Swansea University
Prifysgol Abertawe

Cronfa
Setting Research Free

Cronfa - Swansea University Open Access Repository

_____

This is an author produced version of a paper published in:
Diabetes, Obesity and Metabolism

Cronfa URL for this paper:
http://cronfa.swan.ac.uk/Record/cronfa52246

_____

Paper:

Aroda, V., Capehorn, M., Chaykin, L., Frias, J., Lausvig, N., Macura, S., Lüdemann, J., Madsbad, S., Rosenstock, J., et. al. Impact of baseline characteristics and beta-cell function on the efficacy and safety of subcutaneous once-weekly semaglutide: a patient-level, pooled analysis of the SUSTAIN 1–5 trials. *Diabetes, Obesity and Metabolism*

_____

http://www.swansea.ac.uk/library/researchsupport/ris-support/

Title: Impact of baseline characteristics and beta-cell function on the efficacy and safety of subcutaneous once-weekly semaglutide: a patient-level, pooled analysis of the SUSTAIN 1–5 trials

Short title: Semaglutide: efficacy and safety in patient subgroups of SUSTAIN 1–5

Authors: Vanita R. Aroda MD,[1] Matthew S. Capehorn MD,[2] Louis Chaykin MD,[3] Juan P. Frias MD,[4] Nanna L. Lausvig MSc,[5] Stanislava Macura MD,[5] Jörg Lüdemann MD,[6] Sten Madsbad MD,[7] Julio Rosenstock MD,[8] Omur Tabak MD,[9] Sayeh Tadayon MD,[5] Stephen C. Bain MA MD FRCP[10]

Author affiliations:

[1]Brigham and Women's Hospital, Boston, MA, USA; [2]Rotherham Institute for Obesity, Clifton Medical Centre, Rotherham, UK; [3]Meridien Research, Bradenton, FL, USA; [4]National Research Institute, Los Angeles, CA, USA; [5]Novo Nordisk A/S, Søborg, Denmark; [6]Diabetes-Falkensee, Diabetes-Centre and Centre for Clinical Studies, Falkensee, Germany; [7]Department of Endocrinology, Hvidovre Hospital, Hvidovre, Denmark; [8]Dallas Diabetes Research Center at Medical City, Dallas, TX, USA; [9]Istanbul Kanuni Sultan Suleyman Education and Research Hospital, Kucukcekmece, Istanbul, Turkey; [10]Diabetes Research Unit Cymru, Swansea University Medical School, Swansea, UK.

Contact details for corresponding author:

Vanita R. Aroda, MD

Brigham and Women's Hospital

221 Longwood Avenue, Boston, MA 02115, USA

Phone: +1 (617) 732-5693

Fax: +1 (617) 277-1568

Email: varoda@bwh.harvard.edu

Abstract:	250 words (max 250 words)
Main text:	3652 words (max 3500 words)
Number of references:	41 (max 40 references)
Number of tables:	2
Number of figures:	3
Number of suppl. tables:	2
Number of suppl. figures:	2

Abstract

[250/250 words]

Aims: We evaluated the impact of relevant patient-level characteristics on the efficacy and safety of subcutaneous, once-weekly semaglutide in subjects with T2D.

Materials and Methods: Exploratory *post hoc* analyses of pooled SUSTAIN 1–5 (phase 3a) randomized, controlled trials examined the change from baseline in HbA_{1c} and body weight (BW), and the proportions of subjects achieving the composite endpoint (HbA_{1c} <7.0% [53 mmol/mol], without weight gain or severe/blood glucose-confirmed symptomatic hypoglycaemia) at week 30 with semaglutide (0.5/1.0 mg) across clinically relevant patient subgroups: baseline HbA_{1c} (≤7.5, >7.5–8.0, >8.0–8.5, >8.5–9.0 and >9.0%), background medications, diabetes duration and pancreatic beta-cell function.

Results: Mean HbA_{1c} (%-point) reductions increased from lowest to highest HbA_{1c} subgroups (−0.9, −1.2,−1.5, −1.7 and −2.3% [effect of subgroup within treatment: p=0.247] for semaglutide 0.5 mg, and −1.1, −1.4, −1.9, −2.1 and −2.7% [p=0.045] for semaglutide 1.0 mg), with mean HbA_{1c} ranges at week 30 of 6.3–7.3% and 6.1–6.9%, respectively. The corresponding BW reductions generally decreased with increasing baseline HbA_{1c} (−4.4, −3.9, −3.9, −3.3 and −2.9 kg [p=0.004], and −6.4, −5.9, −5.2, −4.5 and −4.8 kg [p<0.001], respectively). HbA_{1c} and BW reductions were consistently greater for semaglutide 1.0 mg versus 0.5 mg across background medication, diabetes duration and pancreatic beta-cell function subgroups. Adverse events with semaglutide were consistent with the GLP-1RA class, with gastrointestinal events the most common.

Conclusions: Semaglutide was consistently efficacious across the continuum of diabetes care in a broad spectrum of patient subgroups with a range of clinical characteristics.

3

1 Introduction

Current guidelines for type 2 diabetes (T2D) management prioritize the use of glucagon-like peptide-1 receptor agonists (GLP-1RAs) in specific populations and as first injectable therapy before insulin.[1,2] The emphasis is on patient-centred care and individualized treatment, including consideration of patients' clinical characteristics and comorbidities.[1,2] Clinical indicators of disease status in heterogeneous populations of adults with T2D, including glycaemic control (HbA$_{1c}$), duration of disease, background antidiabetes medications and pancreatic beta-cell function, may impact the efficacy and safety of GLP-1RA therapy. An in-depth evaluation of patient subgroups provides insight into whether distinct populations respond differently, and further guides individualization of therapy.

Semaglutide (Novo Nordisk, Bagsværd, Denmark) is a subcutaneous (s.c.), once-weekly (OW) GLP-1 analogue for the treatment of T2D,[3,4] the efficacy and safety of which has been established in the global phase 3a and 3b SUSTAIN (Semaglutide Unabated Sustainability in Treatment of Type 2 Diabetes) clinical trial development programme.[5-11] Semaglutide s.c. OW demonstrated superior reductions in HbA$_{1c}$ and body weight (BW) compared with placebo and active comparators.[5-9] The SUSTAIN 1−5 trials (n=3,918) represented the full continuum of diabetes care, including treatment-naïve subjects, those on a background of oral antidiabetes drugs (OADs;) and on insulin, with differences in baseline characteristics.[5-9]

The present *post hoc* exploratory analyses of data from the SUSTAIN trials aimed to assess the impact of clinical indicators of disease status (baseline HbA$_{1c}$, background antidiabetes medications, diabetes duration and pancreatic beta-cell function) on the efficacy and safety of semaglutide s.c. OW in subjects with inadequately controlled T2D.

2 Materials and Methods

4

2.1 Individual trial designs

The phase 3a, multinational, randomized, controlled SUSTAIN 1–5 trials compared semaglutide s.c. OW (0.5 mg and/or 1.0 mg) with placebo (SUSTAIN 1, monotherapy; SUSTAIN 5, add-on to basal insulin) or active comparators (SUSTAIN 2, sitagliptin 100 mg; SUSTAIN 3, exenatide extended-release 2.0 mg; SUSTAIN 4, insulin glargine titrated-to-target) in subjects with inadequately controlled T2D (comparator data not included in this *post hoc* analysis) over 30 weeks (SUSTAIN 1, 4 and 5) or 56 weeks (SUSTAIN 2 and 3). The trials have been previously published (**Table 1**).[5-9]

2.2 Patient population

Key inclusion and exclusion criteria were similar across the SUSTAIN 1–5 trials.[5-9] Briefly, adult subjects (≥18 years) with T2D (HbA$_{1c}$: ≥7.0–10.0% [53–86 mmol/mol] for SUSTAIN 1, 4 and 5 or ≥7.0–10.5% [53–91 mmol/mol] for SUSTAIN 2 and 3) and an estimated glomerular filtration rate of ≥30 mL/min/1.73 m^2 (SUSTAIN 1, 4 and 5) or ≥60 mL/min/1.73 m^2 (SUSTAIN 2 and 3) were eligible for inclusion.

All trials were registered with ClinicalTrials.gov (NCT02054897, NCT01930188, NCT01885208, NCT02128932 and NCT02305381) and conducted according to the International Conference on Harmonisation Good Clinical Practice guidelines[12] and the Declaration of Helsinki.[13] Trial protocols were approved by the institutional review boards and ethics committees at participating centres. Subjects provided written informed consent before trial-related activities commenced.

2.3 Subgroup analyses

Key indicators of disease status were selected for *post hoc* analyses: baseline HbA$_{1c}$, background antidiabetes medication, baseline diabetes duration and pancreatic beta-cell function.

For baseline HbA$_{1c}$ analyses, subjects were divided into HbA$_{1c}$ categories (≤7.5% [≤58 mmol/mol], >7.5–8.0% [>58–64 mmol/mol], >8.0–8.5% [>64–69 mmol/mol], >8.5%–9.0% [>69–75 mmol/mol] and >9.0% [>75 mmol/mol]). For diabetes duration analyses, diabetes duration categories (≤5 years, >5–10 years and >10 years) were assessed. Both HbA$_{1c}$ and diabetes duration subgroup analyses used pooled SUSTAIN 1–5 data. Categories for HbA$_{1c}$ and diabetes duration analyses were selected based on clinical relevance, with HbA$_{1c}$ categories also reflecting the targets utilised in current clinical guidelines for diabetes management.[1,2,14]

Supporting the diabetes duration analyses, pancreatic beta-cell function (glucose-stimulated insulin secretion) was assessed using the homeostatic model assessment of beta-cell function (HOMA-B),[15,16] including pooled data from SUSTAIN 1–3 only (HOMA-B cannot be applied in subjects taking exogenous insulin, as in SUSTAIN 4 (insulin glargine comparator) and 5 (add-on to basal insulin).[16] No specific thresholds for beta-cell function were used and subjects were categorized into HOMA-B tertiles: low (≤27.21%), intermediate (>27.21 to 51.71%) and high (>51.71%) endogenous beta-cell function.

For background antidiabetes medication analyses, subjects were divided into subgroups (no background medication, metformin monotherapy, other OADs and basal insulin ± metformin). There were differences in background medications across trials: semaglutide was assessed in drug-naïve subjects (SUSTAIN 1); as add-on to existing stable background antidiabetes treatments (metformin, thiazolidinedione or both [SUSTAIN 2]; maximum two of metformin, thiazolidinedione and/or sulphonylurea [SUSTAIN 3]; metformin ± sulphonylurea [SUSTAIN 4]); and as add-on to basal insulin ± metformin (SUSTAIN 5). Pooled SUSTAIN 2–4 data were used for the 'metformin monotherapy' and 'other OADs' subgroups; data by trial was used for 'no background medication' (SUSTAIN 1) and for 'basal insulin ± metformin' (SUSTAIN 5).

2.4   Endpoints and assessments

6

Efficacy endpoints were similar across all trials in the pre-planned analyses; the primary and secondary confirmatory endpoints were change in HbA_{1c} (%-point, hereafter referred to as %) and BW (kg), respectively, from baseline to end of treatment. Week 30 was the latest, common 'on treatment' time point across the SUSTAIN 1–5 trials and was selected as cut-off for these analyses, allowing for inter-trial comparisons. Supportive secondary endpoints included subjects achieving a triple composite endpoint of HbA_{1c} <7.0% (<53 mmol/mol) without weight gain or severe (according to the American Diabetes Association [ADA] classification)[17] or blood glucose (BG)-confirmed symptomatic hypoglycaemia (plasma glucose <3.1 mmol/L [56 mg/dL] with symptoms consistent with hypoglycaemia).[5-9]

Safety was assessed as the numbers of adverse events (AEs), serious AEs and AEs leading to premature treatment discontinuation in the subgroups within each treatment group. Specific AEs of clinical interest analysed included gastrointestinal disorders and hypoglycaemic events.

2.5   Statistical analyses

Post hoc analyses were performed using pooled or by trial data as described in section 2.3. Efficacy analyses included 'on-treatment without rescue medication' data from all subjects contributing to the full analysis sets (randomized and exposed to at least one dose of the trial product) across the SUSTAIN 1–5 trials. Change from baseline analyses were adjusted for trial, country, treatment, baseline value and subgroup, using mixed model for repeated measurements (MMRM) imputations for missing data. Interaction effects were included for country and baseline value by trial and subgroup by treatment. Outcome values are presented as mean (standard error) for each of the categories analysed, unless otherwise stated. The proportions of subjects achieving the composite endpoint (HbA_{1c} <7.0% [<53 mmol/mol], without weight gain or severe/BG-confirmed symptomatic hypoglycaemia) were based on observed data and MMRM imputations for subjects with missing data.

7

The safety analysis set included data from subjects who were exposed to at least one dose of semaglutide and based on 'on treatment' data. The proportions of subjects experiencing at least one AE were adjusted per trial using the Cochran–Mantel–Haenszel method.

3 Results

3.1 Subject disposition and baseline characteristics

Of the 3,918 subjects with T2D who were randomized to subcutaneous, once-weekly semaglutide or comparator treatment in the SUSTAIN 1–5 trials, 2,465 were assigned to semaglutide and received at least one dose of the trial medication (0.5 mg, n=1,031 and 1.0 mg, n=1,434). Baseline characteristics by trial and treatment group (**Table 1**) and according to each subgroup analysis (**Supplementary Table 1**) were broadly similar, with differences reflecting trial eligibility criteria and heterogeneity of the population with respect to the continuum of T2D care.

3.2 Efficacy by subgroup

3.2.1 Effect by baseline HbA$_{1c}$ (SUSTAIN 1–5 pooled)

Overall, the magnitude of the reductions in HbA$_{1c}$ were greater in subgroups with higher baseline HbA$_{1c}$ levels for both semaglutide 0.5 mg and 1.0 mg (**Figure 1A)**. Reductions in HbA$_{1c}$ for semaglutide 0.5 mg ranged from −0.9% (baseline HbA$_{1c}$ ≤7.5%) to −2.3% (baseline HbA$_{1c}$ >9.0%), and for semaglutide 1.0 mg ranged from −1.1% (baseline HbA$_{1c}$ ≤7.5%) to −2.7% (baseline HbA$_{1c}$ >9.0%). There was a significant effect of the HbA$_{1c}$ subgroup within treatment for semaglutide 1.0 mg (p=0.045), but not 0.5 mg (p=0.247) Similar HbA$_{1c}$ concentrations were achieved in all HbA$_{1c}$ subgroup categories, with estimated mean HbA$_{1c}$ levels at week 30 close to or less than 7.0% (53 mmol/mol).

Conversely, the magnitude of the reductions in body weight were generally lower in subgroups with higher baseline HbA_{1c} (**Figure 1B)**. Reductions in body weight from baseline to week 30 were observed across all baseline HbA_{1c} subgroups, ranging from −2.9 kg (baseline HbA_{1c} >9.0%) to −4.4 kg (baseline HbA_{1c} ≤7.5%) with semaglutide 0.5 mg, and from −4.5 kg (baseline HbA_{1c} >8.5–9.0%) to −6.4 kg (baseline HbA_{1c} ≤7.5%) with semaglutide 1.0 mg. There was a significant effect of the HbA_{1c} subgroup within treatment for both semaglutide 0.5 mg (p=0.004), and semaglutide 1.0 mg (p<0.001). The proportions of subjects achieving the composite endpoint (HbA_{1c} <7.0% [<53 mmol/mol], without weight gain or severe/BG-confirmed symptomatic hypoglycaemia) were consistently lower in subgroups with higher baseline HbA_{1c} (**Supplementary Figure 1A**, with ranges of 34.5–76.2% for semaglutide 0.5 mg and 44.9–80.2% for semaglutide 1.0 mg from the highest to lowest baseline HbA_{1c} subgroups.

3.2.2 *Effect by background medication (SUSTAIN 1, SUSTAIN 2–4 pooled,*
SUSTAIN 5)

Overall, reductions in HbA_{1c} (**Figure 2A**) and body weight (**Figure 2B**) were consistent across the four background antidiabetes medication subgroups (no background medication, metformin monotherapy, other OADs and basal insulin plus metformin), with slight variations in the 'other OADs' subgroup category for both semaglutide doses. Reductions in HbA_{1c} for semaglutide 0.5 mg ranged from −1.4% (background of other OADs) to −1.6% (treatment-naïve), and for semaglutide 1.0 mg ranged from −1.7% (metformin monotherapy) to −1.9% (basal insulin ± metformin).

Reductions in body weight for semaglutide 0.5 mg ranged from −3.4 kg (other OADs) to −4.2 kg (treatment-naïve) and for semaglutide 1.0 mg, ranged from −4.9 kg (treatment-naïve) to −6.5 kg (basal insulin plus metformin).

9

Due to the limitations of comparisons using pooled data and data from individual trials (as described in section 2.3), subgroup effects were only analysed in the background medication subgroups of metformin monotherapy and other OADs (SUSTAIN 2–4). There were no significant effects on the change from baseline in HbA_{1c} (p=0.114) or body weight loss (p=0.273) for the 0.5 mg semaglutide dose. For the 1.0 mg dose, a significant difference was observed for body weight loss (p=0.034), but not for change from baseline in HbA_{1c} (p=0.432), between metformin monotherapy and other OADs.

The proportions of subjects achieving the composite endpoint ranged from 42.0% to 66.4% for semaglutide 0.5 mg and 56.8% to 69.5% for semaglutide 1.0 mg (**Supplementary Figure 1B**). The lowest proportions of subjects achieving the composite endpoint were observed in those receiving other OADs for both semaglutide doses.

3.2.3 Effect by baseline diabetes duration (SUSTAIN 1–5 pooled)

Reductions in both HbA_{1c} (**Figure 3A**) and body weight (**Figure 3B**) were consistent, but with no clear pattern across the three diabetes duration subgroups (≤5, >5–10, >10 years at baseline), with greater reductions observed for semaglutide 1.0 mg versus 0.5 mg. Mean reductions were −1.7% to −1.8% and −5.4 kg to −5.7 kg with semaglutide 1.0 mg, and −1.4% and −3.7 kg to −3.8 kg with semaglutide 0.5 mg.

There were no significant effects of diabetes duration for either semaglutide dose on the changes in HbA_{1c} (0.5 mg: p=0.051; 1.0 mg: p=0.441) or body weight loss (0.5 mg: p=0.959; 1.0 mg: p=0.198)

For semaglutide 1.0 mg, the proportions of subjects achieving the composite endpoint were comparable across diabetes duration subgroups (62.5–67.8%). For semaglutide 0.5 mg, the lowest proportion of subjects achieving the composite endpoint was observed with baseline diabetes duration >10 years (49.5%), compared with those with disease duration <10 years (≥58.7%) (**Supplementary Figure 1C**).

10

3.2.4 Baseline HOMA-B (SUSTAIN 1–3 pooled)

Reductions in HbA$_{1c}$ were observed in all baseline HOMA-B tertiles for both semaglutide 0.5 mg and 1.0 mg (**Supplementary Figure 2A**), with the magnitude of reductions decreasing from low to high HOMA-B tertile (ranging from −1.3% to −1.7% and from −1.5% to −2.0%, respectively, for each semaglutide dose). There was no significant effect of HOMA-B on HbA$_{1c}$ reductions with either semaglutide dose (0.5 mg: p=0.948; 1.0 mg: p=0.190).

In general, body weight was reduced in all baseline HOMA-B tertiles (**Supplementary Figure 2B**). There was no apparent difference in the reduction in body weight by tertile, ranging from −3.6 kg to −4.3 kg for semaglutide 0.5 mg, and from −4.9 kg to −6.1 kg for semaglutide 1.0 mg. The greatest reduction (−6.1 kg) was observed in the intermediate tertile group for semaglutide 1.0 mg; however, the effect of subgroup within treatment was non-significant for both semaglutide doses (0.5 mg: p=0.982; 1.0 mg: p=0.116)

The proportions of subjects achieving the composite endpoint were similar across the baseline HOMA-B tertiles (**Supplementary Figure 2C**).

In each of the subgroup analyses, mean HbA$_{1c}$ and mean body weight reductions, as well as the proportions of subjects achieving the composite endpoint, were greater with the higher dose (1.0 mg) than with the lower dose (0.5 mg) of semaglutide (**Figures 1–3**).

3.3 Safety outcomes

An overview of AEs, including gastrointestinal AEs, is presented in **Table 2**. For each semaglutide dose, the proportions of subjects reporting AEs were generally similar across subgroups. The proportions of subjects reporting serious AEs were greater with longer versus shorter duration of diabetes at baseline (**Table 2**) and greater in the highest baseline HOMA-B tertile compared with the other two tertiles for semaglutide 1.0 mg

11

(**Supplementary Table 2**); no trend was observed for baseline HbA_{1c} and background medication subgroups.

The proportions of subjects reporting treatment discontinuations due to AEs and gastrointestinal AEs were generally similar across diabetes duration subgroups (**Table 2**) and baseline HOMA-B tertiles (**Supplementary Table 2**), but varied with no distinctive pattern across baseline HbA_{1c} and background medication subgroups.

Overall, nausea was the most common gastrointestinal AE across all subgroups; nausea was highest in treatment-naïve subjects (not receiving background medication) and lowest in those on basal insulin ± metformin. The proportions of subjects reporting nausea were similar across diabetes duration subgroups with semaglutide 1.0 mg, but decreased with increasing diabetes duration for semaglutide 0.5 mg. There was no consistent pattern in the proportions of subjects reporting nausea across the baseline HbA_{1c} subgroups and HOMA-B tertiles. The incidences of severe/BG glucose-confirmed hypoglycaemia were overall low and similar across HbA_{1c} subgroups and diabetes duration; for background treatment, no incidences of hypoglycaemia were observed in treatment-naïve subjects, i.e. semaglutide monotherapy, while the highest rates were observed in those on a background of other OADs (7.1–10.0%) and basal insulin ± metformin (8.3–10.7%).

4   Discussion

Subcutaneous once-weekly semaglutide demonstrated consistently robust, clinically significant reductions in HbA_{1c} and body weight in the SUSTAIN 1−5 trials.[5-9] Encompassing patients from across the continuum of diabetes care, the SUSTAIN trials represent the heterogeneity of patients with T2D observed in everyday clinical practice, including wide ranging baseline HbA_{1c} levels, background antidiabetes medications and diabetes durations.[5-9] Understanding the impact these different clinical and disease characteristics

12

have on efficacy and safety of semaglutide can help clinical decision-making and individualization of treatment. This exploratory *post hoc* analysis evaluated the effect of semaglutide in the context of selected subgroup characteristics.

Disease progression in diabetes is associated with worsening hyperglycaemia, indicated by increasing levels of HbA_{1c}. Across the range of baseline HbA_{1c} subgroups in this analysis, subjects with higher HbA_{1c} values at baseline had the greatest reductions in $HbA_{1c,}$ with a statistically significant effect of baseline HbA_{1c} in the semaglutide 1.0 mg treatment arm ($p<0.05$). Baseline HbA_{1c} is a well-established predictor of glycaemic response for all antidiabetes treatments, even for non-pharmacological interventions;[18,19] this finding is consistent with published findings for other GLP-1RAs, including dulaglutide,[20,21] liraglutide[22] and lixisenatide.[23] Importantly, from the clinical perspective, these observed differences in the magnitude of change from baseline in HbA_{1c} across HbA_{1c} subgroups resulted in a similar mean end-of-treatment HbA_{1c} level. Indeed, irrespective of baseline HbA_{1c} subgroup, HbA_{1c} levels at week 30 were either close to, or less than, the ADA-recommended target of <7.0% (<53 mmol/mol), reflecting the glucose-dependent, antihyperglycaemic action of semaglutide and other GLP-1RAs.[24]

The GLP-1RA class promotes weight loss,[25] primarily via central, appetite-regulating mechanisms.[24,25] Subjects with highest HbA_{1c} at baseline lost relatively less weight than those with lower HbA_{1c} at baseline, albeit with clinically relevant absolute weight loss. A similar pattern, with less weight loss in subjects with higher baseline HbA_{1c} levels, was also observed with dulaglutide in the AWARD programme,[20,21] and with liraglutide .[26] These findings may be due to treatment-related increases in glycaemic control. In patients with particularly poor glycaemic control at baseline and associated caloric loss due to glucosuria, improving glycaemic control and reducing glucosuria may lead to mitigation of weight reduction.[26,27] Decreased protein turnover and reduced energy expenditure with improved glycaemic control can also lead to weight gain.[27,28] Furthermore, energy expenditure and

13

resting metabolic rate decrease with weight loss, often accompanied by increased appetite.[27-29] Contradicting a previous suggestion that modest weight loss in subjects with higher HbA_{1c} may be related to concomitant insulin treatment and accompanying insulin-related weight gain,[21] the greatest weight loss was observed in these analyses in subjects on a background of basal insulin ± metformin.

GLP-1RAs, such as semaglutide, are recommended as add-on therapy to metformin and other OADs and as first injectable therapy in preference to insulin, unless contraindicated.[1,2] Clinically relevant reductions in HbA_{1c} and body weight were observed in all assessed background medication subgroups of the SUSTAIN 1−5 trials and considerable weight loss was observed with semaglutide 1.0 mg, even in patients on a background of stable basal insulin ± metformin. The proportion of subjects achieving the composite endpoint of HbA_{1c} <7.0% (53 mmol/mol), without weight gain or severe/BG-confirmed symptomatic hypoglycaemia has previously been reported for the SUSTAIN 1−5 trials.[30] In the analysis presented here, the proportion of subjects achieving the triple composite endpoint was lowest in subjects on background medication of other OADs (including thiazolidinedione monotherapy, metformin plus thiazolidinedione or sulphonylurea plus thiazolidinedione), which may be due to preceding weight gain associated with thiazolidinediones and sulphonylureas,[31] or to increased risk of hypoglycaemia associated with concomitant treatment with sulphonylureas.[3]

The intensification of antidiabetes therapy required over time is considered to be an indicator of diabetes severity and progression, and may be closely associated with diabetes duration. A number of published findings for other GLP-1RAs suggest that patients with severe diabetes, i.e. high baseline HbA_{1c} levels,[20,32] or a shorter disease duration, e.g. less than 3 years,[32] may particularly benefit from GLP-1RA treatment. In the analyses presented here, clinically relevant reductions in HbA_{1c} and body weight were consistently observed even in subjects with long-standing diabetes (i.e. those with a duration of diabetes beyond

14

10 years) and the proportions of subjects achieving the triple composite endpoint were comparable across diabetes duration subgroups. There was a clear dose response in favour of semaglutide 1.0 mg versus 0.5 mg, in particular for subjects with baseline diabetes duration of >10 years. The hypothesized diminished insulinotropic effect of GLP-1 in long-standing diabetes, potentially due to poor beta-cell function resulting from secondary effects from other hormonal, metabolic or treatment-related factors,[33-36] may explain the additional benefits that these subjects derive from the higher dose of semaglutide maximising the agonistic effect of the GLP-1RA. Notable in the present analysis, despite the association of diabetes duration with progressively decreasing beta-cell function,[37] similar reductions in HbA$_{1c}$ and body weight with semaglutide were generally observed across all levels of beta-cell function, (assessed by HOMA-B). Consistent with previously reported semaglutide-mediated improvements in beta-cell function and glycaemic control,[38] this finding suggests that even in patients with low beta-cell function, clinically relevant reductions in HbA$_{1c}$ can be achieved with semaglutide treatment.

The safety profile of semaglutide was generally similar across all subgroups, indicating no clear association between baseline profile and risk of AEs. Overall, semaglutide was well tolerated regardless of baseline HbA$_{1c}$, background medication, diabetes duration or baseline HOMA-B, with no or low incidences of hypoglycaemia. As reported with other GLP-1RAs,[39] and for the SUSTAIN 1–5 trials,[5-9] the most common AEs leading to treatment discontinuation with semaglutide were gastrointestinal;[5-9,39] a known class effect of GLP-1RA therapies,[40,41] these GI events typically occur during treatment initiation/escalation, but are transient, mild-to-moderate in severity, and diminish over time.[5-9,39] In these analyses, the proportions of subjects reporting gastrointestinal AEs, were similar across all analysed subgroups. The safety findings with semaglutide are comparable to those previously reported for semaglutide and other GLP-1RAs.[40,41] Lower rates of nausea were observed for

subjects on a background of basal insulin ± metformin, possibly related to compound-specific variation inGLP-1RA-associated gastrointestinal AEs.[39,40]

The strengths of these analyses include the large number of subjects in SUSTAIN 1—5 phase 3a trials from across the continuum of T2D care, representing patients on a range of treatments, from drug-naïve to insulin therapy, with a broad spectrum of baseline characteristics. Although these analyses enable further understanding of the impact of clinical indicators of disease status on efficacy and safety of semaglutide across different trials, limitations include the nature of pooled semaglutide data, which have been analysed without inclusion of comparator data. As such, this is not a randomized comparison, but a comparison across *post hoc*-defined subgroups. Confounding effects from underlying differences, including additive effects of different background therapies, may also be present. Similarly, although HOMA-B analyses can be considered suitable for use in the presence of insulinotropic compounds,[16] the data should be interpreted with caution and complementary to the diabetes duration subgroup analyses, as no adjustments were made for potential confounders, such as differences in baseline characteristics across HOMA-B tertiles. Furthermore, some selection bias may result from trial inclusion/exclusion criteria. The duration of treatment (30 weeks) examined here may not accurately reflect longer-term treatment but provides initial insight into treatment effects.

In conclusion, treatment with subcutaneous once-weekly semaglutide was consistently efficacious, reducing HbA$_{1c}$ and body weight to a clinically important extent, across subgroups by disease severity and progression in subjects with uncontrolled T2D. Semaglutide was well-tolerated, with a low risk of hypoglycaemia, across the continuum of diabetes care and a broad range of clinical characteristics. These analyses show that efficacy and safety of semaglutide is preserved, regardless of these patient characteristics and disease severity, and further support patient-centred decision-making in treatment of T2D.

16

Acknowledgements

Author contributions

All authors contributed to the analysis and interpretation of data, the writing and critical revision of the manuscript at all stages of development. All authors approved the final version.

Conflict of interest

VA received consultant fees from Adocia, AstraZeneca/Bristol Myers-Squibb, Boehringer Ingelheim, Novo Nordisk, Sanofi and Zafgen, and grants from AstraZeneca/Bristol Myers-Squibb, Calibra, Eisai, Fractyl, Janssen, Novo Nordisk, Sanofi and Theracos, and is a partner of an employee of Merck. MC received honoraria from Novo Nordisk, Boehringer Ingelheim, Eli Lilly, Janssen and Merck Sharp & Dohme, and grants from Novo Nordisk, Novartis, Boehringer Ingelheim, Eli Lilly, GlaxoSmithKline, Leo, and Abbott, and served as an expert advisor to the National Institute for Health and Care Excellence (NICE), an unpaid board member of the Association for the Study of Obesity (ASO) and the Primary Care Academy of Diabetes Specialists (PCADS), a part-time Medical Director at LighterLife (a commercial weight-loss company), a partner at Clifton Medical Centre, and a director at RIO Weight Management, Ltd. JPF received honoraria from Eli Lilly, Merck, Novo Nordisk, Sanofi and grants from Astra Zeneca, Boehringer Ingelheim, Eli Lilly, Merck, Novo Nordisk, Pfizer and Theracos. S Madsbad received honoraria from AstraZeneca, Boehringer Ingelheim, Eli Lilly, Merck Sharp & Dohme, Novo Nordisk and Sanofi and grants from Boehringer Ingelheim and Novo Nordisk. JL served as a consultant for Eli Lilly and Novo Nordisk. JR received honoraria

17

References

1. American Diabetes Association. 9. Pharmacologic approaches to glycemic treatment: Standards of Medical Care in Diabetes-2019. *Diabetes Care.* 2019;42(Suppl 1):S90-s102.
2. Davies MJ, D'Alessio DA, Fradkin J, et al. Management of hyperglycemia in type 2 diabetes, 2018. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes Care.* 2018.
3. Novo Nordisk. Ozempic (semaglutide) Prescribing Information. Available at: https://www.novo-pi.com/ozempic.pdf (Accessed July 2019).
4. Lau J, Bloch P, Schäffer L, et al. Discovery of the once-weekly glucagon-like peptide-1 (GLP-1) analogue semaglutide. *J Med Chem.* 2015;58(18):7370-7380.
5. Sorli C, Harashima SI, Tsoukas GM, et al. Efficacy and safety of once-weekly semaglutide monotherapy versus placebo in patients with type 2 diabetes (SUSTAIN 1): a double-blind, randomised, placebo-controlled, parallel-group, multinational, multicentre phase 3a trial. *Lancet Diabetes Endocrinol.* 2017;5(4):251-260.
6. Ahrén B, Masmiquel L, Kumar H, et al. Efficacy and safety of once-weekly semaglutide versus once-daily sitagliptin as an add-on to metformin, thiazolidinediones, or both, in patients with type 2 diabetes (SUSTAIN 2): a 56-week, double-blind, phase 3a, randomised trial. *Lancet Diabetes Endocrinol.* 2017;5(5):341-354.
7. Ahmann AJ, Capehorn M, Charpentier G, et al. Efficacy and safety of once-weekly semaglutide versus exenatide ER in subjects with type 2 diabetes (SUSTAIN 3): a 56-week, open-label, randomized clinical trial. *Diabetes Care.* 2018;41(2):258–266.
8. Aroda VR, Bain SC, Cariou B, et al. Efficacy and safety of once-weekly semaglutide versus once-daily insulin glargine as add-on to metformin (with or without sulfonylureas) in insulin-naive patients with type 2 diabetes (SUSTAIN 4): a randomised, open-label, parallel-group, multicentre, multinational, phase 3a trial. *Lancet Diabetes Endocrinol.* 2017;5(5):355-366.
9. Rodbard HW, Lingvay I, Reed J, et al. Semaglutide added to basal insulin in type 2 diabetes (SUSTAIN 5): a randomized, controlled trial. *J Clin Endocrinol Metab.* 2018;103(6):2291-2301.
10. Marso SP, Bain SC, Consoli A, et al. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. *N Engl J Med.* 2016;375(19):1834-1844.
11. Pratley RE, Aroda VR, Lingvay I, et al. Semaglutide versus dulaglutide once weekly in patients with type 2 diabetes (SUSTAIN 7): a randomised, open-label, phase 3b trial. *Lancet Diabetes Endocrinol.* 2018;6(4):275-286.
12. European Agency for the Evaluation of Medicinal Products. International Conference on Harmonisation-World Health Organization Guideline for Good Clinical Practice [EMEA Web site] ICH Harmonised Tripartite Guideline Good Clinical Practice. 2016. Accessed July, 2019.
13. World Medical Association. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. *JAMA.* 2013;310(20):2191-2194.
14. Garber AJ, Abrahamson MJ, Barzilay JI, et al. Consensus Statement by the American Association of Clinical Endocrinologists and American College of Endocrinology on the Comprehensive Type 2 Diabetes Management Algorithm—2019 Executive Summary. *Endocrine Practice.* 2019;25(1):69-100.
15. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from

19

fasting plasma glucose and insulin concentrations in man. *Diabetologia.* 1985;28(7):412-419.

16. Wallace TM, Levy JC, Matthews DR. Use and abuse of HOMA modeling. *Diabetes Care.* 2004;27(6):1487-1495.

17. Seaquist ER, Anderson J, Childs B, et al. Hypoglycemia and Diabetes: A Report of a Workgroup of the American Diabetes Association and The Endocrine Society. *Diabetes Care.* 2013;36(5):1384-1395.

18. DeFronzo RA, Stonehouse AH, Han J, Wintle ME. Relationship of baseline HbA1c and efficacy of current glucose-lowering therapies: a meta-analysis of randomized clinical trials. *Diabetic Medicine.* 2010;27(3):309-317.

19. Jones AG, Lonergan M, Henley WE, Pearson ER, Hattersley AT, Shields BM. Should studies of diabetes treatment stratification correct for baseline HbA1c? *PLoS One.* 2016;11(4):e0152428.

20. Gallwitz B, Dagogo-Jack S, Thieu V, et al. Effect of once-weekly dulaglutide on glycated haemoglobin (HbA1c) and fasting blood glucose in patient subpopulations by gender, duration of diabetes and baseline HbA1c. *Diabetes Obes Metab.* 2018;20(2):409-418.

21. Pantalone KM, Patel H, Yu M, Fernandez Lando L. Dulaglutide 1.5 mg as an add-on option for patients uncontrolled on insulin: Subgroup analysis by age, duration of diabetes and baseline glycated haemoglobin concentration. *Diabetes Obes Metab.* 2018;20(6):1461-1469.

22. Henry RR, Buse JB, Sesti G, et al. Efficacy of antihyperglycemic therapies and the influence of baseline hemoglobin A(1C): a meta-analysis of the liraglutide development program. *Endocr Pract.* 2011;17(6):906-913.

23. Blonde L, Chava P, Dex T, Lin J, Nikonova EV, Goldenberg RM. Predictors of outcomes in patients with type 2 diabetes in the lixisenatide GetGoal clinical trials. *Diabetes Obes Metab.* 2017;19(2):275-283.

24. Campbell JE, Drucker DJ. Pharmacology, physiology, and mechanisms of incretin hormone action. *Cell Metab.* 2013;17(6):819-837.

25. Shah M, Vella A. Effects of GLP-1 on appetite and weight. *Rev Endocr Metab Disord.* 2014;15(3):181-187.

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

27. Pi-Sunyer FX. Weight loss in type 2 diabetic patients. *Diabetes Care.* 2005;28(6):1526-1527.

28. Nair KS, Halliday D, Garrow JS. Increased energy expenditure in poorly controlled Type 1 (insulin-dependent) diabetic patients. *Diabetologia.* 1984;27(1):13-16.

29. Leibel RL, Rosenbaum M, Hirsch J. Changes in energy expenditure resulting from altered body weight. *N Engl J Med.* 1995;332(10):621-628.

30. DeVries JH, Desouza C, Bellary S, et al. Achieving glycaemic control without weight gain, hypoglycaemia, or gastrointestinal adverse events in type 2 diabetes in the SUSTAIN clinical trial programme. *Diabetes Obes Metab.* 2018;20(10):2426-2434.

31. Cheng V, Kashyap SR. Weight considerations in pharmacotherapy for type 2 diabetes. *J Obes.* 2011;2011.

32. Frías JP, Hardy E, Ahmed A, et al. Effects of exenatide once weekly plus dapagliflozin, exenatide once weekly alone, or dapagliflozin alone added to metformin monotherapy in subgroups of patients with type 2 diabetes in the DURATION-8 randomized controlled trial. *Diabetes Obes Metab.* 2018;20(6):1520-1525.

20

33. Vollmer K, Holst JJ, Baller B, et al. Predictors of incretin concentrations in subjects with normal, impaired, and diabetic glucose tolerance. *Diabetes.* 2008;57(3):678-687.
34. Meier JJ, Nauck MA. Is the diminished incretin effect in type 2 diabetes just an epi-phenomenon of impaired beta-cell function? *Diabetes.* 2010;59(5):1117-1125.
35. Nauck MA, Vardarli I, Deacon CF, Holst JJ, Meier JJ. Secretion of glucagon-like peptide-1 (GLP-1) in type 2 diabetes: what is up, what is down? *Diabetologia.* 2011;54(1):10-18.
36. Jones AG, McDonald TJ, Shields BM, et al. Markers of beta cell failure pedict poor glycemic response to GLP-1 receptor agonist therapy in type 2 diabetes. *Diabetes Care.* 2016;39(2):250-257.
37. UK Prospective Diabetes Study Group. U.K. Prospective Diabetes Study 16: Overview of 6 years' therapy of type II diabetes: a progressive disease. *Diabetes.* 1995;44(11):1249-1258.
38. Kapitza C, Dahl K, Jacobsen JB, Axelsen MB, Flint A. Effects of semaglutide on beta cell function and glycaemic control in participants with type 2 diabetes: a randomised, double-blind, placebo-controlled trial. *Diabetologia.* 2017;60(8):1390-1399.
39. Raccah D. Safety and tolerability of glucagon-like peptide-1 receptor agonists: unresolved and emerging issues. *Expert Opin Drug Saf.* 2017;16(2):227-236.
40. Bettge K, Kahle M, Abd El Aziz MS, Meier JJ, Nauck MA. Occurrence of nausea, vomiting and diarrhoea reported as adverse events in clinical trials studying glucagon-like peptide-1 receptor agonists: A systematic analysis of published clinical trials. *Diabetes Obes Metab.* 2017;19(3):336-347.
41. Madsbad S. Review of head-to-head comparisons of glucagon-like peptide-1 receptor agonists. *Diabetes Obes Metab.* 2016;18(4):317-332.

21

Tables

Table 1. Trial designs and baseline characteristics of subjects receiving semaglutide (SUSTAIN 1

Trial	SUSTAIN 1		SUSTAIN 2		SUSTAIN 3	SUSTAIN 4	
Semaglutide	0.5 mg/1.0 mg		0.5 mg/1.0 mg		1.0 mg	0.5 mg/1.0 mg	
Comparator	Placebo		Sitagliptin 100 mg		Exenatide ER 2.0 mg	Insulin glargine	(a
Trial duration	30 weeks		56 weeks		56 weeks	30 weeks	
RCT design	Double-blind, placebo-controlled		Double-blind, double-dummy		Open-label	Open-label	
Previous therapy	Drug-naïve		OAD		OAD	OAD	
Therapy type	Monotherapy		Add-on: MET ± TZD,		Add-on: 1–2 OADs (MET ± TZD ± SU)	Add-on: MET ± SU	
Semaglutide	**0.5 mg**	**1.0 mg**	**0.5 mg**	**1.0 mg**	**1.0 mg**	**0.5 mg**	**1.0 mg**
Subjects, n	128	130	409	409	404	362	360
Age, years	54.6 ± 11.1	52.7 ± 11.9	54.8 ± 10.2	56.0 ± 9.4	56.4 ± 10.3	56.5 ± 10.3	56.7 ± 10.4	59
Male, %	47	62	51	50	54	54	51
Body weight, kg	89.8 ± 23.0	96.9 ± 25.6	89.9 ± 20.4	89.2 ± 20.7	96.2 ± 22.5	93.7 ± 21.4	94.0 ± 22.5	92
BMI, kg/m^2	32.5 ± 7.6	33.9 ± 8.4	32.4 ± 6.2	32.5 ± 6.6	34.0 ± 7.2	33.1 ± 6.5	33.0 ± 6.5	3
HbA$_{1c}$, %	8.1 ± 0.9	8.1 ± 0.8	8.0 ± 0.9	8.0 ± 0.9	8.4 ± 0.9	8.1 ± 0.8	8.3 ± 0.9	8
Diabetes duration, years	4.8 ± 6.1	3.6 ± 4.9	6.4 ± 4.7	6.7 ± 5.6	9.0 ± 6.0	7.8 ± 5.1	9.3 ± 7.2	1
HOMA-B, %^{a}	39.7 ± 118.8	43.3 ± 114.4	32.8 ± 93.6	33.7 ± 98.1	39.0 ± 97.2	-	-

Data were sourced from original trial reports if not publicly available. Data are means, or mean ± standard deviation, unless otherwis
are geometric mean ± coefficient of variation and were evaluated in SUSTAIN 1, 2 and 3 only. BMI, body mass index; exenatide ER, e
release; HOMA-B, homeostatic model assessment of beta-cell function; MET, metformin; OAD, oral antidiabetes drug; RCT randomize
sulphonylurea; TZD, thiazolidinedione.

22

Table 2. Adverse events by subgroup (SUSTAIN 1–5)

	Semaglutide 0.5 mg					Semaglutide		
	n=1,031 n (%)					n=1,43... n (%)		
HbA$_{1c}$, %	≤7.5	>7.5–8.0	>8.0–8.5	>8.5–9.0	>9.0	≤7.5	>7.5–8.0	>8.0–8.
HbA$_{1c}$, mmol/mol	≤58	>58–64	>64–69	>69–75	>75	≤58	>58–64	>64–69
n	332	216	178	134	171	409	300	250
Total AEs (any grade)	240 (72.3)	155 (71.7)	124 (69.6)	93 (69.7)	120 (70.6)	302 (73.8)	202 (67.9)	172 (68.
Serious AEs	19 (5.7)	16 (7.4)	12 (6.8)	8 (5.9)	12 (7.1)	30 (7.2)	19 (6.5)	21 (8.5
AEs leading to premature treatment discontinuation	25 (7.5)	12 (5.7)	7 (3.9)	12 (9.3)	11 (6.4)	43 (10.4)	26 (8.8)	16 (6.6
Gastrointestinal AEs	133 (40.1)	88 (40.4)	69 (38.8)	51 (39.3)	71 (41.7)	186 (45.5)	116 (39.0)	88 (35.1
Nausea	63 (19.0)	41 (18.7)	26 (14.6)	29 (22.1)	32 (18.7)	101 (24.8)	63 (21.0)	40 (16.0
Diarrhoea	35 (10.6)	32 (14.7)	26 (14.7)	22 (17.2)	20 (11.8)	51 (12.6)	43 (14.5)	30 (12.0
Vomiting	23 (6.9)	12 (5.7)	10 (5.6)	12 (9.2)	13 (7.8)	44 (10.8)	21 (7.1)	18 (7.2
Severe or blood glucose-confirmed hypoglycaemia	8 (2.4)	6 (3.0)	6 (3.3)	7 (4.9)	7 (4.2)	20 (4.9)	13 (4.2)	8 (3.3)
Background medication	None	MET monotherapy	Other OADs[a]	Basal insulin		None	MET monotherapy	
n	128	559	212	132		130	775	
Total AEs (any grade)	82 (64.1)	413 (73.9)	146 (68.8)	91 (68.9)		73 (56.2)	559 (72.1)	
Serious AEs	7 (5.5)	41 (7.3)	11 (5.2)	8 (6.1)		7 (5.4)	63 (8.1)	

23

AEs leading to premature treatment discontinuation	8 (6.3)	44 (7.9)	9 (4.2)	6 (4.5)	7 (5.4)	70 (9.0)
Gastrointestinal AEs	49 (38.3)	238 (42.6)	89 (41.8)	23 (17.4)	50 (38.5)	314 (40.6)
Nausea	26 (20.3)	108 (19.3)	42 (19.8)	15 (11.4)	31 (23.8)	164 (21.2)
Diarrhoea	16 (12.5)	77 (13.8)	36 (16.9)	6 (4.5)	14 (10.8)	98 (12.7)
Vomiting	5 (3.9)	46 (8.2)	11 (5.2)	8 (6.1)	9 (6.9)	69 (8.9)
Severe or blood glucose-confirmed hypoglycaemia	0 (0)	8 (1.4)	15 (7.1)	11 (8.3)	0 (0)	11 (1.4)

Diabetes duration, years	≤5	>5−10	>10	≤5	>5−10
n	420	322	289	519	462
Total AEs (any grade)	301 (71.5)	226 (70.4)	205 (70.9)	360 (69.6)	319 (68.9
Serious AEs	27 (6.4)	17 (5.3)	23 (7.9)	31 (5.9)	37 (8.0
AEs leading to premature treatment discontinuation	26 (6.3)	21 (6.5)	20 (7.1)	41 (7.8)	38 (8.2
Gastrointestinal AEs	179 (42.4)	126 (39.4)	107 (37.2)	205 (39.6)	174 (37.6
Nausea	86 (20.5)	59 (18.6)	46 (15.9)	106 (20.4)	96 (20.7
Diarrhoea	56 (13.3)	40 (12.5)	39 (13.9)	70 (13.5)	64 (13.9
Vomiting	31 (7.3)	17 (5.3)	22 (7.5)	46 (8.9)	40 (8.7
Severe or blood glucose-confirmed hypoglycaemia	11 (2.5)	4 (1.2)	19 (6.7)	14 (2.8)	20 (4.4

ᵃOther OADs included TZD monotherapy, MET+TZD or SU+TZD. Severe or blood glucose-confirmed hypoglycaemia was defined as an
according to the ADA classification or blood glucose-confirmed by a plasma glucose value below 3.1 mmol/L (56 mg/dL) with sympton
hypoglycaemia. %, proportion of subjects experiencing at least one event; ADA, American Diabetes Association; AE, adverse event; N
number of subjects in the safety analysis set; OAD, oral antidiabetes drug; SU, sulphonylurea; TZD, thiazolidinedione.

Figures

Figure legends

Figure 1. Efficacy endpoints at week 30 by baseline HbA$_{1c}$ subgroups (≤7.5%, >7.5–8.0%, >8.0–8.5%, >8.5–9.0%, and >9.0%): (A) change from baseline in HbA$_{1c}$ and (B) change from baseline in body weight.

Data shown are mean ± SEM for the categories analysed. Subgroups are categorized as ≤7.5% [≤58 mmol/mol]; >7.5–8.0% [>58–64 mmol/mol], >8.0–8.5% [>64–69 mmol/mol], >8.5–9.0% [>69–75 mmol/mol] and >9.0% [>75 mmol/mol]. Estimated changes are based on pooled data from the SUSTAIN 1–5 trials. BG, blood glucose; BW, body weight; SEM, standard error of the mean.

Figure 2. Efficacy endpoints at week 30 by background medication subgroups (no background medication [SUSTAIN 1], metformin monotherapy [pooled data from SUSTAIN 2–4], other oral antidiabetes therapy [pooled data from SUSTAIN 2–4] and basal insulin plus metformin [SUSTAIN 5]): (A) change from baseline in HbA$_{1c}$ and (B) change from baseline in body weight.

Data shown are mean ± SEM for the categories analysed. Estimated changes are based on data from the SUSTAIN 1–5 trials, with analyses performed on SUSTAIN 2–4 collectively, but individually for SUSTAIN 1 and 5, so that p-values are provided only for the comparison of metformin monotherapy and other OADs. BG, blood glucose; BW, body weight; OAD, oral antidiabetes drug; SEM, standard error of the mean.

Figure 3. Efficacy endpoints at week 30 by diabetes duration subgroups (≤5 years, >5–10 years and >10 years): (A) change from baseline in HbA$_{1c}$ and (B) change from baseline in body weight.

Data shown are mean ± SEM for the categories analysed. Estimated changes are based on pooled data from the SUSTAIN 1–5 trials. BG, blood glucose; BW, body weight; SEM, standard error of the mean.
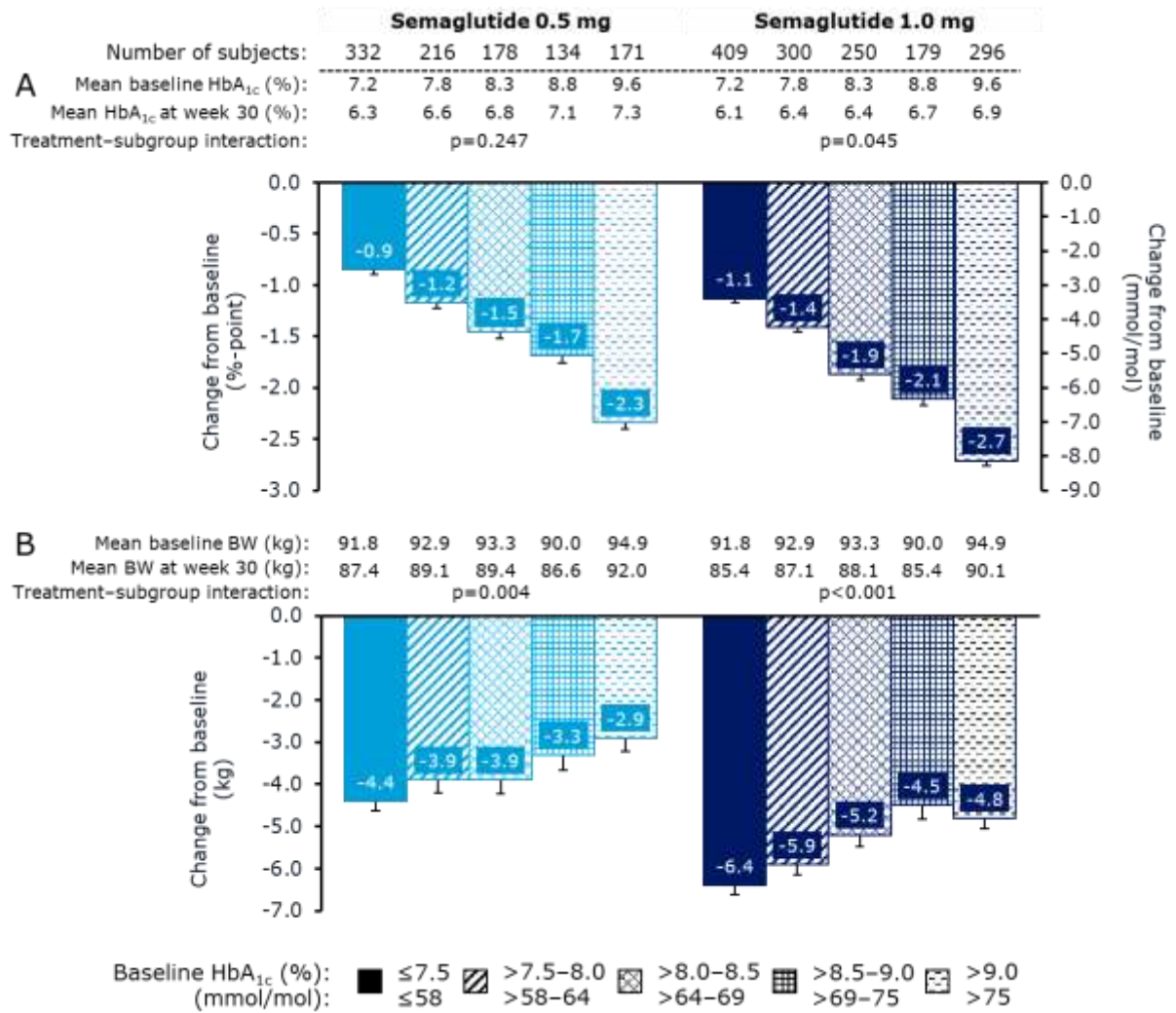
Figure 1. Baseline HbA₁c subgroups

Baseline HbA₁c (%): ■ ≤7.5 ▨ >7.5–8.0 ▦ >8.0–8.5 ▦ >8.5–9.0 ▨ >9.0
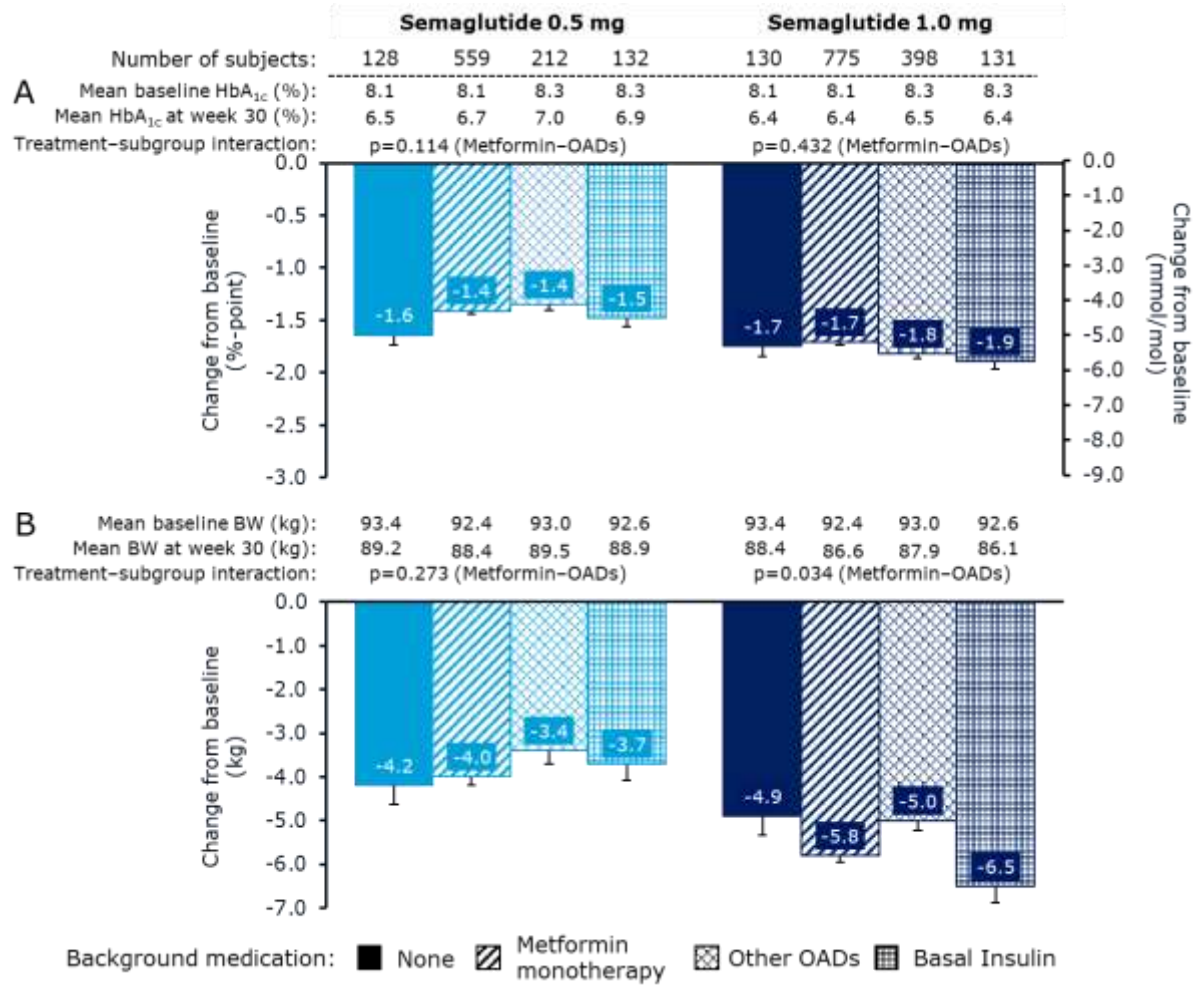(mmol/mol): ≤58 >58–64 >64–69 >69–75 >75

Figure 2. Background medication subgroups

Figure 3. Diabetes duration subgroups