4)
Diarrhoea	160 (13.3)	5 (20.8)	3 (15.8)	3 (18.8)	7 (25.0)
Hypoglycaemia (severe/BG-confirmed)	15 (1.3)	0	1 (5.3)	0	1 (3.6)

Data are presented as number and proportion in percent of subjects with adverse events. Hypoglycaemia was defined as an episode that was severe (according to the American Diabetes Association classification) or BG-confirmed (plasma glucose value <56 mg/dL [3.1 mmol/L]) with symptoms consistent with hypoglycaemia. AE, adverse event; BG, blood glucose; BMI, body mass index; Dula, dulaglutide; n, number of subjects randomised and exposed to at least one dose of trial product as treated (safety analysis set); Sema, semaglutide.

BMJ Open

Impact of patient characteristics on efficacy and safety of once-weekly semaglutide versus dulaglutide: SUSTAIN 7 *post hoc* analyses

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2020-037883.R1
Article Type:	Original research
Date Submitted by the Author:	04-Jul-2020
Complete List of Authors:	Pratley, Richard; AdventHealth Orlando, Translational Research Institute Aroda, Vanita ; Brigham and Women's Hospital Catarig, Andrei-Mircea; Novo Nordisk A/S Lingvay, Ildiko; University of Texas Southwestern Medical Center Lüdemann, Jörg; diabetes-falkensee, Diabetes Centre and Centre for Clinical Studies Yildirim, Emre; Novo Nordisk A/S Viljoen, Adie; Borthwick Diabetes Research Centre, Lister Hospital
Primary Subject Heading:	Diabetes and endocrinology
Secondary Subject Heading:	Evidence based practice
Keywords:	General diabetes < DIABETES & ENDOCRINOLOGY, Diabetes & endocrinology < INTERNAL MEDICINE, Clinical trials < THERAPEUTICS

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

Title page

Full title: Impact of patient characteristics on efficacy and safety of once-weekly semaglutide versus dulaglutide: SUSTAIN 7 *post hoc* analyses

Authors: Pratley Richard E[1], Aroda Vanita R[2], Catarig Andrei M[3], Lingvay Ildiko[4], Lüdemann Jörg[5], Yildirim Emre[3], Viljoen Adie[6]

Author affiliations:

[1]AdventHealth Translational Research Institute for Metabolism and Diabetes, Orlando, FL, USA; [2]Brigham and Women's Hospital, Boston, MA, USA; [3]Novo Nordisk A/S, Søborg, Denmark; [4]University of Texas Southwestern Medical Center, Dallas, TX, USA; [5]diabetes-falkensee, Diabetes Centre and Centre for Clinical Studies, Falkensee, Germany; [6]Borthwick Diabetes Research Centre, Lister Hospital, Stevenage, UK

Keywords: type 2 diabetes, GLP-1, semaglutide, SUSTAIN, age, body mass index

Contact details for corresponding author:

Dr Richard E. Pratley

AdventHealth Translational Research Institute for Metabolism and Diabetes

301 E. Princeton Street, Orlando, FL 32804, USA

Phone: +1-407-303-2519

E-mail: Richard.Pratley.MD@AdventHealth.com

ABSTRACT

OBJECTIVE: In SUSTAIN 7, once-weekly semaglutide demonstrated superior glycated haemoglobin (HbA_{1c}) and body weight (BW) reductions versus once-weekly dulaglutide in subjects with type 2 diabetes (T2D). This *post hoc* analysis investigated the impact of clinically relevant subject characteristics on treatment effects of semaglutide versus dulaglutide.

DESIGN: Analyses by baseline age (<65, ≥65 years), sex (male, female), diabetes duration (≤5, >5-10, >10 years), HbA_{1c} (≤7.5, >7.5-8.5, >8.5% [≤58, >58-69, >69 mmol/mol]) and body mass index (BMI) (<30, 30-<35, ≥35 kg/m^2).

SETTING: 194 sites; 16 countries.

PARTICIPANTS: Subjects with T2D (n=1,199) exposed to treatment.

INTERVENTIONS: Semaglutide 0.5 mg versus dulaglutide 0.75 mg (low-dose comparison); semaglutide 1.0 mg versus dulaglutide 1.5 mg (high-dose comparison), all subcutaneously once weekly.

PRIMARY AND SECONDARY OUTCOME MEASURES: Change in HbA_{1c} (primary endpoint) and BW (confirmatory secondary endpoint) from baseline to week 40; proportion of subjects achieving HbA_{1c} targets (<7%, ≤6.5% [<53, ≤48 mmol/mol]) and weight-loss responses (≥5%, ≥10%) at week 40; and safety.

RESULTS: HbA_{1c} and BW reductions (estimated treatment difference ranges: −0.22 to −0.70%-point; −1.76 to −3.84 kg) and proportion of subjects achieving HbA_{1c} targets and weight-loss responses were statistically significantly greater for the majority of comparisons of semaglutide versus dulaglutide within each subgroup category and, excepting glycaemic control within the low-dose comparison in HbA_{1c} subgroups, this was irrespective of subgroup or dose comparison. Gastrointestinal adverse events, the most common with both treatments, were reported by more females than males and, with semaglutide, decreased with increasing BMI.

CONCLUSIONS: Consistently greater improvements in HbA_{1c} and BW with semaglutide versus dulaglutide, regardless of age, sex, diabetes duration, glycaemic control and BMI, support the efficacy of semaglutide across the continuum of care in a heterogeneous T2D population.

Clinical Trial Registration: NCT02648204 [ClinicalTrials.gov]

STRENGTHS AND LIMITATIONS OF THIS STUDY

- The analysis was designed to provide insight on the influence of five of the most common and relevant patient-level factors from a clinical perspective
- The inclusion of comparator data allows for a more robust analysis and direct comparison of the differences in efficacy and safety of semaglutide versus dulaglutide across the subgroups and subgroup categories
- As the analysis is based on SUSTAIN 7 data alone, it may only be representative of the trial-specific patient population
- The relatively small number of subjects in each subgroup category is a limitation
- As this is a *post hoc* analysis of a randomised clinical trial, there are inherent limitations and, as such, the data should be interpreted with caution

INTRODUCTION

The population of adults with type 2 diabetes (T2D) is heterogeneous, with varying clinical characteristics and comorbidities.(1) The importance of considering this heterogeneity when making treatment decisions is emphasised in guidelines on the management of T2D,(1,2) which recommend individualised patient-centred care considering the presence of comorbidities, including obesity, chronic kidney disease and cardiovascular disease.(2) Some studies have attempted to identify clusters of patients according to their clinical characteristics and risk of complications, in the hope this might enable treatment to be more precisely targeted to those who are likely to benefit most.(3) However, there is an ongoing debate about whether clustering or stratifying patients based on simple clinical characteristics is the most useful approach.(4,5)

Glucagon-like peptide-1 receptor agonists (GLP-1RAs) are an established treatment for T2D, recommended in current management guidelines.(1,2) The efficacy and safety of two once-weekly (OW) subcutaneous medications from the GLP-1RA class, semaglutide and dulaglutide, were respectively investigated in the global phase 3a SUSTAIN (Semaglutide Unabated Sustainability in Treatment of Type 2 Diabetes) (6-10) and AWARD (Assessment of Weekly AdministRation of LY2189265 in Diabetes) (11-20) clinical trial programmes. Both drugs have also been investigated in large-scale cardiovascular outcomes trials.(21,22) *Post hoc* analyses of the SUSTAIN and the AWARD trials have analysed patient subgroups across the continuum of T2D care.(23-35) Such analyses showed consistent, clinically relevant reductions in glycated haemoglobin (HbA_{1c}) and body weight (BW) with semaglutide across patient subgroups based on characteristics including age, baseline body mass index (BMI), baseline HbA_{1c}, diabetes duration, race and ethnicity.(23-26,28) Dulaglutide has also been shown to be efficacious across subgroups based on sex, age, duration of diabetes, beta-cell function, HbA_{1c}, BW and BMI.(29-35)

In the phase 3b SUSTAIN 7 clinical trial, semaglutide and dulaglutide were compared head-to-head in subjects with T2D on background treatment with metformin.(36) The

trial showed superior reductions in HbA_{1c} and BW with semaglutide versus dulaglutide, for both low-dose (semaglutide 0.5 mg versus dulaglutide 0.75 mg) and high-dose (semaglutide 1.0 mg versus dulaglutide 1.5 mg) comparisons.(36) Although both semaglutide and dulaglutide have individually demonstrated efficacy across multiple patient subpopulations,(23-27,29-35) it is as yet unknown whether the treatment differences observed in the SUSTAIN 7 trial are influenced by heterogeneity in the characteristics of the patients with T2D.

To evaluate whether clinically relevant patient characteristics (age, sex, diabetes duration, HbA_{1c} and BMI at baseline) affected the efficacy and safety of semaglutide versus dulaglutide, *post hoc* analyses of data from the SUSTAIN 7 trial were performed.

MATERIALS AND METHODS

Trial design

The design of the SUSTAIN 7 trial has been previously reported.(36) Briefly, this was an open-label trial in which subjects with uncontrolled T2D were randomised to receive semaglutide OW 0.5 mg or 1.0 mg, or dulaglutide OW 0.75 mg or 1.5 mg, as add-on to background treatment with metformin, and were followed throughout a 40-week treatment period. Semaglutide was administered subcutaneously via a prefilled injection device at one of two maintenance dose levels (0.5 mg or 1.0 mg OW), following a fixed-dose escalation regimen.(36) Dulaglutide was administered subcutaneously in accordance with the regimen used in the phase 3 clinical trial programme (0.75 mg or 1.5 mg OW), without dose escalation.(37)

The trial was registered with ClinicalTrials.gov (NCT02648204) and conducted in accordance with the International Conference on Harmonisation Good Clinical Practice guidelines and the Declaration of Helsinki. The trial protocol (see Supplement) was approved by the central ethics committees (Eticka komisia, Nemocnica Svateho Michala, a.s., Bratislava, Slovakia and, for Portugal, Comissão de Ética para a Investigação

Clínica) and by the institutional review boards and ethics committees at each participating centre (**Supplementary Table 1**) and subjects provided written informed consent before trial-related activities commenced.

Patient and public involvement

The research question and endpoints, such as efficacy and safety, were informed indirectly by patients' priorities, experiences and preferences, via input from clinicians during advisory board meetings. No patients were involved directly in the design, recruitment and conduct of the trial. Furthermore, the trial results were not directly disseminated to trial patients, but were publicly communicated and available via press release, trial portal and journal publication. In the trial, the burden of intervention was not assessed by the patients, nor were there any patient advisers involved.

Patient population

The inclusion and exclusion criteria for the SUSTAIN 7 trial are described in detail elsewhere.(36) Key inclusion criteria were: diagnosis of T2D; age ≥18 years; HbA_{1c} ≥7.0-10.5% (53-91 mmol/mol). Key exclusion criteria were: estimated glomerular filtration rate <60 mL/min/1.73 m^2; history of chronic or idiopathic acute pancreatitis; known proliferative retinopathy or maculopathy requiring acute treatment (determined by fundoscopy/fundus photography performed within 90 days before randomisation according to local practice); screening calcitonin value ≥50 ng/L; personal/family history of medullary thyroid carcinoma or multiple endocrine neoplasia syndrome type 2; acute coronary or cerebrovascular event within 90 days before randomisation; heart failure (New York Heart Association Class IV); and any of the following: myocardial infarction, stroke, or hospitalisation for unstable angina and/or transient ischaemic attack within the past 180 days prior to screening.(36)

Endpoints

The primary endpoint was change in HbA_{1c} (%-point) from baseline to end of treatment at week 40 and the secondary confirmatory endpoint was change in BW (kg) over the

same period. Predefined HbA_{1c} treatment targets (proportion of subjects achieving HbA_{1c} targets of <7% [53 mmol/mol] and ≤6.5% [48 mmol/mol]) and weight-loss responses (proportion of subjects achieving ≥5% and ≥10% weight loss) were also assessed.

The numbers of adverse events (AEs), serious AEs and AEs leading to premature treatment discontinuation were reported. Specific AEs of clinical interest, such as gastrointestinal (GI) disorders and hypoglycaemic events, were also evaluated.

Subgroup analyses

For this *post hoc* analysis, subjects were stratified into subgroups selected for potential clinical relevance: age at baseline (<65 years, ≥65 years), sex (male, female), diabetes duration at baseline (≤5 years, >5–10 years, >10 years), baseline HbA_{1c} (≤7.5%, >7.5-8.5%, >8.5% [≤58, >58-69, >69 mmol/mol]) and baseline BMI (<30 kg/m^2, 30–<35 kg/m^2, ≥35 kg/m^2). The baseline BMI <25 kg/m^2 subgroup category was also evaluated; however, due to the small number of subjects (representing less than 10% of the total trial population), these data are not included in the Results, but are provided in the Supplement.

Statistical analyses

The efficacy analyses were based on the full analysis set, comprising all subjects randomised and exposed to at least one dose of the trial product, using 'on-treatment without rescue medication' data (as randomised). Analysis of covariance (ANCOVA) was performed for each endpoint, including the interaction between treatment and subgroup as a factor. Multiple imputation was used to account for missing data. Specifically, using a sequential multiple-imputation approach, missing values for the underlying continuous assessments were imputed by treatment group, assuming missing data were missing at random, and based on a linear-regression model. A sequential conditional-regression approach was applied whereby missing observations at any post-baseline visits were imputed based on a linear-regression model and incorporating observations from

previous visits including baseline. Binary endpoints were created and logistic-regression models run on the complete data set; inference was drawn using Rubin's rule.(38)

Values for the mean change from baseline for HbA_{1c} and BW were calculated, and the data are presented as mean and standard error. Estimated treatment differences (ETDs) for the change from baseline in HbA_{1c} and BW, and odds ratios (ORs) for the proportions of subjects achieving HbA_{1c} targets or weight-loss responses, both with 95% confidence intervals, were also calculated for the low-dose (semaglutide 0.5 mg versus dulaglutide 0.75 mg) and high-dose (semaglutide 1.0 mg versus dulaglutide 1.5 mg) comparisons. To evaluate the evidence of heterogeneity of treatment effects across the clinical characteristics, a p-value for interaction between treatment effect and subgroup categories was calculated for both dose comparisons in all subgroup analyses, without adjustment for multiplicity.

Safety analyses were based on the safety analysis set, which included all randomised subjects who were exposed to at least one dose of trial product, based on 'as-treated' data and summarised descriptively. Safety was assessed within each treatment arm (semaglutide 0.5 mg, dulaglutide 0.75 mg, semaglutide 1.0 mg, dulaglutide 1.5 mg) in each of the subgroup categories.

Analyses were conducted using SAS version 9.4. Baseline characteristics and AEs are provided as descriptive data only.

RESULTS

Subject disposition and baseline characteristics

Baseline characteristics are summarised by treatment arm within each subgroup category (**Table 1; Supplementary Tables 2–6**). Subject characteristics were generally comparable across subgroup categories with some exceptions. In all treatment arms, diabetes duration was longer, and BW and BMI were lower in the elderly (≥65 years) subgroup compared with the non-elderly (<65 years) subgroup (**Table 1**). Males

were generally heavier but with a lower BMI, and had a longer diabetes duration than females (**Supplementary Table 2**). In the diabetes duration subgroup categories (≤5 years, >5-10 years, >10 years), age increased with increasing diabetes duration and, in the semaglutide 1.0 mg treatment arm, BW and BMI decreased with increasing diabetes duration (**Supplementary Table 3**). Across the baseline HbA_{1c} subgroups (≤7.5%, >7.5-8.5, >8.5% [≤58, >58-69, >69 mmol/mol]), subjects in the semaglutide 0.5 mg treatment arm exhibited decreasing BW and BMI with increasing HbA_{1c} (**Supplementary Table 4**). In keeping with the distribution of subjects in the sex subgroup categories, there was a greater proportion of females versus males in the two highest BMI subgroups, and the proportion of Asian subjects was higher in the subgroup with the lowest BMI versus the subgroup with the highest BMI (**Supplementary Table 5**). When compared with the other BMI subgroup categories, subjects with BMI <25 kg/m^2 had the highest HbA_{1c} levels, the highest proportions of male and Asian subjects and, as expected, the lowest BW (**Supplementary Table 6**).

Table 1. Subject demographics and baseline characteristics by age

		<65 years				≥65 years			
	All subjects	**Sema 0.5 mg**	**Dula 0.75 mg**	**Sema 1.0 mg**	**Dula 1.5 mg**	**Sema 0.5 mg**	**Dula 0.75 mg**	**Sema 1.0 mg**	**Dula 1.5 mg**
n	**1,199**	**222**	**238**	**247**	**232**	**79**	**61**	**53**	**67**
Age, years	56 (10.6)	51.6 (8.4)	51.7 (8.3)	52.4 (9.0)	52.0 (8.5)	69.4 (4.4)	69.1 (3.9)	69.3 (4.2)	69.4 (3.9)
Sex, n (%)									
Male	662 (55.2)	119 (53.6)	131 (55.0)	132 (53.4)	130 (56.0)	50 (63.3)	29 (47.5)	30 (56.6)	41 (61.2)
Female	537 (44.8)	103 (46.4)	107 (45.0)	115 (46.6)	102 (44.0)	29 (36.7)	32 (52.5)	23 (43.4)	26 (38.8)
Diabetes duration, years	7.4 (5.7)	6.8 (5.4)	6.3 (5.2)	6.6 (5.3)	6.9 (5.2)	10.2 (6.7)	9.8 (5.9)	10.2 (6.6)	10.3 (6.3)
HbA_{1c}, %	8.2 (0.9)	8.4 (1.0)	8.2 (0.9)	8.3 (0.9)	8.3 (0.9)	8.1 (0.9)	8.0 (0.8)	7.9 (0.8)	8.0 (0.8)
HbA_{1c}, mmol/mol	66.4 (10.0)	68.2 (10.7)	66.2 (10.1)	66.9 (10.1)	66.7 (9.9)	65.4 (9.7)	63.6 (9.0)	62.8 (9.2)	64.1 (8.7)
Body weight, kg	95.2(22.6)	97.8 (25.6)	96.5 (23.6)	97.2 (20.7)	94.3 (23.2)	92.4 (20.1)	92.1 (20.4)	87.4 (20.2)	90.2 (15.8)
BMI, kg/m^2	33.5 (6.8)	34.4 (7.7)	34.0 (7.1)	34.2 (6.6)	33.4 (6.9)	31.7 (4.5)	32.4 (5.9)	30.9 (5.1)	32.1 (5.4)
Race, n (%)									
Asian	191 (15.9)	44 (19.8)	45 (18.9)	34 (13.8)	52 (22.4)	6 (7.6)	3 (4.9)	4 (7.5)	3 (4.5)
Black/African American	70 (5.8)	13 (5.9)	13 (5.5)	14 (5.7)	16 (6.9)	4 (5.1)	4 (6.6)	4 (7.5)	2 (3.0)
White	928 (77.4)	164 (73.9)	178 (74.8)	198 (80.2)	158 (68.1)	69 (87.3)	54 (88.5)	45 (84.9)	62 (92.5)
Other	10 (0.8)	1 (0.5)	2 (0.8)	1 (0.4)	6 (2.6)	0	0	0	0
Ethnic group, n (%)									
Hispanic/Latino	138 (11.5)	23 (10.4)	30 (12.6)	30 (12.1)	38 (16.4)	6 (7.6)	1 (1.6)	5 (9.4)	5 (7.5)
Non-Hispanic/Latino	1,061 (88.5)	199 (89.6)	208 (87.4)	217 (87.9)	194 (83.6)	73 (92.4)	60 (98.4)	48 (90.6)	62 (92.5)

'On-treatment without rescue medication' data. Subgroup data are presented as mean (standard deviation) unless otherwise indicated. BMI: body mass index; Dula: dulaglutide; HbA_{1c}: glycated haemoglobin; n: number of subjects randomised and exposed to at least one dose of trial product as randomised (full analysis set); Sema: semaglutide.

Glycaemic control and body weight changes

Missing observations in the efficacy analyses were mainly due to subjects who discontinued treatment or received rescue medication. At week 40, between 81% and 86% of subjects were on treatment without initiation of rescue medication in the four treatment arms (**Supplementary Figure 1**).

Overall, the mean changes from baseline in HbA_{1c} and BW (**Supplementary Figure 2**) and the proportions of subjects achieving HbA_{1c} targets of <7% (53 mmol/mol) and ≤ 6.5% (48 mmol/mol) and weight-loss responses of ≥5% and ≥10% (**Figures 1 and 2**) were of greater magnitude with semaglutide versus dulaglutide treatment. This observation was confirmed by the ETDs for change from baseline (**Figure 3**) and the ORs for proportions of subjects (**Supplementary Figures 3 and 4**) which significantly favoured semaglutide in the majority of both the low-dose and high-dose comparisons within each subgroup category.

For the individual analyses by subgroup, the findings were as follows:

Age at baseline (<65 years, ≥65 years): the proportion of elderly versus non-elderly subjects achieving glycaemic targets and weight-loss response of ≥5% was consistently numerically higher with both semaglutide and dulaglutide (**Figure 1A and B, and 2A**), despite elderly subjects having a lower baseline HbA_{1c} and BMI than non-elderly subjects (**Table 1**). Proportions of subjects achieving ≥10% weight loss were comparable between the two age subgroups for both treatment arms (**Figure 2B**). Absolute changes in HbA_{1c} and BW from baseline at week 40 by age are shown in **Supplementary Figure 2A and B**.

Sex (male, female): reductions in HbA_{1c} and BW were generally numerically greater in female than in male subjects (**Supplementary Figure 2C and D**), as was baseline BMI (**Supplementary Table 2**). This was reflected in the correspondingly greater proportions of female versus male subjects achieving the glycaemic targets and weight-loss responses (**Figure 1C and D, and 2C and D**).

Diabetes duration at baseline (≤5 years, >5–10 years, >10 years): comparatively smaller numeric reductions in HbA_{1c} and BW were observed with semaglutide 1.0 mg in subjects with diabetes duration of >10 years versus ≤10 years, with no apparent differences observed in the other treatment arms (**Supplementary Figure 2E and F**). A similar pattern was observed for the proportions of subjects achieving glycaemic targets and weight-loss responses in the semaglutide 1.0 mg treatment group (**Figure 1E and F, and 2E and F**).

Baseline HbA_{1c} (≤7.5%, >7.5-8.5%, >8.5% [≤58, >58-69, >69 mmol/mol]): with semaglutide 0.5 mg, and to a greater degree with semaglutide 1.0 mg, the magnitude of the mean reduction in HbA_{1c} from baseline increased numerically with increasing baseline HbA_{1c}; the converse was apparent for BW, whereby the amount of weight lost was less with increasing baseline HbA_{1c} (**Supplementary Figure 2G and H**). A similar though less apparent pattern was observed with dulaglutide (**Supplementary Figure 2G and H**), and this was reflected in the proportions of subjects achieving glycaemic targets (**Figure 1G and H**). Across baseline HbA_{1c} subgroups, the greatest proportion of subjects achieving ≥5% weight loss was observed in those subjects receiving semaglutide 1.0 mg, particularly in the HbA_{1c} subgroup categories of ≤7.5% (58 mmol/mol) and >7.5-8.5% (58-69 mmol/mol) (**Figure 2G**). There were no other apparent differences across the subgroup categories regarding the proportions of subjects achieving weight-loss responses (**Figure 2G and H**).

Baseline BMI (<30 kg/m^2, 30–<35 kg/m^2, ≥35 kg/m^2): There were no apparent trends in glycaemic outcomes across the BMI categories for either dose comparison (**Figure 1I and J; Supplementary Figure 2I**). Mean reductions in BW for both semaglutide and dulaglutide increased numerically with increasing baseline BMI, with the greatest reductions in the ≥35 kg/m^2 BMI subgroup category for all treatment arms (**Supplementary Figure 2J**). There were no apparent trends in other BW outcomes across the BMI categories for either dose comparison (**Figure 2I and J; Supplementary Figure 2J**), or when BW reduction was expressed as percentage

change (**Supplementary Figure 5**). Changes in the <25 kg/m^2 BMI subgroup were largely consistent with those observed in the broader population (**Supplementary Figures 6 and 7**).

Treatment–subgroup interaction effects

For each of the subgroups, analysis of the ETDs for the change from baseline in HbA_{1c} in the age, sex, diabetes duration, baseline HbA_{1c} and baseline BMI subgroups, the p-values for the low-dose and high-dose comparisons were nonsignificant, except in the analysis of the HbA_{1c} subgroups within the low-dose comparison ($p<0.05$ for the treatment–subgroup interaction effect) (**Figure 3A and B**). The change from baseline in BW in the age, sex, diabetes duration, baseline HbA_{1c} and baseline BMI subgroups was similar, with nonsignificant treatment–subgroup interactions for both dose comparisons (**Figure 3C**). Similarly, treatment–subgroup interactions were nonsignificant for the analysis of the ORs for the proportions of subjects achieving glycaemic targets and weight-loss responses (**Supplementary Figures 3 and 4**).

Safety outcomes

Overall, AEs were reported in more than half of subjects irrespective of the subgroup category (ranging from 55.3% [dulaglutide 0.75 mg; diabetes duration >5–10 years] to 80.6% [dulaglutide 1.5 mg; elderly]) and were generally more common with semaglutide 0.5 mg than with dulaglutide 0.75 mg, and less common with semaglutide 1.0 mg than with dulaglutide 1.5 mg. Premature treatment discontinuations due to AEs were higher with semaglutide than with dulaglutide, and were primarily due to GI AEs (**Table 2**; **Supplementary Tables 7–10**).

Table 2. Adverse events by age

n (%)	All subjects	<65 years				≥65 years			
		Sema 0.5 mg	Dula 0.75 mg	Sema 1.0 mg	Dula 1.5 mg	Sema 0.5 mg	Dula 0.75 mg	Sema 1.0 mg	Dula 1.5 mg
	1,199	222	238	247	232	79	61	53	67
AEs	818 (68.2)	152 (68.5)	150 (63.0)	166 (67.2)	167 (72.0)	52 (65.8)	36 (59.0)	41 (77.4)	54 (80.6)
Serious AEs	86 (7.2)	10 (4.5)	18 (7.6)	20 (8.1)	16 (6.9)	7 (8.9)	6 (9.8)	3 (5.7)	6 (9.0)
AEs leading to premature treatment discontinuation	87 (7.3)	17 (7.7)	12 (5.0)	19 (7.7)	16 (6.9)	7 (8.9)	2 (3.3)	10 (18.9)	4 (6.0)
Gastrointestinal AEs leading to premature treatment discontinuation	54 (4.5)	12 (5.4)	5 (2.1)	13 (5.2)	13 (5.6)	4 (5.1)	1 (1.6)	5 (9.4)	1 (1.5)
Gastrointestinal AEs	505 (42.1)	99 (44.6)	80 (33.6)	105 (42.5)	108 (46.6)	30 (38.0)	20 (32.8)	28 (52.8)	35 (52.2)
Vomiting	103 (8.6)	23 (10.4)	7 (2.9)	27 (10.9)	21 (9.1)	8 (10.1)	5 (8.2)	4 (7.5)	8 (11.9)
Nausea	230 (19.2)	49 (22.1)	33 (13.9)	52 (21.1)	43 (18.5)	19 (24.1)	6 (9.8)	11 (20.8)	17 (25.4)
Diarrhoea	160 (13.3)	32 (14.4)	21 (8.8)	32 (13.0)	42 (18.1)	11 (13.9)	2 (3.3)	9 (17.0)	11 (16.4)
Hypoglycaemia (severe/BG-confirmed)	15 (1.3)	2 (0.9)	1 (0.4)	4 (1.6)	5 (2.2)	0	2 (3.3)	1 (1.9)	0

Data are presented as number and proportion (%) of subjects with adverse events. Hypoglycaemia was defined as an episode that was severe (according to the American Diabetes Association classification) or BG-confirmed (plasma glucose value <56 mg/dL [3.1 mmol/L]) with symptoms consistent with hypoglycaemia. AE: adverse event; BG: blood glucose; Dula: dulaglutide; n: number of subjects randomised and exposed to at least one dose of trial product as treated (safety analysis set); Sema: semaglutide.

GI AEs were the most frequently reported events, with generally higher rates with semaglutide 0.5 mg versus dulaglutide 0.75 mg, and dulaglutide 1.5 mg versus semaglutide 1.0 mg, across the subgroups and subgroup categories (ranging from 27.7% [dulaglutide 0.75 mg; diabetes duration >5–10 years] to 59.5% [dulaglutide 1.5 mg; HbA_{1c} ≤7.5% [58 mmol/mol]), with nausea being the most common (ranging from 8.1% [dulaglutide 0.75 mg; male] to 29.5% [semaglutide 0.5 mg; female]) (**Table 2**; **Supplementary Tables 7–10**). Across the subgroup categories, more female than male subjects reported GI AEs overall, with GI AEs generally decreasing with increasing BMI in subjects treated with semaglutide (**Supplementary Tables 7 and 10**). The highest proportion of GI AEs were reported by subjects with BMI <25 kg/m^2 (**Supplementary Table 11**).

DISCUSSION

Given the heterogeneous profile of patients with T2D and the guidance for such differences to be considered when making treatment choices,(2,3) this *post hoc* analysis of SUSTAIN 7 data assessed the impact of individual clinical characteristics on the effect of semaglutide versus dulaglutide treatment. The analyses indicate that the effect of semaglutide versus dulaglutide was not influenced by age, sex, diabetes duration, HbA_{1c} or BMI at baseline, with the exception of the low-dose comparison for HbA_{1c} in the baseline HbA_{1c} subgroup, which showed increasing efficacy for semaglutide 0.5 mg versus dulaglutide 0.75 mg in subjects with increasing HbA_{1c} at baseline.

This *post hoc* analysis supports the finding from the overall SUSTAIN 7 trial that semaglutide was superior to dulaglutide in reducing HbA_{1c} and BW;(36) the same was observed across each of the subgroups and within the various subgroup categories presented here.

This *post hoc* analysis also supports findings from similar subgroup analyses of SUSTAIN trials. An analysis of SUSTAIN 1–5 data showed greater reductions in HbA_{1c} and BW with

semaglutide versus comparators, and comparable efficacy in elderly subjects (a population often presenting with comorbidities) and non-elderly subjects, without an increased risk of hypoglycaemia.(25) Similarly, analyses of pooled SUSTAIN data showed clinically relevant reductions in HbA_{1c} and BW with semaglutide, regardless of baseline BW, HbA_{1c}, diabetes duration, race and ethnicity.(23-26,28)

HbA_{1c} reductions were greater with increasing baseline HbA_{1c} for both semaglutide and dulaglutide in the present analyses, which has been observed with dulaglutide previously,(29,31-33) as well as with liraglutide,(39) lixisenatide (40) and other antihyperglycaemic agents. Furthermore, a converse relationship between weight loss and baseline HbA_{1c} levels was observed, whereby increasing baseline HbA_{1c} was associated with greater reductions in HbA_{1c} but a decreasing magnitude of weight loss. A similar pattern has been observed with liraglutide as an add-on to insulin treatment,(41) with exenatide alone (42) and with dulaglutide.(31,32) These findings have relevance for clinical practice, indicating that there may be an effect with GLP-1RAs (and potentially other antihyperglycaemic therapies) in predicting treatment responses based on HbA_{1c} levels.(41) Conversely, a recent analysis of the AWARD trials found a weak positive correlation between HbA_{1c} reduction and weight loss with dulaglutide.(43) Several mechanisms, also associated with other antihyperglycaemic agents, may contribute to these results.(44) Improved treatment-related glycaemic control is associated with decreased glycosuria,(41,44) normalised protein turnover and a decreased catabolic effect,(44) in addition to decreased energy expenditure and resting metabolic rate.(44) As GLP-1RAs exhibit a glucose-dependent mechanism of action, the greater post-treatment reductions in HbA_{1c} from a higher initial baseline HbA_{1c} may contribute to the retention of glucose calories and, thereby, moderation of the achievable weight loss. In these analyses, greater weight loss was observed with increasing baseline BMI for both semaglutide and dulaglutide, aligning with what has been previously reported for semaglutide (23) and dulaglutide.(35) While percentage weight loss was also greater with semaglutide versus dulaglutide, the percentage change in weight loss was generally

of a similar magnitude across BMI categories, indicating that the weight-loss pattern observed across the HbA_{1c} subgroup categories may be associated with subjects' baseline BMI. High BMI is associated with an insulin-resistant phenotype in some patients,(3) and less weight loss is observed in patients with diabetes who are insulin resistant than in those with insulin sensitivity.(45) However, clinically relevant reductions in BW were achieved for all BMI subgroup categories, and the magnitude of weight loss was comparatively greater for semaglutide than for dulaglutide. This is an important consideration for clinical practice, given the increasing interest in weight management as a key aspect of treatment for T2D.(1)

Analysis of the ETDs for change from baseline in HbA_{1c} and BW and ORs for the proportions of subjects achieving HbA_{1c} targets or weight-loss responses indicated a consistent effect of semaglutide versus dulaglutide across subgroup categories. These findings are aligned with previous analyses of subpopulations treated with GLP-1RAs, including semaglutide and dulaglutide, which also reported a nonsignificant impact of age, sex or diabetes duration on treatment effect,(23-27,29-35) although weight loss tended to be greater in women than in men with dulaglutide,(31) as was also observed in this analysis.

Consistent with the known class effect of GLP-1RAs,(46) both semaglutide and dulaglutide reported relatively high levels of GI AEs. The rate of GI AEs was higher with semaglutide versus dulaglutide in the low-dose comparison; in the high-dose comparison it was higher with dulaglutide versus semaglutide.(36) Premature treatment discontinuations due to AEs were higher with semaglutide than with dulaglutide, which may be due to the higher levels of moderate GI AEs observed in the overall SUSTAIN 7 trial.(36) The occurrence of some GIs AEs may be dose-dependent, and nausea (and also vomiting for semaglutide) is usually transient with both semaglutide (47) and dulaglutide;(14) furthermore, the dose-escalation regimen approved for semaglutide has been shown to mitigate these AEs.(47) In the subgroups in the present analyses, GI AEs were higher with dulaglutide 1.5 mg versus semaglutide 1.0 mg in elderly subjects with

longer diabetes duration, and lower in subjects with HbA_{1c} >8.5% (69 mmol/mol) and higher BMI. There were no other associations between subjects' baseline characteristics with the incidence of GI AEs. Subjects who experience GI AEs, specifically nausea and vomiting, have greater weight loss compared with those who do not.(23,48) While this hypothesised association might be considered an explanation for the observed greater weight loss with semaglutide versus dulaglutide in the low-dose comparison, a mediation analysis has previously shown that the direct effects of semaglutide on BW are the main contributors to weight loss with very little effect attributable to GI AEs.(48,49). Our analyses support this finding as, overall, there were no clear trends between the incidence of GI AEs and the greater efficacy of semaglutide in terms of HbA_{1c} reduction and weight loss versus dulaglutide.(31) With semaglutide, there was a trend towards decreasing GI AEs with increasing baseline BMI, which has also been previously reported for the SUSTAIN 1–5 (23) and the AWARD 1–6 (50) trials, and may be due to differences in exposure–response levels associated with BW as has been demonstrated with semaglutide.(51) Similarly, an analysis has shown that elderly patients with a lower BMI are more likely to experience side effects (including GI AEs) with dulaglutide than younger patients with a higher BMI.(50) However, it is noted that this was a *post hoc* analysis in Japanese patients, with low event rates for some GI AEs, and so the results may not be generalizable to a wider diabetes population. In either case, a dose-escalation regimen may be beneficial.

A strength of the present analysis is the inclusion of comparator data, which allows for a more robust analysis and direct comparison of the differences in efficacy and safety of semaglutide versus dulaglutide across the subgroups and subgroup categories, and also the use of multiple imputation that helps to conserve randomisation. However, the *post hoc* nature of this analysis means there are inherent limitations and, as such, the data should be interpreted with caution. Also, as the analysis is based on SUSTAIN 7 alone, it may only be representative of the trial-specific patient population. A further limitation is the relatively small number of subjects in each subgroup category, which means that the

findings should be interpreted with caution. Additionally, in the age subgroups, there was an imbalance in subject numbers (elderly versus non-elderly), with relatively few patients in the elderly subgroup (260; 22% of the analysis population). However, given the overall consistency of the age-subgroup analyses, as well as the general limitations of these *post hoc* analyses, the difference in subject numbers between the age subgroup categories seemed to have had little or no impact. Furthermore, elderly subjects in previous pooled analyses of the SUSTAIN 1–5 (26) and AWARD (30,32) trials have demonstrated similar efficacy and safety, supporting the results obtained here.

Understanding the impact of heterogeneity in patient characteristics on treatment effects is important for clinical practice. This analysis provides insight on the influence of five of the most common and relevant patient-level factors from a clinical perspective and highlights semaglutide as an effective choice across these patient subgroups that are commonly encountered in clinical practice.

CONCLUSIONS

Semaglutide was associated with superior efficacy to dulaglutide across various clinically relevant patient subgroups that are commonly encountered in clinical practice, with a safety profile similar to other GLP-1RAs and in line with previously published data for semaglutide. The treatment effect for semaglutide versus dulaglutide did not appear to be influenced by age, sex, diabetes duration, HbA_{1c} or BMI at baseline. Together with results from other studies and from experience in clinical practice, these findings support the efficacy of semaglutide across the continuum of care in a heterogeneous T2D population.

ACKNOWLEDGEMENTS

We thank all the trial subjects, investigators and trial-site staff members who were involved in the SUSTAIN trials; Charlotte Hindsberger and Thomas Hansen (both

Novo Nordisk) for review and suggestions for revising the manuscript; and Stacy Carl-McGrath (AXON Communications) for medical writing and editorial assistance. This study and the associated trials were supported by Novo Nordisk A/S, Denmark. The funding sources contributed to the design and conduct of the trials, the analysis and interpretation of the data and the preparation, review and approval of the manuscript.

COMPETING INTERESTS

The authors received no grants or funding for the writing of this article. In relation to the submitted work, RP reports grants from Novo Nordisk to his institution, AdventHealth, a nonprofit organisation, and VA also reports grants from Novo Nordisk to her institution.

Outside of this work, RP reports speaker and consulting fees from AstraZeneca; consulting fees from Boehringer Ingelheim; consulting fees from Eisai, Inc.; consulting fees from GlaxoSmithKline; consulting fees from Glytec, LLC; consulting fees from Janssen; grants from Lexicon Pharmaceuticals; grants and consulting fees from Ligand Pharmaceuticals, Inc;, grants and consulting fees from Lilly; grants and consulting fees from Merck; consulting fees from Mundipharma; grants, speaker fees and consulting fees from Novo Nordisk; consulting fees from Pfizer; grants and consulting fees from Sanofi; grants, speaker fees and consulting fees from Takeda; and personal consulting fees from Sanofi US Services, Inc. Except for consulting fees in February 2018 and June 2018 from Sanofi US Services, Inc., RP's services were paid for directly to AdventHealth. VA has received consulting fees (to her institution) from Adocia; grants (to her institution) and consulting fees (to her institution) from AstraZeneca/BMS; consulting fees from Becton-Dickinson; grants (to her institution) from Boehringer Ingelheim; grants (to her institution) from Calibra; consulting fees from Duke University; grants (to her institution) from Eisai; grants (to her institution) from Fractyl; grants (to her institution) from Janssen; grants (to her institution) and consulting fees from Novo Nordisk; grants (to her institution) and consulting fees from Sanofi; grants (to her institution) from Theracos; and consulting fees from Zafgen, all outside of the submitted work; and is the

spouse of an employee of Merck Research Laboratories. AMC is an employee of Novo Nordisk. In relation to the submitted work, IL reports grants to her institution from Novo Nordisk. Outside of the submitted work, IL has received consulting fees from AstraZeneca; consulting fees from Boehringer Ingelheim; grants from GI Dynamics; consulting fees from Intarcia; consulting fees from Janssen; consulting fees from Lilly; consulting fees from Mannkind; grants from Merck; grants from Mylan; grants from Novartis; grants and consulting fees from Novo Nordisk; grants from Pfizer; consulting fees from Sanofi; consultant fees from TARGETPharma; and consulting fees from Valeritas, all outside of the submitted work. JL reports being an investigator in clinical studies for Eli Lilly and Novo Nordisk outside of the submitted work. EY is an employee and minor shareholder of Novo Nordisk. AV has received lecture/other fees and non-financial (clinical research) support from AstraZeneca; non-financial (clinical research) support from Amgen; lecture/other fees from Boehringer Ingelheim; lecture/other fees and non-financial (clinical research) support from Eli Lilly; lecture/other fees from Merck Sharp & Dohme; lecture/other fees from Napp, lecture/other fees and non-financial (clinical research) support from Novo Nordisk; non-financial (clinical research) support from Novartis; and lecture/other fees and non-financial (clinical research) support from Sanofi, all outside of the submitted work.

FUNDING

This work was supported by Novo Nordisk A/S. Editorial support was provided by Stacy Carl-McGrath PhD (AXON Communications), funded by Novo Nordisk A/S.

DATA SHARING STATEMENT

Individual participant data will be shared in datasets in a deidentified format, including datasets from Novo Nordisk-sponsored clinical research completed after 2001 for product indications approved in both the European Union and USA. The study protocol and

redacted clinical study report will be available according to Novo Nordisk data sharing commitments. Data will be available permanently after research completion and approval of product and product use in the European Union and USA. Data will only be shared with *bona fide* researchers submitting a research proposal and requesting access to data, for use as approved by the independent review board and according to its charter. The access request proposal form and the access criteria can be found online. Data will be made available on a specialised Statistical Analysis System data platform.

AUTHOR CONTRIBUTIONS

RP: conduct of trial, data collection, data analysis, data interpretation, manuscript preparation, approval of submitted version; VA: conduct of trial, data collection, data interpretation, manuscript preparation, approval of submitted version; AMC: data interpretation, manuscript preparation, approval of submitted version; IL: conduct of trial, data collection, data interpretation, manuscript preparation, approval of submitted version; JL: conduct of the trial, data collection, data interpretation, manuscript preparation, approval of submitted version; EY: data interpretation, manuscript preparation, approval of submitted version; AV: data interpretation, manuscript preparation, approval of submitted version.

REFERENCES

1. American Diabetes Association. Standards of Medical Care in Diabetes–2019. Diabetes Care. 2019;42(Suppl 1).
2. Cosentino F, Grant PJ, Aboyans V, et al. 2019 ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD. *Eur Heart J* 2019; doi: 10.1093/eurheartj/ehz486. [Epub ahead of print].
3. Ahlqvist E, Storm P, Käräjämäki A, et al. Novel subgroups of adult-onset diabetes and their association with outcomes: a data-driven cluster analysis of six variables. Lancet *Diabetes Endocrinol* 2018;6(5):361–9.
4. Pearson ER. Type 2 diabetes: a multifaceted disease. *Diabetologia* 2019;62(7):1107–12.
5. Dennis JM, Shields BM, Henley WE, et al. Disease progression and treatment response in data-driven subgroups of type 2 diabetes compared with models based on simple clinical features: an analysis using clinical trial data. *Lancet Diabetes Endocrinol* 2019;7(6):442–51.
6. Rodbard HW, Lingvay I, Reed J, et al. Semaglutide added to basal insulin in type 2 diabetes (SUSTAIN 5): a randomized, controlled trial. *J Clin Endocrinol Metab* 2018;103(6):2291–301.
7. Sorli C, Harashima SI, Tsoukas GM, et al. Efficacy and safety of once-weekly semaglutide monotherapy versus placebo in patients with type 2 diabetes (SUSTAIN 1): a double-blind, randomised, placebo-controlled, parallel-group, multinational, multicentre phase 3a trial. *Lancet Diabetes Endocrinol* 2017;5(4):251–60.
8. Ahmann AJ, Capehorn M, Charpentier G, et al. Efficacy and safety of once-weekly semaglutide versus exenatide ER in subjects with type 2 diabetes (SUSTAIN 3): a 56-week, open-label, randomized clinical trial. *Diabetes Care* 2018;41(2):258–66.
9. Ahrén B, Masmiquel L, Kumar H, et al. Efficacy and safety of once-weekly semaglutide versus once-daily sitagliptin as an add-on to metformin, thiazolidinediones, or both, in patients with type 2 diabetes (SUSTAIN 2): a 56-week, double-blind, phase 3a, randomised trial. *Lancet Diabetes Endocrinol* 2017;5(5):341–54.
10. Aroda VR, Bain SC, Cariou B, et al. Efficacy and safety of once-weekly semaglutide versus once-daily insulin glargine as add-on to metformin (with or without sulfonylureas) in insulin-naive patients with type 2 diabetes (SUSTAIN 4): a

randomised, open-label, parallel-group, multicentre, multinational, phase 3a trial. *Lancet Diabetes Endocrinol* 2017;5(5):355–66.

11. Dungan KM, Weitgasser R, Perez Manghi F, et al. A 24-week study to evaluate the efficacy and safety of once-weekly dulaglutide added on to glimepiride in type 2 diabetes (AWARD-8). *Diabetes Obes Metab* 2016;18(5):475–82.
12. Ludvik B, Frías JP, Tinahones FJ, et al. Dulaglutide as add-on therapy to SGLT2 inhibitors in patients with inadequately controlled type 2 diabetes (AWARD-10): a 24-week, randomised, double-blind, placebo-controlled trial. *Lancet Diabetes Endocrinol* 2018;6(5):370–81.
13. Tuttle KR, Lakshmanan MC, Rayner B, et al. Dulaglutide versus insulin glargine in patients with type 2 diabetes and moderate-to-severe chronic kidney disease (AWARD-7): a multicentre, open-label, randomised trial. *Lancet Diabetes Endocrinol* 2018;6(8):605–17.
14. Wysham C, Blevins T, Arakaki R, et al. Efficacy and safety of dulaglutide added onto pioglitazone and metformin versus exenatide in type 2 diabetes in a randomized controlled trial (AWARD-1). *Diabetes Care* 2014;37(8):2159–67.
15. Umpierrez G, Tofé Povedano S, Pérez Manghi F, et al. Efficacy and safety of dulaglutide monotherapy versus metformin in type 2 diabetes in a randomized controlled trial (AWARD-3). *Diabetes Care* 2014;37(8):2168–76.
16. Nauck M, Weinstock RS, Umpierrez GE, et al. Efficacy and safety of dulaglutide versus sitagliptin after 52 weeks in type 2 diabetes in a randomized controlled trial (AWARD-5). *Diabetes Care* 2014;37(8):2149–58.
17. Giorgino F, Benroubi M, Sun JH, et al. Efficacy and safety of once-weekly dulaglutide versus insulin glargine in patients with type 2 diabetes on metformin and glimepiride (AWARD-2). *Diabetes Care* 2015;38(12):2241–9.
18. Blonde L, Jendle J, Gross J, et al. Once-weekly dulaglutide versus bedtime insulin glargine, both in combination with prandial insulin lispro, in patients with type 2 diabetes (AWARD-4): a randomised, open-label, phase 3, non-inferiority study. *Lancet* 2015;385(9982):2057–66.
19. Dungan KM, Povedano ST, Forst T, et al. Once-weekly dulaglutide versus once-daily liraglutide in metformin-treated patients with type 2 diabetes (AWARD-6): a randomised, open-label, phase 3, non-inferiority trial. *Lancet* 2014;384(9951):1349–57.
20. Pozzilli P, Norwood P, Jódar E, et al. Placebo-controlled, randomized trial of the addition of once-weekly glucagon-like peptide-1 receptor agonist dulaglutide to

titrated daily insulin glargine in patients with type 2 diabetes (AWARD-9). *Diabetes Obes Metab* 2017;19(7):1024–31.

21. Marso SP, Bain SC, Consoli A, et al. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. *N Engl J Med* 2016;375(19):1834–44.
22. Gerstein HC, Colhoun HM, Dagenais GR, et al. Dulaglutide and cardiovascular outcomes in type 2 diabetes (REWIND): a double-blind, randomised placebo-controlled trial. *Lancet* 2019;394(10193):121–30.
23. Ahrén B, Atkin SL, Charpentier G, et al. Semaglutide induces weight loss in subjects with type 2 diabetes regardless of baseline BMI or gastrointestinal adverse events in the SUSTAIN 1 to 5 trials. *Diabetes Obes Metab* 2018;20(9):2210–9.
24. Bain SC, Araki E, Desouza C, et al. Semaglutide reduces HbA_{1c} across baseline HbA_{1c} subgroups in the SUSTAIN 1–5 clinical trials. 77th Scientific Sessions of the American Diabetes Association, San Diego, CA, USA, June 9–13, 2017 (Poster 1123P).
25. Warren M, Chaykin L, Trachtenbarg D, et al. Semaglutide as a therapeutic option for elderly patients with type 2 diabetes: pooled analysis of the SUSTAIN 1-5 trials. *Diabetes Obes Metab* 2018;20(9):2291–7.
26. Rosenstock J, Chaykin L, Lüdemann J, et al. Consistent HbA_{1c} and body weight reduction with semaglutide independent of diabetes duration: SUSTAIN 1–5 and 7 patient-level meta-analysis. 78th Scientific Sessions of the American Diabetes Association, Orlando, FL, USA, 22–26 June, 2018 (Poster 1081-P).
27. Hramiak I, Desouza C, Seufert J, et al. Semaglutide consistently reduces cardiovascular events in both male and female subjects with type 2 diabetes. 78th Scientific Sessions of the American Diabetes Association, Orlando, FL, USA, 22–26 June, 2018 (Poster 1085-P).
28. Desouza C, Garg SK, Cariou B, et al. Efficacy and safety of semaglutide in subjects with type 2 diabetes across race and ethnicity subgroups: a *post hoc* analysis of the SUSTAIN trials. 27th Annual Scientific & Clinical Congress of the American Association of Clinical Endocrinologists, Boston, MA, USA, 16–20 May, 2018 (Poster 298).
29. Wysham C, Guerci B, D'Alessio D, et al. Baseline factors associated with glycaemic response to treatment with once-weekly dulaglutide in patients with type 2 diabetes. *Diabetes Obes Metab* 2016;18(11):1138–42.

30. Boustani MA, Pittman I 4th, Yu M, et al. Similar efficacy and safety of once-weekly dulaglutide in patients with type 2 diabetes aged ≥65 and <65 years. *Diabetes Obes Metab* 2016;18(8):820–8.

31. Gallwitz B, Dagogo-Jack S, et al. Effect of once-weekly dulaglutide on glycated haemoglobin (HbA1c) and fasting blood glucose in patient subpopulations by gender, duration of diabetes and baseline HbA1c. *Diabetes Obes Metab* 2018;20(2):409–18.

32. Pantalone KM, Patel H, Yu M, et al. Dulaglutide 1.5 mg as an add-on option for patients uncontrolled on insulin: subgroup analysis by age, duration of diabetes and baseline glycated haemoglobin concentration. *Diabetes Obes Metab* 2018;20(6):1461–9.

33. Gentilella R, Romera I, Nicolay C, et al. Change in HbA_{1c} across the baseline HbA_{1c} range in type 2 diabetes patients receiving once-weekly dulaglutide versus other incretin agents. *Diabetes Ther* 2019;10(3):1113–25.

34. Mathieu C, Del Prato S, Botros FT, et al. Effect of once weekly dulaglutide by baseline beta-cell function in people with type 2 diabetes in the AWARD programme. *Diabetes Obes Metab* 2018;20(8):2023–8.

35. Fuechtenbusch M, Aberle J, Heitmann E, et al. Weight loss in patients with type 2 diabetes receiving once-weekly dulaglutide plus insulin lispro or insulin glargine plus insulin lispro: a post-hoc analysis of the AWARD-4 study across baseline body mass index subgroups. *Diabetes Obes Metab* 2019;21(6):1340–8.

36. Pratley RE, Aroda VR, Lingvay I, et al. Semaglutide versus dulaglutide once weekly in patients with type 2 diabetes (SUSTAIN 7): a randomised, open-label, phase 3b trial. *Lancet Diabetes Endocrinol* 2018;6(4):275–86.

37. Jendle J, Grunberger G, Blevins T, et al. Efficacy and safety of dulaglutide in the treatment of type 2 diabetes: a comprehensive review of the dulaglutide clinical data focusing on the AWARD phase 3 clinical trial program. *Diabetes Metab Res Rev* 2016;32(8):776–90.

38. Little RJA, Rubin DB. Statistical analysis with missing data. New York: John Wiley & Sons, 1987.

39. Henry RR, Buse JB, Sesti G, et al. Efficacy of antihyperglycemic therapies and the influence of baseline hemoglobin A(1C): a meta-analysis of the liraglutide development program. *Endocr Pract* 2011;17(6):906–13.

40. Blonde L, Chava P, Dex T, et al. Predictors of outcomes in patients with type 2 diabetes in the lixisenatide GetGoal clinical trials. *Diabetes Obes Metab* 2017;19(2):275–83.

41. Dahlqvist S, Ahlén E, Filipsson K, et al. Variables associated with HbA1c and weight reductions when adding liraglutide to multiple daily insulin injections in persons with type 2 diabetes (MDI Liraglutide trial 3). *BMJ Open Diabetes Res Care* 2018;6(1):e000464.

42. Frías JP, Hardy E, Ahmed A, et al. Effects of exenatide once weekly plus dapagliflozin, exenatide once weekly alone, or dapagliflozin alone added to metformin monotherapy in subgroups of patients with type 2 diabetes in the DURATION-8 randomized controlled trial. *Diabetes Obes Metab* 2018;20(6):1520–5.

43. Umpierrez GE, Pantalone KM, Kwan AY, et al. Relationship between weight change and glycaemic control in patients with type 2 diabetes receiving once-weekly dulaglutide treatment. *Diabetes Obes Metab* 2016;18(6):615–22.

44. Pi-Sunyer FX. Weight loss in type 2 diabetic patients. *Diabetes Care* 2005;28(6):1526–27.

45. Fonseca VA, Capehorn MS, Garg SK, et al. Reductions in insulin resistance are mediated primarily via weight loss in subjects with type 2 diabetes on semaglutide. *J Clin Endocrinol Metab* 2019. doi: 10.1210/jc.2018-02685. [Epub ahead of print].

46. Bettge K, Kahle M, Abd El Aziz MS, et al. Occurrence of nausea, vomiting and diarrhoea reported as adverse events in clinical trials studying glucagon-like peptide-1 receptor agonists: a systematic analysis of published clinical trials. *Diabetes Obes Metab* 2017;19(3):336–47.

47. Nauck MA, Petrie JR, Sesti G, et al. A phase 2, randomized, dose-finding study of the novel once-weekly human GLP-1 analog, semaglutide, compared with placebo and open-label liraglutide in patients with type 2 diabetes. *Diabetes Care* 2016;39(2):231–41.

48. Atkin S, Woo V, de la Rosa R, et al. The impact of gastrointestinal adverse events on weight loss with semaglutide in subjects with type 2 diabetes. 53rd Annual Meeting of the European Association for the Study of Diabetes (EASD), Lisbon, Portugal, 11–15 September 2017 (Poster 821).

49. Ahrén B, Atkin SL, Charpentier G, et al. Semaglutide induces weight loss in subjects with type 2 diabetes regardless of baseline BMI or gastrointestinal adverse events in the SUSTAIN 1 to 5 trials. *Diabetes Obes Metab* 2018;20(9):2210–9.

50. Hamano K, Nishiyama H, Matsui A, et al. Efficacy and safety analyses across 4 subgroups combining low and high age and body mass index groups in Japanese phase 3 studies of dulaglutide 0.75 mg after 26 weeks of treatment. *Endocr J* 2017;64(4):449-45.

685 51. Petri KCC, Ingwersen SH, Flint A, et al. Exposure-response analysis for evaluation of
686 semaglutide dose levels in type 2 diabetes. *Diabetes Obes Metab* 2018;20(9):
687 2238–45.

Figure Legends

Figure 1. Proportion of subjects achieving HbA_{1c} < 7.0% (53 mmol/mol; A, C, E, G and I) and HbA_{1c} ≤6.5% (48 mmol/mol; B, D, F, H and J) at 40 weeks. *p<0.05, **p<0.001, ***p<0.0001. Values are estimated proportions from ANCOVAs with multiple imputations using 'on-treatment without rescue medication' data from all randomised subjects exposed to at least one dose of trial product as randomised (full analysis set) obtained while on treatment and prior to onset of rescue medication. P-values are based on ETDs; statistical analyses were not performed for change from baseline. ANCOVA: analysis of covariance; BMI: body mass index; BW: body weight; ETD: estimated treatment differences; HbA_{1c}: glycated haemoglobin.

Figure 2. Proportion of subjects achieving weight loss ≥5% (A, C, E, G and I) and weight loss ≥10% (B, D, F, H and J) at 40 weeks

*p<0.05, **p<0.001, ***p<0.0001. Values are estimated proportions from ANCOVAs with multiple imputations using 'on-treatment without rescue medication' data from all randomised subjects exposed to at least one dose of trial product as randomised (full analysis set) obtained while on treatment and prior to onset of rescue medication. P-values are based on ETDs; statistical analyses were not performed for change from baseline. ANCOVA: analysis of covariance; BMI: body mass index; BW: body weight; ETD: estimated treatment difference.

Figure 3. Estimated treatment differences for change from baseline in HbA_{1c} shown as %-points (A), HbA_{1c} shown as mmol/mol (B) and body weight (C) at week 40 by age, sex, diabetes duration, HbA_{1c} and BMI at baseline. *p<0.05, **p<0.001, ***p<0.0001; †p-values represent the test for treatment by subgroup interaction. Values are ETDs [95% CIs] for semaglutide versus dulaglutide (low-dose comparison [semaglutide 0.5 mg versus dulaglutide 0.75 mg] and high-dose comparison

[semaglutide 1.0 mg versus dulaglutide 1.5 mg]) from ANCOVAs with multiple imputations using data from all randomised subjects exposed to at least one dose of trial product and did not discontinue treatment or receive any non-investigational antihyperglycaemic treatment (full analysis set) obtained while on treatment and prior to onset of rescue medication. ANCOVA controlled for baseline HbA_{1c} (A) or body weight (B) and interaction between randomised treatment and subgroup. ANCOVA: analysis of covariance; BMI: body mass index; CI: confidence interval; ETD: estimated treatment difference; HbA_{1c}: glycated haemoglobin.

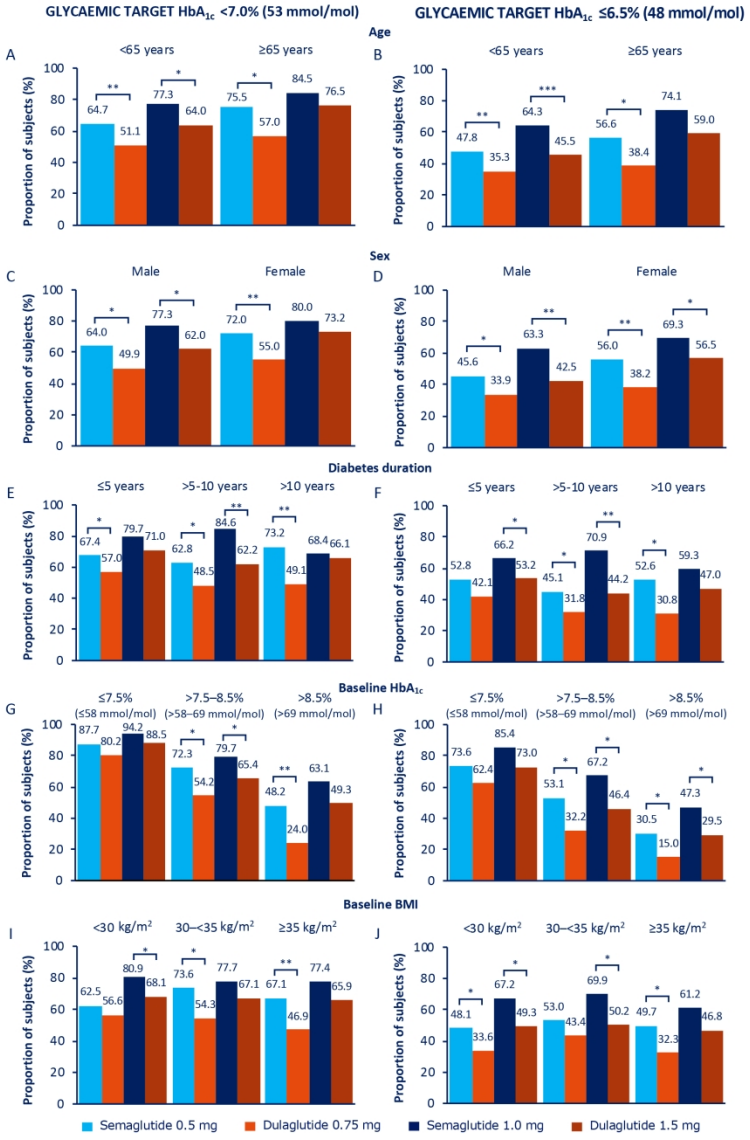


Figure 1. Proportion of subjects achieving HbA_{1c} < 7.0% (53 mmol/mol; A, C, E, G and I) and HbA_{1c} ≤6.5% (48 mmol/mol; B, D, F, H and J) at 40 weeks. *p<0.05, **p<0.001, ***p<0.0001. Values are estimated proportions from ANCOVAs with multiple imputations using 'on-treatment without rescue medication' data from all randomised subjects exposed to at least one dose of trial product as randomised (full analysis set) obtained while on treatment and prior to onset of rescue medication. P-values are based on ETDs; statistical analyses were not performed for change from baseline. ANCOVA: analysis of covariance; BMI: body mass index; BW: body weight; ETD: estimated treatment differences; HbA_{1c}: glycated haemoglobin.

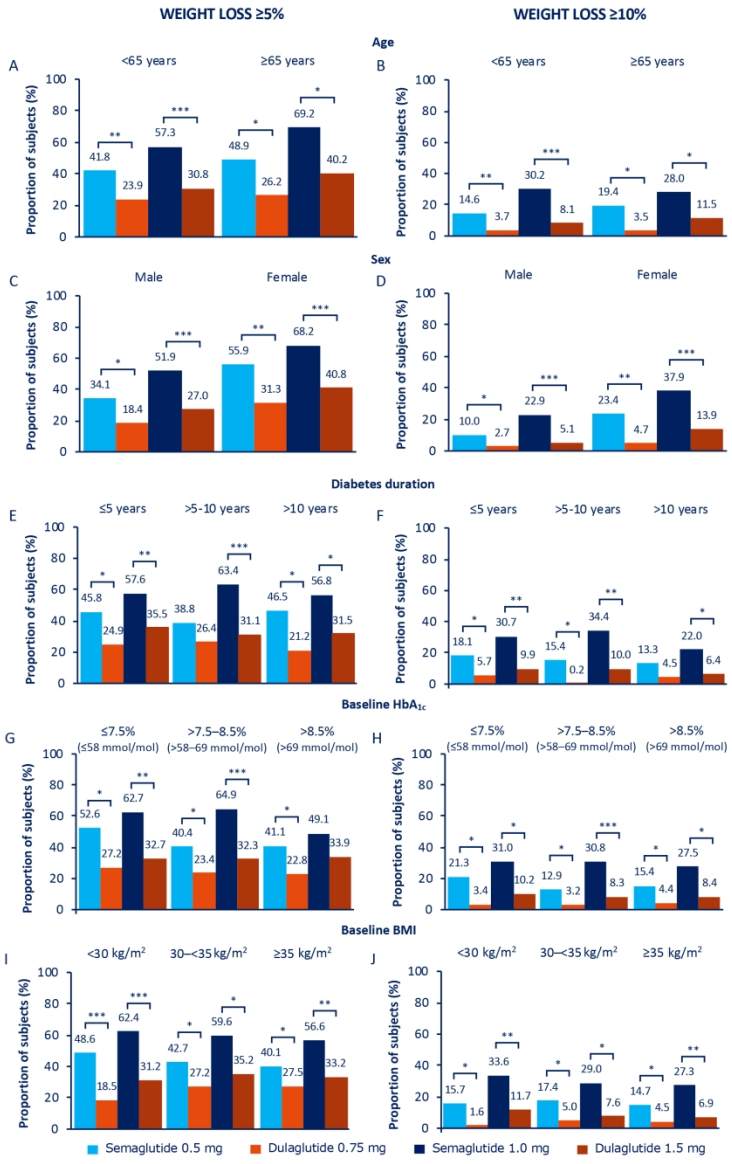


Figure 2. Proportion of subjects achieving weight loss ≥5% (A, C, E, G and I) and weight loss ≥10% (B, D, F, H and J) at 40 weeks. *p<0.05, **p<0.001, ***p<0.0001. Values are estimated proportions from ANCOVAs with multiple imputations using 'on-treatment without rescue medication' data from all randomised subjects exposed to at least one dose of trial product as randomised (full analysis set) obtained while on treatment and prior to onset of rescue medication. P-values are based on ETDs; statistical analyses were not performed for change from baseline. ANCOVA: analysis of covariance; BMI: body mass index; BW: body weight; ETD: estimated treatment difference.

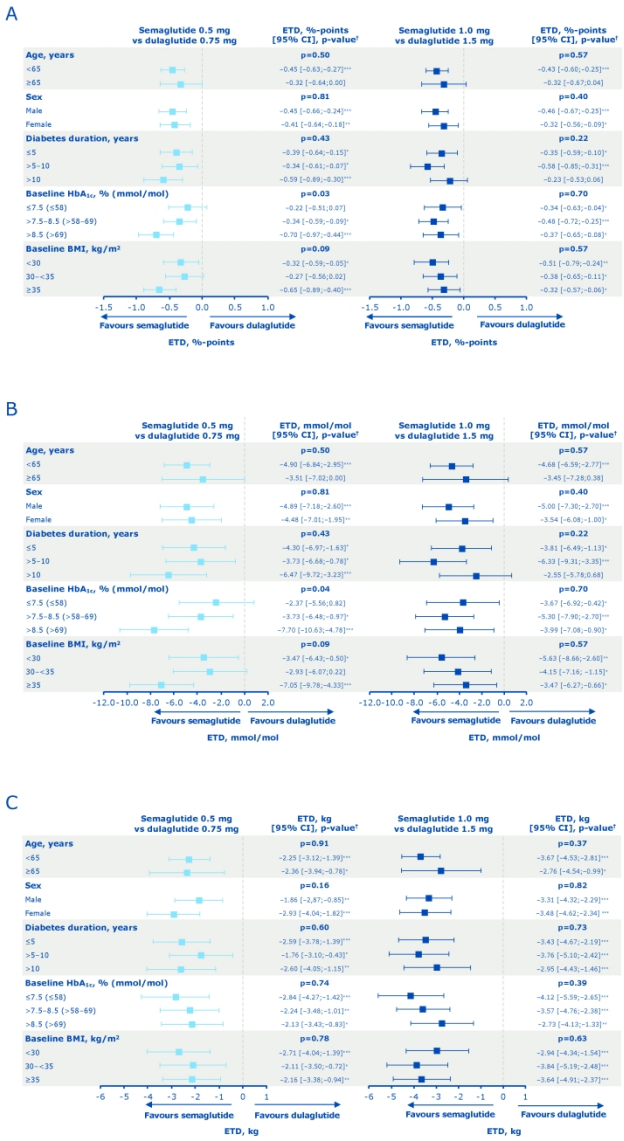


Figure 3. Estimated treatment differences for change from baseline in HbA_{1c} shown as %-points (A), HbA_{1c} shown as mmol/mol (B) and body weight (C) at week 40 by age, sex, diabetes duration, HbA_{1c} and BMI at baseline. *p<0.05, **p<0.001, ***p<0.0001; †p values represent the test for treatment by subgroup interaction. Values are ETDs [95% CIs] for semaglutide versus dulaglutide (low-dose comparison [semaglutide 0.5 mg versus dulaglutide 0.75 mg] and high-dose comparison [semaglutide 1.0 mg versus dulaglutide 1.5 mg]) from ANCOVAs with multiple imputations using data from all randomised subjects exposed to at least one dose of trial product and did not discontinue treatment or receive any non-investigational antihyperglycaemic treatment (full analysis set) obtained while on treatment and prior to onset of rescue medication. ANCOVA controlled for baseline HbA_{1c} (A) or body weight (B) and interaction between randomised treatment and subgroup. ANCOVA: analysis of covariance; BMI: body mass index; CI: confidence interval; ETD: estimated treatment difference; HbA_{1c}: glycated haemoglobin.

Supplementary Materials

Full title:

Impact of patient characteristics on efficacy and safety of once-weekly semaglutide versus dulaglutide: SUSTAIN 7 *post hoc* analyses

Authors:

Pratley Richard E[1], Aroda Vanita R[2], Catarig Andrei M[3], Lingvay Ildiko[4], Lüdemann Jörg[5], Yildirim Emre[3], Viljoen Adie[6]

Author affiliations:

[1]AdventHealth Translational Research Institute for Metabolism and Diabetes, Orlando, FL, USA; [2]Brigham and Women's Hospital, Boston, MA, USA; [3]Novo Nordisk A/S, Søborg, Denmark; [4]University of Texas Southwestern Medical Center, Dallas, TX, USA; [5]diabetes-falkensee, Diabetes Centre and Centre for Clinical Studies, Falkensee, Germany; [6]Borthwick Diabetes Research Centre, Lister Hospital, Stevenage, UK

Contact details for corresponding author:

Dr Richard E. Pratley

AdventHealth Translational Research Institute for Metabolism and Diabetes

301 E. Princeton Street, Orlando, FL 32804, USA

Phone: +1-407-303-2519

E-mail: Richard.Pratley.MD@AdventHealth.com

Supplementary Section I: Independent Ethics Committees

Supplementary Table 1. Independent ethics committees for SUSTAIN 7

Country	Independent ethics committees
Bulgaria	• Ethics Committee for Multicenter Clinical Trials
Croatia	• Agencija za lijekove i medicinske proizvode
Finland	• Ethics Committee of the Hospital District of Southwest Finland
Germany	• Ethikkommission der Ärztekammer des Saarlandes
Greece	• National Ethics Committee • Private Clinic, Iatriko Palaiou Falirou • General Hospital of Thessaloniki "G. Papanikolaou" Exohi • General University Hospital of Chalkida • General Hospital of Piraeus "Tzaneio" 1 • "THERMI" Clinic 14th km of National Road Thessaloniki • General University Hospital of Thessaloniki "Ahepa" 1 • University Hospital of Ioannina • Private Clinic, Iatriko Psychikou 1
Hong Kong	• Joint Chinese University of Hong Kong – New Territories East Cluster Clinical Research Ethics Committee
India	• Park Clinic Ethics Committee • Institutional Ethics Committee, Amrita Institute of Medical and Research Centre • Institutional Ethics Committee, Inamdar Multispeciality Hospital • IPGME&R Research Oversight Committee, Institute of Post-graduate Medical Education and Research • Institutional Ethics Committee, Deenanath Mangeshkar Hospital and Research Centre • Ethics Committee For Human Research, Lady Hardinge Medical College & Associated Hospitals • Institutional Human Ethics Committee, Office of the SOCOMER • Institutional Ethics Committee, Goa Medical College • Institutional Ethics Committee, Lokmanya Tilak Municipal Medical College • Ethics Committee, Apollo Hospital • Ethics Committee Silver, Christian Medical College • Ethics Committee, Endolife Speciality Hospitals Pvt. Ltd • Academic Research Projects, Medical College and BYL Nair Hospital • Institutional Ethics Committee, M/s. King George Hospital • Institutional Ethics Committee, Global Hospitals • Ethics Committee, Marwari Hospital & Research Center • Integrity Ethics Committee, Convenient Hospitals Ltd

	• Institutional Ethics Committee of Madras, Diabetes Research Foundation • The JMSHF and BMRC Institutional Ethics Committee, The Jivraj Mehta Hospital • Institutional Ethics Committee, Fortis Hospital • Institutional Ethics Committee, Maulana Azad Medical College • Drug Trial Ethics Committee, Dayanand Medical College and Hospital • Ethics Committee of Bangalore, Medical College & Research Institute • Institutional Ethics Committee, Osmania Medical College • Ethics Committee, Government Medical College • Institutional Ethics Committee, Postgraduate Institute of Medical Education & Research • Institute of Ethics Committee AIIMS
Ireland	• Clinical Research Ethics Committee of the Cork Teaching Hospitals • Mater Misericordiae Hospital • Galway University Hospital • Connolly Hospital • St Vincent's Healthcare Ethics and Medical Research Committee • The Palms Surgery
Latvia	• Ethics Committee for Clinical Research at Pauls Stradins Clinical University Hospital Development Society
Lithuania	• Lithuanian Bioethics Committee
Portugal	• Comissão de Ética para a Investigação Clínica
Romania	• National Bioethics Committee for Medicine and Medical Devices
Slovakia	• Eticka komisia, Sabinovska 16 • Eticka komisia, Nemocnica Svateho Michala, a.s. **(Central IEC)** • Eticka komisia, Trencianskeho samospravneho kraja • Eticka komisia, Nitrianskeho samospravneho kraja • Etická komisia, Presovskeho samospravneho kraja • Eticka komisia, Trnavskeho samospravneho kraja
Spain	• Comité Coordinador de Ética de la Investigación Biomédica de Andalucía • CEI Provincial de Málaga
UK	• NRES Committee East of England – Cambridge Central • Research and Development Department East and North Hertfordshire NHS Trust • RMG Office, NHS Cambridgeshire and Peterborough CCG • Clinical Research Network North Thames • East of England – Cambridge Central Research Ethics Committee • Room 4, 112, 1 West University of Bath

	• Research and Development Department Clinical Trial Facility, Moorgreen Hospital • R&D Department, University Hospital Southampton NHS Foundation Trust
USA	• Sterling Institutional Review Board • Western International Review Board • University of Texas Southwestern Medical Center Institutional Review Board • Schulman Associates IRB, Inc. • Florida Hospital Institutional Review Board

Supplementary Section II: Baseline Characteristics

Supplementary Table 2. Baseline characteristics by sex subgroups

		Male				Female			
	All subjects	Sema 0.5 mg	Dula 0.75 mg	Sema 1.0 mg	Dula 1.5 mg	Sema 0.5 mg	Dula 0.75 mg	Sema 1.0 mg	Dula 1.5 mg
n	**1,199**	**169**	**160**	**162**	**171**	**132**	**139**	**138**	**128**
Age, years	56 (10.6)	57.0 (10.9)	55.6 (10.1)	55.6 (10.3)	56.8 (10.5)	55.3 (10.9)	54.9 (10.7)	55.1 (11.0)	54.7 (10.7)
Sex, n (%)									
Male	662 (55.2)	169 (100)	160 (100)	162 (100)	171 (100)	-	-	-	-
Female	537 (44.8)	-	-	-	-	132 (100)	139 (100)	138 (100)	128 (100)
Diabetes duration, years	7.4 (5.7)	7.8 (5.8)	7.1 (5.7)	7.4 (5.5)	8.0 (5.6)	7.7 (6.1)	6.9 (5.2)	7.1 (5.9)	7.2 (5.7)
HbA_{1c}, %	8.2 (0.9)	8.4 (1.0)	8.2 (0.9)	8.2 (0.9)	8.2 (0.8)	8.3 (1.0)	8.1 (0.9)	8.2 (0.9)	8.2 (1.0)
HbA_{1c}, mmol/mol	66.4 (10.0)	67.8 (10.5)	66.2 (10.0)	66.0 (10.2)	65.8 (9.0)	67.1 (10.4)	66.4 (9.9)	65.2 (9.9)	66.6 (10.6)
Body weight, kg	95.2 (22.6)	102.3 (23.9)	100.6 (23.4)	100.8 (21.0)	96.9 (21.5)	88.9 (23.0)	89.9 (21.3)	89.3 (19.0)	88.8 (21.3)
BMI, kg/m^2	33.5 (6.8)	33.3 (6.8)	32.8 (6.6)	32.7 (6.2)	32.0 (5.8)	34.2 (7.5)	34.6 (7.2)	34.7 (6.7)	34.5 (7.2)
Race, n (%)									
Asian	191 (15.9)	24 (14.2)	31 (19.4)	25 (15.4)	32 (18.7)	26 (19.7)	17 (12.2)	13 (9.4)	23 (18.0)
Black/African American	70 (5.8)	5 (3.0)	4 (2.5)	7 (4.3)	6 (3.5)	12 (9.1)	13 (9.4)	11 (8.0)	12 (9.4)
White	928 (77.4)	139 (82.2)	124 (77.5)	130 (80.2)	128 (74.9)	94 (71.2)	108 (77.7)	113 (81.9)	92 (71.9)
Other	10 (0.8)	1 (0.6)	1 (0.6)	0	5 (2.9)	0	1 (0.7)	1 (0.7)	1 (0.8)
Ethnic group, n (%)									
Hispanic/Latino	138 (11.5)	18 (10.7)	15 (9.4)	14 (8.6)	24 (14.0)	11 (8.3)	16 (11.5)	21 (15.2)	19 (14.8)
Non-Hispanic/ Latino	1,061 (88.5)	151 (89.3)	145 (90.6)	148 (91.4)	147 (86.0)	121 (91.7)	123 (88.5)	117 (84.8)	109 (85.2)

'On-treatment without rescue medication' data. Subgroup data are presented as mean (standard deviation) unless otherwise indicated. BMI: body mass index; Dula: dulaglutide; HbA_{1c}: glycated haemoglobin; n: number of subjects randomised and exposed to at least one dose of trial product as randomised (full analysis set); Sema: semaglutide.

Supplementary Table 3. Baseline characteristics by diabetes duration subgroups

		≤5 years				>5–10 years				>10 years			
	All subjects	Sema 0.5 mg	Dula 0.75 mg	Sema 1.0 mg	Dula 1.5 mg	Sema 0.5 mg	Dula 0.75 mg	Sema 1.0 mg	Dula 1.5 mg	Sema 0.5 mg	Dula 0.75 mg	Sema 1.0 mg	Dula 1.5 mg
n	**1,199**	**113**	**128**	**122**	**114**	**101**	**94**	**103**	**92**	**87**	**77**	**75**	**93**
Age, years	56 (10.6)	52.3 (11.0)	51.7 (10.1)	51.1 (11.6)	51.8 (10.2)	55.5 (9.8)	57.0 (8.5)	56.8 (7.9)	57.0 (10.3)	62.3 (9.3)	58.9 (11.0)	60.4 (9.4)	59.9 (9.7)
Sex, n (%)													
Male	662 (55.2)	62 (54.9)	71 (55.5)	61 (50.0)	53 (46.5)	55 (54.5)	46 (48.9)	58 (56.3)	64 (69.6)	52 (59.8)	43 (55.8)	43 (57.3)	54 (58.1)
Female	537 (44.8)	51 (45.1)	57 (44.5)	61 (50.0)	61 (53.5)	46 (45.5)	48 (51.1)	45 (43.7)	28 (30.4)	35 (40.2)	34 (44.2)	32 (42.7)	39 (41.9)
Diabetes duration, years	7.4 (5.7)	2.6 (1.3)	2.5 (1.3)	2.5 (1.4)	2.6 (1.4)	7.0 (1.4)	7.1 (1.3)	7.3 (1.3)	7.0 (1.4)	15.3 (4.9)	14.5 (4.5)	14.9 (5.3)	14.5 (4.4)
HbA_{1c}, %	8.2 (0.9)	8.2 (1.0)	8.1 (0.9)	8.2 (0.9)	8.2 (0.9)	8.3 (1.0)	8.2 (0.9)	8.2 (1.0)	8.2 (0.8)	8.4 (0.9)	8.2 (0.9)	8.2 (0.9)	8.2 (0.9)
HbA_{1c}, mmol/mol	66.4 (10.0)	66.6 (10.8)	65.3 (10.2)	66.6 (9.6)	65.9 (10.1)	67.5 (10.4)	66.1 (9.8)	65.9 (10.5)	66.4 (9.0)	68.6 (10.1)	66.0 (9.8)	65.9 (10.3)	66.2 (10.0)
Body weight, kg	95.2 (22.6)	97.2 (27.6)	96.8 (24.0)	100.4 (23.6)	92.0 (22.9)	95.1 (21.8)	96.6 (23.7)	94.7 (18.1)	95.1 (23.3)	96.8 (23.0)	92.4 (20.3)	88.6 (17.7)	93.5 (18.8)
BMI, kg/m^2	33.5 (6.8)	34.0 (7.9)	34.3 (7.3)	35.1 (7.8)	33.0 (6.7)	33.3 (6.3)	33.9 (7.2)	33.3 (5.4)	33.2 (6.9)	33.7 (7.1)	32.3 (5.7)	31.6 (4.7)	33.1 (6.1)
Race, n (%)													
Asian	191 (15.9)	25 (22.1)	30 (23.4)	19 (15.6)	35 (30.7)	18 (17.8)	11 (11.7)	9 (8.7)	13 (14.1)	7 (8.0)	7 (9.1)	10 (13.3)	7 (7.5)
Black/African American	70 (5.8)	2 (1.8)	8 (6.3)	5 (4.1)	6 (5.3)	6 (5.9)	4 (4.3)	7 (6.8)	1 (1.1)	9 (10.3)	5 (6.5)	6 (8.0)	11 (11.8)
White	928 (77.4)	86 (76.1)	89 (69.5)	97 (79.5)	72 (63.2)	76 (75.2)	79 (84.0)	87 (84.5)	77 (83.7)	71 (81.6)	64 (83.1)	59 (78.7)	71 (76.3)
Other	10 (0.8)	0	1 (0.8)	1 (0.8)	1 (0.9)	1 (1.0)	0	0	1 (1.1)	0	1 (1.3)	0	4 (4.3)

Ethnic group, n (%)													
Hispanic/Latino	138 (11.5)	11 (9.7)	9 (7.0)	13 (10.7)	17 (14.9)	5 (5.0)	7 (7.4)	12 (11.7)	15 (16.3)	13 (14.9)	15 (19.5)	10 (13.3)	11 (11.8)
Non-Hispanic/Latino	1,061 (88.5)	102 (90.3)	119 (93.0)	109 (89.3)	97 (85.1)	96 (95.0)	87 (92.6)	91 (88.3)	77 (83.7)	74 (85.1)	62 (80.5)	65 (86.7)	82 (88.2)

'On-treatment without rescue medication' data. Subgroup data are presented as mean (standard deviation) unless otherwise indicated. BMI: body mass index; Dula: dulaglutide; HbA_{1c}: glycated haemoglobin; n: number of subjects randomised and exposed to at least one dose of trial product as randomised (full analysis set); Sema: semaglutide.

Supplementary Table 4. Baseline characteristics by baseline HbA_{1c} subgroups

		≤7.5% (≤58 mmol/mol)				>7.5–8.5% (>58–69 mmol/mol)				>8.5% (>69 mmol/mol)			
	All subjects	Sema 0.5 mg	Dula 0.75 mg	Sema 1.0 mg	Dula 1.5 mg	Sema 0.5 mg	Dula 0.75 mg	Sema 1.0 mg	Dula 1.5 mg	Sema 0.5 mg	Dula 0.75 mg	Sema 1.0 mg	Dula 1.5 mg
n	**1,199**	**74**	**94**	**83**	**84**	**120**	**105**	**124**	**120**	**107**	**100**	**93**	**95**
Age, years	56 (10.6)	57.5 (12.2)	57.0 (10.4)	57.7 (11.1)	58.1 (10.2)	57.3 (10.1)	53.3 (10.6)	55.6 (9.7)	55.4 (10.5)	54.3 (10.7)	53.5 (9.9)	53.1 (10.9)	54.5 (10.9)
Sex, n (%)													
Male	662 (55.2)	39 (52.7)	50 (53.2)	48 (57.8)	45 (53.6)	69 (57.5)	53 (50.5)	67 (54.0)	69 (57.5)	61 (57.0)	57 (57.0)	47 (50.5)	57 (60.0)
Female	537 (44.8)	35 (47.3)	44 (46.8)	35 (42.2)	39 (46.4)	51 (42.5)	52 (49.5)	57 (46.0)	51 (42.5)	46 (43.0)	43 (43.0)	46 (49.5)	38 (40.0)
Diabetes duration, years	7.4 (5.7)	6.7 (4.6)	7.0 (6.2)	8.0 (5.9)	8.0 (6.5)	7.8 (6.1)	6.9 (4.8)	6.3 (5.0)	7.4 (5.5)	8.3 (6.5)	7.1 (5.5)	7.9 (6.1)	7.6 (5.0)
HbA_{1c}, %	8.2 (0.9)	7.3 (0.2)	7.2 (0.2)	7.2 (0.2)	7.2 (0.2)	8.0 (0.3)	8.0 (0.3)	8.0 (0.3)	8.0 (0.3)	9.4 (0.6)	9.3 (0.5)	9.4 (0.6)	9.3 (0.5)
HbA_{1c}, mmol/mol	66.4 (10.0)	55.8 (2.4)	55.4 (2.3)	55.6 (2.3)	55.7 (2.3)	64.0 (3.1)	63.5 (2.9)	63.9 (3.0)	64.1 (3.1)	79.4 (6.5)	77.7 (5.8)	78.7 (6.6)	78.0 (5.7)
Body weight, kg	95.2 (22.6)	99.1 (24.1)	96.9 (21.9)	97.9 (24.3)	93.0 (21.5)	97.4 (22.9)	94.8 (23.0)	94.8 (18.9)	93.8 (21.5)	93.4 (26.1)	95.3 (24.2)	94.3 (20.3)	93.3 (22.7)
BMI, kg/m^2	33.5 (6.8)	34.2 (6.9)	34.0 (6.3)	34.6 (8.3)	33.4 (6.7)	34.1 (6.7)	33.4 (7.4)	33.1 (4.9)	33.1 (6.7)	32.8 (7.7)	33.5 (7.0)	33.4 (6.5)	32.8 (6.3)
Race, n (%)													
Asian	191 (15.9)	5 (6.8)	12 (12.8)	12 (14.5)	17 (20.2)	18 (15.0)	15 (14.3)	13 (10.5)	23 (19.2)	27 (25.2)	21 (21.0)	13 (14.0)	15 (15.8)
Black/African American	70 (5.8)	8 (10.8)	6 (6.4)	8 (9.6)	6 (7.1)	5 (4.2)	6 (5.7)	6 (4.8)	9 (7.5)	4 (3.7)	5 (5.0)	4 (4.3)	3 (3.2)
White	928 (77.4)	61 (82.4)	76 (80.9)	63 (75.9)	60 (71.4)	96 (80.0)	84 (80.0)	105 (84.7)	87 (72.5)	76 (71.0)	72 (72.0)	75 (80.6)	73 (76.8)
Other	10 (0.8)	0	0	0	1 (1.2)	1 (0.8)	0	0	1 (0.8)	0	2 (2.0)	1 (1.1)	4 (4.2)

Ethnic group, n (%)													
Hispanic/Latino	138 (11.5)	6 (8.1)	8 (8.5)	8 (9.6)	7 (8.3)	8 (6.7)	8 (7.6)	15 (12.1)	15 (12.5)	15 (14.0)	15 (15.0)	12 (12.9)	21 (22.1)
Non-Hispanic/Latino	1,061 (88.5)	68 (91.9)	86 (91.5)	75 (90.4)	77 (91.7)	112 (93.3)	97 (92.4)	109 (87.9)	105 (87.5)	92 (86.0)	85 (85.0)	81 (87.1)	74 (77.9)

'On-treatment without rescue medication' data. Subgroup data are presented as mean (standard deviation) unless otherwise indicated. BMI: body mass index; Dula: dulaglutide; n: number of subjects randomised and exposed to at least one dose of trial product as randomised (full analysis set); Sema: semaglutide.

Supplementary Table 5. Subject demographics and baseline characteristics by baseline BMI

		<30 kg/m²				30–<35 kg/m²				≥35 kg/m²			
	All subjects	Sema 0.5 mg	Dula 0.75 mg	Sema 1.0 mg	Dula 1.5 mg	Sema 0.5 mg	Dula 0.75 mg	Sema 1.0 mg	Dula 1.5 mg	Sema 0.5 mg	Dula 0.75 mg	Sema 1.0 mg	Dula 1.5 mg
n	**1,199**	**99**	**100**	**91**	**109**	**90**	**86**	**105**	**81**	**112**	**113**	**104**	**108**
Age, years	56 (10.6)	57.4 (11.2)	56.0 (11.4)	57.5 (10.4)	56.9 (10.5)	58.7 (10.1)	55.3 (9.6)	54.4 (11.8)	57.9 (10.7)	53.3 (10.7)	54.5 (10.0)	54.6 (9.3)	53.5 (10.4)
Sex, n (%)													
Male	662 (55.2)	57 (57.6)	60 (60.0)	56 (61.5)	71 (65.1)	53 (58.9)	44 (51.2)	62 (59.0)	47 (58.0)	59 (52.7)	56 (49.6)	44 (42.3)	52 (48.1)
Female	537 (44.8)	42 (42.4)	40 (40.0)	35 (38.5)	38 (34.9)	37 (41.1)	42 (48.8)	43 (41.0)	34 (42.0)	53 (47.3)	57 (50.4)	60 (57.7)	56 (51.9)
Diabetes duration, years	7.4 (5.7)	8.0 (6.9)	8.0 (6.3)	9.0 (6.9)	7.3 (5.8)	7.5 (5.1)	6.2 (4.6)	7.0 (4.9)	7.9 (5.7)	7.7 (5.6)	6.7 (5.3)	6.0 (4.8)	7.8 (5.5)
HbA_{1c}, %	8.2 (0.9)	8.4 (1.0)	8.2 (0.9)	8.3 (1.0)	8.1 (0.9)	8.2 (1.0)	8.2 (1.0)	8.1 (0.8)	8.2 (0.8)	8.3 (0.9)	8.1 (0.9)	8.2 (0.9)	8.3 (0.9)
HbA_{1c}, mmol/mol	66.4 (10.0)	68.6 (10.9)	65.7 (9.6)	66.9 (10.8)	65.5 (9.8)	66.2 (10.6)	66.4 (10.8)	65.5 (9.1)	65.9 (8.7)	67.4 (9.9)	65.1 (9.6)	66.3 (10.3)	66.9 (10.3)
Body weight, kg	95.2 (22.6)	73.8 (12.4)	75.1 (12.4)	78.4 (13.0)	74.7 (12.6)	94.1 (12.6)	91.8 (11.6)	92.8 (12.3)	93.5 (11.3)	118.2 (20.1)	116.8 (18.2)	113.2 (19.7)	112.3 (18.5)
BMI, kg/m²	33.5 (6.8)	26.5 (2.5)	26.8 (2.3)	27.2 (2.2)	26.7 (2.5)	32.6 (1.4)	32.3 (1.4)	32.4 (1.5)	32.7 (1.5)	40.9 (5.5)	40.7 (5.1)	40.5 (5.5)	39.8 (4.9)
Race, n (%)													
Asian	191 (15.9)	37 (37.4)	31 (31.0)	23 (25.3)	41 (37.6)	9 (10.0)	14 (16.3)	13 (12.4)	7 (8.6)	4 (3.6)	3 (2.7)	2 (1.9)	6 (5.6)
Black/African American	70 (5.8)	2 (2.0)	7 (7.0)	9 (9.9)	4 (3.7)	5 (5.6)	3 (3.5)	5 (4.8)	6 (7.4)	10 (8.9)	7 (6.2)	4 (3.8)	8 (7.4)
White	928 (77.4)	60 (60.6)	62 (62.0)	59 (64.8)	63 (57.8)	76 (84.4)	69 (80.2)	87 (82.9)	67 (82.7)	97 (86.6)	101 (89.4)	97 (93.3)	90 (83.3)
Other	10 (0.8)	0	0	0	1 (0.9)	0	0	0	1 (1.2)	1 (0.9)	2 (1.8)	1 (1.0)	4 (3.7)

Ethnic group, n (%)													
Hispanic/Latino	138 (11.5)	8 (8.1)	15 (15.0)	13 (14.3)	18 (16.5)	10 (11.1)	7 (8.1)	13 (12.4)	11 (13.6)	11 (9.8)	9 (8.0)	9 (8.7)	14 (13.0)
Non-Hispanic/Latino	1,061 (88.5)	91 (91.9)	85 (85.0)	78 (85.7)	91 (83.5)	80 (88.9)	79 (91.9)	92 (87.6)	70 (86.4)	101 (90.2)	104 (92.0)	95 (91.3)	94 (87.0)

'On-treatment without rescue medication' data. Subgroup data are presented as mean (standard deviation) unless otherwise indicated. BMI: body mass index; Dula: dulaglutide; HbA_{1c}: glycated haemoglobin; n: number of subjects randomised and exposed to at least one dose of trial product as randomised (full analysis set); Sema: semaglutide.

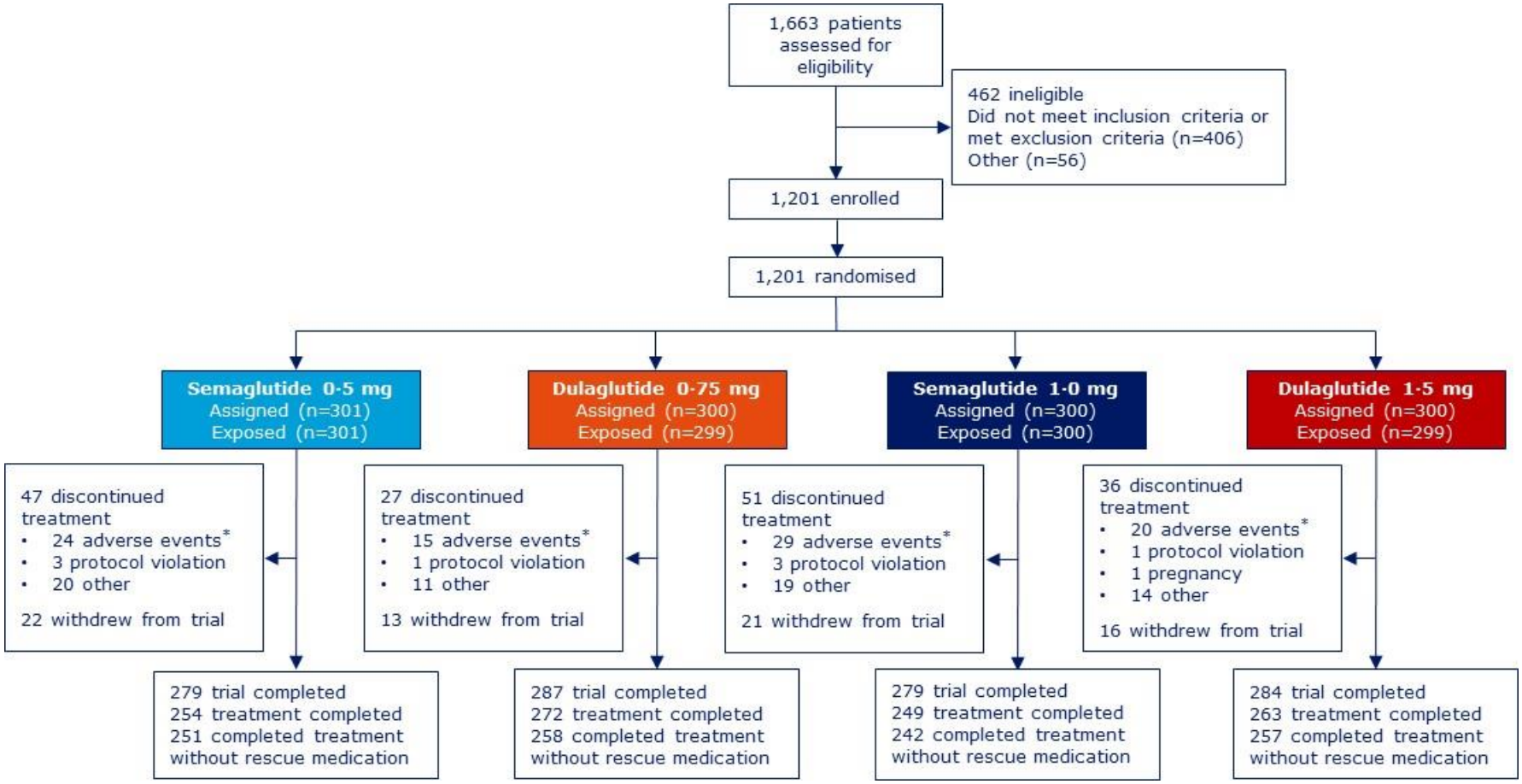
Supplementary Table 6. Baseline characteristics of subjects with BMI <25 kg/m² at baseline

	All subjects	Sema 0.5 mg	Dula 0.75 mg	Sema 1.0 mg	Dula 1.5 mg
n	**1,199**	**24**	**19**	**16**	**28**
Age, years	56 (10.6)	56.9 (10.0)	51.2 (12.1)	61.8 (11.5)	56.8 (11.8)
Sex, n (%)					
Male	662 (55.2)	15 (62.5)	13 (68.4)	8 (50.0)	18 (64.3)
Female	537 (44.8)	9 (37.5)	6 (31.6)	8 (50.0)	10 (35.7)
Diabetes duration, years	7.4 (5.7)	6.8 (6.4)	7.8 (6.6)	12.2 (9.2)	7.3 (5.7)
HbA_{1c}, %	8.2 (0.9)	8.8 (1.1)	8.5 (0.8)	8.4 (1.1)	8.3 (1.1)
HbA_{1c}, mmol/mol	66.4 (10.0)	72.4 (11.5)	69.6 (8.6)	68.2 (12.1)	67.6 (11.5)
Body weight, kg	95.2 (22.6)	62.9 (8.2)	61.8 (9.7)	64.5 (8.4)	62.4 (7.8)
BMI, kg/m²	33.5 (6.8)	23.0 (1.6)	23.1 (1.6)	23.4 (1.6)	23.1 (1.2)
Race, n (%)					
Asian	191 (15.9)	17 (70.8)	9 (47.4)	7 (43.8)	16 (57.1)
Black/African American	70 (5.8)	0	0	0	1 (3.6)
White	928 (77.4)	7 (29.2)	10 (52.6)	9 (56.3)	11 (39.3)
Other	10 (0.8)	0	0	0	0
Ethnic group, n (%)					
Hispanic/Latino	138 (11.5)	2 (8.3)	5 (26.3)	3 (18.8)	3 (10.7)
Non-Hispanic/Latino	1,061 (88.5)	22 (91.7)	14 (73.7)	13 (81.3)	25 (89.3)

'On-treatment without rescue medication' data. Subgroup data are presented as mean (standard deviation) unless otherwise indicated. BMI: body mass index; Dula: dulaglutide; HbA_{1c}: glycated haemoglobin; n: number of subjects randomised and exposed to at least one dose of trial product as randomised (full analysis set); Sema: semaglutide.

Supplementary Section III: Subject Disposition

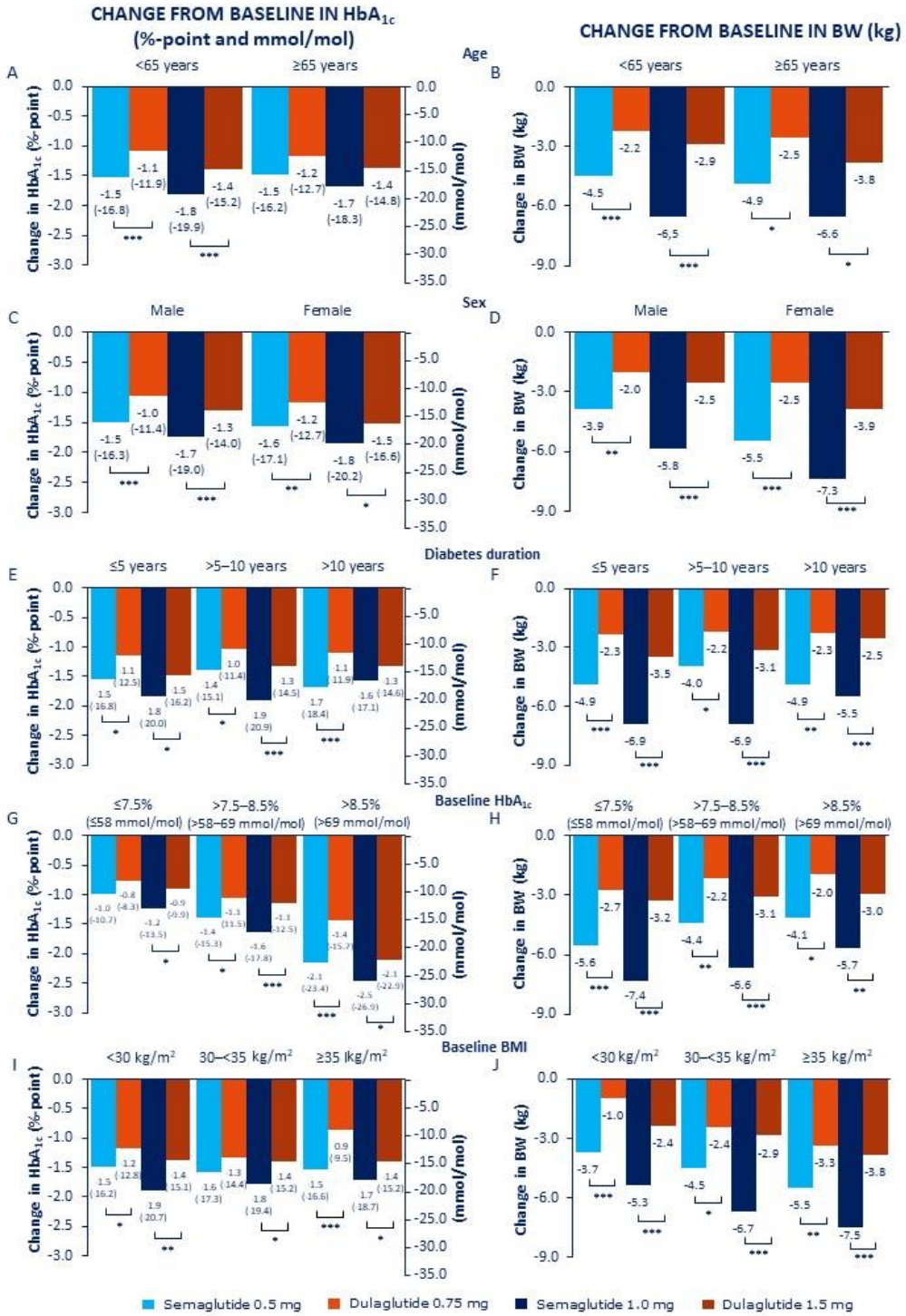
Supplementary Figure 1. Subject disposition in SUSTAIN 7.



*Reflects primary reason for treatment discontinuation, as judged by the investigator. 'Completed trial' refers to those patients who attended the follow-up visit. 'Completed treatment' refers to those patients who did not discontinue treatment prematurely (with or without the addition of rescue medication).

Supplementary Section IV: Glycaemic Targets & Weight-Loss Responses

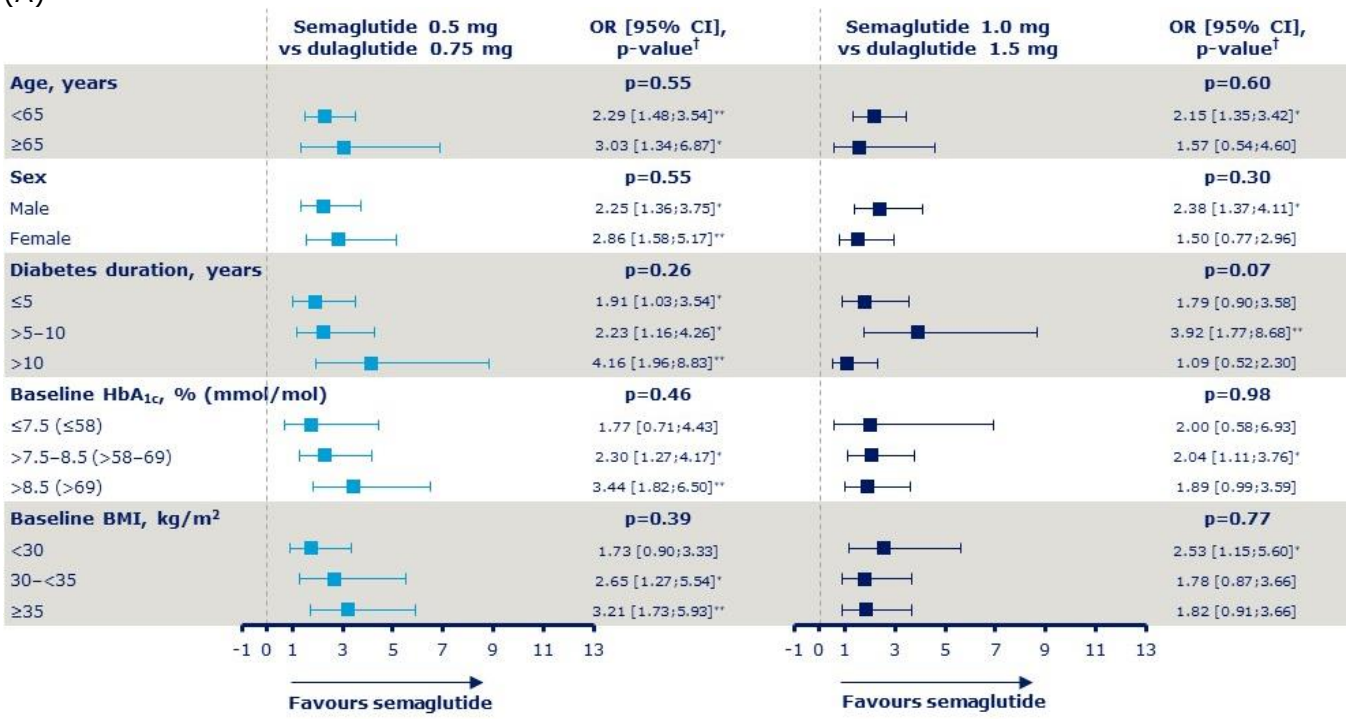
Supplementary Figure 2. Change from baseline in HbA_{1c} (A, C, E, G, I) and body weight (B, D, F, H, J) at week 40 by age (A, B), sex (C, D), diabetes duration (E, F), HbA_{1c} (G, H) and BMI (I, J) at baseline.



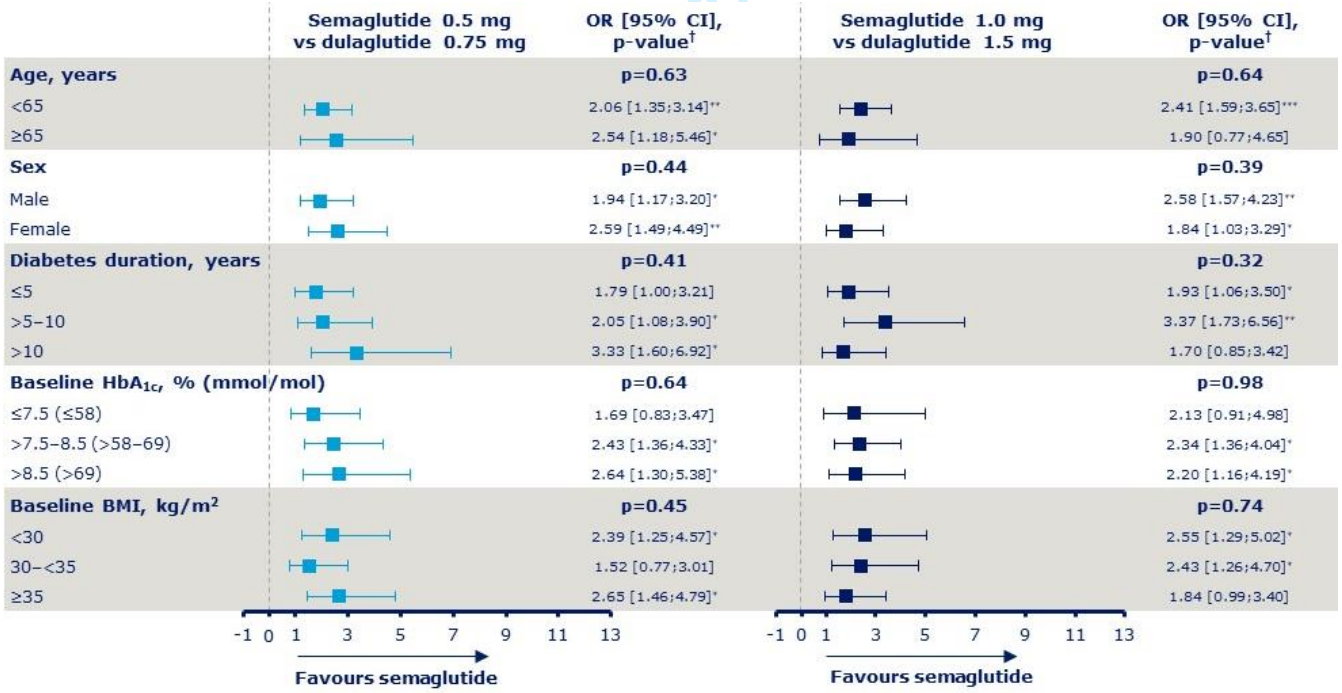
*p<0.05, **p<0.001, ***p<0.0001. Values are estimated means from ANCOVAs controlled for baseline HbA_{1c} (A, C, E, G, I) or BW (B, D, F, H, I) with multiple imputations using data from all randomised subjects exposed to at least one dose of trial product and did not discontinue treatment or receive any non-investigational antihyperglycaemic treatment (full analysis set) obtained while on treatment and prior to onset of rescue medication. P-values are based on ETDs; statistical analyses were not performed for change from baseline.
ANCOVA: analysis of covariance; BMI: body mass index; BW: body weight; ETD: estimated treatment difference; HbA_{1c}: glycated haemoglobin.

Supplementary Figure 3. Odds ratios for the proportion of subjects achieving HbA_{1c} <7.0% (53 mmol/mol; A) and HbA_{1c} ⩽6.5% (48 mmol/mol; B) at 40 weeks by age, sex, diabetes duration, HbA_{1c} and BMI at baseline

(A)



(B)

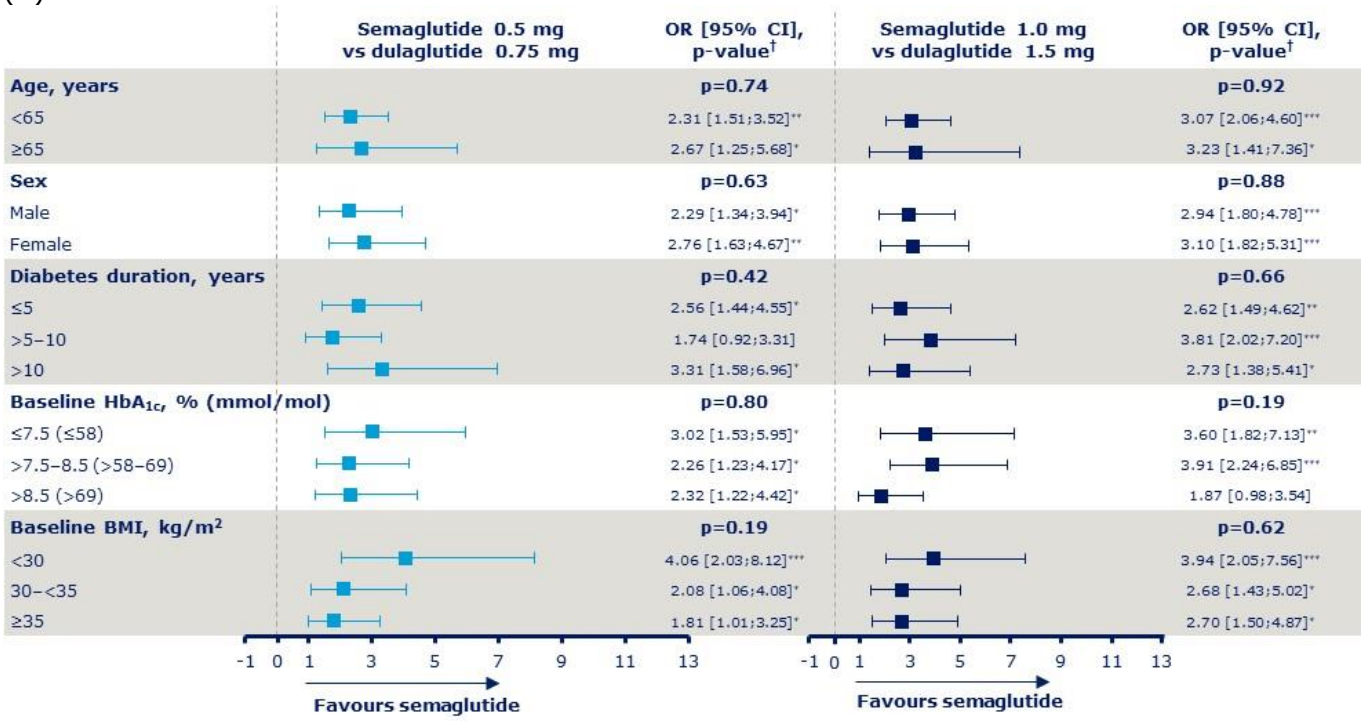


*p<0.05, **p<0.001, ***p<0.0001; †p-values represent the test for treatment by subgroup interaction. Values are ORs [95% CIs] from ANCOVAs with multiple imputations using 'on-treatment without rescue medication' data

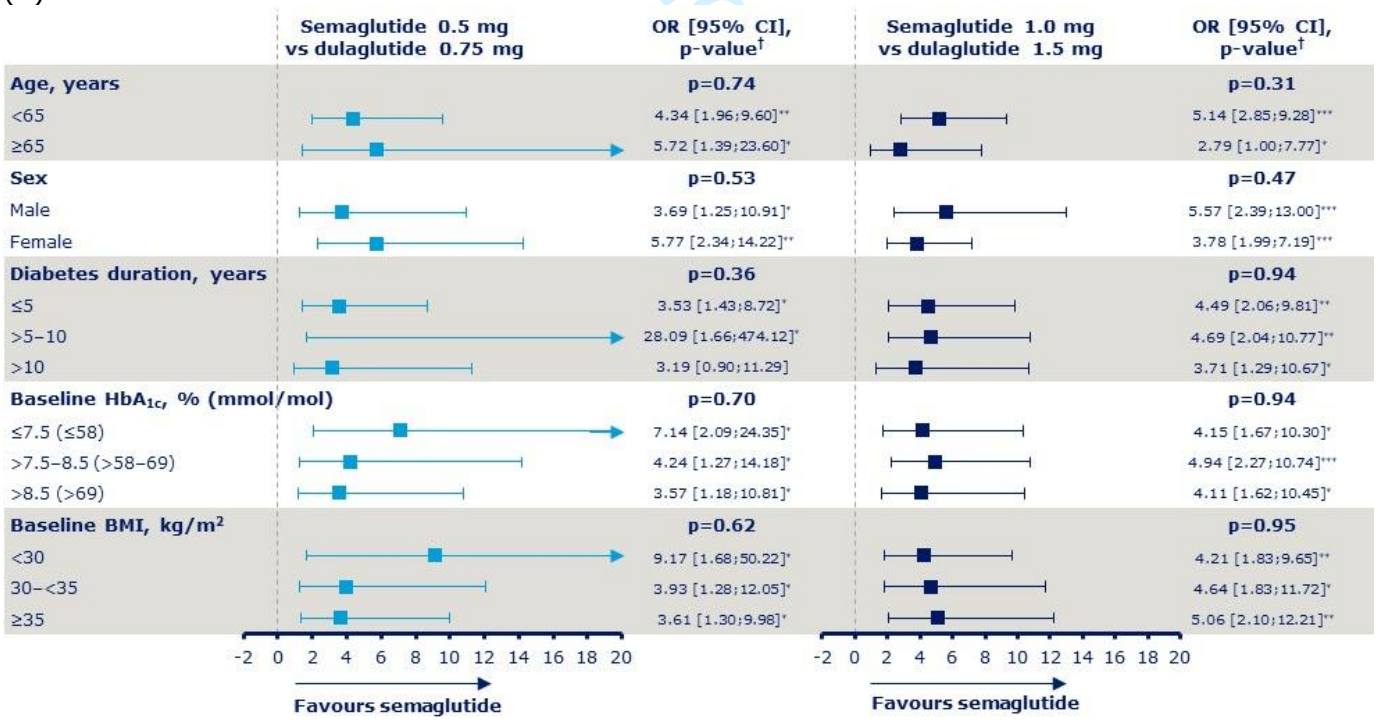
from all randomised subjects exposed to at least one dose of trial product as randomised (full analysis set) obtained while on treatment and prior to onset of rescue medication. ANCOVA controlled for baseline HbA_{1c} and interaction between randomised treatment and subgroup. ANCOVA: analysis of covariance; BMI: body mass index; CI: confidence interval; HbA_{1c}: glycated haemoglobin; OR: odds ratio.

Supplementary Figure 4. Odds ratios for the proportion of subjects achieving weight loss ⩾5% (A) and weight loss ⩾10% (B) at 40 weeks by age, sex, diabetes duration, HbA_{1c} and BMI at baseline

(A)

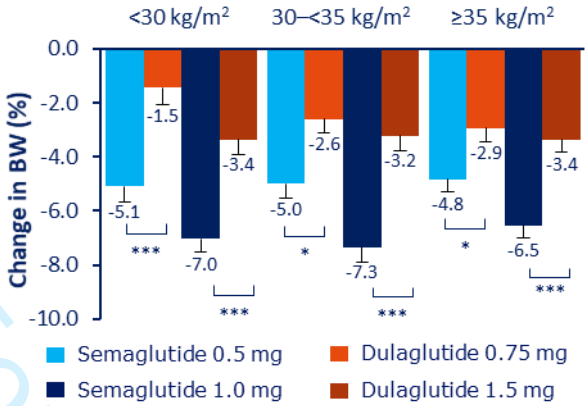


(B)



*p<0.05, **p<0.001, ***p<0.0001; †p-values represent the test for treatment by subgroup interaction. Values are ORs [95% CIs] from ANCOVA analyses with multiple imputations using 'on-treatment without rescue medication' data from all randomised subjects exposed to at least one dose of trial product as randomised (full analysis set) obtained while on treatment and prior to onset of rescue medication. ANCOVA controlled for baseline HbA_{1c} and interaction between randomised treatment and subgroup. ANCOVA: analysis of covariance; BMI: body mass index; CI: confidence interval; HbA_{1c}: glycated haemoglobin; OR: odds ratio.

Supplementary Figure 5: Change in body weight (%) from baseline to week 40 by baseline BMI category



*p<0.05, ***p<0.0001. Values are estimated means from ANCOVAs with multiple imputations using 'on-treatment without rescue medication' data from all randomised subjects exposed to at least one dose of trial product as randomised (full analysis set) obtained while on treatment and prior to onset of rescue medication. ANCOVA: analysis of covariance; BMI: body mass index; BW: body weight.

Supplementary Section V: Adverse Events

Supplementary Table 7. Adverse events by sex subgroups

n (%)	All subjects	Male				Female			
		Sema 0.5 mg	Dula 0.75 mg	Sema 1.0 mg	Dula 1.5 mg	Sema 0.5 mg	Dula 0.75 mg	Sema 1.0 mg	Dula 1.5 mg
	1,199	**169**	**160**	**162**	**171**	**132**	**139**	**138**	**128**
AEs	818 (68.2)	111 (65.7)	97 (60.6)	113 (69.8)	129 (75.4)	93 (70.5)	89 (64.0)	94 (68.1)	92 (71.9)
Serious AEs	86 (7.2)	11 (6.5)	15 (9.4)	10 (6.2)	12 (7.0)	6 (4.5)	9 (6.5)	13 (9.4)	10 (7.8)
AEs leading to premature treatment discontinuation	87 (7.3)	13 (7.7)	8 (5.0)	15 (9.3)	12 (7.0)	11 (8. 3)	6 (4.3)	14 (10.1)	8 (6.3)
Gastrointestinal AEs leading to premature treatment discontinuation	54 (4.5)	8 (4.7)	1 (0.6)	9 (5.6)	8 (4.7)	8 (6.1)	5 (3.6)	9 (6.5)	6 (4.8)
Gastrointestinal AEs	505 (42.1)	67 (39.6)	47 (29.4)	67 (41.4)	81 (47.4)	62 (47.0)	53 (38.1)	66 (47.8)	62 (48.4)
Vomiting	103 (8.6)	13 (7.7)	5 (3.1)	11 (6.8)	16 (9.4)	18 (13.6)	7 (5.0)	20 (14.5)	13 (10.2)
Nausea	230 (19.2)	29 (17.2)	13 (8.1)	25 (15.4)	33 (19.3)	39 (29.5)	26 (18.7)	38 (27.5)	27 (21.1)
Diarrhoea	160 (13.3)	21 (12.4)	10 (6.3)	19 (11.7)	33 (19.3)	22 (16.7)	13 (9.4)	22 (15.9)	20 (15.6)
Hypoglycaemia (severe/BG-confirmed)	15 (1.3)	1 (0.6)	3 (1.9)	3 (1.9)	3 (1.8)	1 (0.8)	0	2 (1.4)	2 (1.6)

Data are presented as number and proportion in percent of subjects with adverse events. Hypoglycaemia was defined as an episode that was severe (according to the American Diabetes Association classification) or BG-confirmed (plasma glucose value <56 mg/dL [3.1 mmol/L]) with symptoms consistent with hypoglycaemia. AE: adverse event; BG: blood glucose; Dula: dulaglutide; n: number of subjects randomised and exposed to at least one dose of trial product as treated (safety analysis set); Sema: semaglutide.

Supplementary Table 8. Adverse events by diabetes duration subgroups

n (%)	All subjects	≤5 years				>5–10 years				>10 years			
		Sema 0.5 mg	Dula 0.75 mg	Sema 1.0 mg	Dula 1.5 mg	Sema 0.5 mg	Dula 0.75 mg	Sema 1.0 mg	Dula 1.5 mg	Sema 0.5 mg	Dula 0.75 mg	Sema 1.0 mg	Dula 1.5 mg
	1,199	113	128	122	114	101	94	103	92	87	77	75	93
AEs	818 (68.2)	76 (67.3)	81 (63.3)	79 (64.8)	76 (66.7)	66 (65.3)	52 (55.3)	74 (71.8)	73 (79.3)	62 (71.3)	53 (68.8)	54 (72.0)	72 (77.4)
Serious AEs	86 (7.2)	5 (4.4)	9 (7.0)	10 (8.2)	9 (7.9)	4 (4.0)	6 (6.4)	7 (6.8)	6 (6.5)	8 (9.2)	9 (11.7)	6 (8.0)	7 (7.5)
AEs leading to premature treatment discontinuation	87 (7.3)	9 (8.0)	3 (2.3)	9 (7.4)	5 (4.4)	10 (9.9)	5 (5.3)	9 (8.7)	8 (8.7)	5 (5.7)	6 (7.8)	11 (14.7)	7 (7.5)
Gastrointestinal AEs leading to premature treatment discontinuation	54 (4.5)	7 (6.2)	1 (0.8)	6 (4.9)	3 (2.6)	6 (5.9)	1 (1.1)	5 (4.9)	5 (5.4)	3 (3.4)	4 (5.2)	7 (9.3)	6 (6.5)
Gastrointestinal AEs	505 (42.1)	52 (46.0)	44 (34.4)	57 (46.7)	52 (45.6)	44 (43.6)	26 (27.7)	42 (40.8)	48 (52.2)	33 (37.9)	30 (39.0)	34 (45.3)	43 (46.2)
Vomiting	103 (8.6)	14 (12.4)	5 (3.9)	18 (14.8)	8 (7.0)	10 (9.9)	4 (4.3)	6 (5.8)	9 (9.8)	7 (8.0)	3 (3.9)	7 (9.3)	12 (12.9)
Nausea	230 (19.2)	25 (22.1)	17 (13.3)	24 (19.7)	21 (18.4)	22 (21.8)	10 (10.6)	24 (23.3)	20 (21.7)	21 (24.1)	12 (15.6)	15 (20.0)	19 (20.4)
Diarrhoea	160 (13.3)	16 (14.2)	14 (10.9)	22 (18.0)	20 (17.5)	18 (17.8)	4 (4.3)	11 (10.7)	18 (19.6)	9 (10.3)	5 (6.5)	8 (10.7)	15 (16.1)
Hypoglycaemia (severe/BG-confirmed)	15 (1.3)	0	1 (0.8)	2 (1.6)	2 (1.8)	0	0	2 (1.9)	2 (2.2)	2 (2.3)	2 (2.6)	1 (1.3)	1 (1.1)

Data are presented as number and proportion in percent of subjects with adverse events. Hypoglycaemia was defined as an episode that was severe (according to the American Diabetes Association classification) or BG-confirmed (plasma glucose value <56 mg/dL [3.1 mmol/L]) with symptoms consistent with hypoglycaemia. AE: adverse event; BG: blood glucose; Dula: dulaglutide; n: number of subjects randomised and exposed to at least one dose of trial product as treated (safety analysis set); Sema: semaglutide.

Supplementary Table 9. Adverse events by baseline HbA_{1c} subgroups

n (%)	All subjects	≤7.5% (≤58 mmol/mol)				>7.5–8.5% (>58–69 mmol/mol)				>8.5% (>69 mmol/mol)			
		Sema 0.5 mg	Dula 0.75 mg	Sema 1.0 mg	Dula 1.5 mg	Sema 0.5 mg	Dula 0.75 mg	Sema 1.0 mg	Dula 1.5 mg	Sema 0.5 mg	Dula 0.75 mg	Sema 1.0 mg	Dula 1.5 mg
	1,199	74	94	83	84	120	105	124	120	107	100	93	95
AEs	818 (68.2)	51 (68.9)	62 (66.0)	57 (68.7)	66 (78.6)	80 (66.7)	65 (61.9)	83 (66.9)	94 (78.3)	73 (68.2)	59 (59.0)	67 (72.0)	61 (64.2)
Serious AEs	86 (7.2)	3 (4.1)	9 (9.6)	6 (7.2)	3 (3.6)	7 (5.8)	8 (7.6)	9 (7.3)	7 (5.8)	7 (6.5)	7 (7.0)	8 (8.6)	12 (12.6)
AEs leading to premature treatment discontinuation	88 (7.3)	6 (8.1)	5 (5.3)	8 (9.6)	11 (13.1)	11 (9.2)	5 (4.8)	12 (9.7)	4 (3.3)	7 (6.5)	4 (4.0)	9 (9.7)	5 (5.3)
Gastrointestinal AEs leading to premature treatment discontinuation	54 (4.5)	5 (6.8)	2 (2.1)	6 (7.2)	9 (10.7)	6 (5.0)	2 (1.9)	8 (6.5)	1 (0.8)	5 (4.7)	2 (2.0)	4 (4.3)	4 (4.2)
Gastrointestinal AEs	505 (42.1)	33 (44.6)	32 (34.0)	38 (45.8)	50 (59.5)	52 (43.3)	40 (38.1)	53 (42.7)	55 (45.8)	44 (41.1)	28 (28.0)	42 (45.2)	38 (40.0)
Vomiting	103 (8.6)	7 (9.5)	5 (5.3)	8 (9.6)	7 (8.3)	14 (11.7)	2 (1.9)	14 (11.3)	11 (9.2)	10 (9.3)	5 (5.0)	9 (9.7)	11 (11.6)
Nausea	230 (19.2)	16 (21.6)	11 (11.7)	16 (19.3)	19 (22.6)	28 (23.3)	14 (13.3)	28 (22.6)	22 (18.3)	24 (22.4)	14 (14.0)	19 (20.4)	19 (20.0)
Diarrhoea	160 (13.3)	12 (16.2)	6 (6.4)	14 (16.9)	25 (29.8)	20 (16.7)	11 (10.5)	17 (13.7)	17 (14.2)	11 (10.3)	6 (6.0)	10 (10.8)	11 (11.6)
Hypoglycaemia (severe/BG-confirmed)	15 (1.3)	0	1 (1.1)	2 (2.4)	1 (1.2)	2 (1.7)	1 (1.0)	1 (0.8)	2 (1.7)	0	1 (1.0)	2 (2.2)	2 (2.1)

Data are presented as number and proportion in percent of subjects with adverse events. Hypoglycaemia was defined as an episode that was severe (according to the American Diabetes Association classification) or BG-confirmed (plasma glucose value <56 mg/dL [3.1 mmol/L]) with symptoms consistent with hypoglycaemia. AE: adverse event; BG: blood glucose; Dula: dulaglutide; n: number of subjects randomised and exposed to at least one dose of trial product as treated (safety analysis set); Sema: semaglutide.

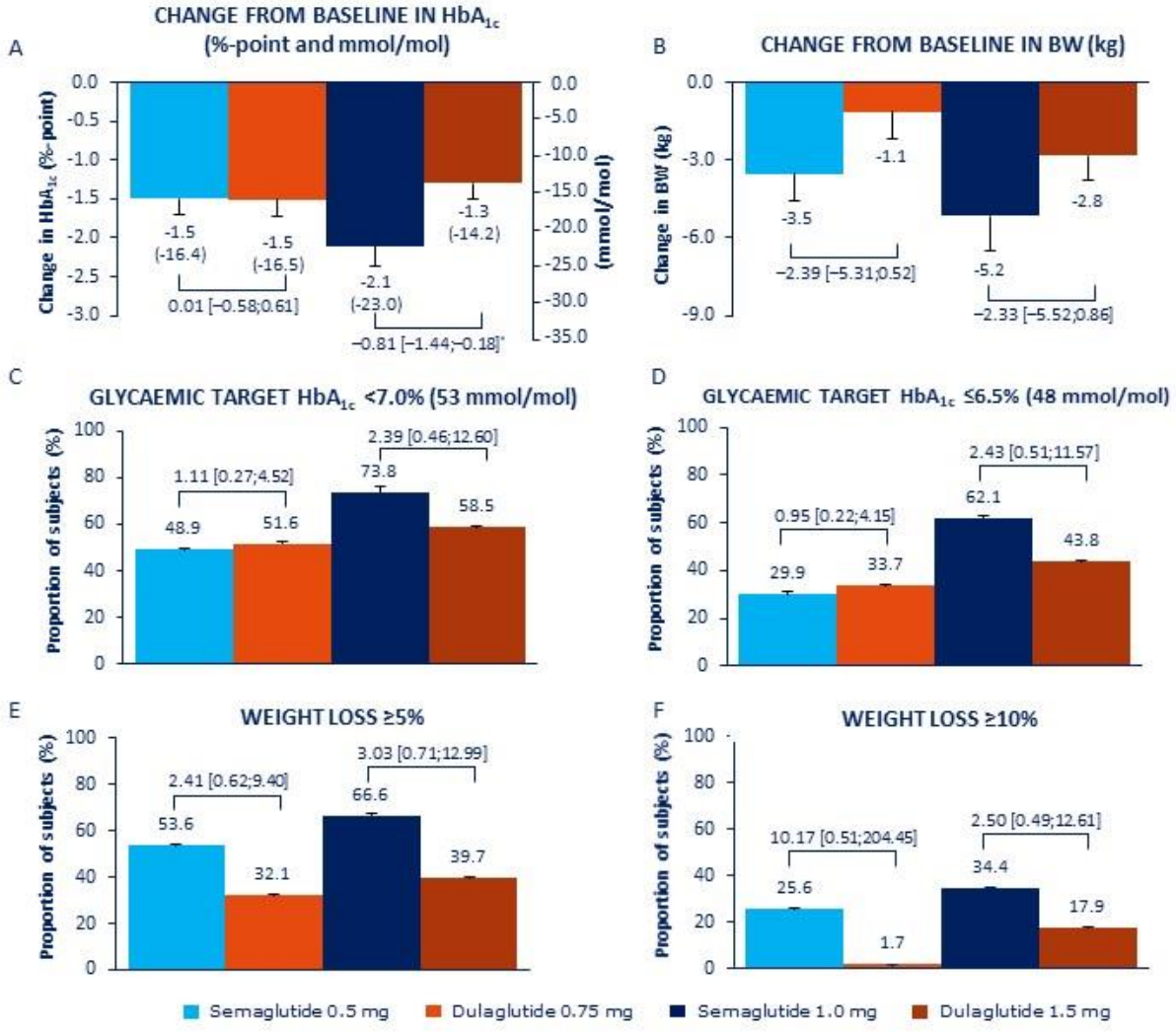
Supplementary Table 10. Adverse events by baseline BMI

n (%)	All subjects	<30 kg/m²				30–<35 kg/m²				≥35 kg/m²			
		Sema 0.5 mg	Dula 0.75 mg	Sema 1.0 mg	Dula 1.5 mg	Sema 0.5 mg	Dula 0.75 mg	Sema 1.0 mg	Dula 1.5 mg	Sema 0.5 mg	Dula 0.75 mg	Sema 1.0 mg	Dula 1.5 mg
	1,199	99	100	91	109	90	86	105	81	112	113	104	108
AEs	818 (68.2)	65 (65.7)	60 (60.0)	65 (71.4)	84 (77.1)	60 (66.7)	54 (62.8)	66 (62.9)	65 (80.2)	79 (70.5)	72 (63.7)	76 (73.1)	71 (65.7)
Serious AEs	86 (7.2)	4 (4.0)	4 (4.0)	5 (5.5)	4 (3.7)	6 (6.7)	6 (7.0)	5 (4.8)	12 (14.8)	7 (6.3)	14 (12.4)	13 (12.5)	6 (5.6)
AEs leading to premature treatment discontinuation	87 (7.3)	12 (12.1)	8 (8.0)	12 (13.2)	16 (14.7)	8 (8.9)	5 (5.8)	8 (7.6)	2 (2.5)	4 (3.6)	1 (0.9)	9 (8.7)	2 (1.9)
Gastrointestinal AEs leading to premature treatment discontinuation	54 (4.5)	9 (9.1)	4 (4.0)	9 (9.9)	11 (10.1)	5 (5.6)	2 (2.3)	5 (4.8)	2 (2.5)	2 (1.8)	0	4 (3.8)	1 (0.9)
Gastrointestinal AEs	505 (42.1)	48 (48.5)	32 (32.0)	44 (48.4)	59 (54.1)	39 (43.3)	27 (31.4)	44 (41.9)	41 (50.6)	42 (37.5)	41 (36.3)	45 (43.3)	42 (38.9)
Vomiting	103 (8.6)	16 (16.2)	5 (5.0)	11 (12.1)	15 (13.8)	6 (6.7)	3 (3.5)	12 (11.4)	4 (4.9)	9 (8.0)	4 (3.5)	8 (7.7)	10 (9.3)
Nausea	230 (19.2)	25 (25.3)	9 (9.0)	19 (20.9)	24 (22.0)	21 (23.3)	11 (12.8)	24 (22.9)	19 (23.5)	22 (19.6)	19 (16.8)	20 (19.2)	17 (15.7)
Diarrhoea	160 (13.3)	18 (18.2)	6 (6.0)	14 (15.4)	28 (25.7)	13 (14.4)	9 (10.5)	14 (13.3)	14 (17.3)	12 (10.7)	8 (7.1)	13 (12.5)	10 (9.3)
Hypoglycaemia (severe/BG-confirmed)	15 (1.3)	0	1 (1.0)	0	3 (2.8)	0	1 (1.2)	2 (1.9)	0	2 (1.8)	1 (0.9)	3 (2.9)	2 (1.9)

Data are presented as number and proportion (%) in percent of subjects with adverse events. Hypoglycaemia was defined as an episode that was severe (according to the American Diabetes Association classification) or BG-confirmed (plasma glucose value <56 mg/dL [3.1 mmol/L]) with symptoms consistent with hypoglycaemia. AE: adverse event; BG: blood glucose; BMI: body mass index; Dula: dulaglutide; n: number of subjects randomised and exposed to at least one dose of trial product as treated (safety analysis set); Sema: semaglutide.

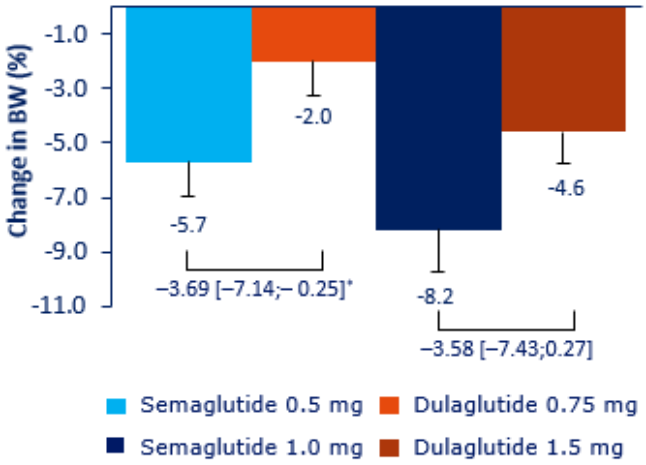
Supplementary Section VI: Results in subjects with BMI <25 kg/m^2

Supplementary Figure 6. Change in HbA_{1c} (A) and body weight (B) from baseline to week 40 and the proportion of subjects achieving HbA_{1c} <7.0% (53 mmol/mol; C), HbA_{1c} ⩽6.5% (48 mmol/mol; D), weight loss ⩾5% (E) and weight loss ⩾10% (F) in subjects with BMI <25 kg/m² at baseline



*p<0.05. Values are estimated means (A, B), estimated proportions (C–F), ETDs [95% CIs] (A, B) or ORs [95% CIs] (C–F) from ANCOVAs with multiple imputations using 'on-treatment without rescue medication' data from all randomised subjects exposed to at least one dose of trial product as randomised (full analysis set). ANCOVA analyses were controlled for baseline HbA_{1c} and interaction between randomised treatment and subgroup. ANCOVA: analysis of covariance; BMI: body mass index, BW: body weight; CI: confidence interval; ETD: estimated treatment difference; HbA_{1c}: glycated haemoglobin; OR: odds ratio.

Supplementary Figure 7. Change in body weight (%) from baseline to week 40 in subjects with BMI <25 kg/m^2 at baseline



*p<0.05. Values are estimated means from ANCOVAs with multiple imputations using 'on-treatment without rescue medication' data from all randomised subjects exposed to at least one dose of trial product as randomised (full analysis set). ANCOVAs were controlled for baseline HbA_{1c} and interaction between randomised treatment and subgroup. ANCOVA: analysis of covariance; BMI: body mass index; BW: body weight; CI: confidence interval; ETD: estimated treatment difference.

Supplementary Table 11. Adverse events in subjects with BMI <25 kg/m² at baseline

n (%)	All subjects	Sema 0.5 mg	Dula 0.75 mg	Sema 1.0 mg	Dula 1.5 mg
	1,199	**24**	**19**	**16**	**28**
AEs	818 (68.2)	18 (75.0)	14 (73.7)	12 (75.0)	23 (82.1)
Serious AEs	86 (7.2)	1 (4.2)	1 (5.3)	2 (12.5)	2 (7.1)
AEs leading to premature treatment discontinuation	87 (7.3)	5 (20.8)	2 (10.5)	4 (25.0)	6 (21.4)
Gastrointestinal AEs leading to premature treatment discontinuation	54 (4.5)	4 (16.7)	0	2 (12.5)	2 (7.1)
Gastrointestinal AEs	505 (42.1)	14 (58.3)	6 (31.6)	10 (62.5)	17 (60.7)
Vomiting	103 (8.6)	6 (25.0)	1 (5.3)	2 (12.5)	3 (10.7)
Nausea	230 (19.2)	6 (25.0)	1 (5.3)	4 (25.0)	6 (21.4)
Diarrhoea	160 (13.3)	5 (20.8)	3 (15.8)	3 (18.8)	7 (25.0)
Hypoglycaemia (severe/BG-confirmed)	15 (1.3)	0	1 (5.3)	0	1 (3.6)

Data are presented as number and proportion in percent of subjects with adverse events. Hypoglycaemia was defined as an episode that was severe (according to the American Diabetes Association classification) or BG-confirmed (plasma glucose value <56 mg/dL [3.1 mmol/L]) with symptoms consistent with hypoglycaemia. AE: adverse event; BG: blood glucose; BMI: body mass index; Dula: dulaglutide; n: number of subjects randomised and exposed to at least one dose of trial product as treated (safety analysis set); Sema: semaglutide.