Received: 23 December 2019 | Revised: 18 March 2020 | Accepted: 26 March 2020

DOI: 10.1111/dom.14039

WILEY

ORIGINAL ARTICLE

Semaglutide improves health-related quality of life versus placebo when added to standard of care in patients with type 2 diabetes at high cardiovascular risk (SUSTAIN 6)

Esteban Jódar MD[1,2] | Marie Michelsen MD[3] | William Polonsky PhD[4,5] | Rosangela Réa MD[6] | Anna Sandberg MMSc[3] | Tina Vilsbøll MD[7] | Mark Warren MD[8] | Signe Harring MD[3] | Uwe Ziegler MSc[3] | Stephen Bain MD[9]

[1]Faculty of Medicine, Universidad Europea de Madrid, Madrid, Spain

[2]Department of Endocrinology and Nutrition Service, Hospital Universitario QuironSalud Madrid, Madrid, Spain

[3]Novo Nordisk A/S, Søborg, Denmark

[4]Behavioral Diabetes Institute, San Diego, California

[5]Department of Psychiatry, University of California San Diego, La Jolla, California

[6]Department of Clinical Medicine, SEMPR, Universidade Federal do Paraná, Curitiba, Brazil

[7]Steno Diabetes Center Copenhagen, University of Copenhagen, Hellerup, Denmark

[8]Department of Endocrinology, Physicians East, Greenville, North Carolina

[9]Diabetes Research Unit Cymru, Swansea University Medical School, Swansea, UK

Correspondence
Professor E. Jódar, MD, PhD, Universidad Europea de Madrid, Calle Tajo, s/n, 28670 Villaviciosa de Odón, Madrid, Spain.
Email: esteban.jodar@gmail.com

Funding information
Novo Nordisk

Peer Review
The peer review history for this article is available at https://publons.com/publon/10.1111/dom.14039.

Abstract

Aim: To assess what drives change in health-related quality of life (HRQoL) in type 2 diabetes in the SUSTAIN 6 trial and identify potential mediators of the treatment effect of semaglutide on HRQoL scores.

Materials and Methods: The Short Form (SF)-36v2® questionnaire [comprising physical component summary (PCS) and mental component summary (MCS)] was used to assess changes in HRQoL from baseline to week 104, by treatment, in a prespecified analysis. This post-hoc analysis assessed change in PCS and MCS using the following factors as parameter/covariate, using descriptive statistics and linear regressions: major adverse cardiac events, hypoglycaemia, gastrointestinal adverse events, at least one episode of nausea, vomiting or diarrhoea, and change in glycated haemoglobin (HbA1c), body weight, blood pressure, heart rate and estimated glomerular filtration rate.

Results: Mean change in overall PCS score was +1.0 with semaglutide versus +0.4 with placebo, and +0.5 versus −0.2 for MCS. The treatment effect of semaglutide versus placebo (unadjusted estimate) was 0.7 [(95% confidence interval 0.1, 1.2); P = 0.018] on PCS and this was reduced when adjusted for change in HbA1c [0.4 (−0.2, 1.0), P = .167] and body weight [0.3 (−0.3, 0.9), P = .314]. The unadjusted treatment effect on MCS [0.7 (−0.0, 1.5), P = .054] was only reduced when adjusted for change in HbA1c [0.3 (−0.4, 1.1), P = .397]. When adjusting for all other parameters separately, the estimated effect of semaglutide on PCS and MCS qualitatively did not change.

Conclusions: Semaglutide improved HRQoL versus placebo; greater improvements with semaglutide versus placebo were possibly mediated, in part, by change in HbA1c and body weight.

Clinicaltrials.gov: NCT01720446 (SUSTAIN 6).

KEYWORDS

cardiovascular disease, GLP-1 analogue, hypoglycaemia, incretin therapy, type 2 diabetes, weight control

1 | INTRODUCTION

Type 2 diabetes (T2D) is often associated with reduced health-related quality of life (HRQoL), including factors such as depression, worries, self-care and functional ability.[1–3] As per American Diabetes Association (ADA)/European Association for the Study of Diabetes (EASD) guidelines, one of the goals of care for T2D is to optimize and maintain the quality of life of patients.[4] To understand better how diabetes management may affect HRQoL, it is now routinely included as an endpoint in clinical and observational trials. The Short Form-36 health survey, version 2® (SF-36v2®) is a validated and widely used tool to assess patient-reported HRQoL in such trials.[5]

Therapy with glucagon-like peptide-1 receptor agonists (GLP-1RAs) has been shown to have a beneficial effect on HRQoL and treatment satisfaction in both randomized controlled trials (RCTs) and real-world observational studies.[6–10] Semaglutide (Novo Nordisk, Denmark) is a GLP-1 analogue approved as a once-weekly subcutaneous (s.c.) treatment for T2D,[11,12] and as a daily oral treatment for T2D.[13,14] In the SUSTAIN phase 3a global clinical trial programme, larger, clinically relevant reductions in glycated haemoglobin (HbA1c) and body weight were seen with once-weekly s.c. semaglutide versus comparators (GLP-1RA, dipeptidyl peptidase 4 inhibitor, basal insulin or placebo), together with a low risk of hypoglycaemia.[15–21] In SUSTAIN 6 and PIONEER 6 trials, once-weekly and oral semaglutide reduced the occurrence of major adverse cardiovascular events (MACE) versus placebo in patients with T2D and high cardiovascular disease (CVD) risk.[20,22]

In the SUSTAIN 2–5 and 7 trials, HRQoL, as measured by SF-36v2®, was generally similar or improved significantly with semaglutide versus comparators.[16–19,21]

SUSTAIN 6 was a 2-year, randomized, double-blind, placebo-controlled, event- and time-driven, pre-approval, cardiovascular (CV) outcomes trial with once-weekly s.c. semaglutide (n = 1648) versus placebo (n = 1649) in patients with T2D at high risk of CV events.[20] Change in HRQoL, as measured by SF-36v2®, was a prespecified secondary endpoint in the trial. Changes from baseline to week 104 were significantly greater for semaglutide 1.0 mg compared with placebo (physical component summary [PCS]: 1.7 versus 0.3; $P = 0.0004$ and mental component summary [MCS] 0.9 versus −0.1; $P = 0.0489$).[23]

The aim of this post-hoc analysis of the SUSTAIN 6 trial was to understand better what drives change in HRQoL for patients with T2D and to investigate the potential mediators of the treatment effect of semaglutide on HRQoL scores. Specifically, we evaluated: (a) association of relevant factors [occurrence of MACE, hypoglycaemia and gastrointestinal (GI) adverse events (AEs) during the trial, as well as change in HbA1c, body weight, systolic and diastolic blood pressure (SBP, DBP), heart rate and estimated glomerular filtration rate (eGFR) at end of trial] with change from baseline in HRQoL outcomes in the overall (pooled) trial population, irrespective of treatment; (b) effect of semaglutide (pooled) versus placebo (pooled) on HRQoL outcomes; and (c) whether the above-named relevant factors mediate the effect of semaglutide on HRQoL outcomes.

2 | MATERIALS AND METHODS

2.1 | Trial design

The trial design of SUSTAIN 6 has been reported previously in detail.[20] Briefly, in total, 3297 patients were randomized 1:1:1:1 to receive once-weekly s.c. semaglutide 0.5 or 1.0 mg or volume-matched placebo, which maintained blinding within dose, added to standard of care (Figure S1; see Supporting Information). Patients with T2D and HbA1c ≥7% (53 mmol/mol) were eligible if they had not been treated with an antihyperglycaemic drug or had been treated with no more than two oral antihyperglycaemic agents, with or without basal or premixed insulin. Key inclusion criteria were age ≥50 years with established CVD (previous CV, cerebrovascular or peripheral vascular disease), chronic heart failure (New York Heart Association class II or III) or chronic kidney disease stage 3 or higher or age ≥60 years with at least one CV risk factor.[20] The trial was conducted in compliance with the International Conference on Harmonisation Good Clinical Practice guidelines and the Declaration of Helsinki.[24] The protocols were approved by local ethics committees and institutional review boards. Written informed consent was obtained from all patients before trial commencement.[20]

2.2 | Study endpoints

Key prespecified endpoints of SUSTAIN 6 have been described previously.[23] Change from baseline in patient-reported HRQoL was a prespecified secondary endpoint.[23]

2.3 | Health-related quality of life assessment

The SF-36v2® questionnaire was used to assess changes in HRQoL from baseline to week 104. The SF-36v2® measures HRQoL across two distinct concepts, PCS and MCS, and comprises 36 items across four physical health domains (general health; role: physical; physical functioning; bodily pain) and four mental health domains (mental health; vitality; role: emotional; social functioning).[25] The items in each domain are listed in the user's manual for the SF-36v2® Health Survey (3rd edition).[26] A norm-based scoring is used for the SF-36v2®, setting the general population mean to 50 for each domain, with higher and increasing scores indicating better health.[27] The means, standard deviations and factor score coefficients used in scoring come from the general US population.[28] There is no single overall score for SF-36v2®. The two individual summary scores for PCS and MCS scores are used as the highest score for each group.[25] Of note, the SF-36v2® is a generic scale, validated in the population with T2D and population/countries that contributed to SUSTAIN 6. It does not specifically address CV outcomes, but it has shown good validity and reliability in T2D populations.[29]

The SF-36v2® questionnaire was completed by patients at randomization, then at weeks 56 and 104, preferably before any other trial-

related activities. Each patient completed a paper version of the questionnaire, which was kept at site as source documentation. Data were then transcribed into the electronic case report form by site staff. Clarifications of entries or discrepancies were referred to the patient and a conclusion made in the medical records. Care was taken not to bias the patient. The investigator reviewed the SF-36 v2® scales to ensure that AEs, including overall change in health, were reported.

2.4 | Post-hoc analysis

All analyses used observed SF-36v2® values, and missing values were imputed using a mixed model for repeated measurements, except for patients who died.

2.4.1 | Observed change from baseline in Short Form-36v2® score by relevant factors (irrespective of treatment)

Both semaglutide doses (0.5 and 1.0 mg) and both placebo doses (0.5 and 1.0 mg) were pooled for this post-hoc analysis. Change from baseline in HRQoL (PCS and MCS scores) was assessed using descriptive statistics in patients (all treatment groups pooled) at week 104, and reported in the following subgroups: MACE (yes/no), hypoglycaemia (yes/no); GI AEs (yes/no); at least one episode of nausea or vomiting or diarrhoea (yes/no); body weight loss ≥5% (yes/no); HbA1c reduction ≥1% (yes/no). Body weight was measured throughout the trial in SUSTAIN 6, but weight change at week 104 was used as a covariate for this post-hoc analysis. *P*-values to assess the impact of each factor on change from baseline in SF-36v2® scores were obtained from linear regression models.

2.4.2 | Observed changes from baseline in Short Form-36v2® scores by treatment

Change from baseline to week 104 in PCS and MCS scores was assessed using descriptive statistics and reported by treatment group (semaglutide pooled versus placebo pooled) for PCS and MCS overall and by subdomains.

2.4.3 | Estimated treatment effect on Short Form-36v2® scores and the impact of relevant factors (mediator analysis)

The estimated treatment effect of semaglutide (pooled) versus placebo was calculated for change from baseline in PCS and MCS SF-36v2® scores at week 104 using multiple linear regression models. $P < 0.05$ indicated a significant treatment effect for semaglutide versus placebo. Mediator analysis was then used to evaluate the potential mediating effect of each factor by adjusting treatment effect for the particular factor and comparing with the unadjusted treatment effect. A mediator will reduce the size of the treatment effect, reducing the regression coefficient for the treatment variable, increase its *P*-value and may reduce the Akaike information criterion (AIC) value.

AIC is an estimator of the relative goodness of fit of statistical models for a given set of data, and the lower the AIC, the higher the goodness of fit of that model.[30] While evaluating the estimated effect of semaglutide on PCS and MCS scores, using the value for AIC of the unadjusted model as a reference, a score lower than the value of the unadjusted model indicates a higher quality model and a score higher than the value of the unadjusted model indicates a lower quality model.

3 | RESULTS

3.1 | Patient disposition and baseline characteristics

Key baseline characteristics, patient demographics, baseline CV risk factors and history of CVD are shown in Table 1. These were similar between treatment arms.

3.2 | Observed change from baseline in Short Form-36v2® overall scores by relevant factors (irrespective of treatment)

3.2.1 | Physical component summary

In this pooled treatment (semaglutide and placebo) analysis, the overall PCS score increased by a mean of 0.7 [standard error (SE): 0.1; 95% confidence interval (CI): 0.4, 1.0] from baseline to week 104 (Figure 1A). When analysed by the presence or absence of relevant factors, the mean PCS score increased numerically in all subgroups, but increases were generally smaller in patients with the occurrence of MACE or GI AEs during the trial, as well as in patients without HbA1c reduction ≥1% or without weight loss ≥5% from baseline to end of trial compared with patients without MACE/GI AEs and patients with HbA1c reduction ≥1% or weight loss ≥5% (Figure 1A). The PCS score increased more from baseline in patients with hypoglycaemia [1.4 (SE: 0.3; 95% CI: 0.8, 2.0)] compared with those without hypoglycaemia [0.5 (SE: 0.2; 95% CI: 0.2, 0.8)] ($P < 0.01$) (Figure 1A).

3.2.2 | Mental component summary

In the pooled treatment (semaglutide and placebo) analysis, the change in overall MCS score was 0.2 (SE: 0.2; 95% CI: −0.2, 0.5) from baseline to week 104 for all patients in the trial (Figure 1B). When analysed by the presence or absence of relevant factors, generally the mean MCS score was reduced from baseline in patients with the occurrence of MACE, hypoglycaemia or GI AEs during the trial, as well as in patients without HbA1c reduction ≥1% or without weight loss ≥5% at the end of the trial (Figure 1B).

TABLE 1 Patient disposition and baseline characteristics

	Semaglutide (0.5 + 1.0 mg)	Placebo (0.5 + 1.0 mg)	Total
Patient disposition			
Randomized, n	1648	1649	3297
Trial completers, n (%)	1623 (98.5)	1609 (97.6)	3232 (98.0)
Treatment completers, n (%)	1297 (78.7)	1339 (81.2)	2636 (80.0)
Baseline characteristics			
Age, years	64.7 ± 7.2	64.6 ± 7.5	64.6 ± 7.4
Male, n (%)	1013 (61.5)	989 (60.0)	2002 (60.7)
Diabetes duration, years	14.2 ± 8.2	13.6 ± 8.0	13.9 ± 8.1
HbA1c, %	8.7 ± 1.5	8.7 ± 1.5	8.7 ± 1.5
HbA1c, mmol/mol	71.6 ± 15.9	71.5 ± 16.1	71.6 ± 16.0
BMI, kg/m^2	32.8 ± 6.2	32.8 ± 6.2	32.8 ± 6.2
Body weight, kg	92.3 ± 20.7	91.9 ± 20.5	92.1 ± 20.6
CV risk factors			
SBP, mmHg	136.0 ± 17.5	135.3 ± 16.8	135.6 ± 17.1
DBP, mmHg	77.0 ± 10.0	77.1 ± 10.0	77.0 ± 10.0
Pulse rate, beats/min	72.1 ± 11.1	72.0 ± 10.8	72.0 ± 10.9
Total cholesterol, mmol/L [mean (CoV)]†	4.3 (27.5)	4.3 (27.1)	4.3 (26.7)
eGFR, mL/min/1.73 m^2	75.9 ± 25.9	76.4 ± 27.2	76.1 ± 26.5
Current smoker, n (%)	204 (12.4)	202 (12.2)	406 (12.3)
History of CVD at screening, n (%)			
Prior myocardial infarction	530 (32.2)	542 (32.9)	1072 (32.5)
Ischaemic heart disease	988 (60.0)	1006 (61.0)	1994 (60.5)
Previous ischaemic stroke	178 (10.8)	205 (12.4)	383 (11.6)
Prior arterial disease	226 (13.7)	227 (13.8)	453 (13.7)
≥50% arterial stenosis	567 (34.4)	600 (36.4)	1167 (35.4)
Percutaneous coronary intervention	490 (29.7)	522 (31.7)	1012 (30.7)
Coronary artery bypass graft	288 (17.5)	289 (17.5)	577 (17.5)
Heart failure	381 (23.1)	396 (24.0)	777 (23.6)

Data presented as arithmetic mean ± SD unless otherwise indicated.
†Geometric means.
Abbreviations: BMI, body mass index; CoV, coefficient of variation; CV, cardiovascular; CVD, cardiovascular disease; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HbA1c, glycated haemoglobin; SBP, systolic blood pressure; SD, standard deviation.

3.3 | Observed and estimated change from baseline in Short Form-36v2® overall scores and domains with semaglutide versus placebo and effect when adjusting for relevant factors

3.3.1 | Physical component summary

In the semaglutide group, the mean overall PCS score and its domains increased from baseline (1.0 for change in overall PCS score; SE: 0.2; 95% CI: 0.6, 1.4), and the improvement was numerically greater compared with placebo (0.4; SE: 0.2; 95% CI: −0.0, 0.8) (Figure 2).

The unadjusted estimated treatment effect of semaglutide versus placebo for change in overall PCS score was 0.7 (95% CI: 0.1, 1.2; P = 0.018) (Table 2). When adjusted for change in HbA1c, the treatment effect was reduced to 0.4 (95% CI: −0.2, 1.0; P = 0.167) and when adjusted for body weight, it was reduced to 0.3 (95% CI: −0.3, 0.9; P = 0.314) (Table 2). When adjusting for the occurrence of MACE, GI AEs, hypoglycaemia, nausea/vomiting/diarrhoea and change in SBP, DBP, heart rate and eGFR during the trial, the estimated significant effect of semaglutide versus placebo on PCS was maintained (Table 2).

3.3.2 | Mental component summary

The MCS score and its domains increased from baseline with semaglutide (0.5 for change in overall score; SE: 0.3; 95% CI: 0.0,

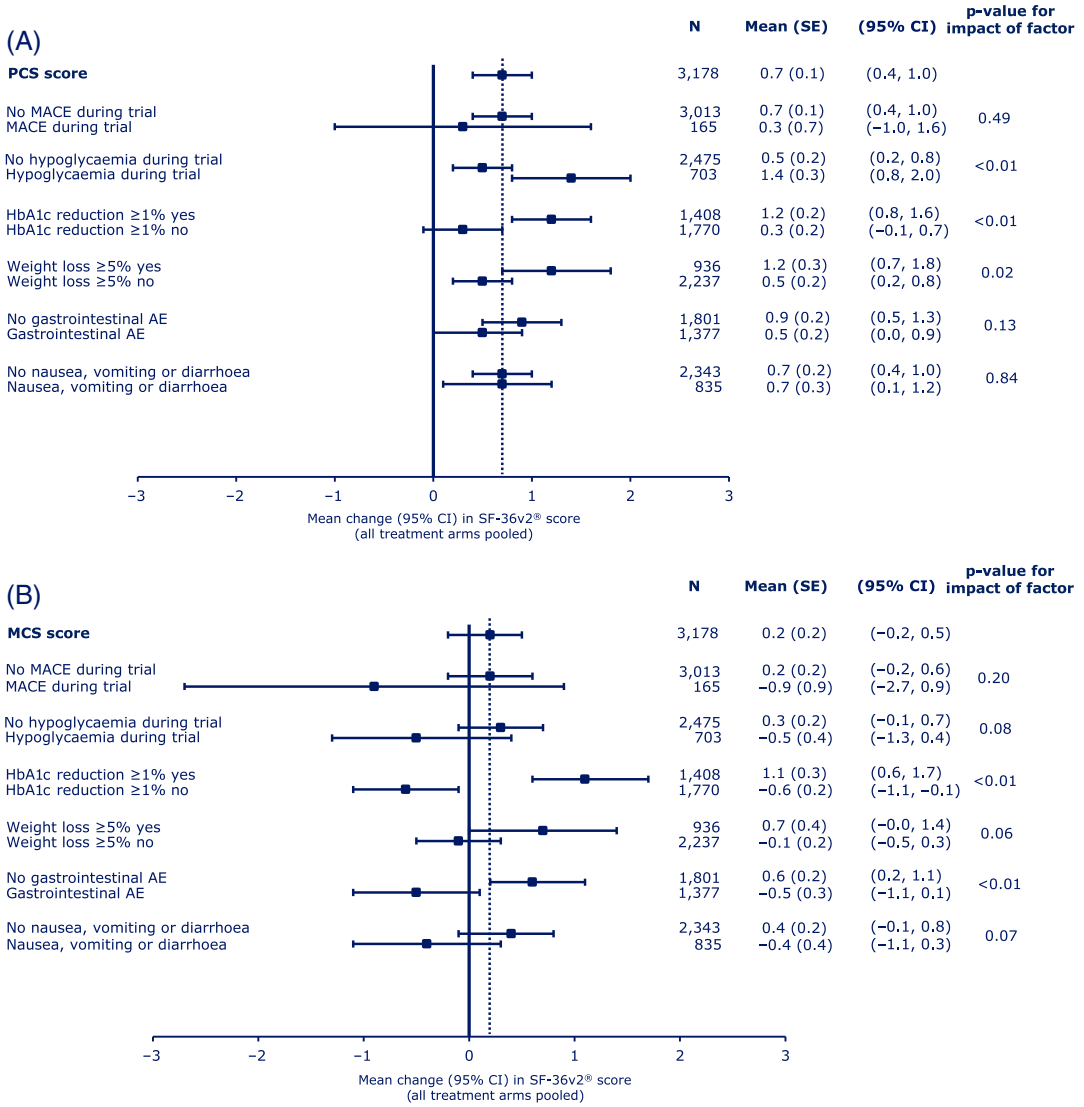

FIGURE 1 A, PCS. B, MCS. Mean change from baseline in SF-36v2® overall PCS and MCS scores by occurrence of relevant factors (yes/no) in all patients (all treatment arms pooled) at week 104. Mean values and 95% CI were assessed using descriptive statistics in patients at week 104 by relevant factors. Observed and MMRM imputed values, excluding MMRM imputed values for patients who died. *P* values were obtained from linear regression models. Dashed vertical line indicates the mean score for the total population. AE, adverse event; CI, confidence interval; MACE, major adverse cardiovascular event; MCS, mental component summary; MMRM, mixed model for repeated measurements; N, number of patients; PCS, physical component summary; SE, standard error; SF-36v2®, Short Form-36 health survey, version 2®

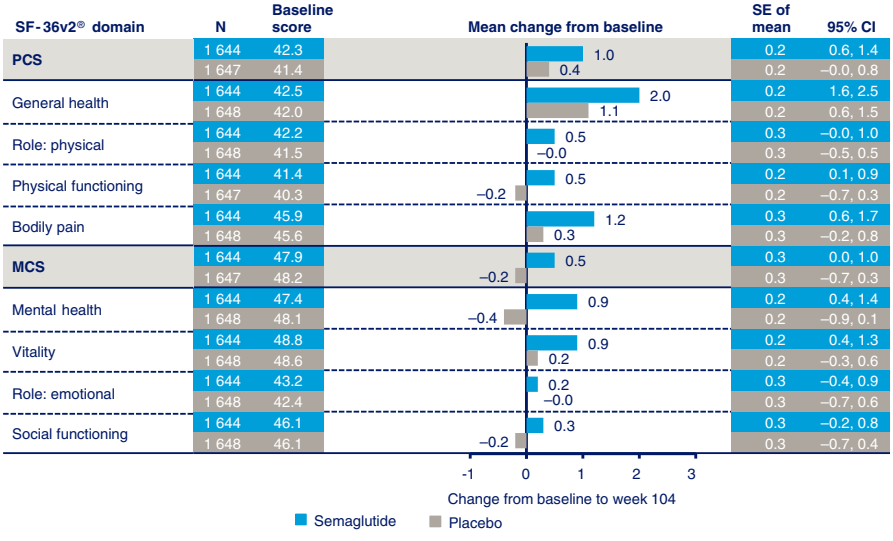

FIGURE 2 Mean change from baseline in SF-36v2® PCS and MCS scores and domains with semaglutide versus placebo at week 104 by treatment. Observed and MMRM imputed values, excluding MMRM imputed values for patients who died. Bars may appear larger or smaller than the number indicated due to rounding. CI, confidence interval; MCS, mental component summary; MMRM, mixed model for repeated measurements; PCS, physical component summary; SE, standard error; SF-36v2®, Short Form-36 health survey, version 2®

TABLE 2 Estimated treatment effect (semaglutide versus placebo) – unadjusted and adjusted by relevant factors – on change from baseline in SF-36v2® overall PCS and MCS scores at week 104

	Estimated effect of semaglutide (95% CI)	*P*-value	AIC (goodness of fit)
PCS score			
Unadjusted	0.7 (0.1, 1.2)	0.018	22 220
Adjusted for:			
MACE	0.7 (0.1, 1.2)	0.020	22 219
Hypoglycaemia	0.7 (0.1, 1.2)	0.020	22 214
GI AE	0.8 (0.2, 1.3)	0.008	22 217
Nausea/vomiting/diarrhoea	0.7 (0.1, 1.3)	0.015	22 220
HbA1c reduction ≥1%	0.5 (−0.1, 1.0)	0.125	22 214
Change in HbA1c	0.4 (−0.2, 1.0)	0.167	22 211
Weight loss ≥5%	0.5 (−0.0, 1.1)	0.061	22 183
% change in weight	0.3 (−0.3, 0.9)	0.314	22 174
Change in SBP	0.7 (0.1, 1.2)	0.020	22 228
Change in DBP	0.7 (0.1, 1.2)	0.018	22 227
Change in heart rate	0.8 (0.2, 1.3)	0.008	22 218
Change in eGFR	0.7 (0.1, 1.2)	0.018	22 227
MCS score			
Unadjusted	0.7 (−0.0, 1.5)	0.054	23 995
Adjusted for:			
MACE	0.7 (−0.0, 1.4)	0.062	23 992
Hypoglycaemia	0.7 (−0.0, 1.5)	0.050	23 992
GI AE	0.9 (0.2, 1.7)	0.014	23 984
Nausea/vomiting/diarrhoea	0.9 (0.1, 1.6)	0.022	23 990
HbA1c reduction ≥1%	0.3 (−0.5, 1.0)	0.516	23 977
Change in HbA1c	0.3 (−0.4, 1.1)	0.397	23 982
Weight loss ≥5%	0.6 (−0.2, 1.3)	0.135	23 956
% change in weight	0.7 (−0.1, 1.4)	0.086	23 963
Change in SBP	0.7 (0.0, 1.5)	0.047	24 002
Change in DBP	0.7 (−0.0, 1.5)	0.054	24 001
Change in heart rate	0.8 (0.1, 1.5)	0.034	23 998
Change in eGFR	0.7 (−0.0, 1.5)	0.053	24 002

Patients experienced at least one event during the trial. Observed and MMRM imputed values, excluding MMRM imputed values for patients who died. Statistical analysis using PROC MIXED, modelling change of SF-36v2® dependent on the respective effects/covariates. AIC describes how well a statistical model fits a set of observations – lower AIC values indicate a better fit. $P < 0.05$ was considered as significant.

Abbreviations: AE, adverse event; AIC, Akaike information criterion; CI, confidence interval; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; GI, gastrointestinal; HbA1c, glycated haemoglobin; MACE, major adverse cardiovascular event; MCS, mental component summary; MMRM, mixed model for repeated measurements; PCS, physical component summary; SBP, systolic blood pressure; SF-36v2®, Short Form-36 health survey, version 2®.

1.0), whereas MCS score decreased for patients on placebo (−0.2; SE: 0.3; 95% CI: −0.7, 0.3) and all domains except vitality (Figure 2).

The unadjusted estimated treatment effect of semaglutide versus placebo on change in overall MCS score was 0.7 (95% CI: −0.0, 1.5; $P = 0.054$) (Table 2). This was only reduced when adjusted for change in HbA1c: 0.3 (95% CI: −0.4, 1.1; $P = 0.397$) (Table 2). When adjusting for the occurrence of MACE, hypoglycaemia, nausea/vomiting/diarrhoea, change in body weight, SBP, DBP, heart rate and eGFR, the estimated effect of semaglutide versus placebo on MCS did not change qualitatively (Table 2).

4 | DISCUSSION

In this post-hoc analysis of the SUSTAIN 6 trial, the overall mean PCS score and MCS score of the SF-36v2® scale generally increased from baseline in all treatment arms (pooled). When analysed by treatment, semaglutide resulted in greater increases in PCS and MCS scores versus placebo; these improvements were in part, possibly mediated by change in HbA1c and body weight. Presence of MACE or GI AEs during the trial did not affect the increase in PCS scores in the pooled treatment group (treatment-independent analysis).

A US cohort study estimated the clinical and social benchmarks for interpretation of SF-36 scores in people with diabetes. It showed that a one-point lower score on the physical function, general health and PCS scales of the SF-36 Health Survey is associated with an excess risk of up to 9% for mortality. A one-point lower score on the physical function, role physical, bodily pain, general health, vitality, social function and PCS scales is associated with an excess risk of up to 12% for inability to work.[27] Hence, as per this study, the benchmark for the interpretation of SF-36v2® scores in diabetes is one point for each domain on the various components of PCS or MCS.

Semaglutide reduces CV complications and improves glycaemic control in patients with T2D, as shown in the SUSTAIN 6 trial.[20] This may have a positive effect on a patient's HRQoL both physically and mentally. However, in that trial, semaglutide treatment was associated with GI AEs, particularly during the escalation phase.[20] Although most events were mild or moderate in severity and of short duration,[20] these may affect HRQoL negatively. When semaglutide was used in combination with sulphonylureas or insulin in the SUSTAIN 3–6 trials, there was a slight increase in episodes of hypoglycaemia with semaglutide versus comparators,[17–20] which could also negatively affect HRQoL.[31] We therefore examined the influence of these factors on HRQoL and the effect of semaglutide versus placebo on HRQoL.

The overall PCS score increased from baseline regardless of the occurrence of MACE or GI AEs during the trial and for patients with and without HbA1c reduction ≥1% or weight loss ≥5%. The increase was less pronounced in patients without HbA1c reduction ≥1% or without weight loss ≥5% and when MACE or GI AEs were present. The overall MCS score was reduced in patients with occurrence of MACE, hypoglycaemia or GI AEs during the trial, as well as in patients without HbA1c reduction ≥1% or without weight loss ≥5%, suggesting that some of these factors, if not all, were associated with the patients' mental health. Hence, in the whole study population, the

occurrence of MACE or GI AEs during the trial and achieving HbA1c reduction ≥1% or weight loss ≥5% at end of trial seemed to be associated with the change in HRQoL.

The reduction in overall MCS score with the occurrence of hypoglycaemia aligns with the results of a European-based observational, cross-sectional study in which patients with T2D with or without reported hypoglycaemia were assessed for HRQoL and fear of hypoglycaemia using the hypoglycaemia fear survey-II worry scale (HFS-II).[31] Patients with hypoglycaemia (45%), versus those without, scored significantly higher on the HFS-II scale ($P < 0.01$), and the overall impact of T2D on their HRQoL was more negative ($P < 0.01$).[31] Patients reporting hypoglycaemia during the current trial actually had a greater increase in the overall PCS score than those not reporting hypoglycaemia. The reason for this is unclear and may be a spurious finding. It could be an indirect increase from increased attention from health care professionals following a hypoglycaemic episode. It might also be that hypoglycaemia is an indirect measure of intensified treatment, resulting in an increased PCS score.

The overall PCS and MCS scores and the domain scores increased from baseline in the pooled semaglutide treatment group, whereas scores either decreased from baseline with placebo or increased numerically less than with semaglutide. Based on the benchmark of a one-point change in SF-36v2® scores in patients with diabetes,[27] the positive change in overall PCS score as well as the bodily pain and general health domains of the PCS with semaglutide and positive change in the general health domain with placebo may be associated with reduced risk of hospitalization and inability to work. The change in overall MCS scores and its domains were all below the one-point benchmark.

In the mediator analysis, we found that HbA1c reduction ≥1%, change in HbA1c, weight loss ≥5% and percentage change in body weight may possibly mediate some of the treatment effects of semaglutide versus placebo on change in PCS. HbA1c reduction, in part, might mediate the effects of semaglutide on change in MCS. The mediation effect was small and this may be because of other positive effects of semaglutide, suggesting that semaglutide improves HRQoL via multiple mechanisms, and not just by reducing HbA1c and body weight. Although adjusting for weight loss had a small impact on the semaglutide versus placebo treatment effect on PCS scores, it did not have an impact on the semaglutide versus placebo treatment effect on MCS scores. This is in line with a review demonstrating that HRQoL outcomes, including depression, were not consistently improved in RCTs of weight loss (from ≤5% to ≥10%), although there is no indication as to whether the lack of improvement is related to the magnitude of weight loss. The review concluded that the available compelling RCT data do not support the notion that HRQoL is consistently and robustly improved following weight loss.[32]

Adjusting for the occurrence of hypoglycaemia did not affect the semaglutide versus placebo treatment effect on the MCS score, indicating that the mental wellbeing of patients receiving semaglutide versus placebo was not sensitive to hypoglycaemia events.

Other glucose-lowering agents have also shown improvements in HRQoL in patients with T2D. In the AWARD-1 study, dulaglutide 0.75 and 1.5 mg as an add-on to metformin and pioglitazone significantly improved HRQoL and treatment satisfaction, compared with placebo.[33] In the DURATION-2 study, weight-related HRQoL and general health utility scores (EQ-5D) improved significantly for patients receiving exenatide extended release or sitagliptin but not pioglitazone.[33] The AWARD-6 study showed that there were no significant differences between dulaglutide and liraglutide in improving HRQoL (EQ-5D).[33] The PAGE1 study showed that liraglutide resulted in significant improvements in glycaemic control and body weight without deteriorating the QoL of patients although the treatment modality had changed from injection to non-injection therapy.[10] A real-world inception cohort study assessing HRQoL (EQ-5D) scores in people initiating one of the new glucose-lowering drugs in daily practice demonstrated that over 26 weeks, patients starting with or switching to a new drug maintained or modestly increased their HRQoL.[34]

There are limitations to our analysis, e.g. the SF-36v2® is a generic, non-disease-specific questionnaire. Therefore, it is unlikely to be sensitive enough to detect all changes in HRQoL that are specific to the diabetes population. A questionnaire that includes questions on diabetes-specific aspects of life would have been preferable; however, compared with disease-specific measures, generic measures such as SF-36v2® are more comprehensive in their coverage of different health status domains and are necessary to compare outcomes across different populations and interventions.[35,36] The changes in the mean SF-36v2® scores are small compared with the standard deviations and this limits the conclusions that can be drawn. The SUSTAIN 6 trial compared semaglutide with placebo, hence these results cannot be extrapolated to other interventions. The statistical models supporting the mediator analysis are of limited use for assessing the effects of factors of interest, i.e. for identifying moderators.

The strength of this analysis is that it is based on long-term patient outcomes data, which can reinforce the conclusions that are made from the initial main trial or can provide completely new information.[37] This post-hoc analysis reinforces the finding from SUSTAIN 6 that semaglutide improves HRQoL versus placebo in patients with T2D at high CV risk, and demonstrates that patients on semaglutide and placebo feel better physically after participation in the trial, regardless of the presence of MACE or GI AEs.

As HRQoL is an important contributor to patient satisfaction, further studies are warranted to understand which factors have an impact on HRQoL in patients with diabetes. This would help guide clinical practice and better aid clinical decision making.

5 | CONCLUSIONS

This post-hoc analysis of SUSTAIN 6 showed that semaglutide was associated with greater improvements in HRQoL scores compared with placebo. The overall PCS score of SF-36v2® increased in patients treated with semaglutide and with placebo, regardless of the presence of MACE or GI AEs during the trial. The MCS score reduced with the occurrence of MACE, hypoglycaemia or GI AEs during the trial, as well as in patients without HbA1c reduction ≥1% or weight loss ≥5% at the end of the trial. Greater improvements in HRQoL with

semaglutide versus placebo were possibly mediated, in part, by change in HbA1c and body weight, but other mechanisms are probably also involved.

ACKNOWLEDGEMENTS

We thank all the patients, investigators and trial-site staff members who were involved in the SUSTAIN 6 trial, and Priya Talluri of AXON Communications for medical writing and editorial assistance, who received compensation from Novo Nordisk. This study and the associated trial were supported by Novo Nordisk A/S, Denmark.

CONFLICT OF INTEREST

E.J. reports receiving grants and personal fees from Novo Nordisk for the work for publication; grants and personal fees from Novo Nordisk, MSD, Lilly, Janssen, Pfizer, AstraZeneca, Sanofi, UCB, Amgen, grants from FAES and Shire, personal fees from Mundipharma and Novartis, all outside the submitted work. W.H.P. reports serving as a consultant for Novo Nordisk outside the submitted work; R.R. reports serving on the advisory panel and speaker's bureau of Novo Nordisk, AstraZeneca, Boehringer Ingelheim, Eli Lilly and Sanofi and serving on the speaker's bureau of Takeda. T.V. reports serving as a consultant on the advisory panel of Amgen, Boehringer Ingelheim, Eli Lilly, AstraZeneca, MSD and Sun Pharmaceuticals and receiving grants from Boehringer Ingelheim and Eli Lilly; all outside the submitted work. M.W. reports receiving non-financial support from Novo Nordisk for the work for publication; receiving grants and personal fees from Novo Nordisk, Eli Lilly and Sanofi Aventis, grants from Gan and Lee and personal fees from AstraZeneca, all outside the submitted work. S.C.B. reports receiving honoraria, teaching and research sponsorship/grants from Abbott, AstraZeneca, Boehringer Ingelheim, Cellnovo, Eli Lilly, MSD, Novo Nordisk and Sanofi-Aventis; receiving funding for the development of educational programmes from Cardiff University, Doctors.net, Elsevier, Onmedica, Omnia-Med and Medscape; providing expert advice for the All-Wales Medicines Strategy Group and NICE UK; owning a share in Glycosmedia; all outside the submitted work. All other authors: nothing to disclose.

AUTHOR CONTRIBUTIONS

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

ORCID

Esteban Jódar https://orcid.org/0000-0002-1234-8560
Tina Vilsbøll https://orcid.org/0000-0002-0456-6787
Mark Warren https://orcid.org/0000-0001-6693-9860
Stephen Bain https://orcid.org/0000-0001-8519-4964

REFERENCES

1. Luscombe FA. Health-related quality of life measurement in type 2 diabetes. *Value Health*. 2000;3(Suppl 1):15-28.
2. Grandy S, Chapman RH, Fox KM, SHIELD Study Group. Quality of life and depression of people living with type 2 diabetes mellitus and those at low and high risk for type 2 diabetes: findings from the Study to Help Improve Early evaluation and management of risk factors Leading to Diabetes (SHIELD). *Int J Clin Pract*. 2008;62(4):562-568.
3. Grandy S, Fox KM, SHIELD Study Group. Change in health status (EQ-5D) over 5 years among individuals with and without type 2 diabetes mellitus in the SHIELD longitudinal study. *Health Qual Life Outcomes*. 2012;10:99.
4. 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;41(12):2669-2701.
5. Speight J, Reaney MD, Barnard KD. Not all roads lead to Rome-a review of quality of life measurement in adults with diabetes. *Diabet Med*. 2009;26(4):315-327.
6. Bode BW, Testa MA, Magwire M, et al. Patient-reported outcomes following treatment with the human GLP-1 analogue liraglutide or glimepiride in monotherapy: results from a randomized controlled trial in patients with type 2 diabetes. *Diabetes Obes Metab*. 2010;12(7):604-612.
7. Bergenstal RM, Garrison LP, Miller LA, et al. Exenatide BID Observational Study (ExOS): results for primary and secondary endpoints of a prospective research study to evaluate the clinical effectiveness of exenatide BID use in patients with type 2 diabetes in a real-world setting. *Curr Med Res Opin*. 2011;27(12):2335-2342.
8. Grant P, Lipscomb D, Quin J. Psychological and quality of life changes in patients using GLP-1 analogues. *J Diabetes Complications*. 2011;25(4):244-246.
9. Reaney M, Mathieu C, Ostenson CG, et al. Patient-reported outcomes among patients using exenatide twice daily or insulin in clinical practice in six European countries: the CHOICE prospective observational study. *Health Qual Life Outcomes*. 2013;11:217.
10. Ishii H, Niiya T, Ono Y, Inaba N, Jinnouchi H, Watada H. Improvement of quality of life through glycemic control by liraglutide, a GLP-1 analog, in insulin-naive patients with type 2 diabetes mellitus: the PAGE1 study. *Diabetol Metab Syndr*. 2017;9:3.
11. European Medicines Agency. *Ozempic® (semaglutide) Summary of Product Characteristics*. 2018. https://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/004174/WC500244163.pdf. Accessed April 2020.
12. Novo Nordisk. *Ozempic® (semaglutide) Prescribing Information*. 2020. https://www.novo-pi.com/ozempic.pdf. Accessed April 2020.
13. US Food and Drug Administration. News release: FDA approves first oral GLP-1 treatment for type 2 diabetes. 2019. https://www.fda.gov/news-events/press-announcements/fda-approves-first-oral-glp-1-treatment-type-2-diabetes. Accessed April 2020.
14. GlobeNewswire. *Rybelsus® (oral semaglutide) approved for the treatment of adults with type 2 diabetes in the EU*. April 2020. https://www.globenewswire.com/news-release/2020/04/04/2011789/0/en/Rybelsus-oral-semaglutide-approved-for-the-treatment-of-adults-with-type-2-diabetes-in-the-EU.html. Accessed April 2020.
15. 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.
16. 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.
17. 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.

18. 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.
19. 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.
20. 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.
21. 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.
22. Husain M, Birkenfeld AL, Donsmark M, et al. Oral Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes. *N Engl J Med*. 2019;381(19):841-851.
23. Jódar E, Polonsky W, Réa R, et al. Semaglutide improves health-related quality of life vs placebo when added to standard-of-care in patients with type 2 diabetes. Poster presented at 54th Annual Meeting of the European Association for the Study of Diabetes (EASD, Berlin, Germany; 1–5 October 2018.
24. Novo Nordisk. Data on file.
25. Lins L, Carvalho FM. SF-36 total score as a single measure of health-related quality of life: Scoping review. *SAGE Open Med*. 2016;4:2050312116671725.
26. Maruish M. *User's Manual for the SF-36v2 Health Survey*. 3rd ed. Quality Metric Incorporated: Lincoln, RI; 2011.
27. Bjorner JB, Lyng Wolden M, Gundgaard J, Miller KA. Benchmarks for interpretation of score differences on the SF-36 health survey for patients with diabetes. *Value Health*. 2013;16(6):993-1000.
28. Ware JE, Kosinski M, Keller S. *SF-36 Physical and Mental Health Summary Scales: A User's Manual*. Boston, MA: The Health Institute; 1994.
29. Clinical Review Report: Insulin Degludec (Tresiba): (Novo Nordisk Canada Inc). *Indication: For Once-daily Treatment of Adults with Diabetes Mellitus to Improve Glycemic Control*. Canadian Agency for Drugs and Technologies in Health, Ottawa, ON, Canada; 2017.
30. Mohammed EA, Naugler C, Far BH. Emerging business intelligence framework for a clinical laboratory through big data analytics. In: Tran QN, Arabnia H, eds. *Emerging Trends in Computer Science and Applied Computing, Emerging Trends in Computational Biology, Bioinformatics, and Systems Biology*. Morgan Kaufmann, Burlington, MA, USA; 2015:577-602.
31. Jódar-Gimeno E, Álvarez-Guisasola F, Ávila-Lachica L, Palomares-Ortega R, Roldán-Suárez C, Lizán-Tudela L. Quality of life and fear for hypoglycaemia in patients with type 2 diabetes mellitus. *Rev Clin Esp*. 2015;215(2):91-97.
32. Kolotkin RL, Andersen JR. A systematic review of reviews: exploring the relationship between obesity, weight loss and health-related quality of life. *Clin Obes*. 2017;7(5):273-289.
33. Billings LK, Handelsman Y, Heile M, Schneider D, Wyne K. Health-related quality of life assessments with once-weekly glucagon-like peptide-1 receptor agonists in type 2 diabetes mellitus. *J Manag Care Spec Pharm*. 2018;24(9-a Suppl):S30-S41.
34. Torre C, Guerreiro J, Longo P, Raposo JF, Leufkens H, Martins AP. Health-related quality of life in adults with type 2 diabetes mellitus starting with new glucose lowering drugs: An inception cohort study. *Prim Care Diabetes*. 2019;13(3):221-232.
35. Patrick DL, Deyo RA. Generic and disease-specific measures in assessing health status and quality of life. *Med Care*. 1989;27(3 Suppl):S217-S232.
36. Wolinsky FD, Wyrwich KW, Nienaber NA, Tierney WM. Generic versus disease-specific health status measures. An example using coronary artery disease and congestive heart failure patients. *Eval Health Prof*. 1998;21(2):216-243.
37. Knight BP. The long-term benefits of long-term follow-up in clinical trials. https://www.eplabdigest.com/articles/Long-Term-Benefits-Long-Term-Follow-Clinical-Trials. Accessed April 2020.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

How to cite this article: Jódar E, Michelsen M, Polonsky W, et al. Semaglutide improves health-related quality of life versus placebo when added to standard of care in patients with type 2 diabetes at high cardiovascular risk (SUSTAIN 6). *Diabetes Obes Metab*. 2020;1–9. https://doi.org/10.1111/dom.14039