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

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4 1 **Title page**

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8 3 dulaglutide: SUSTAIN 7 *post hoc* analyses
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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/m²).

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

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3 52 and BMI; supporting the efficacy of semaglutide across the continuum of care in a
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5 53 heterogeneous T2D population.
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8 54 Clinical Trial Registration: NCT02648204 [ClinicalTrials.gov]
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13 56 **STRENGTHS AND LIMITATIONS OF THIS STUDY**

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15 57 • The analysis was designed to provide insight on the influence of five of the most
16
17 58 common and relevant patient-level factors from a clinical perspective
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19 59 • The inclusion of comparator data allows for a more robust analysis and direct
20
21 60 comparison of the differences in efficacy and safety of semaglutide vs dulaglutide
22
23 61 across the subgroups and subgroup categories
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25 62 • As the analysis is based on SUSTAIN 7 data alone, it may only be representative
26
27 63 of the trial-specific patient population
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29 64 • The relatively small number of subjects in each subgroup category is a limitation
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31 65 • As this is a *post hoc* analysis of a randomised clinical trial, there are inherent
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33 66 limitations and, as such, the data should be interpreted with caution
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67 INTRODUCTION

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

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

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

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3 95 trial showed superior reductions in HbA_{1c} and BW with semaglutide vs dulaglutide, for
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5 96 both low-dose (semaglutide 0.5 mg vs dulaglutide 0.75 mg) and high-dose (semaglutide
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7 97 1.0 mg vs dulaglutide 1.5 mg) comparisons.(36) Although both semaglutide and
8
9 98 dulaglutide have individually demonstrated efficacy across multiple patient
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11 99 subpopulations,(23-27,29-35) it is as yet unknown whether the treatment differences
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13 100 observed in the SUSTAIN 7 trial are influenced by heterogeneity in the characteristics of
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15 101 the patients with T2D.

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18 102 To evaluate whether clinically relevant patient characteristics (age, sex, diabetes
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20 103 duration, HbA_{1c} and BMI at baseline) affected the efficacy and safety of semaglutide vs
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22 104 dulaglutide, *post hoc* analyses of data from the SUSTAIN 7 trial were performed.
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26 27 106 **MATERIALS AND METHODS**

28 29 107 **Trial design**

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32 108 The design of the SUSTAIN 7 trial has been previously reported.(36) Briefly, this was an
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34 109 open-label trial in which subjects with uncontrolled T2D were randomised to receive
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36 110 semaglutide OW 0.5 mg or 1.0 mg, or dulaglutide OW 0.75 mg or 1.5 mg, as add-on to
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38 111 background treatment with metformin, and were followed throughout a 40-week
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40 112 treatment period. Semaglutide was administered subcutaneously via a prefilled injection
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42 113 device at one of two maintenance dose levels (0.5 mg or 1.0 mg OW), after following a
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44 114 fixed-dose escalation regimen, as previously reported.(36) Dulaglutide was administered
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46 115 subcutaneously in accordance with the regimen used in the phase 3 clinical trial
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48 116 programme (0.75 mg or 1.5 mg OW), without dose escalation.(37)

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51 117 The trial was registered with ClinicalTrials.gov (NCT02648204) and conducted in
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53 118 accordance with the International Conference on Harmonisation Good Clinical Practice
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55 119 guidelines and the Declaration of Helsinki. The trial protocol (see Supplement) was
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57 120 approved by the institutional review boards and ethics committees at each participating
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3 121 centre and subjects provided written informed consent before trial-related activities
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5 122 commenced.

8 123 **Patient and public involvement**

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10 124 The research question and endpoints, such as efficacy and safety, were informed
11
12 125 indirectly by patients' priorities, experiences and preferences, via input from clinicians
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14 126 during advisory board meetings. No patients were involved directly in the design,
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16 127 recruitment and conduct of the trial. Furthermore, the trial results were not directly
17
18 128 disseminated to trial patients, but were publicly communicated and available via press
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20 129 release, trial portal and journal publication. In the trial, the burden of intervention was
21
22 130 not assessed by the patients, nor were there any patient advisers involved.

25 131 **Patient population**

26
27 132 The inclusion and exclusion criteria for the SUSTAIN 7 trial are described in detail
28
29 133 elsewhere.⁽³⁶⁾ Key inclusion criteria were: diagnosis of T2D; age ≥ 18 years; HbA_{1c}
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31 134 ≥ 7.0 – 10.5% (53–91 mmol/mol). Key exclusion criteria were: estimated glomerular
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33 135 filtration rate < 60 mL/min/1.73 m²; history of chronic or idiopathic acute pancreatitis;
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35 136 known proliferative retinopathy or maculopathy requiring acute treatment (determined
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37 137 by fundoscopy/fundus photography performed within 90 days before randomisation
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39 138 according to local practice); screening calcitonin value ≥ 50 ng/L; personal/family history
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41 139 of medullary thyroid carcinoma or multiple endocrine neoplasia syndrome type 2; acute
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43 140 coronary or cerebrovascular event within 90 days before randomisation; heart failure
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45 141 (New York Heart Association Class IV); and any of the following: myocardial infarction,
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47 142 stroke, or hospitalisation for unstable angina and/or transient ischaemic attack within
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49 143 the past 180 days prior to screening.⁽³⁶⁾

52 144 **Endpoints**

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55 145 The primary endpoint was change in HbA_{1c} (%-point) from baseline to end of treatment
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57 146 at week 40 and the secondary confirmatory endpoint was change in BW (kg) over the
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59 147 same period. Predefined clinical treatment targets were assessed; proportion of subjects
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3 148 achieving HbA_{1c} targets of <7% (53 mmol/mol) and ≤6.5% (48 mmol/mol). The
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5 149 proportion of subjects achieving weight-loss responses of ≥5% and ≥10% was also
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7 150 assessed.
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10 151 The numbers of adverse events (AEs), serious AEs and AEs leading to premature
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12 152 treatment discontinuation were reported. Specific AEs of clinical interest, such as
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14 153 gastrointestinal (GI) disorders and hypoglycaemic events, were also evaluated.
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16 154 **Subgroup analyses**

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19 155 For this *post hoc* analysis, subjects were stratified into subgroups selected for potential
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21 156 clinical relevance: age at baseline (<65 years, ≥65 years), sex (male, female), diabetes
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23 157 duration at baseline (≤5 years, >5–10 years, >10 years), baseline HbA_{1c} (≤7.5%, >7.5–
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25 158 8.5%, >8.5% [≤58, >58–69, >69 mmol/mol]) and baseline BMI (<30 kg/m²,
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27 159 30–<35 kg/m², ≥35 kg/m²). The baseline BMI <25 kg/m² subgroup category was also
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29 160 evaluated; however, due to the small number of subjects (representing less than 10% of
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31 161 the total trial population), these data are not included in the Results, but are provided in
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33 162 the Supplement.
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35 163 **Statistical analyses**

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38 164 The efficacy analyses were based on the full analysis set, comprising all subjects
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40 165 randomised and exposed to at least one dose of the trial product, using 'on-treatment
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42 166 without rescue medication' data (as randomised). Analysis of covariance was performed
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44 167 for each endpoint, including the interaction between treatment and subgroup as a factor.
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46 168 Multiple imputation was used to account for missing data. Specifically, using a sequential
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48 169 multiple-imputation approach, missing values for the underlying continuous assessments
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50 170 were imputed by treatment group, assuming missing data were missing at random, and
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52 171 based on a linear-regression model. A sequential conditional-regression approach was
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54 172 applied whereby missing observations at any post-baseline visits were imputed based on
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56 173 a linear-regression model and incorporating observations from previous visits including
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3 174 baseline. Binary endpoints were created and logistic-regression models run on the
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5 175 complete data set; inference was drawn using Rubin's rule.
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8 176 Values for the mean change from baseline for HbA_{1c} and BW were calculated, and the
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10 177 data are presented as mean and standard error. Estimated treatment differences (ETDs)
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12 178 for the change from baseline in HbA_{1c} and BW, and odds ratios (ORs) for the proportions
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14 179 of subjects achieving HbA_{1c} targets or weight-loss responses, both with 95% confidence
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16 180 intervals, were also calculated for the low-dose (semaglutide 0.5 mg vs dulaglutide
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18 181 0.75 mg) and high-dose (semaglutide 1.0 mg vs dulaglutide 1.5 mg) comparisons. To
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20 182 evaluate the evidence of heterogeneity of treatment effects across the clinical
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22 183 characteristics, a p-value for interaction between treatment effect and subgroup
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24 184 categories was calculated for both dose comparisons in all subgroup analyses, without
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26 185 adjustment for multiplicity.

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28 186 Safety analyses were based on the safety analysis set, which included all randomised
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30 187 subjects who were exposed to at least one dose of trial product, based on 'as-treated'
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32 188 data and summarised descriptively. Safety was assessed within each treatment arm
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34 189 (semaglutide 0.5 mg, dulaglutide 0.75 mg, semaglutide 1.0 mg, dulaglutide 1.5 mg) in
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36 190 each of the subgroup categories.

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39 191 Baseline characteristics and AEs are provided as descriptive data only.
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43 44 193 **RESULTS**

45 46 194 **Subject disposition and baseline characteristics**

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49 195 Baseline characteristics are summarised by treatment arm within each subgroup
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51 196 category (**Tables 1 and 2; Supplementary Section I, Tables 1–3**). Subject
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53 197 characteristics were generally comparable across subgroup categories with some
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55 198 exceptions. In all treatment arms, diabetes duration was longer, and BW and BMI were
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57 199 lower in the elderly (≥ 65 years) subgroup compared with the non-elderly (< 65 years)
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59 200 subgroup (**Table 1**). Males were generally heavier but with a lower BMI, and had a
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2
3 201 longer diabetes duration than females (**Supplementary Table 1**). In the diabetes
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5 202 duration subgroup categories (≤ 5 years, >5 – 10 years, >10 years), age increased with
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7 203 increasing diabetes duration and, in the semaglutide 1.0 mg treatment arm, BW and BMI
8
9 204 decreased with increasing diabetes duration (**Supplementary Table 2**). Across the
10
11 205 baseline HbA_{1c} subgroups ($\leq 7.5\%$, >7.5 – 8.5 , $>8.5\%$ [≤ 58 , >58 – 69 , >69 mmol/mol]),
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13 206 subjects in the semaglutide 0.5 mg treatment arm exhibited decreasing BW and BMI
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15 207 with increasing HbA_{1c} (**Supplementary Table 3**). In keeping with the distribution of
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17 208 subjects in the sex subgroup categories, there was a greater proportion of females vs
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19 209 males in the two highest BMI subgroups, and the proportion of Asian subjects was higher
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21 210 in the subgroup with the lowest BMI vs the subgroup with the highest BMI (**Table 2**).
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23 211 When compared with the other BMI subgroup categories, subjects with BMI <25 kg/m²
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25 212 had the highest HbA_{1c} levels, the highest proportions of male and Asian subjects and, as
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27 213 expected, the lowest BW (**Supplementary Table 4**).
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214 **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)

215 'On-treatment without rescue medication' data. Subgroup data are presented as mean (standard deviation) unless otherwise indicated. BMI, body mass index; Dula,
 216 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,
 217 semaglutide.

218 **Table 2. Subject demographics and baseline characteristics by baseline BMI**

		<30 kg/m ²				30–<35 kg/m ²				≥35 kg/m ²			
	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/m ²	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)

219 'On-treatment without rescue medication' data. Subgroup data are presented as mean (standard deviation) unless otherwise indicated. BMI, body mass index; Dula,
 220 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,
 221 semaglutide.

222 **Glycaemic control and body weight changes**

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

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

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

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

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

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3 249 responses in the semaglutide 1.0 mg treatment group (**Supplementary Figure 2E and**
4
5 250 **F, and 3E and F**).

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8 251 Baseline HbA_{1c} (<7.5%, >7.5–8.5%, >8.5% [≤ 58 , >58–69, >69 mmol/mol]): with

9
10 252 semaglutide 0.5 mg, and to a greater degree with semaglutide 1.0 mg, the magnitude of
11
12 253 the mean reduction in HbA_{1c} from baseline increased with increasing baseline HbA_{1c}; the
13
14 254 converse was apparent for BW, whereby the amount of weight lost was less with
15
16 255 increasing baseline HbA_{1c} (**Supplementary Figure 1G and H**). A similar though less
17
18 256 apparent pattern was observed with dulaglutide, (**Supplementary Figure 1G and H**),
19
20 257 and this was reflected in the proportions of subjects achieving glycaemic targets
21
22 258 (**Supplementary Figure 2G and H**). Across baseline HbA_{1c} subgroups, the greatest
23
24 259 proportion of subjects achieving $\geq 5\%$ weight loss was observed in those subjects
25
26 260 receiving semaglutide 1.0 mg, particularly in the HbA_{1c} subgroup categories of $\leq 7.5\%$
27
28 261 (58 mmol/mol) and >7.5–8.5% (58–69 mmol/mol) (**Supplementary Figure 3G**). There
29
30 262 were no other apparent differences across the subgroup categories regarding the
31
32 263 proportions of subjects achieving weight-loss responses (**Supplementary Figure 3G**
33
34 264 **and H**).

35
36 265 Baseline BMI (<30 kg/m², 30–<35 kg/m², ≥ 35 kg/m²): mean reductions in BW for both

37
38 266 semaglutide and dulaglutide increased with increasing baseline BMI, with the greatest
39
40 267 reductions in the ≥ 35 kg/m² BMI subgroup category for all treatment arms
41
42 268 (**Supplementary Figure 1J**). There were no apparent trends in other BW or glycaemic
43
44 269 outcomes across the BMI categories for either dose comparison (**Supplementary**
45
46 270 **Figure 1I; Supplementary Figure 2I and J; Supplementary Figure 3I and J;**
47
48 271 **Supplementary Figure 6**), or when BW reduction was expressed as percentage change
49
50 272 (**Supplementary Figure 6**). Changes in the <25 kg/m² BMI subgroup were largely
51
52 273 consistent with those observed in the broader population (**Supplementary Section IV,**
53
54 274 **Figures 7 and 8**).

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56
57 275 **Treatment–subgroup interaction effects**
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3 276 For each of the subgroups, analysis of the ETDs for the change from baseline in HbA_{1c} in
4
5 277 the age, sex, diabetes duration, baseline HbA_{1c} and baseline BMI subgroups, the
6
7 278 p-values for the low-dose and high-dose comparisons were nonsignificant, except in the
8
9 279 analysis of the HbA_{1c} subgroups within the low-dose comparison (p<0.05 for the
10
11 280 treatment–subgroup interaction effect) (**Figure 1A**). The change from baseline in BW in
12
13 281 the age, sex, diabetes duration, baseline HbA_{1c} and baseline BMI subgroups was similar,
14
15 282 with nonsignificant treatment–subgroup interactions for both dose comparisons
16
17 283 (**Figure 1B**). Similarly, treatment–subgroup interactions were nonsignificant for the
18
19 284 analysis of the ORs for the proportions of subjects achieving glycaemic targets and
20
21 285 weight-loss responses (**Supplementary Section II, Figures 4 and 5**).

23 24 286 **Safety outcomes**

25
26 287 Overall, AEs were reported in more than half of subjects irrespective of the subgroup
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28 288 category (ranging from 55.3% [dulaglutide 0.75 mg; diabetes duration >5–10 years] to
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30 289 80.6% [dulaglutide 1.5 mg; elderly]) and were generally more common with
31
32 290 semaglutide 0.5 mg than with dulaglutide 0.75 mg, and less common with semaglutide
33
34 291 1.0 mg than with dulaglutide 1.5 mg. Premature treatment discontinuations due to AEs
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36 292 were higher with semaglutide than with dulaglutide, and were primarily due to GI AEs
37
38 293 (**Tables 3 and 4; Supplementary Section III, Tables 5–7**).

294 **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

295 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
 296 Diabetes Association classification) or BG-confirmed (plasma glucose value <56 mg/dL [3.1 mmol/L]) with symptoms consistent with hypoglycaemia. AE, adverse event;
 297 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,
 298 semaglutide.

299 **Table 4. Adverse events by baseline BMI**

n (%)	All subjects	<30 kg/m ²				30–<35 kg/m ²				≥35 kg/m ²			
		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)

300 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
 301 American Diabetes Association classification) or BG-confirmed (plasma glucose value <56 mg/dL [3.1 mmol/L]) with symptoms consistent with hypoglycaemia. AE, adverse
 302 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
 303 analysis set); Sema, semaglutide.

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4 304 GI AEs were the most frequently reported events, with generally higher rates with
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6 305 semaglutide 0.5 mg vs dulaglutide 0.75 mg, and dulaglutide 1.5 mg vs semaglutide
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8 306 1.0 mg, across the subgroups and subgroup categories (ranging from 27.7%
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10 307 [dulaglutide 0.75 mg; diabetes duration >5–10 years] to 59.5% [dulaglutide 1.5 mg;
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12 308 HbA_{1c} ≤7.5% [58 mmol/mol]), with nausea being the most common (ranging from 8.1%
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14 309 [dulaglutide 0.75 mg; male] to 29.5% [semaglutide 0.5 mg; female]) (**Tables 3 and 4;**
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16 310 **Supplementary Section III, Tables 5–7**). Across the subgroup categories, more
17
18 311 female than male subjects reported GI AEs overall, with GI AEs generally decreasing
19
20 312 with increasing BMI in subjects treated with semaglutide (**Table 4 and Supplementary**
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22 313 **Section III, Table 4**). The highest proportion of GI AEs were reported by subjects with
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24 314 BMI <25 kg/m² (**Supplementary Section V, Table 8**).

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29 316 **DISCUSSION**

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32 317 Given the heterogeneous profile of patients with T2D and the guidance for such
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34 318 differences to be considered when making treatment choices,(2-3) this *post hoc* analysis
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36 319 of SUSTAIN 7 data assessed the impact of individual clinical characteristics on the effect
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38 320 of semaglutide vs dulaglutide treatment. The analyses indicate that the effect of
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40 321 semaglutide vs dulaglutide was not influenced by age, sex, diabetes duration, HbA_{1c} or
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42 322 BMI at baseline, with the exception of the low-dose comparison for HbA_{1c} in the baseline
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44 323 HbA_{1c} subgroup, which showed increasing efficacy for semaglutide 0.5 mg vs dulaglutide
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46 324 0.75 mg in subjects with increasing HbA_{1c} at baseline.

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48 325 This *post hoc* analysis supports the finding from the overall SUSTAIN 7 trial that
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50 326 semaglutide was superior to dulaglutide in reducing HbA_{1c} and BW;(36) the same was
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52 327 observed across each of the subgroups and within the various subgroup categories
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54 328 presented here.

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57 329 This *post hoc* analysis also supports findings from similar subgroup analyses of SUSTAIN
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59 330 trials. An analysis of SUSTAIN 1–5 data showed greater reductions in HbA_{1c} and BW with
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3 331 semaglutide vs comparators, and comparable efficacy in elderly subjects (a population
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5 332 often presenting with comorbidities) and non-elderly subjects, without an increased risk
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7 333 of hypoglycaemia.(25) Similarly, analyses of pooled SUSTAIN data showed clinically
8
9 334 relevant reductions in HbA_{1c} and BW with semaglutide, regardless of baseline BW, HbA_{1c},
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11 335 diabetes duration, race and ethnicity.(23-26,28)
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13
14 336 HbA_{1c} reductions were greater with increasing baseline HbA_{1c} for both semaglutide and
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16 337 dulaglutide in the present analyses, which has been observed with dulaglutide
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18 338 previously,(29,31-33) as well as with liraglutide,(38) lixisenatide (39) and other
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20 339 antihyperglycaemic agents. Furthermore, a converse relationship between weight loss
21
22 340 and baseline HbA_{1c} levels was observed, whereby increasing baseline HbA_{1c} was
23
24 341 associated with greater reductions in HbA_{1c} but a decreasing magnitude of weight loss. A
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26 342 similar pattern has been observed with liraglutide as an add-on to insulin treatment,(40)
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28 343 with exenatide alone (41) and with dulaglutide.(31,32) These findings have relevance for
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30 344 clinical practice, indicating that there may be an effect with GLP-1RAs (and potentially
31
32 345 other antihyperglycaemic therapies) in predicting treatment responses based on HbA_{1c}
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34 346 levels.(40) Conversely, a recent analysis of the AWARD trials found a weak positive
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36 347 correlation between HbA_{1c} reduction and weight loss with dulaglutide.(42) Several
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38 348 mechanisms, also associated with other antihyperglycaemic agents, may contribute to
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40 349 these results.(43) Improved treatment-related glycaemic control is associated with
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42 350 decreased glycosuria,(40,43) normalised protein turnover and a decreased catabolic
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44 351 effect,(43) in addition to decreased energy expenditure and resting metabolic rate.(43)
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46 352 As GLP-1RAs exhibit a glucose-dependent mechanism of action, the greater post-
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48 353 treatment reductions in HbA_{1c} from a higher initial baseline HbA_{1c} may contribute to the
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50 354 retention of glucose calories and, thereby, moderation of the achievable weight loss. In
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52 355 these analyses, greater weight loss was observed with increasing baseline BMI for both
53
54 356 semaglutide and dulaglutide, aligning with what has been previously reported for
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56 357 semaglutide (23) and dulaglutide.(35) While percentage weight loss was also greater
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58 358 with semaglutide vs dulaglutide, the percentage change in weight loss was generally of a
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3 359 similar magnitude across BMI categories, indicating that the weight-loss pattern
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5 360 observed across the HbA_{1c} subgroup categories may be associated with subjects'
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7 361 baseline BMI. High BMI is associated with an insulin resistant-phenotype in some
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9 362 patients,(3) and less weight loss is observed in patients with diabetes who are insulin
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11 363 resistant than in those with insulin sensitivity.(44) However, clinically relevant reductions
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13 364 in BW were achieved for all BMI subgroup categories, and the magnitude of weight loss
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15 365 was comparatively greater for semaglutide than for dulaglutide. This is an important
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17 366 consideration for clinical practice, given the increasing interest in weight management as
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19 367 a key aspect of treatment for T2D.(1)

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22 368 Analysis of the ETDs for change from baseline in HbA_{1c} and BW and ORs for the
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24 369 proportions of subjects achieving HbA_{1c} targets or weight-loss responses indicated a
25
26 370 consistent effect of semaglutide vs dulaglutide across subgroup categories. These
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28 371 findings are aligned with previous analyses of subpopulations treated with GLP-1RAs,
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30 372 including semaglutide and dulaglutide, which also reported a nonsignificant impact of
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32 373 age, sex or diabetes duration on treatment effect,(23-27,29-35) although weight loss
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34 374 tended to be greater in women than in men with dulaglutide,(31) as was also observed
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36 375 in this analysis.

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38 376 Consistent with the known class effect of GLP-1RAs,(45) both semaglutide and
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40 377 dulaglutide reported relatively high levels of GI AEs. The rate of GI AEs was higher with
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42 378 semaglutide vs dulaglutide in the low-dose comparison; in the high-dose comparison it
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44 379 was higher with dulaglutide vs semaglutide.(36) Premature treatment discontinuations
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46 380 due to AEs were higher with semaglutide than with dulaglutide, which may be due to the
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48 381 higher levels of moderate GI AEs observed in the overall SUSTAIN 7 trial.(36) The
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50 382 occurrence of some GIs AEs may be dose-dependent and nausea (and also vomiting for
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52 383 semaglutide) is usually transient with both semaglutide (46) and dulaglutide;(14)
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54 384 furthermore, the dose-escalation regimen approved for semaglutide has been shown to
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56 385 mitigate these AEs.(46) In the subgroups in the present analyses, GI AEs were higher
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58 386 with dulaglutide 1.5 mg vs semaglutide 1.0 mg in elderly subjects with longer diabetes
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3 387 duration, and lower in subjects with HbA_{1c} >8.5% (69 mmol/mol) and higher BMI. There
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5 388 were no other associations between subjects' baseline characteristics with the incidence
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7 389 of GI AEs. Subjects who experience GI AEs, specifically nausea and vomiting, have
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9 390 greater weight loss compared with those who do not.(23,47) While this hypothesised
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11 391 association might be considered an explanation for the observed greater weight loss with
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13 392 semaglutide vs dulaglutide in the low-dose comparison, a mediation analysis has
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15 393 previously shown that the direct effects of semaglutide on BW are the main contributors
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17 394 to weight loss with very little effect attributable to GI AEs.(47,48). Our analyses support
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19 395 this finding as, overall, there were no clear trends between the incidence of GI AEs and
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21 396 the greater efficacy of semaglutide in terms of HbA_{1c} reduction and weight loss vs
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23 397 dulaglutide.(31) With semaglutide, there was a trend towards decreasing GI AEs with
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25 398 increasing baseline BMI, which has also been previously reported for the SUSTAIN 1–5
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27 399 (23) and the AWARD 1–6 (49) trials, and may be due to differences in exposure–
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29 400 response levels associated with BW as has been demonstrated with semaglutide.(50)
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31 401 Similarly, an analysis has shown that elderly patients with a lower BMI are more likely to
32
33 402 experience side effects (including GI AEs) with dulaglutide than younger patients with a
34
35 403 higher BMI.(49) However, it is noted that this was a *post hoc* analysis in Japanese
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37 404 patients, with low event rates for some GI AEs, and so the results may not be
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39 405 generalizable to a wider diabetes population. In either case, a dose-escalation regimen
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41 406 may be beneficial.

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43
44 407 A strength of the present analysis is the inclusion of comparator data, which allows for a
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46 408 more robust analysis and direct comparison of the differences in efficacy and safety of
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48 409 semaglutide vs dulaglutide across the subgroups and subgroup categories. However, the
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50 410 *post hoc* nature of this analysis means there are inherent limitations and, as such, the
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52 411 data should be interpreted with caution. Also, as the analysis is based on SUSTAIN 7
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54 412 alone, it may only be representative of the trial-specific patient population. A further
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56 413 limitation is the relatively small number of subjects in each subgroup category.
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58 414 Additionally, in the age subgroups, there was an imbalance in subject numbers (elderly
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3 415 vs non-elderly), with relatively few patients in the elderly subgroup (260; 22% of the
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5 416 analysis population). However, given the overall consistency of the age-subgroup
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7 417 analyses, as well as the general limitations of these *post hoc* analyses, the difference in
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9 418 subject numbers between the age subgroup categories seemed to have had little or no
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11 419 impact. Furthermore, elderly subjects in previous pooled analyses of the SUSTAIN 1–5
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13 420 (26) and AWARD (30,32) trials have demonstrated similar efficacy and safety,
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15 421 supporting the results obtained here.

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18 422 This analysis provides insight on the influence of five of the most common and relevant
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20 423 patient-level factors from a clinical perspective and highlights semaglutide as an
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22 424 effective choice across these patient subgroups that are commonly encountered in
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24 425 clinical practice. Understanding the impact of heterogeneity in clinical characteristics on
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26 426 the treatment differences between GLP-1RAs further supports patient-centred decision-
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28 427 making in clinical practice.

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31 32 33 429 **CONCLUSIONS**

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35 430 Semaglutide was associated with superior efficacy to dulaglutide across various clinically
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37 431 relevant patient subgroups that are commonly encountered in clinical practice, with a
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39 432 safety profile similar to other GLP-1RAs and in line with previously published data for
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41 433 semaglutide. The treatment effect for semaglutide vs dulaglutide did not appear to be
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43 434 influenced by age, sex, diabetes duration, HbA_{1c} or BMI at baseline. This indicates that
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45 435 the efficacy of semaglutide vs dulaglutide is retained across a range of diverse clinical
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47 436 characteristics, thereby increasing the evidence base available to clinicians to guide care.

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492 **DATA SHARING STATEMENT**

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

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3 497 commitments. Data will be available permanently after research completion and
4
5 498 approval of product and product use in the European Union and USA. Data will only be
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7 499 shared with *bona fide* researchers submitting a research proposal and requesting access
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9 500 to data, for use as approved by the independent review board and according to its
10
11 501 charter. The access request proposal form and the access criteria can be found online.
12
13 502 Data will be made available on a specialised Statistical Analysis System data platform.
14
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16 503

17 18 504 **AUTHOR CONTRIBUTIONS**

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21 505 RP: conduct of trial, data collection, data analysis, data interpretation, manuscript
22
23 506 preparation, approval of submitted version; VA: conduct of trial, data collection, data
24
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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.

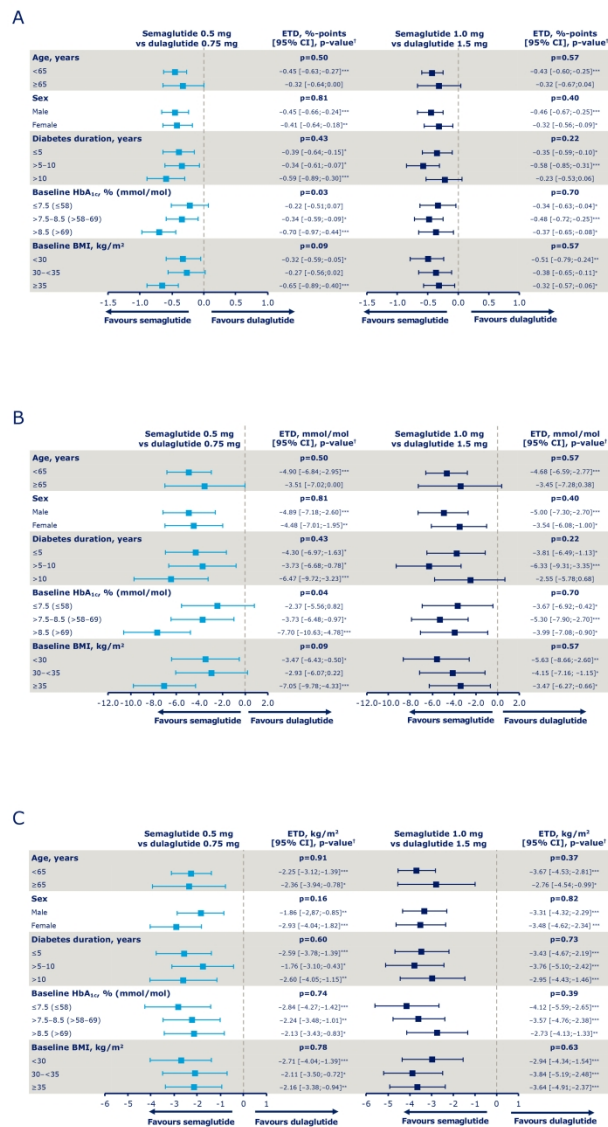


Figure 1. Estimated treatment differences for change from baseline in HbA_{1c} shown as %-points (A), HbA_{1c} shown as mmol/mol (B) and body weight (C) at week 40 by age, sex, diabetes duration, HbA_{1c} and BMI at baseline. *p<0.05, **p<0.001, ***p<0.0001; †p values represent the test for treatment 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

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3 **SUPPLEMENTARY SECTION I: BASELINE CHARACTERISTICS**
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Supplementary Table 1. Baseline characteristics by sex subgroups

	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
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

	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
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.

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

	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
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)

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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.

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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/m ²	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)

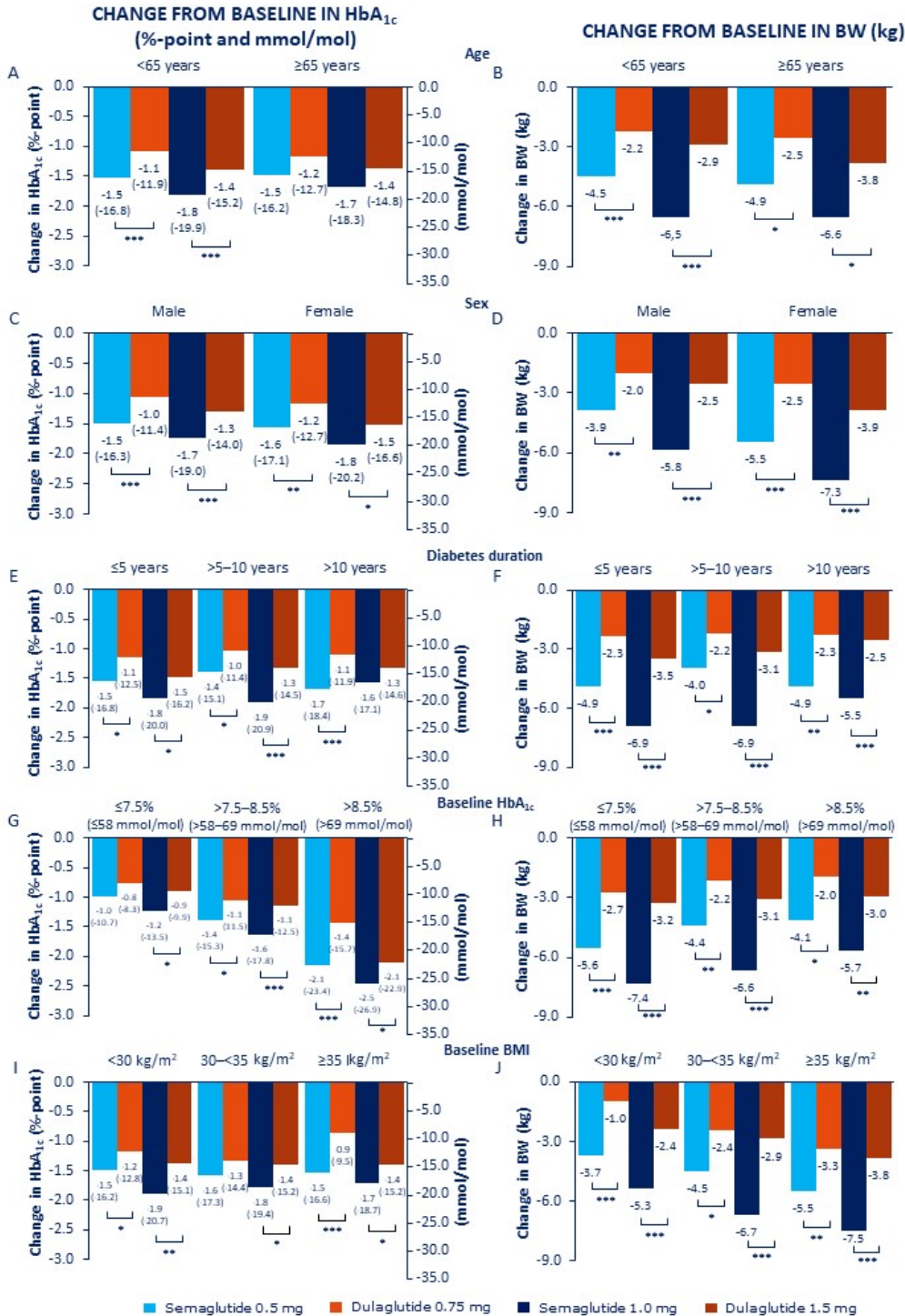
'On-treatment without rescue medication' data. Subgroup data are presented as mean (standard deviation) unless otherwise indicated. BMI, body mass index; Dula, dulaglutide; HbA_{1c}, glycosylated haemoglobin; n, number of subjects randomised and exposed to at least one dose of trial product as randomised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

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SUPPLEMENTARY SECTION II : GLYCAEMIC TARGETS & WEIGHT-LOSS RESPONSES

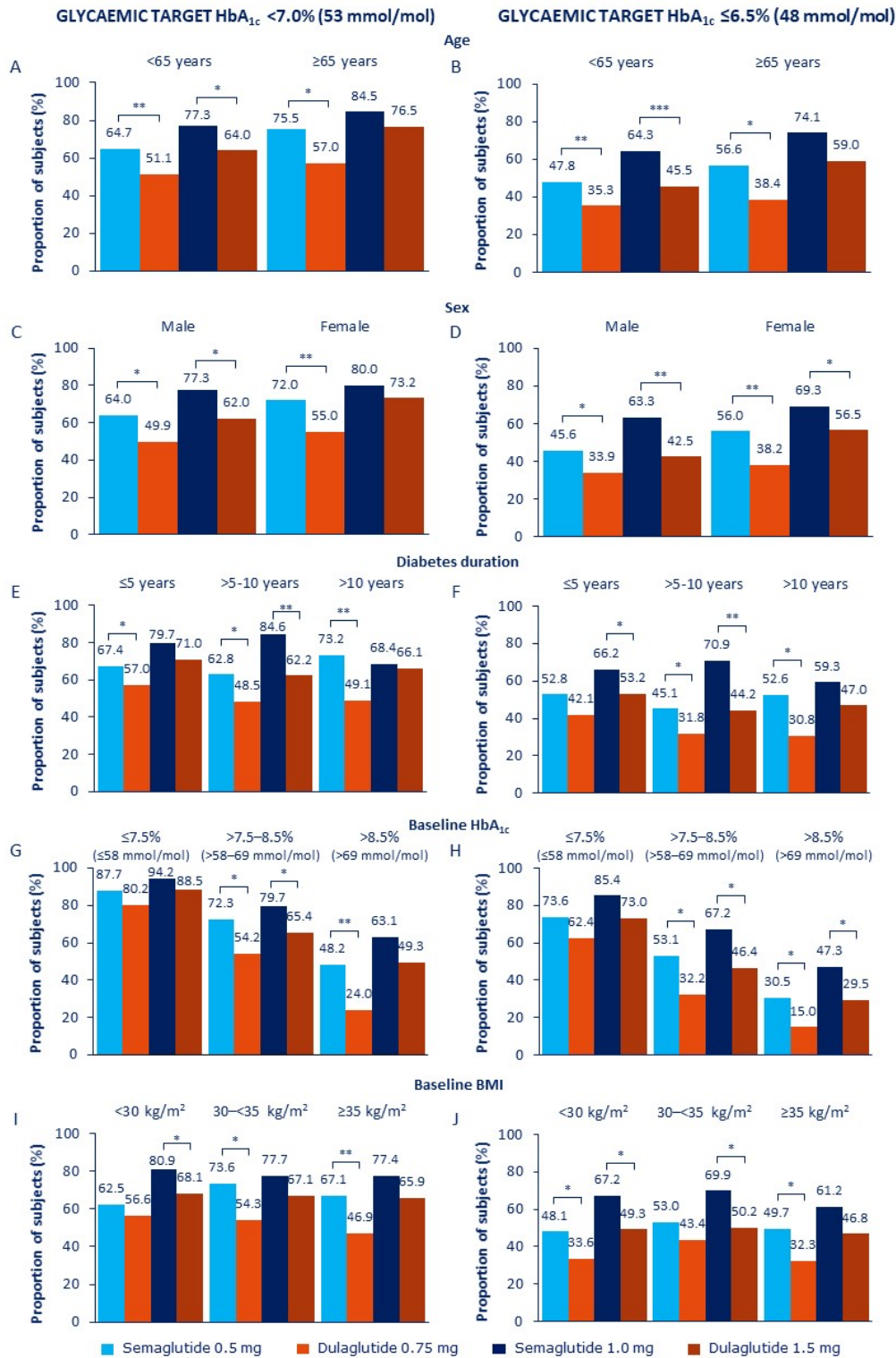
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Supplementary Figure 1. Change from baseline in HbA_{1c} (A, C, E, G, I) and body weight (B, D, F, H, J) at week 40 by age (A, B), sex (C, D), diabetes duration (E, F), HbA_{1c} (G, H) and BMI (I, J) at baseline.



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3 *p<0.05, **p<0.001, ***p<0.0001. Values are estimated means from ANCOVAs controlled for baseline HbA_{1c}
4 (A, C, E, G, I) or BW (B, D, F, H, I) with multiple imputations using data from all randomised subjects exposed to
5 at least one dose of trial product and did not discontinue treatment or receive any non-investigational
6 antihyperglycaemic treatment (full analysis set) obtained while on treatment and prior to onset of rescue
7 medication. P-values are based on ETDs; statistical analyses were not performed for change from baseline.
8 ANCOVA, analysis of covariance; BMI, body mass index; BW, body weight; ETD, estimated treatment difference;
9 HbA_{1c}, glycated haemoglobin.
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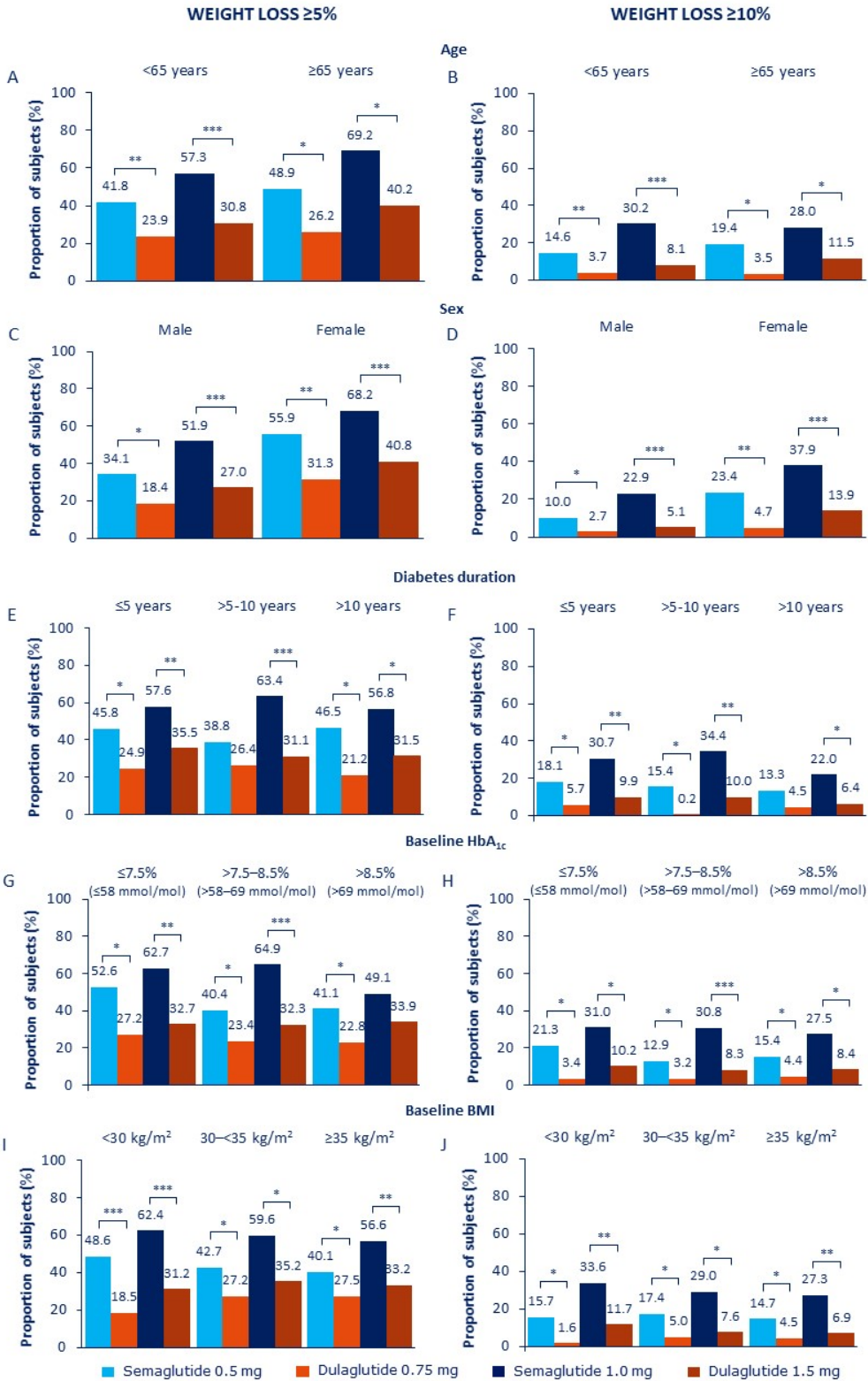
Supplementary Figure 2. Proportion of subjects achieving HbA_{1c} < 7.0% (53 mmol/mol; A, C, E, G and I) and HbA_{1c} ≤6.5% (48 mmol/mol; B, D, F, H and J) at 40 weeks



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3 *p<0.05, **p<0.001, ***p<0.0001. Values are estimated proportions from ANCOVAs with multiple imputations
4 using 'on-treatment without rescue medication' data from all randomised subjects exposed to at least one dose of
5 trial product as randomised (full analysis set) obtained while on treatment and prior to onset of rescue medication.
6 ANCOVA, analysis of covariance; BMI, body mass index; BW, body weight; HbA_{1c}, glycated haemoglobin.
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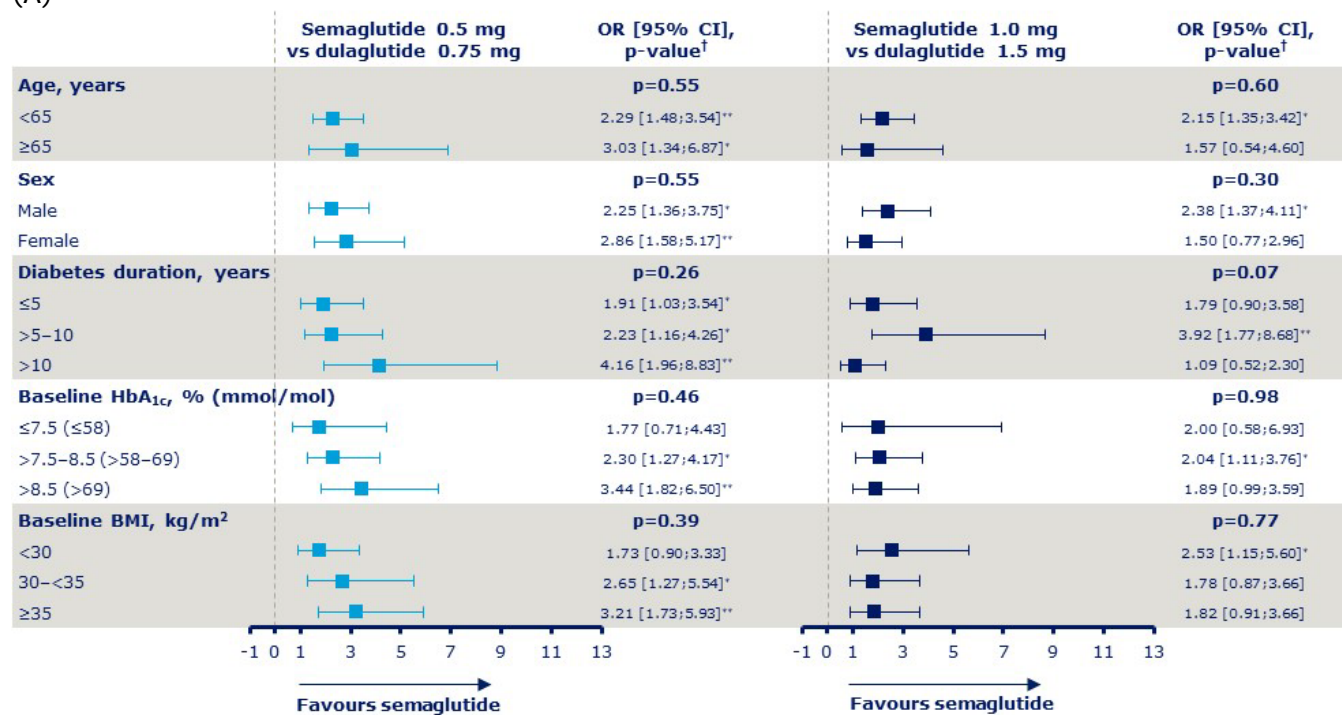
Supplementary Figure 3. Proportion of subjects achieving weight loss $\geq 5\%$ (A, C, E, G and I) and weight loss $\geq 10\%$ (B, D, F, H and J) at 40 weeks



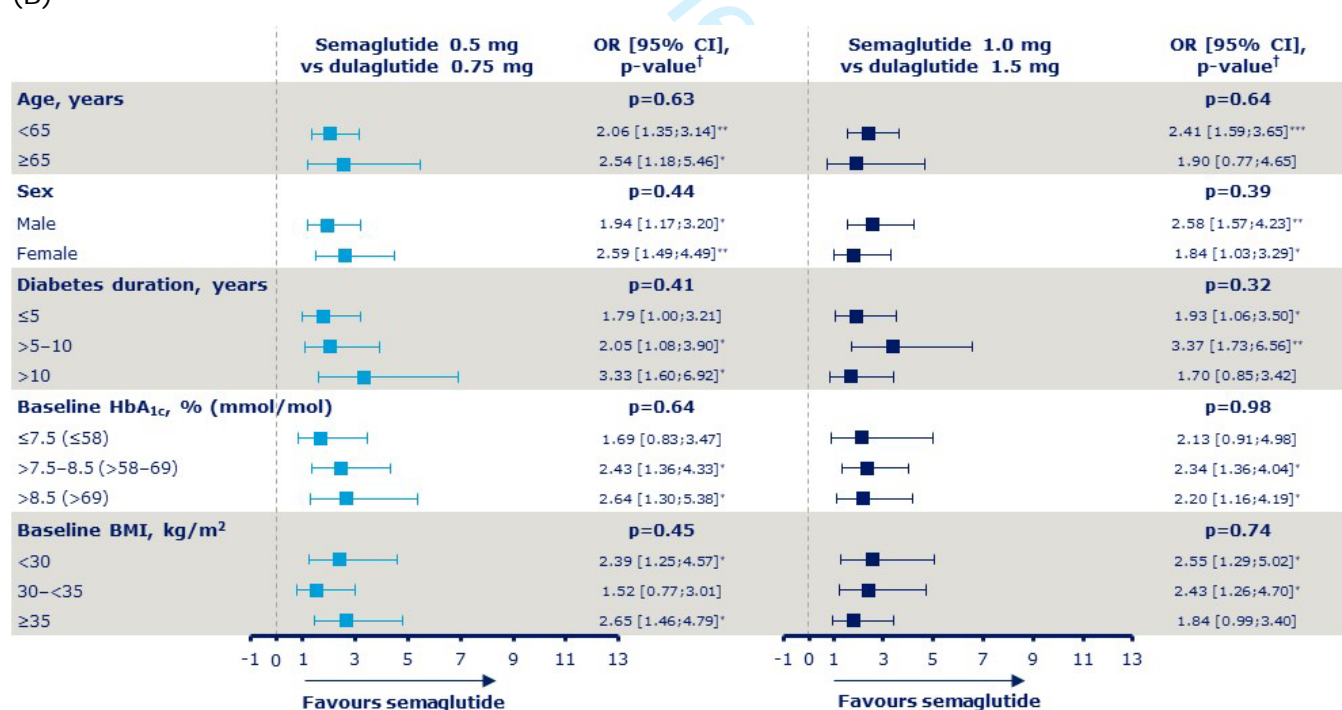
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3 *p<0.05, **p<0.001, ***p<0.0001. Values are estimated proportions from ANCOVAs with multiple imputations
4 using 'on-treatment without rescue medication' data from all randomised subjects exposed to at least one dose of
5 trial product as randomised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



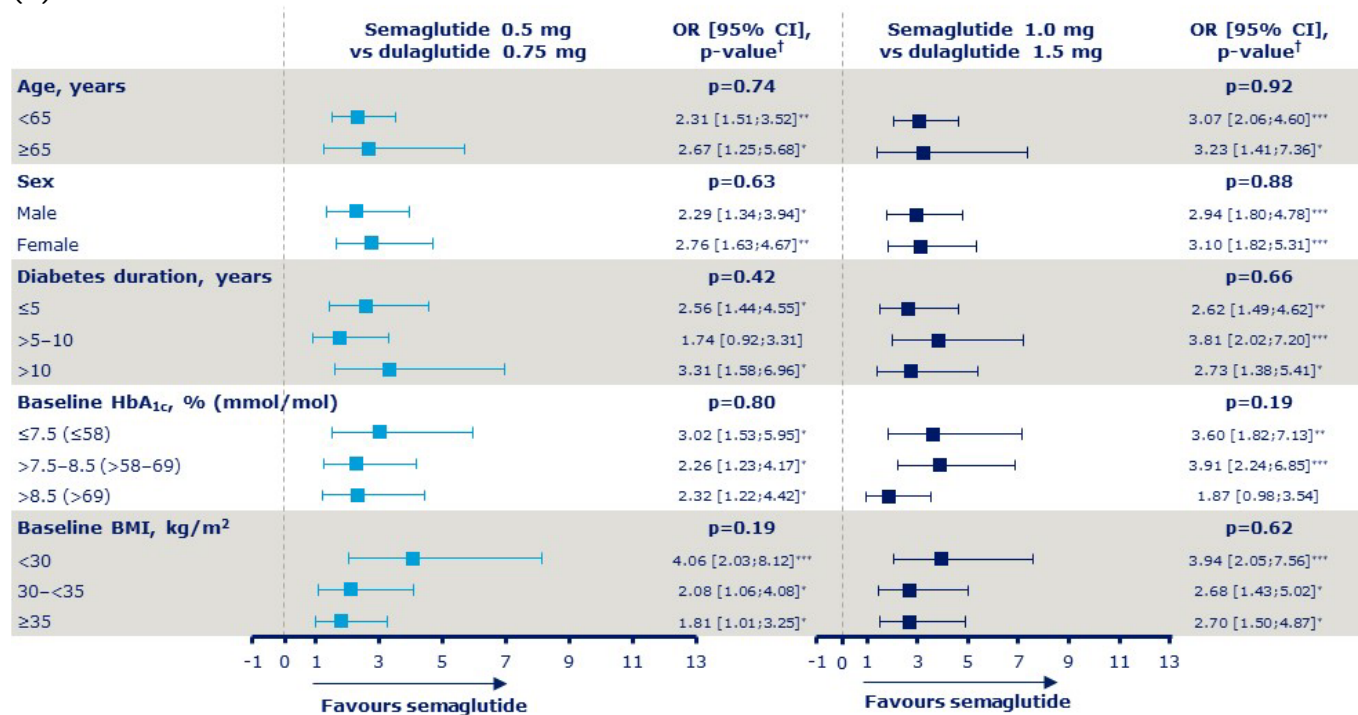
*p<0.05, **p<0.001, ***p<0.0001; [†]p-values represent the test for treatment by subgroup interaction. Values are ORs [95% CIs] from ANCOVAs with multiple imputations using 'on-treatment without rescue medication' data

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3 from all randomised subjects exposed to at least one dose of trial product as randomised (full analysis set)
4 obtained while on treatment and prior to onset of rescue medication. ANCOVA controlled for baseline HbA_{1c} and
5 interaction between randomised treatment and subgroup. ANCOVA, analysis of covariance; BMI, body mass index;
6 CI, confidence interval; HbA_{1c}, glycated haemoglobin; OR, odds ratio.
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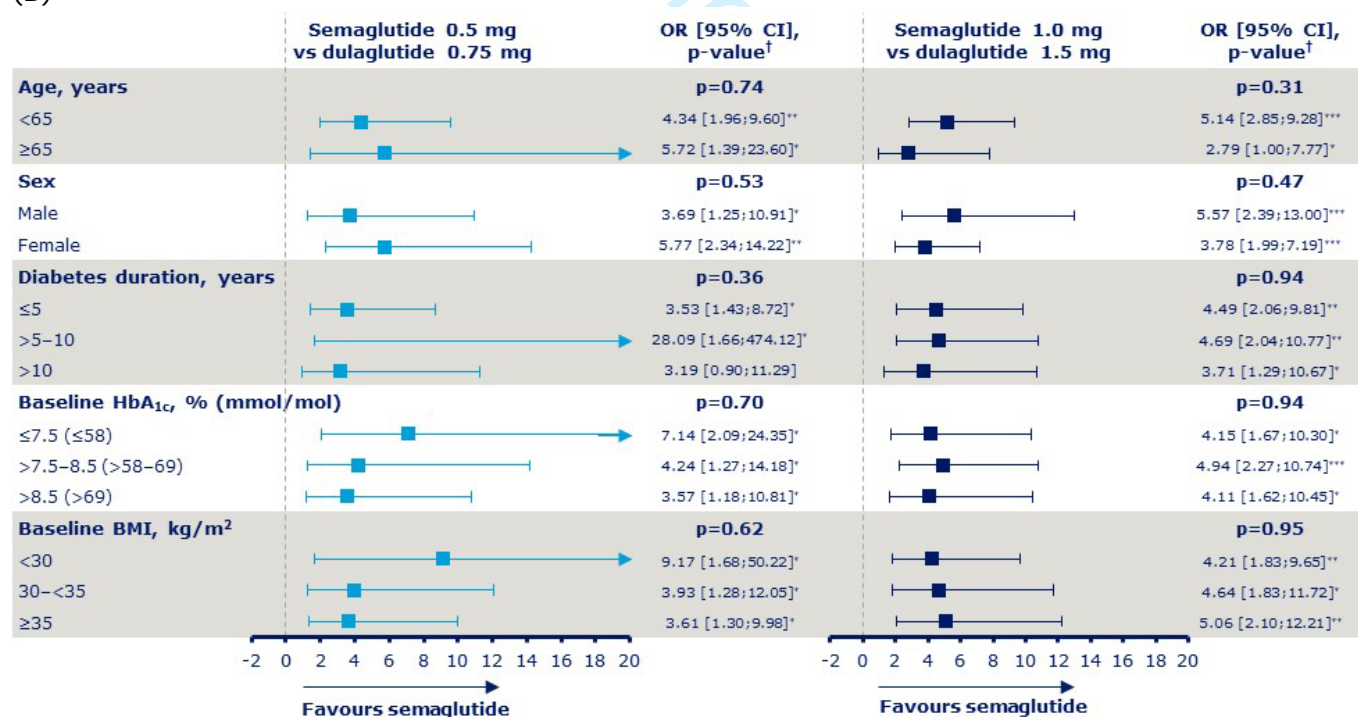
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Supplementary Figure 5. Odds ratios for the proportion of subjects achieving weight loss $\geq 5\%$ (A) and weight loss $\geq 10\%$ (B) at 40 weeks by age, sex, diabetes duration, HbA_{1c} and BMI at baseline

(A)

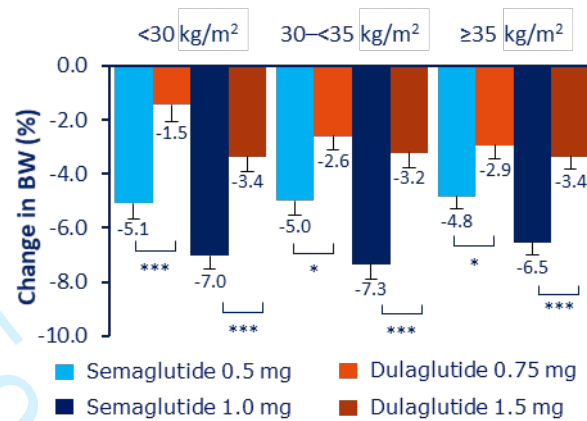


(B)



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

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SUPPLEMENTARY SECTION III: ADVERSE EVENTS

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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)

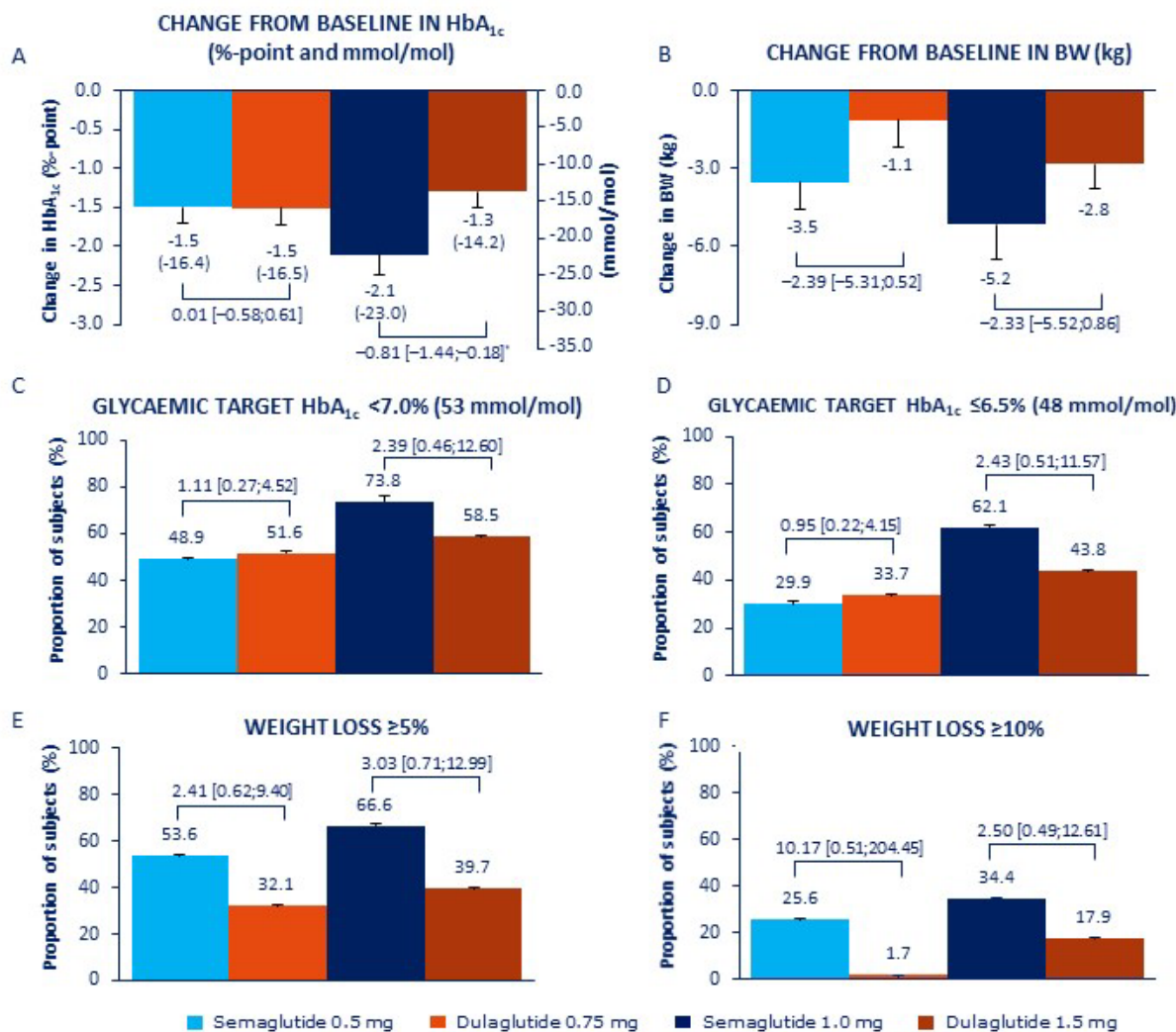
Data are presented as number and proportion in percent of subjects with adverse events. Hypoglycaemia was defined as an episode that was severe (according to the American Diabetes Association classification) or BG-confirmed (plasma glucose value <56 mg/dL [3.1 mmol/L]) with symptoms consistent with hypoglycaemia. 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/m²

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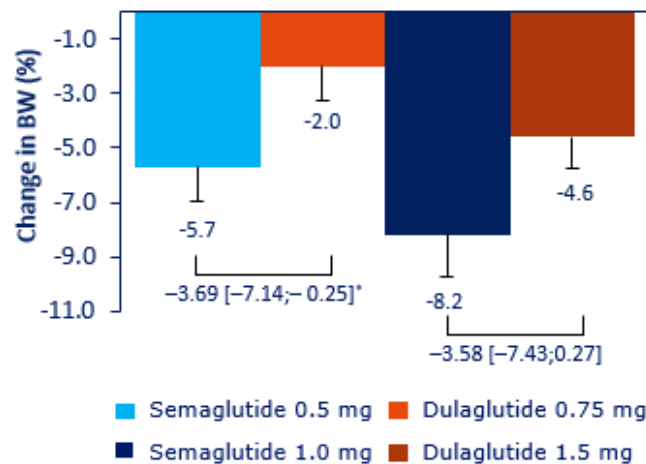
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Supplementary Figure 7. Change in HbA_{1c} (A) and body weight (B) from baseline to week 40 and the proportion of subjects achieving HbA_{1c} <7.0% (53 mmol/mol; C), HbA_{1c} ≤6.5% (48 mmol/mol; D), weight loss ≥5% (E) and weight loss ≥10% (F) in subjects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

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

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4 1 **Title page**

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8 3 semaglutide versus dulaglutide: SUSTAIN 7 *post hoc* analyses
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35 15 **Keywords:** type 2 diabetes, GLP-1, semaglutide, SUSTAIN, age, body mass index
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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% [\leq 58, >58-69, >69 mmol/mol]) and body mass index (BMI) (<30, 30-<35, ≥35 kg/m²).

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% [\leq 53, \leq 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.

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3 51 CONCLUSIONS: Consistently greater improvements in HbA_{1c} and BW with semaglutide
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5 52 versus dulaglutide, regardless of age, sex, diabetes duration, glycaemic control and BMI,
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7 53 support the efficacy of semaglutide across the continuum of care in a heterogeneous T2D
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9 54 population.

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11 55 Clinical Trial Registration: NCT02648204 [ClinicalTrials.gov]
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16 57 **STRENGTHS AND LIMITATIONS OF THIS STUDY**

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19 58 • The analysis was designed to provide insight on the influence of five of the most
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21 59 common and relevant patient-level factors from a clinical perspective
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23 60 • The inclusion of comparator data allows for a more robust analysis and direct
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25 61 comparison of the differences in efficacy and safety of semaglutide versus
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27 62 dulaglutide across the subgroups and subgroup categories
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29 63 • As the analysis is based on SUSTAIN 7 data alone, it may only be representative
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31 64 of the trial-specific patient population
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33 65 • The relatively small number of subjects in each subgroup category is a limitation
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35 66 • As this is a *post hoc* analysis of a randomised clinical trial, there are inherent
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37 67 limitations and, as such, the data should be interpreted with caution
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68 INTRODUCTION

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

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

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

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3 96 trial showed superior reductions in HbA_{1c} and BW with semaglutide versus dulaglutide,
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5 97 for both low-dose (semaglutide 0.5 mg versus dulaglutide 0.75 mg) and high-dose
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7 98 (semaglutide 1.0 mg versus dulaglutide 1.5 mg) comparisons.(36) Although both
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9 99 semaglutide and dulaglutide have individually demonstrated efficacy across multiple
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11 100 patient subpopulations,(23-27,29-35) it is as yet unknown whether the treatment
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13 101 differences observed in the SUSTAIN 7 trial are influenced by heterogeneity in the
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15 102 characteristics of the patients with T2D.

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18 103 To evaluate whether clinically relevant patient characteristics (age, sex, diabetes
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20 104 duration, HbA_{1c} and BMI at baseline) affected the efficacy and safety of semaglutide
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22 105 versus dulaglutide, *post hoc* analyses of data from the SUSTAIN 7 trial were performed.
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25 26 27 107 **MATERIALS AND METHODS**

28 29 108 **Trial design**

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32 109 The design of the SUSTAIN 7 trial has been previously reported.(36) Briefly, this was an
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34 110 open-label trial in which subjects with uncontrolled T2D were randomised to receive
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36 111 semaglutide OW 0.5 mg or 1.0 mg, or dulaglutide OW 0.75 mg or 1.5 mg, as add-on to
37
38 112 background treatment with metformin, and were followed throughout a 40-week
39
40 113 treatment period. Semaglutide was administered subcutaneously via a prefilled injection
41
42 114 device at one of two maintenance dose levels (0.5 mg or 1.0 mg OW), following a fixed-
43
44 115 dose escalation regimen.(36) Dulaglutide was administered subcutaneously in
45
46 116 accordance with the regimen used in the phase 3 clinical trial programme (0.75 mg or
47
48 117 1.5 mg OW), without dose escalation.(37)

49
50 118 The trial was registered with ClinicalTrials.gov (NCT02648204) and conducted in
51
52 119 accordance with the International Conference on Harmonisation Good Clinical Practice
53
54 120 guidelines and the Declaration of Helsinki. The trial protocol (see Supplement) was
55
56 121 approved by the central ethics committees (Eticka komisia, Nemocnica Svateho Michala,
57
58 122 a.s., Bratislava, Slovakia and, for Portugal, Comissão de Ética para a Investigação
59
60

1
2
3 123 Clínica) and by the institutional review boards and ethics committees at each
4
5 124 participating centre (**Supplementary Table 1**) and subjects provided written informed
6
7 125 consent before trial-related activities commenced.
8
9

10 126 **Patient and public involvement**

11
12 127 The research question and endpoints, such as efficacy and safety, were informed
13
14 128 indirectly by patients' priorities, experiences and preferences, via input from clinicians
15
16 129 during advisory board meetings. No patients were involved directly in the design,
17
18 130 recruitment and conduct of the trial. Furthermore, the trial results were not directly
19
20 131 disseminated to trial patients, but were publicly communicated and available via press
21
22 132 release, trial portal and journal publication. In the trial, the burden of intervention was
23
24 133 not assessed by the patients, nor were there any patient advisers involved.
25
26

27 134 **Patient population**

28
29 135 The inclusion and exclusion criteria for the SUSTAIN 7 trial are described in detail
30
31 136 elsewhere.(36) Key inclusion criteria were: diagnosis of T2D; age ≥ 18 years; HbA_{1c}
32
33 137 ≥ 7.0 -10.5% (53-91 mmol/mol). Key exclusion criteria were: estimated glomerular
34
35 138 filtration rate < 60 mL/min/1.73 m²; history of chronic or idiopathic acute pancreatitis;
36
37 139 known proliferative retinopathy or maculopathy requiring acute treatment (determined
38
39 140 by fundoscopy/fundus photography performed within 90 days before randomisation
40
41 141 according to local practice); screening calcitonin value ≥ 50 ng/L; personal/family history
42
43 142 of medullary thyroid carcinoma or multiple endocrine neoplasia syndrome type 2; acute
44
45 143 coronary or cerebrovascular event within 90 days before randomisation; heart failure
46
47 144 (New York Heart Association Class IV); and any of the following: myocardial infarction,
48
49 145 stroke, or hospitalisation for unstable angina and/or transient ischaemic attack within
50
51 146 the past 180 days prior to screening.(36)
52
53

54 147 **Endpoints**

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56
57 148 The primary endpoint was change in HbA_{1c} (%-point) from baseline to end of treatment
58
59 149 at week 40 and the secondary confirmatory endpoint was change in BW (kg) over the
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1
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3 150 same period. Predefined HbA_{1c} treatment targets (proportion of subjects achieving HbA_{1c}
4
5 151 targets of <7% [53 mmol/mol] and ≤6.5% [48 mmol/mol]) and weight-loss responses
6
7 152 (proportion of subjects achieving ≥5% and ≥10% weight loss) were also assessed.
8
9

10 153 The numbers of adverse events (AEs), serious AEs and AEs leading to premature
11
12 154 treatment discontinuation were reported. Specific AEs of clinical interest, such as
13
14 155 gastrointestinal (GI) disorders and hypoglycaemic events, were also evaluated.
15

16 156 **Subgroup analyses**

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18
19 157 For this *post hoc* analysis, subjects were stratified into subgroups selected for potential
20
21 158 clinical relevance: age at baseline (<65 years, ≥65 years), sex (male, female), diabetes
22
23 159 duration at baseline (≤5 years, >5–10 years, >10 years), baseline HbA_{1c} (≤7.5%, >7.5–
24
25 160 8.5%, >8.5% [≤58, >58–69, >69 mmol/mol]) and baseline BMI (<30 kg/m²,
26
27 161 30–<35 kg/m², ≥35 kg/m²). The baseline BMI <25 kg/m² subgroup category was also
28
29 162 evaluated; however, due to the small number of subjects (representing less than 10% of
30
31 163 the total trial population), these data are not included in the Results, but are provided in
32
33 164 the Supplement.
34
35

36 165 **Statistical analyses**

37
38
39 166 The efficacy analyses were based on the full analysis set, comprising all subjects
40
41 167 randomised and exposed to at least one dose of the trial product, using 'on-treatment
42
43 168 without rescue medication' data (as randomised). Analysis of covariance (ANCOVA) was
44
45 169 performed for each endpoint, including the interaction between treatment and subgroup
46
47 170 as a factor. Multiple imputation was used to account for missing data. Specifically, using
48
49 171 a sequential multiple-imputation approach, missing values for the underlying continuous
50
51 172 assessments were imputed by treatment group, assuming missing data were missing at
52
53 173 random, and based on a linear-regression model. A sequential conditional-regression
54
55 174 approach was applied whereby missing observations at any post-baseline visits were
56
57 175 imputed based on a linear-regression model and incorporating observations from
58
59
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1
2
3 176 previous visits including baseline. Binary endpoints were created and logistic-regression
4
5 177 models run on the complete data set; inference was drawn using Rubin's rule.(38)
6
7
8 178 Values for the mean change from baseline for HbA_{1c} and BW were calculated, and the
9
10 179 data are presented as mean and standard error. Estimated treatment differences (ETDs)
11
12 180 for the change from baseline in HbA_{1c} and BW, and odds ratios (ORs) for the proportions
13
14 181 of subjects achieving HbA_{1c} targets or weight-loss responses, both with 95% confidence
15
16 182 intervals, were also calculated for the low-dose (semaglutide 0.5 mg versus dulaglutide
17
18 183 0.75 mg) and high-dose (semaglutide 1.0 mg versus dulaglutide 1.5 mg) comparisons.
19
20 184 To evaluate the evidence of heterogeneity of treatment effects across the clinical
21
22 185 characteristics, a p-value for interaction between treatment effect and subgroup
23
24 186 categories was calculated for both dose comparisons in all subgroup analyses, without
25
26 187 adjustment for multiplicity.

27
28 188 Safety analyses were based on the safety analysis set, which included all randomised
29
30 189 subjects who were exposed to at least one dose of trial product, based on 'as-treated'
31
32 190 data and summarised descriptively. Safety was assessed within each treatment arm
33
34 191 (semaglutide 0.5 mg, dulaglutide 0.75 mg, semaglutide 1.0 mg, dulaglutide 1.5 mg) in
35
36 192 each of the subgroup categories.

37
38
39 193 Analyses were conducted using SAS version 9.4. Baseline characteristics and AEs are
40
41 194 provided as descriptive data only.

42
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44 195

45 46 196 **RESULTS**

47 48 49 197 **Subject disposition and baseline characteristics**

50
51 198 Baseline characteristics are summarised by treatment arm within each subgroup
52
53 199 category (**Table 1; Supplementary Tables 2–6**). Subject characteristics were
54
55 200 generally comparable across subgroup categories with some exceptions. In all treatment
56
57 201 arms, diabetes duration was longer, and BW and BMI were lower in the elderly (≥65
58
59 202 years) subgroup compared with the non-elderly (<65 years) subgroup (**Table 1**). Males

1
2
3 203 were generally heavier but with a lower BMI, and had a longer diabetes duration than
4
5 204 females (**Supplementary Table 2**). In the diabetes duration subgroup categories (≤ 5
6
7 205 years, $>5-10$ years, >10 years), age increased with increasing diabetes duration and, in
8
9 206 the semaglutide 1.0 mg treatment arm, BW and BMI decreased with increasing diabetes
10
11 207 duration (**Supplementary Table 3**). Across the baseline HbA_{1c} subgroups ($\leq 7.5\%$,
12
13 208 $>7.5-8.5$, $>8.5\%$ [≤ 58 , $>58-69$, >69 mmol/mol]), subjects in the semaglutide 0.5 mg
14
15 209 treatment arm exhibited decreasing BW and BMI with increasing HbA_{1c} (**Supplementary**
16
17 210 **Table 4**). In keeping with the distribution of subjects in the sex subgroup categories,
18
19 211 there was a greater proportion of females versus males in the two highest BMI
20
21 212 subgroups, and the proportion of Asian subjects was higher in the subgroup with the
22
23 213 lowest BMI versus the subgroup with the highest BMI (**Supplementary Table 5**). When
24
25 214 compared with the other BMI subgroup categories, subjects with BMI <25 kg/m² had the
26
27 215 highest HbA_{1c} levels, the highest proportions of male and Asian subjects and, as
28
29 216 expected, the lowest BW (**Supplementary Table 6**).

217 **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)

218 'On-treatment without rescue medication' data. Subgroup data are presented as mean (standard deviation) unless otherwise indicated. BMI: body mass index; Dula:
 219 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:
 220 semaglutide.

221 **Glycaemic control and body weight changes**

222 Missing observations in the efficacy analyses were mainly due to subjects who
223 discontinued treatment or received rescue medication. At week 40, between 81% and
224 86% of subjects were on treatment without initiation of rescue medication in the four
225 treatment arms (**Supplementary Figure 1**).

226 Overall, the mean changes from baseline in HbA_{1c} and BW (**Supplementary Figure 2**)
227 and the proportions of subjects achieving HbA_{1c} targets of <7% (53 mmol/mol) and ≤
228 6.5% (48 mmol/mol) and weight-loss responses of ≥5% and ≥10% (**Figures 1 and 2**)
229 were of greater magnitude with semaglutide versus dulaglutide treatment. This
230 observation was confirmed by the ETDs for change from baseline (**Figure 3**) and the
231 ORs for proportions of subjects (**Supplementary Figures 3 and 4**) which significantly
232 favoured semaglutide in the majority of both the low-dose and high-dose comparisons
233 within each subgroup category.

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

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

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

1
2
3 248 Diabetes duration at baseline (≤ 5 years, $>5-10$ years, >10 years): comparatively
4
5 249 smaller numeric reductions in HbA_{1c} and BW were observed with semaglutide 1.0 mg in
6
7 250 subjects with diabetes duration of >10 years versus ≤ 10 years, with no apparent
8
9 251 differences observed in the other treatment arms (**Supplementary Figure 2E and F**).
10
11 252 A similar pattern was observed for the proportions of subjects achieving glycaemic
12
13 253 targets and weight-loss responses in the semaglutide 1.0 mg treatment group (**Figure**
14
15 254 **1E and F, and 2E and F**).

16
17
18 255 Baseline HbA_{1c} ($\leq 7.5\%$, $>7.5-8.5\%$, $>8.5\%$ [≤ 58 , $>58-69$, >69 mmol/mol]): with
19
20 256 semaglutide 0.5 mg, and to a greater degree with semaglutide 1.0 mg, the magnitude of
21
22 257 the mean reduction in HbA_{1c} from baseline increased numerically with increasing baseline
23
24 258 HbA_{1c}; the converse was apparent for BW, whereby the amount of weight lost was less
25
26 259 with increasing baseline HbA_{1c} (**Supplementary Figure 2G and H**). A similar though
27
28 260 less apparent pattern was observed with dulaglutide (**Supplementary Figure 2G and**
29
30 261 **H**), and this was reflected in the proportions of subjects achieving glycaemic targets
31
32 262 (**Figure 1G and H**). Across baseline HbA_{1c} subgroups, the greatest proportion of
33
34 263 subjects achieving $\geq 5\%$ weight loss was observed in those subjects receiving
35
36 264 semaglutide 1.0 mg, particularly in the HbA_{1c} subgroup categories of $\leq 7.5\%$ (58
37
38 265 mmol/mol) and $>7.5-8.5\%$ (58-69 mmol/mol) (**Figure 2G**). There were no other
39
40 266 apparent differences across the subgroup categories regarding the proportions of
41
42 267 subjects achieving weight-loss responses (**Figure 2G and H**).

43
44
45 268 Baseline BMI (<30 kg/m², $30- <35$ kg/m², ≥ 35 kg/m²): There were no apparent trends in
46
47 269 glycaemic outcomes across the BMI categories for either dose comparison (**Figure 1I**
48
49 270 **and J; Supplementary Figure 2I**). Mean reductions in BW for both semaglutide and
50
51 271 dulaglutide increased numerically with increasing baseline BMI, with the greatest
52
53 272 reductions in the ≥ 35 kg/m² BMI subgroup category for all treatment arms
54
55 273 (**Supplementary Figure 2J**). There were no apparent trends in other BW outcomes
56
57 274 across the BMI categories for either dose comparison (**Figure 2I and J;**
58
59 275 **Supplementary Figure 2J**), or when BW reduction was expressed as percentage

1
2
3 276 change (**Supplementary Figure 5**). Changes in the <25 kg/m² BMI subgroup were
4
5 277 largely consistent with those observed in the broader population (**Supplementary**
6
7 278 **Figures 6 and 7**).

279 **Treatment–subgroup interaction effects**

11
12 280 For each of the subgroups, analysis of the ETDs for the change from baseline in HbA_{1c} in
13
14 281 the age, sex, diabetes duration, baseline HbA_{1c} and baseline BMI subgroups, the
15
16 282 p-values for the low-dose and high-dose comparisons were nonsignificant, except in the
17
18 283 analysis of the HbA_{1c} subgroups within the low-dose comparison (p<0.05 for the
19
20 284 treatment–subgroup interaction effect) (**Figure 3A and B**). The change from baseline in
21
22 285 BW in the age, sex, diabetes duration, baseline HbA_{1c} and baseline BMI subgroups was
23
24 286 similar, with nonsignificant treatment–subgroup interactions for both dose comparisons
25
26 287 (**Figure 3C**). Similarly, treatment–subgroup interactions were nonsignificant for the
27
28 288 analysis of the ORs for the proportions of subjects achieving glycaemic targets and
29
30 289 weight-loss responses (**Supplementary Figures 3 and 4**).

32 33 290 **Safety outcomes**

34
35 291 Overall, AEs were reported in more than half of subjects irrespective of the subgroup
36
37 292 category (ranging from 55.3% [dulaglutide 0.75 mg; diabetes duration >5–10 years] to
38
39 293 80.6% [dulaglutide 1.5 mg; elderly]) and were generally more common with
40
41 294 semaglutide 0.5 mg than with dulaglutide 0.75 mg, and less common with semaglutide
42
43 295 1.0 mg than with dulaglutide 1.5 mg. Premature treatment discontinuations due to AEs
44
45 296 were higher with semaglutide than with dulaglutide, and were primarily due to GI AEs
46
47 297 (**Table 2; Supplementary Tables 7–10**).

298 **Table 2. Adverse events by age**

n (%)	<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
	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

299 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
300 Diabetes Association classification) or BG-confirmed (plasma glucose value <56 mg/dL [3.1 mmol/L]) with symptoms consistent with hypoglycaemia. AE: adverse event;
301 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:
302 semaglutide.

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4 303 GI AEs were the most frequently reported events, with generally higher rates with
5
6 304 semaglutide 0.5 mg versus dulaglutide 0.75 mg, and dulaglutide 1.5 mg versus
7
8 305 semaglutide 1.0 mg, across the subgroups and subgroup categories (ranging from
9
10 306 27.7% [dulaglutide 0.75 mg; diabetes duration >5–10 years] to 59.5% [dulaglutide 1.5
11
12 307 mg; HbA_{1c} ≤7.5% [58 mmol/mol]), with nausea being the most common (ranging from
13
14 308 8.1% [dulaglutide 0.75 mg; male] to 29.5% [semaglutide 0.5 mg; female]) (**Table 2;**
15
16 309 **Supplementary Tables 7–10**). Across the subgroup categories, more female than
17
18 310 male subjects reported GI AEs overall, with GI AEs generally decreasing with increasing
19
20 311 BMI in subjects treated with semaglutide (**Supplementary Tables 7 and 10**). The
21
22 312 highest proportion of GI AEs were reported by subjects with BMI <25 kg/m²
23
24 313 (**Supplementary Table 11**).

25
26 314

29 315 **DISCUSSION**

31
32 316 Given the heterogeneous profile of patients with T2D and the guidance for such
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34 317 differences to be considered when making treatment choices,(2,3) this *post hoc* analysis
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36 318 of SUSTAIN 7 data assessed the impact of individual clinical characteristics on the effect
37
38 319 of semaglutide versus dulaglutide treatment. The analyses indicate that the effect of
39
40 320 semaglutide versus dulaglutide was not influenced by age, sex, diabetes duration, HbA_{1c}
41
42 321 or BMI at baseline, with the exception of the low-dose comparison for HbA_{1c} in the
43
44 322 baseline HbA_{1c} subgroup, which showed increasing efficacy for semaglutide 0.5 mg
45
46 323 versus dulaglutide 0.75 mg in subjects with increasing HbA_{1c} at baseline.

47
48 324 This *post hoc* analysis supports the finding from the overall SUSTAIN 7 trial that
49
50 325 semaglutide was superior to dulaglutide in reducing HbA_{1c} and BW;(36) the same was
51
52 326 observed across each of the subgroups and within the various subgroup categories
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54 327 presented here.

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56
57 328 This *post hoc* analysis also supports findings from similar subgroup analyses of SUSTAIN
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59 329 trials. An analysis of SUSTAIN 1–5 data showed greater reductions in HbA_{1c} and BW with
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3 330 semaglutide versus comparators, and comparable efficacy in elderly subjects (a
4
5 331 population often presenting with comorbidities) and non-elderly subjects, without an
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7 332 increased risk of hypoglycaemia.(25) Similarly, analyses of pooled SUSTAIN data showed
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9 333 clinically relevant reductions in HbA_{1c} and BW with semaglutide, regardless of baseline
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11 334 BW, HbA_{1c}, diabetes duration, race and ethnicity.(23-26,28)
12
13
14 335 HbA_{1c} reductions were greater with increasing baseline HbA_{1c} for both semaglutide and
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16 336 dulaglutide in the present analyses, which has been observed with dulaglutide
17
18 337 previously,(29,31-33) as well as with liraglutide,(39) lixisenatide (40) and other
19
20 338 antihyperglycaemic agents. Furthermore, a converse relationship between weight loss
21
22 339 and baseline HbA_{1c} levels was observed, whereby increasing baseline HbA_{1c} was
23
24 340 associated with greater reductions in HbA_{1c} but a decreasing magnitude of weight loss. A
25
26 341 similar pattern has been observed with liraglutide as an add-on to insulin treatment,(41)
27
28 342 with exenatide alone (42) and with dulaglutide.(31,32) These findings have relevance for
29
30 343 clinical practice, indicating that there may be an effect with GLP-1RAs (and potentially
31
32 344 other antihyperglycaemic therapies) in predicting treatment responses based on HbA_{1c}
33
34 345 levels.(41) Conversely, a recent analysis of the AWARD trials found a weak positive
35
36 346 correlation between HbA_{1c} reduction and weight loss with dulaglutide.(43) Several
37
38 347 mechanisms, also associated with other antihyperglycaemic agents, may contribute to
39
40 348 these results.(44) Improved treatment-related glycaemic control is associated with
41
42 349 decreased glycosuria,(41,44) normalised protein turnover and a decreased catabolic
43
44 350 effect,(44) in addition to decreased energy expenditure and resting metabolic rate.(44)
45
46 351 As GLP-1RAs exhibit a glucose-dependent mechanism of action, the greater post-
47
48 352 treatment reductions in HbA_{1c} from a higher initial baseline HbA_{1c} may contribute to the
49
50 353 retention of glucose calories and, thereby, moderation of the achievable weight loss. In
51
52 354 these analyses, greater weight loss was observed with increasing baseline BMI for both
53
54 355 semaglutide and dulaglutide, aligning with what has been previously reported for
55
56 356 semaglutide (23) and dulaglutide.(35) While percentage weight loss was also greater
57
58 357 with semaglutide versus dulaglutide, the percentage change in weight loss was generally
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3 358 of a similar magnitude across BMI categories, indicating that the weight-loss pattern
4
5 359 observed across the HbA_{1c} subgroup categories may be associated with subjects'
6
7 360 baseline BMI. High BMI is associated with an insulin-resistant phenotype in some
8
9 361 patients,(3) and less weight loss is observed in patients with diabetes who are insulin
10
11 362 resistant than in those with insulin sensitivity.(45) However, clinically relevant reductions
12
13 363 in BW were achieved for all BMI subgroup categories, and the magnitude of weight loss
14
15 364 was comparatively greater for semaglutide than for dulaglutide. This is an important
16
17 365 consideration for clinical practice, given the increasing interest in weight management as
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19 366 a key aspect of treatment for T2D.(1)

21
22 367 Analysis of the ETDs for change from baseline in HbA_{1c} and BW and ORs for the
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24 368 proportions of subjects achieving HbA_{1c} targets or weight-loss responses indicated a
25
26 369 consistent effect of semaglutide versus dulaglutide across subgroup categories. These
27
28 370 findings are aligned with previous analyses of subpopulations treated with GLP-1RAs,
29
30 371 including semaglutide and dulaglutide, which also reported a nonsignificant impact of
31
32 372 age, sex or diabetes duration on treatment effect,(23-27,29-35) although weight loss
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34 373 tended to be greater in women than in men with dulaglutide,(31) as was also observed
35
36 374 in this analysis.

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38
39 375 Consistent with the known class effect of GLP-1RAs,(46) both semaglutide and
40
41 376 dulaglutide reported relatively high levels of GI AEs. The rate of GI AEs was higher with
42
43 377 semaglutide versus dulaglutide in the low-dose comparison; in the high-dose comparison
44
45 378 it was higher with dulaglutide versus semaglutide.(36) Premature treatment
46
47 379 discontinuations due to AEs were higher with semaglutide than with dulaglutide, which
48
49 380 may be due to the higher levels of moderate GI AEs observed in the overall SUSTAIN 7
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51 381 trial.(36) The occurrence of some GI AEs may be dose-dependent, and nausea (and
52
53 382 also vomiting for semaglutide) is usually transient with both semaglutide (47) and
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55 383 dulaglutide;(14) furthermore, the dose-escalation regimen approved for semaglutide has
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57 384 been shown to mitigate these AEs.(47) In the subgroups in the present analyses, GI AEs
58
59 385 were higher with dulaglutide 1.5 mg versus semaglutide 1.0 mg in elderly subjects with
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3 386 longer diabetes duration, and lower in subjects with HbA_{1c} >8.5% (69 mmol/mol) and
4
5 387 higher BMI. There were no other associations between subjects' baseline characteristics
6
7 388 with the incidence of GI AEs. Subjects who experience GI AEs, specifically nausea and
8
9 389 vomiting, have greater weight loss compared with those who do not.(23,48) While this
10
11 390 hypothesised association might be considered an explanation for the observed greater
12
13 391 weight loss with semaglutide versus dulaglutide in the low-dose comparison, a mediation
14
15 392 analysis has previously shown that the direct effects of semaglutide on BW are the main
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17 393 contributors to weight loss with very little effect attributable to GI AEs.(48,49). Our
18
19 394 analyses support this finding as, overall, there were no clear trends between the
20
21 395 incidence of GI AEs and the greater efficacy of semaglutide in terms of HbA_{1c} reduction
22
23 396 and weight loss versus dulaglutide.(31) With semaglutide, there was a trend towards
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25 397 decreasing GI AEs with increasing baseline BMI, which has also been previously reported
26
27 398 for the SUSTAIN 1–5 (23) and the AWARD 1–6 (50) trials, and may be due to differences
28
29 399 in exposure–response levels associated with BW as has been demonstrated with
30
31 400 semaglutide.(51) Similarly, an analysis has shown that elderly patients with a lower BMI
32
33 401 are more likely to experience side effects (including GI AEs) with dulaglutide than
34
35 402 younger patients with a higher BMI.(50) However, it is noted that this was a *post hoc*
36
37 403 analysis in Japanese patients, with low event rates for some GI AEs, and so the results
38
39 404 may not be generalizable to a wider diabetes population. In either case, a dose-
40
41 405 escalation regimen may be beneficial.

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43
44 406 A strength of the present analysis is the inclusion of comparator data, which allows for a
45
46 407 more robust analysis and direct comparison of the differences in efficacy and safety of
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48 408 semaglutide versus dulaglutide across the subgroups and subgroup categories, and also
49
50 409 the use of multiple imputation that helps to conserve randomisation. However, the *post*
51
52 410 *hoc* nature of this analysis means there are inherent limitations and, as such, the data
53
54 411 should be interpreted with caution. Also, as the analysis is based on SUSTAIN 7 alone, it
55
56 412 may only be representative of the trial-specific patient population. A further limitation is
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58 413 the relatively small number of subjects in each subgroup category, which means that the
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3 414 findings should be interpreted with caution. Additionally, in the age subgroups, there was
4
5 415 an imbalance in subject numbers (elderly versus non-elderly), with relatively few
6
7 416 patients in the elderly subgroup (260; 22% of the analysis population). However, given
8
9 417 the overall consistency of the age-subgroup analyses, as well as the general limitations
10
11 418 of these *post hoc* analyses, the difference in subject numbers between the age subgroup
12
13 419 categories seemed to have had little or no impact. Furthermore, elderly subjects in
14
15 420 previous pooled analyses of the SUSTAIN 1-5 (26) and AWARD (30,32) trials have
16
17 421 demonstrated similar efficacy and safety, supporting the results obtained here.
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19
20 422 Understanding the impact of heterogeneity in patient characteristics on treatment effects
21
22 423 is important for clinical practice. This analysis provides insight on the influence of five of
23
24 424 the most common and relevant patient-level factors from a clinical perspective and
25
26 425 highlights semaglutide as an effective choice across these patient subgroups that are
27
28 426 commonly encountered in clinical practice.
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31 32 33 428 **CONCLUSIONS**

34
35 429 Semaglutide was associated with superior efficacy to dulaglutide across various clinically
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37 430 relevant patient subgroups that are commonly encountered in clinical practice, with a
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39 431 safety profile similar to other GLP-1RAs and in line with previously published data for
40
41 432 semaglutide. The treatment effect for semaglutide versus dulaglutide did not appear to
42
43 433 be influenced by age, sex, diabetes duration, HbA_{1c} or BMI at baseline. Together with
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45 434 results from other studies and from experience in clinical practice, these findings support
46
47 435 the efficacy of semaglutide across the continuum of care in a heterogeneous T2D
48
49 436 population.
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491

492 **DATA SHARING STATEMENT**

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

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3 496 redacted clinical study report will be available according to Novo Nordisk data sharing
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5 497 commitments. Data will be available permanently after research completion and
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7 498 approval of product and product use in the European Union and USA. Data will only be
8
9 499 shared with *bona fide* researchers submitting a research proposal and requesting access
10
11 500 to data, for use as approved by the independent review board and according to its
12
13 501 charter. The access request proposal form and the access criteria can be found online.
14
15 502 Data will be made available on a specialised Statistical Analysis System data platform.
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18 503

20 504 **AUTHOR CONTRIBUTIONS**

22
23 505 RP: conduct of trial, data collection, data analysis, data interpretation, manuscript
24
25 506 preparation, approval of submitted version; VA: conduct of trial, data collection, data
26
27 507 interpretation, manuscript preparation, approval of submitted version; AMC: data
28
29 508 interpretation, manuscript preparation, approval of submitted version; IL: conduct of
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31 509 trial, data collection, data interpretation, manuscript preparation, approval of submitted
32
33 510 version; JL: conduct of the trial, data collection, data interpretation, manuscript
34
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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

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9 treatment (full analysis set) obtained while on treatment and prior to onset of rescue
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11 medication. ANCOVA controlled for baseline HbA_{1c} (A) or body weight (B) and interaction
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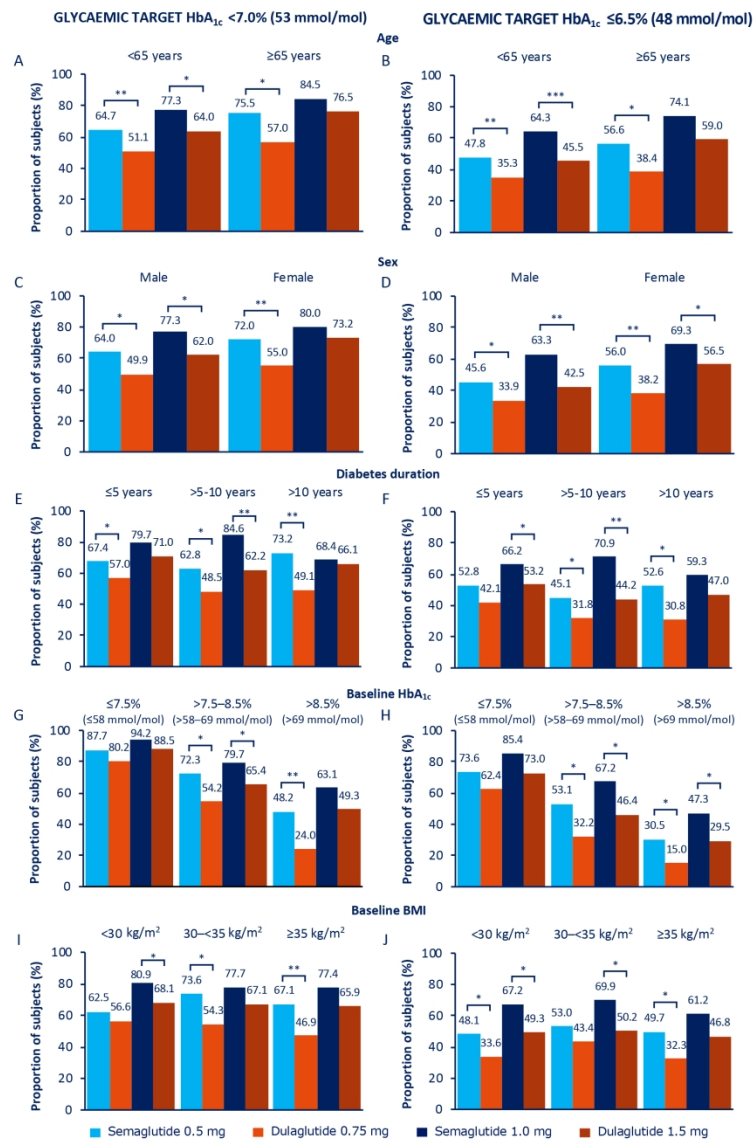


Figure 1. Proportion of subjects achieving HbA_{1c} < 7.0% (53 mmol/mol; A, C, E, G and I) and HbA_{1c} ≤6.5% (48 mmol/mol; B, D, F, H and J) at 40 weeks. *p<0.05, **p<0.001, ***p<0.0001. Values are estimated proportions from ANCOVAs with multiple imputations using 'on-treatment without rescue medication' 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.

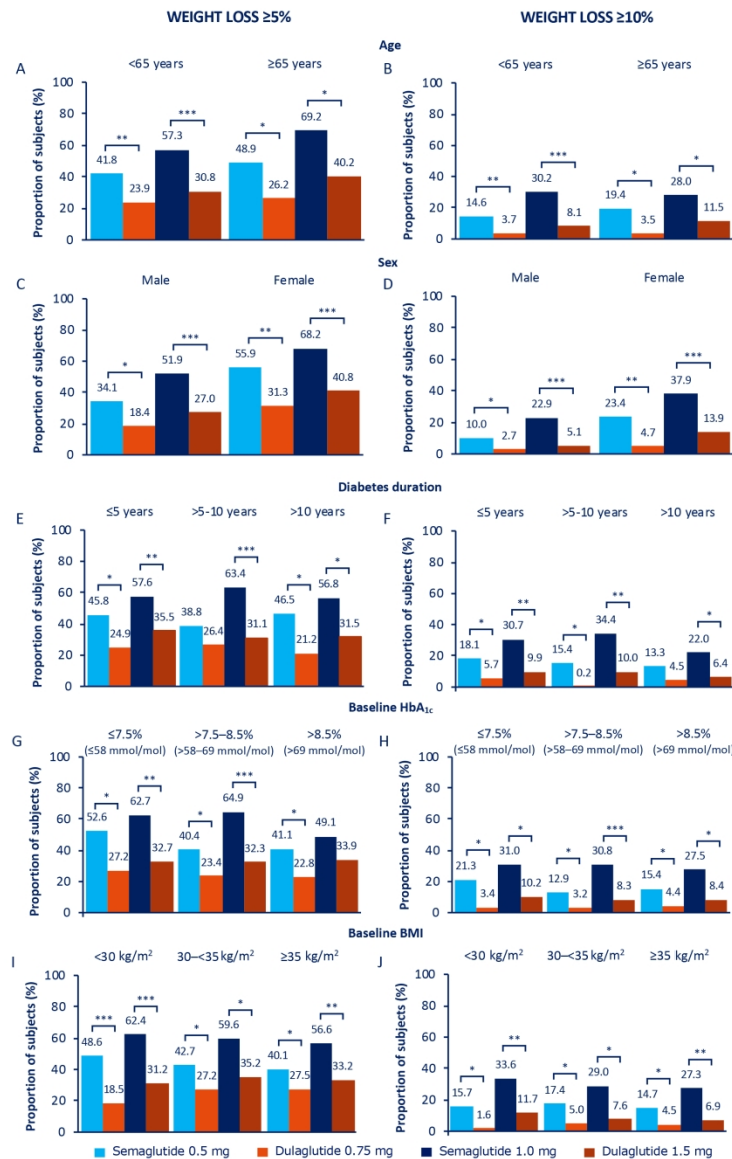


Figure 2. Proportion of subjects achieving weight loss $\geq 5\%$ (A, C, E, G and I) and weight loss $\geq 10\%$ (B, D, F, H and J) at 40 weeks. * $p < 0.05$, ** $p < 0.001$, *** $p < 0.0001$. Values are estimated proportions from ANCOVAs with multiple imputations using 'on-treatment without rescue medication' 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.

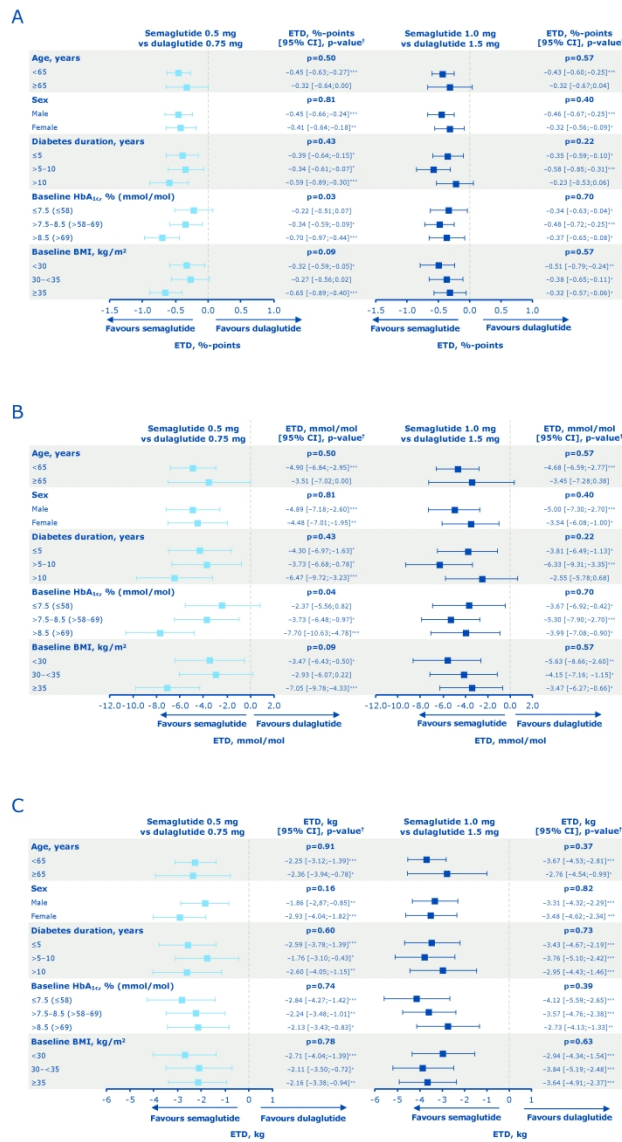


Figure 3. Estimated treatment differences for change from baseline in HbA_{1c} shown as %-points (A), HbA_{1c} shown as mmol/mol (B) and body weight (C) at week 40 by age, sex, diabetes duration, HbA_{1c} and BMI at baseline. *p<0.05, **p<0.001, ***p<0.0001; †p values represent the test for treatment 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

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3 **SUPPLEMENTARY SECTION I: INDEPENDENT ETHICS COMMITTEES**
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Supplementary Table 1. Independent ethics committees for SUSTAIN 7

Country	Independent ethics committees
Bulgaria	<ul style="list-style-type: none"> Ethics Committee for Multicenter Clinical Trials
Croatia	<ul style="list-style-type: none"> Agencija za lijekove i medicinske proizvode
Finland	<ul style="list-style-type: none"> Ethics Committee of the Hospital District of Southwest Finland
Germany	<ul style="list-style-type: none"> Ethikkommission der Ärztekammer des Saarlandes
Greece	<ul style="list-style-type: none"> National Ethics Committee Private Clinic, Iatriko Palaiau 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	<ul style="list-style-type: none"> Joint Chinese University of Hong Kong – New Territories East Cluster Clinical Research Ethics Committee
India	<ul style="list-style-type: none"> 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

	<ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> • Ethics Committee for Clinical Research at Pauls Stradins Clinical University Hospital Development Society
Lithuania	<ul style="list-style-type: none"> • Lithuanian Bioethics Committee
Portugal	<ul style="list-style-type: none"> • Comissão de Ética para a Investigação Clínica
Romania	<ul style="list-style-type: none"> • National Bioethics Committee for Medicine and Medical Devices
Slovakia	<ul style="list-style-type: none"> • Eticka komisia, Sabinovska 16 • Eticka komisia, Nemocnica Svateho Michala, a.s. (Central IEC) • Eticka komisia, Trencianskeho samospravného kraja • Eticka komisia, Nitrianskeho samospravného kraja • Etická komisia, Presovskeho samospravného kraja • Eticka komisia, Trnavskeho samospravného kraja
Spain	<ul style="list-style-type: none"> • Comité Coordinador de Ética de la Investigación Biomédica de Andalucía • CEI Provincial de Málaga
UK	<ul style="list-style-type: none"> • 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

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	<ul style="list-style-type: none">• Research and Development Department Clinical Trial Facility, Moorgreen Hospital• R&D Department, University Hospital Southampton NHS Foundation Trust
USA	<ul style="list-style-type: none">• 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

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3 **SUPPLEMENTARY SECTION II: BASELINE CHARACTERISTICS**
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Supplementary Table 2. Baseline characteristics by sex subgroups

	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
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

	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
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.

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

	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
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.

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

		<30 kg/m ²				30–<35 kg/m ²				≥35 kg/m ²			
	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/m ²	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)

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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.

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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/m ²	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)

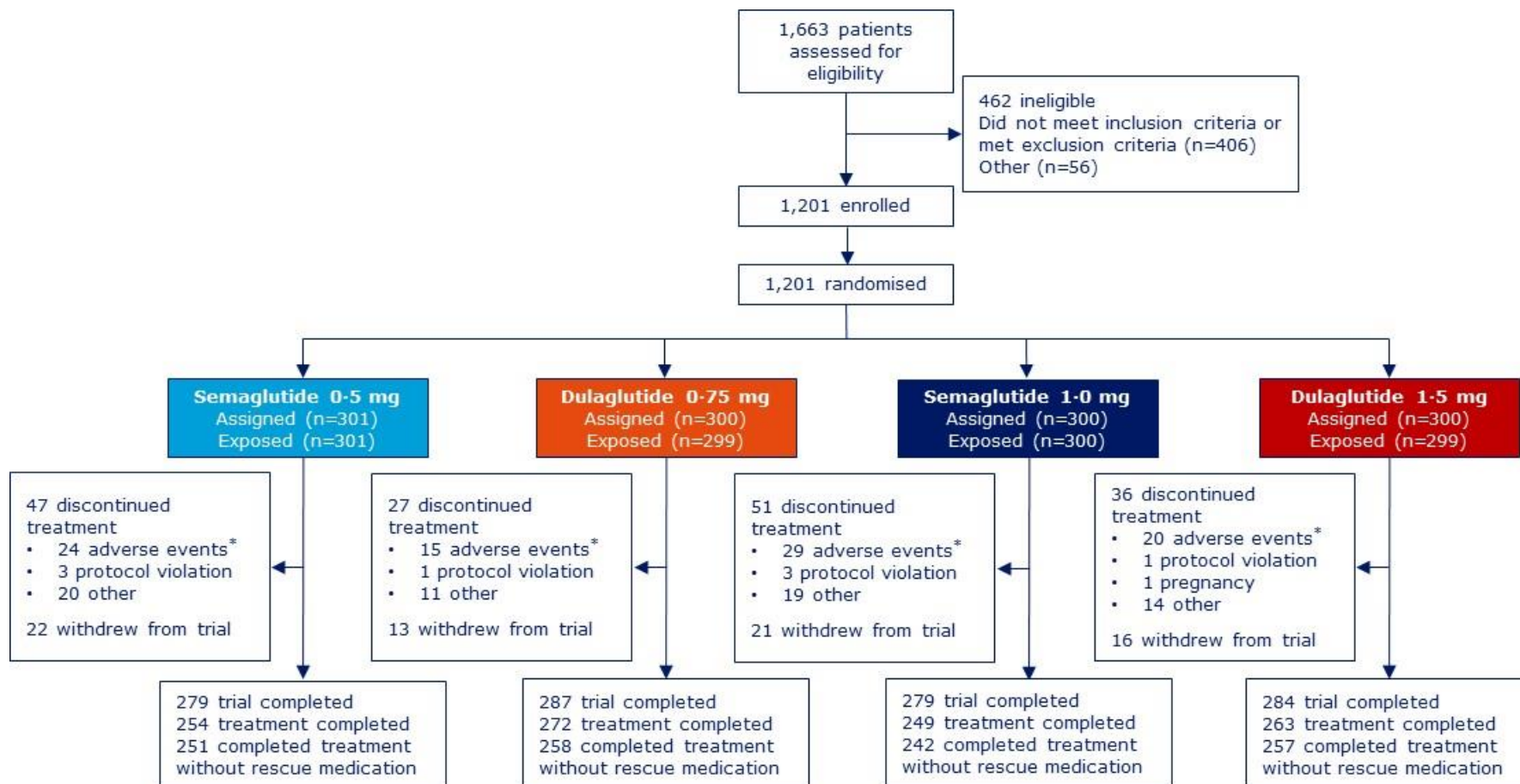
'On-treatment without rescue medication' data. Subgroup data are presented as mean (standard deviation) unless otherwise indicated. BMI: body mass index; Dula: dulaglutide; HbA_{1c}: glycated haemoglobin; n: number of subjects randomised and exposed to at least one dose of trial product as randomised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

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SUPPLEMENTARY SECTION III: SUBJECT DISPOSITION

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Supplementary Figure 1. Subject disposition in SUSTAIN 7.



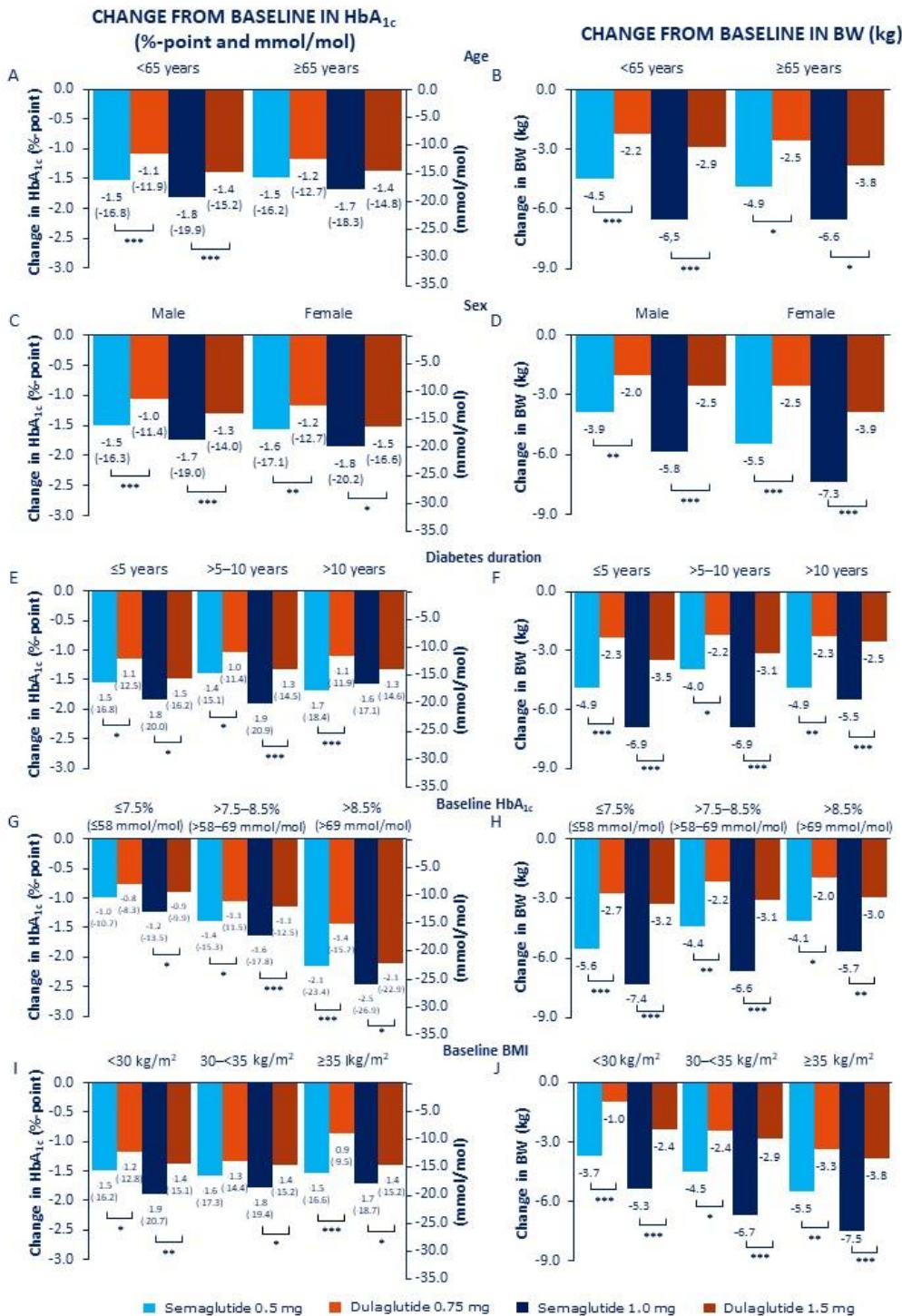
*Reflects primary reason for treatment discontinuation, as judged by the investigator. 'Completed trial' refers to those patients who attended the follow-up visit. 'Completed treatment' refers to those patients who did not discontinue treatment prematurely (with or without the addition of rescue medication).

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SUPPLEMENTARY SECTION IV: GLYCAEMIC TARGETS & WEIGHT-LOSS RESPONSES

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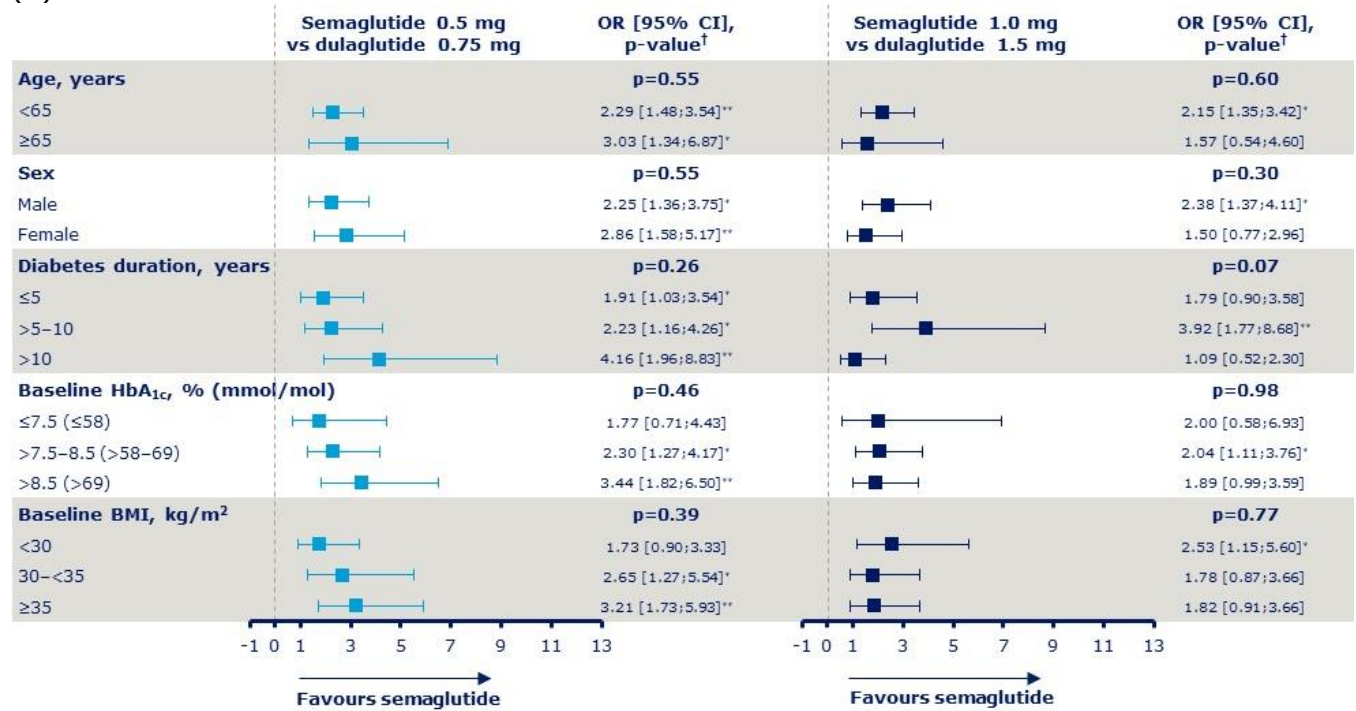
Supplementary Figure 2. Change from baseline in HbA_{1c} (A, C, E, G, I) and body weight (B, D, F, H, J) at week 40 by age (A, B), sex (C, D), diabetes duration (E, F), HbA_{1c} (G, H) and BMI (I, J) at baseline.



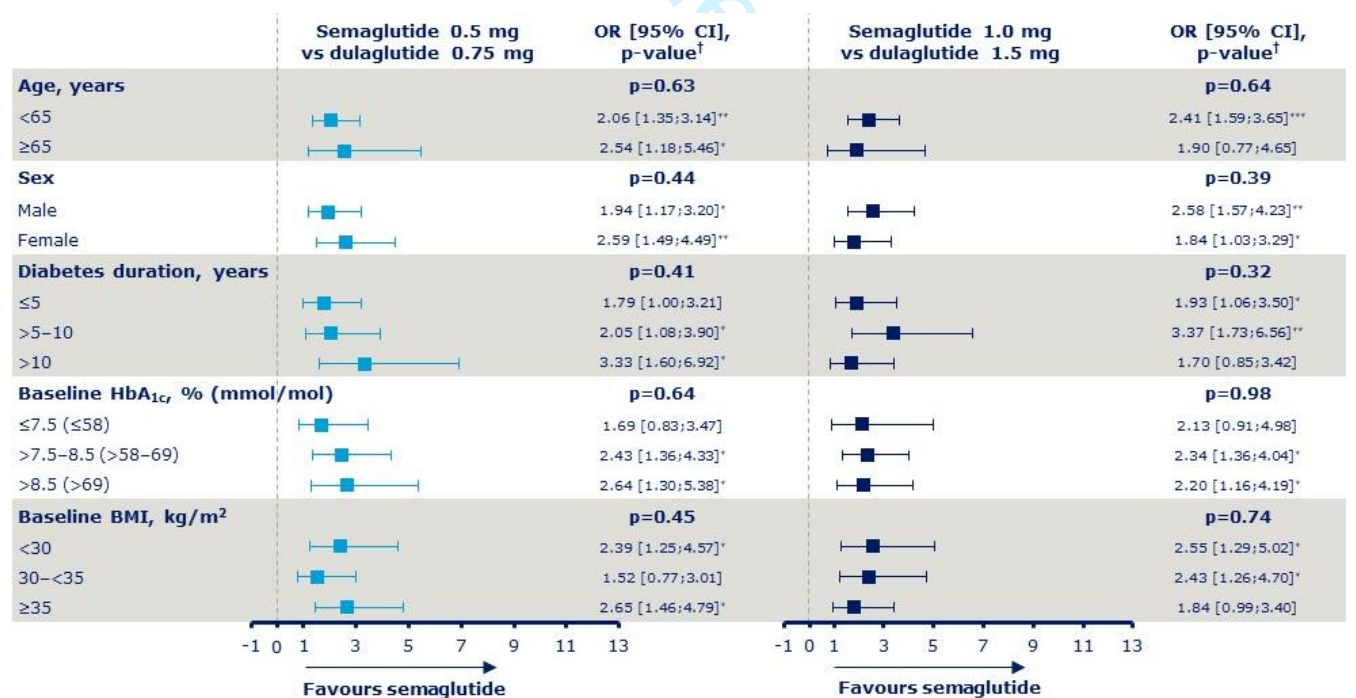
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3 *p<0.05, **p<0.001, ***p<0.0001. Values are estimated means from ANCOVAs controlled for baseline HbA_{1c}
4 (A, C, E, G, I) or BW (B, D, F, H, I) with multiple imputations using data from all randomised subjects exposed to
5 at least one dose of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



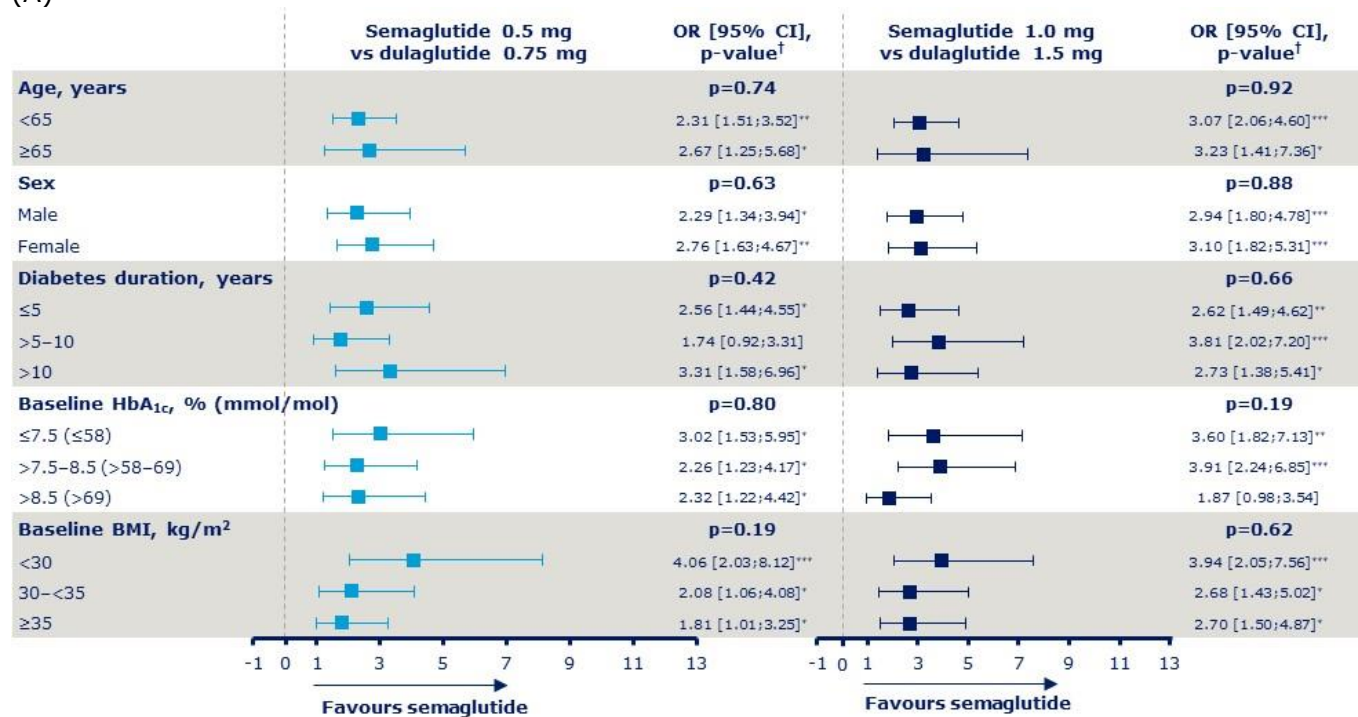
*p<0.05, **p<0.001, ***p<0.0001; †p-values represent the test for treatment by subgroup interaction. Values are ORs [95% CIs] from ANCOVAs with multiple imputations using 'on-treatment without rescue medication' data

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3 from all randomised subjects exposed to at least one dose of trial product as randomised (full analysis set)
4 obtained while on treatment and prior to onset of rescue medication. ANCOVA controlled for baseline HbA_{1c} and
5 interaction between randomised treatment and subgroup. ANCOVA: analysis of covariance; BMI: body mass index;
6 CI: confidence interval; HbA_{1c}: glycated haemoglobin; OR: odds ratio.
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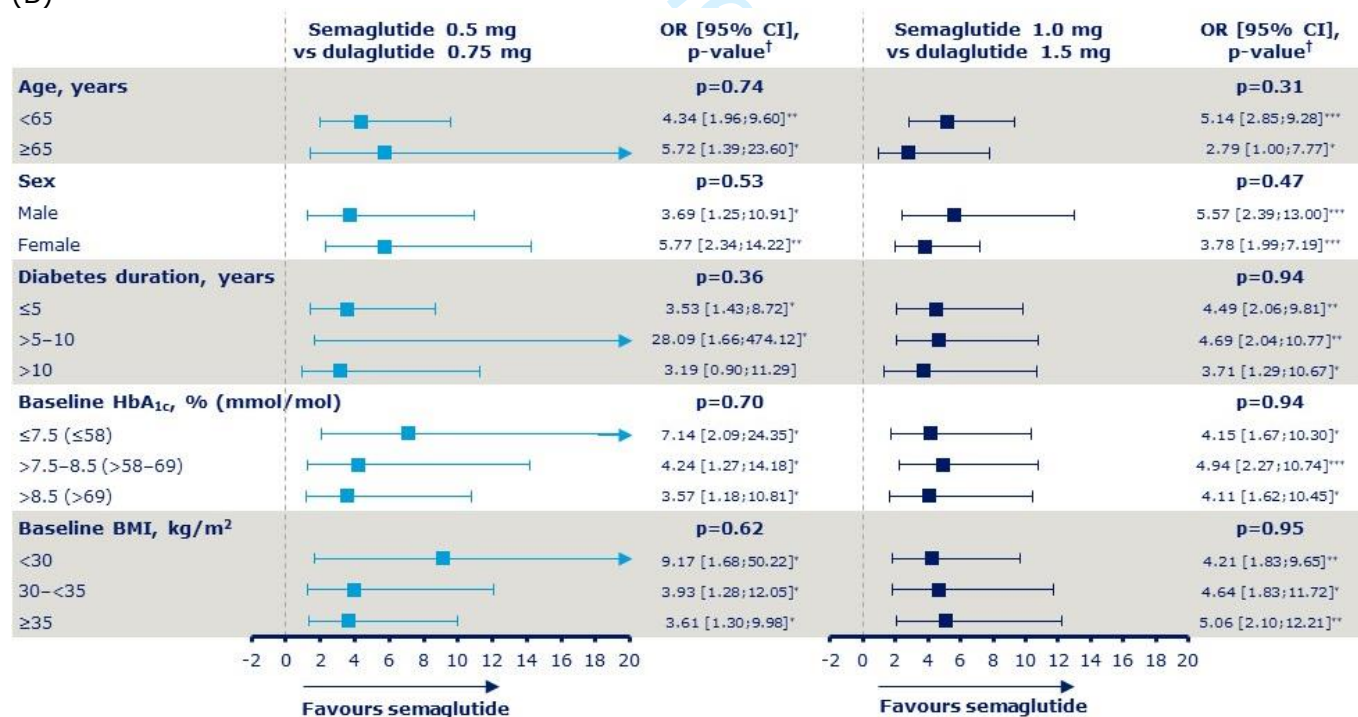
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Supplementary Figure 4. Odds ratios for the proportion of subjects achieving weight loss $\geq 5\%$ (A) and weight loss $\geq 10\%$ (B) at 40 weeks by age, sex, diabetes duration, HbA_{1c} and BMI at baseline

(A)

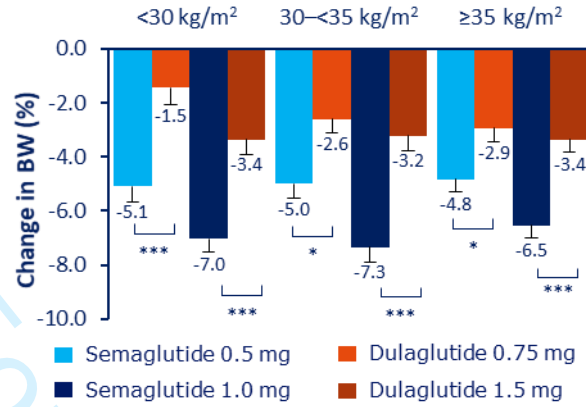


(B)



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

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SUPPLEMENTARY SECTION V: ADVERSE EVENTS

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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/m ²				30–<35 kg/m ²				≥35 kg/m ²			
		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)

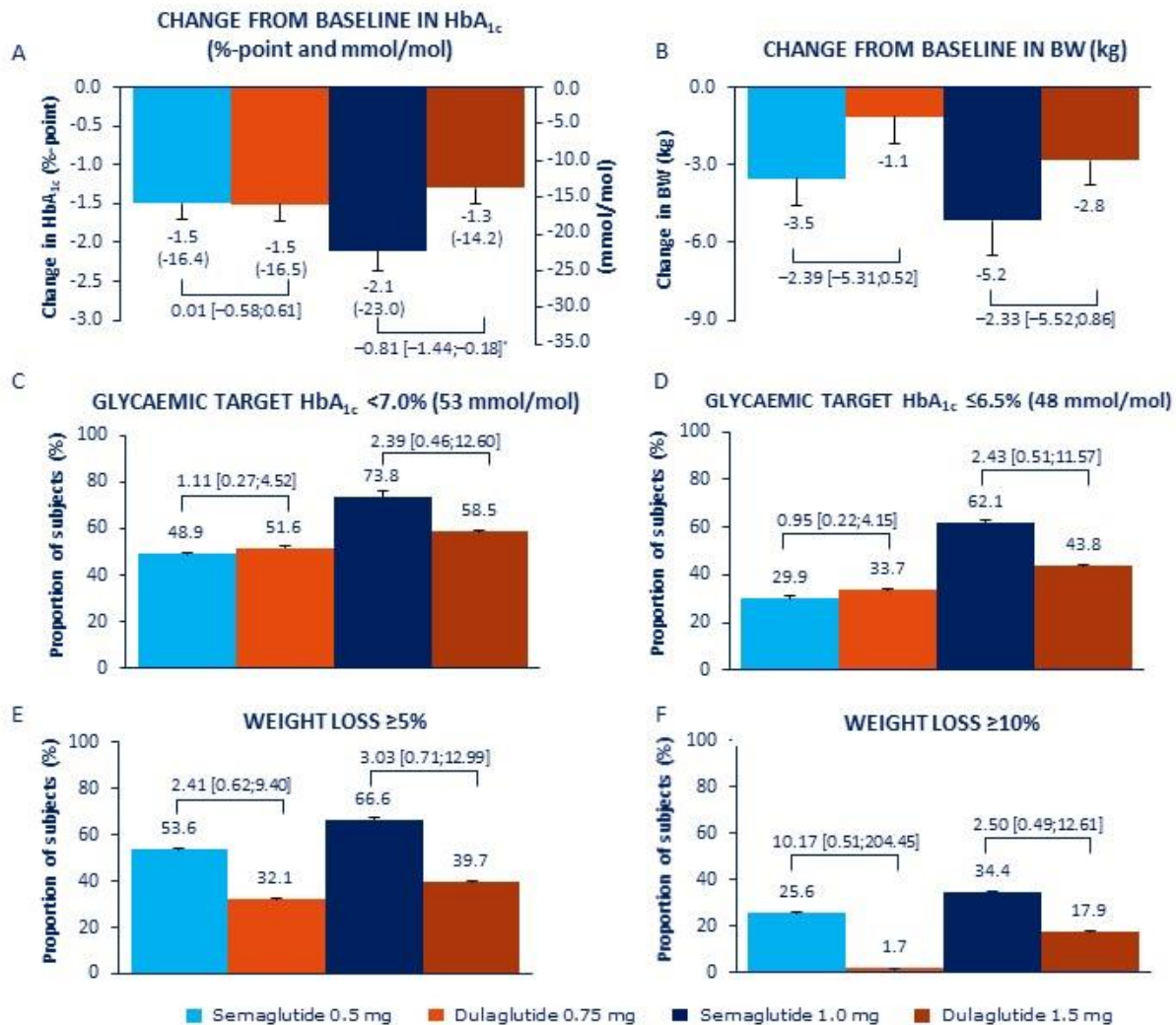
Data are presented as number and proportion (%) in percent of subjects with adverse events. Hypoglycaemia was defined as an episode that was severe (according to the American Diabetes Association classification) or BG-confirmed (plasma glucose value <56 mg/dL [3.1 mmol/L]) with symptoms consistent with 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/m²

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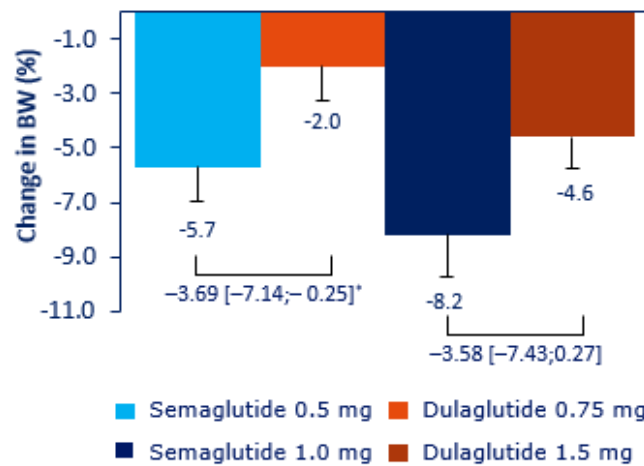
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Supplementary Figure 6. Change in HbA_{1c} (A) and body weight (B) from baseline to week 40 and the proportion of subjects achieving HbA_{1c} <7.0% (53 mmol/mol; C), HbA_{1c} ≤6.5% (48 mmol/mol; D), weight loss ≥5% (E) and weight loss ≥10% (F) in subjects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