Superior weight loss with once-weekly semaglutide versus other glucagon-like peptide-1 receptor agonists is independent of gastrointestinal adverse events

Ildiko Lingvay, Thomas Hansen, Stanislava Macura, Michel Marre, Michael A Nauck, Raymond de la Rosa, Vincent Woo, Emre Yildirim, John Wilding

ABSTRACT

Introduction Gastrointestinal (GI) adverse events (AEs) are the most common AEs with glucagon-like peptide-1 receptor agonists (GLP-1RAs). Weight loss (WL) is slightly greater in people who experience GI AEs than those who do not. A previous mediation analysis of the SUSTAIN 1–5 trials indicated minor contribution of nausea/vomiting to the greater WL with once-weekly semaglutide versus comparators. Semaglutide demonstrated superior glycated hemoglobin and body weight (BW) reductions versus other GLP-1RAs in SUSTAIN 3 (versus exenatide extended release 2.0 mg), SUSTAIN 7 (versus dulaglutide) and SUSTAIN 10 (iraglutide 1.2 mg). The objective of this analysis was to assess if significantly greater WL with semaglutide versus other GLP-1RAs is mediated by nausea/vomiting and other GI AEs (diarrhea, constipation, dyspepsia) during dose escalation (baseline to week 12, when GI AEs are generally most prevalent) and from baseline to end of treatment (EOT: week 56 (SUSTAIN 3), 40 (SUSTAIN 7) or 30 (SUSTAIN 10)).

Research design and methods Subjects within trials were subdivided into those who reported (yes/no) nausea/vomiting or any other GI AE. Change from baseline in BW was assessed within each trial and subgroup. A mediation analysis separated WL into direct or indirect (mediated by GI AEs) effects.

Results From baseline to week 12 or EOT, the nausea/vomiting-mediated difference in WL was, respectively: 0.05 or 0.09 kg of 3.78 kg at EOT (SUSTAIN 3); 0.06 or 0.03 kg of 2.26 kg at EOT (low-dose comparison) and 0.08 or 0.04 kg of 3.55 kg at EOT (high-dose comparison) (SUSTAIN 7) and 0.05 or 0.09 kg of 3.82 kg at EOT (SUSTAIN 10).

Conclusions In SUSTAIN 3, 7 and 10, nausea/vomiting by week 12 (end of dose escalation) or throughout treatment contributed minimally (<0.1 kg) to the superior WL with semaglutide versus GLP-1RA comparators at EOT.

INTRODUCTION

The association between type 2 diabetes (T2D) and overweight/obesity is well established, with more than 90% of people with T2D being overweight. Individuals with T2D and overweight/obesity are at increased risk of developing T2D complications compared with people who are not overweight/obese. Body weight (BW) reductions of ≥5% improve glycemic control, lipid levels and
blood pressure. BW control is an important component of an individualized, multifactorial approach to T2D management, as recommended in current treatment guidelines.

Glucagon-like peptide-1 receptor agonists (GLP-1RAs) are recommended as second-line therapy (add-on to metformin) where minimizing weight gain, promoting weight loss or when hypoglycemia and cardiovascular risk reduction are considerations. All available GLP-1RAs (dulaglutide, exenatide, lixisenatide and semaglutide) have demonstrated weight loss in people with T2D. Semaglutide (Novo Nordisk, Denmark) is a GLP-1RA approved for the treatment of T2D as once-weekly (OW) subcutaneous and once-daily oral formulations. The efficacy and safety of OW semaglutide have been established in the global phase 3 SUSTAIN clinical trial program, encompassing subjects from across the continuum of T2D care. In addition to significantly greater reductions in glycated hemoglobin (HbA1c), semaglutide demonstrated superior reductions in BW versus all comparators across all SUSTAIN trials.

The SUSTAIN 3, 7 and 10 trials compared semaglutide with the GLP-1RAs OW exenatide extended release (exenatide ER), OW dulaglutide and once-daily lixisenatide, respectively. In these trials, mean BW loss was significantly greater with semaglutide versus comparators at end of treatment (EOT: weeks 56, 40 and 30 for SUSTAIN 3, 7 and 10, respectively): SUSTAIN 3: –5.6 kg vs –1.9 kg with semaglutide 1.0 mg vs exenatide ER 2.0 mg; SUSTAIN 7: –4.6 kg vs –2.3 kg with semaglutide 0.5 mg vs dulaglutide 0.75 mg and –6.5 kg vs –3.0 kg with semaglutide 1.0 mg vs dulaglutide 1.5 mg; SUSTAIN 10: –5.8 kg vs –1.9 kg with semaglutide 1.0 mg vs liraglutide 1.2 mg; all p<0.0001. Consistent with the GLP-1RA class, gastrointestinal (GI) adverse events (AEs) were the most frequently reported AEs in the SUSTAIN 3, 7 and 10 trials: 42% with semaglutide 1.0 mg vs 33% with exenatide ER 2.0 mg in SUSTAIN 3; 43% with semaglutide 0.5 mg vs 33% with dulaglutide 0.75 mg and 44% with semaglutide 1.0 mg vs 48% with dulaglutide 1.5 mg in SUSTAIN 7; 44% with semaglutide 1.0 mg vs 38% with liraglutide 1.2 mg in SUSTAIN 10. The five most commonly reported GI AEs in SUSTAIN 3, 7 and 10 were: nausea (23% with semaglutide 0.5 mg, 21%–22% with semaglutide 1.0 mg and 12%–20% with comparators); vomiting (10% with semaglutide 0.5 mg, 7%–10% with semaglutide 1.0 mg and 4%–10% with comparators); diarrhea (14% with semaglutide 0.5 mg, 11%–16% with semaglutide 1.0 mg and 8%–18% with comparators); dyspepsia (3% with semaglutide 0.5 mg, 4%–7% with semaglutide 1.0 mg and 3%–5% with comparators) and constipation (5% with semaglutide 0.5 mg, 5%–6% with semaglutide 1.0 mg and 3%–5% with comparators). Given the clinical significance of weight loss in T2D management, it is important to understand the mechanism by which semaglutide provides greater weight loss versus class comparators and, in particular, whether it is mediated by GI AEs. A previous mediation analysis examining superior weight loss with semaglutide versus mixed class comparators by GI AEs in the SUSTAIN 1–5 trials showed that only 0.07 kg of 2.3 kg (semaglutide 0.5 mg) and 0.5 kg of 6.3 kg (semaglutide 1.0 mg) of the treatment difference in weight loss was mediated by nausea/vomiting.

To further determine if GI AEs of nausea/vomiting and others are associated with weight loss, we performed a post hoc mediation analysis to examine the extent to which the treatment difference with semaglutide versus the other GLP-1RAs in the SUSTAIN 3, 7 and 10 trials might be driven by a difference in GI AEs (indirect effects) or treatment (direct effect). Data on nausea and/or vomiting were pooled and data on nausea, vomiting, diarrhea, constipation and dyspepsia were analyzed individually.

**MATERIALS AND METHODS SUSTAIN 3, 7 and 10 trial designs**

The designs of the SUSTAIN 3, 7 and 10 trials have been previously published. Briefly, subjects with inadequately controlled T2D were randomized to receive: (1) in SUSTAIN 3, semaglutide 1.0 mg or exenatide ER 2.0 mg, in addition to existing oral antidiabetes drugs, over 56 weeks; (2) in SUSTAIN 7, semaglutide 0.5 mg or 1.0 mg, or dulaglutide 0.75 mg or 1.5 mg in addition to metformin monotherapy, over 40 weeks; (3) in SUSTAIN 10, semaglutide 1.0 mg or liraglutide 1.2 mg, in addition to 1–3 oral antidiabetes drugs, over 30 weeks.

Semaglutide-treated subjects followed a fixed dose-escalation regimen. The 0.5 mg maintenance dose was reached after 4 weeks of 0.25 mg OW and the 1.0 mg maintenance dose was reached after 4 weeks of 0.25 mg OW, followed by 4 weeks of 0.5 mg OW. Exenatide ER was administered in accordance with its prescribing information (ie, no dose escalation) and dulaglutide was administered in accordance with its phase III clinical trial program (ie, no dose escalation). The liraglutide 1.2 mg maintenance dose was reached after 1 week of 0.6 mg once daily.

For all three trials, prior to trial initiation, the protocol, the consent form and the subject information sheet were reviewed and approved according to local regulations by appropriate health authorities and by an independent ethics committee/institutional review board. Written informed consent was obtained from all participants.
As with the previous analysis, a mediation analysis was performed to separate the overall effect of the GLP-1RAs on BW into direct or indirect (mediated by nausea or vomiting) effects, estimated using natural effect models with imputation-based estimation. Missing BW data were imputed using observed data within the same treatment group assuming that data were missing at random. The question assessed by the direct effect was: what is the effect of changing the treatment from comparator to semaglutide while maintaining the mediator at a value observed in the comparator arm? Conversely, the question assessed by the indirect effect was: what is the effect of changing the level of mediator between semaglutide and comparator (exenatide ER, dulaglutide or liraglutide)? As some of these factors are counterfactual (ie, things that did not occur but were possible) and non-observable, a model was required to obtain estimates of the direct and indirect effects. The natural effect model for the estimation of direct and indirect effects included the interaction between treatment and GI AEs together with the baseline variables of BW and country as main effects, assuming no interaction between natural effects and baseline variables; standard errors of treatment differences were estimated by the bootstrap method. The model used to impute counterfactual values of BW also included the interaction between treatment and each baseline variable and the interaction between any GI AE and each baseline variable.

RESULTS

The presented results of the SUSTAIN 3, 7 and 10 trials focus on the category of subjects with/without nausea/vomiting, regardless of severity or duration (table 1; figures 1 and 2). The results, according to the common individual GI AEs associated with semaglutide (nausea, vomiting, diarrhea, constipation or dyspepsia), are provided in detail in the online supplemental material 1.

Change from baseline in BW by GI AEs

The change in BW from baseline to EOT (week 56 for SUSTAIN 3; week 40 for SUSTAIN 7; week 30 for SUSTAIN 10) in subjects who experienced GI AEs versus those who did not experience GI AEs was estimated from a mixed model for repeated measurements. The effect of GI AEs on the change from baseline in BW at EOT was compared in subjects with versus without GI AEs from baseline to week 12 (when GI AEs were found to peak and decline thereafter) and from baseline to EOT. The effect on the change in BW was analyzed by each of the five most common GI AEs (nausea, vomiting, diarrhea, constipation or dyspepsia) individually and by nausea/vomiting. Analyses for BW change were performed on the full analysis set. Subjects who discontinued treatment/initiated rescue medication contributed to the analysis based on the data observed prior to their discontinuation of treatment or initiation of rescue medication.

Mediation analysis

As with the previous analysis, a mediation analysis was performed to separate the overall effect of the GLP-1RAs on BW into direct or indirect (mediated by nausea or vomiting) effects, estimated using natural effect models with imputation-based estimation. Missing BW data were imputed using observed data within the same treatment group assuming that data were missing at random. The question assessed by the direct effect was: what is the effect of changing the treatment from comparator to semaglutide while maintaining the mediator at a value observed in the comparator arm? Conversely, the question assessed by the indirect effect was: what is the effect of changing the level of mediator between semaglutide and comparator (exenatide ER, dulaglutide or liraglutide)? As some of these factors are counterfactual (ie, things that did not occur but were possible) and non-observable, a model was required to obtain estimates of the direct and indirect effects. The natural effect model for the estimation of direct and indirect effects included the interaction between treatment and GI AEs together with the baseline variables of BW and country as main effects, assuming no interaction between natural effects and baseline variables; standard errors of treatment differences were estimated by the bootstrap method. The model used to impute counterfactual values of BW also included the interaction between treatment and each baseline variable and the interaction between any GI AE and each baseline variable.
Table 1  Baseline characteristics and subject disposition of subjects with onset of nausea/vomiting from baseline to week 12 and at any time from baseline to end of treatment (yes/no) in the SUSTAIN 3, 7 and 10 trials

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Semaglutide 0.5 mg (SUSTAIN 7)</th>
<th>Semaglutide 1.0 mg (pooled)</th>
<th>Exenatide ER 2.0 mg (SUSTAIN 3)</th>
<th>Dulaglutide 0.75 mg (SUSTAIN 7)</th>
<th>Dulaglutide 1.5 mg (SUSTAIN 7)</th>
<th>Liraglutide 1.2 mg (SUSTAIN 10)</th>
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<tr>
<td>N (total)</td>
<td>301</td>
<td>994</td>
<td>405</td>
<td>299</td>
<td>299</td>
<td>287</td>
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<tr>
<td>Nausea/vomiting Yes/No</td>
<td>Y</td>
<td>N</td>
<td>Y</td>
<td>N</td>
<td>Y</td>
<td>Y</td>
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<td><strong>Baseline to week 12</strong></td>
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<td>N</td>
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<td>230</td>
<td>213</td>
<td>781</td>
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<td>262</td>
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<td>Race, n (%)</td>
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<td>15 (21.1)</td>
<td>35 (15.2)</td>
<td>13 (6.1)</td>
<td>38 (4.9)</td>
<td>1 (2.0)</td>
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<td></td>
<td>Black or African American</td>
<td>3 (4.2)</td>
<td>14 (6.1)</td>
<td>11 (5.2)</td>
<td>37 (4.7)</td>
<td>2 (4.0)</td>
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<td>53 (74.6)</td>
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<td>179 (84.0)</td>
<td>669 (85.7)</td>
<td>44 (88.0)</td>
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<td>Ethnic group, n (%)</td>
<td>Hispanic or Latino</td>
<td>8 (11.3)</td>
<td>21 (9.1)</td>
<td>25 (11.7)</td>
<td>107 (13.7)</td>
<td>11 (22.0)</td>
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<tr>
<td></td>
<td>Not Hispanic or Latino</td>
<td>63 (88.7)</td>
<td>209 (90.9)</td>
<td>185 (86.9)</td>
<td>661 (84.6)</td>
<td>39 (78.0)</td>
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<td>13 (1.7)</td>
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<td>Baseline HbA1c, %</td>
<td>8.3 (1.0)</td>
<td>8.3 (1.0)</td>
<td>8.2 (0.9)</td>
<td>8.3 (0.9)</td>
<td>8.4 (1.1)</td>
<td>8.3 (0.9)</td>
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<td>Baseline BMI, kg/m²</td>
<td>32.5 (7.2)</td>
<td>34.0 (7.1)</td>
<td>33.1 (6.3)</td>
<td>34.0 (7.0)</td>
<td>32.7 (6.2)</td>
<td>33.7 (6.2)</td>
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<td>Baseline BW, kg</td>
<td>92.1 (28.4)</td>
<td>97.7 (22.9)</td>
<td>92.4 (19.4)</td>
<td>97.1 (22.0)</td>
<td>90.2 (16.7)</td>
<td>96.1 (20.9)</td>
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<td>Duration of diabetes, years</td>
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<td>7.8 (5.9)</td>
<td>8.8 (6.5)</td>
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<td>9.6 (7.2)</td>
<td>9.4 (6.6)</td>
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<td>Onset of rescue, n (%)</td>
<td>0 (0.0)</td>
<td>3 (1.3)</td>
<td>3 (1.4)</td>
<td>36 (4.6)</td>
<td>3 (6.0)</td>
<td>45 (12.7)</td>
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<tr>
<td>Discontinued treatment, n (%)</td>
<td>21 (29.6)</td>
<td>26 (11.3)</td>
<td>61 (28.6)</td>
<td>111 (14.2)</td>
<td>12 (24.0)</td>
<td>73 (20.6)</td>
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<td>Withdrawal from trial, n (%)</td>
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<td>17 (7.4)</td>
<td>17 (8.0)</td>
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<td>6 (12.0)</td>
<td>30 (8.5)</td>
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<td>Lost to follow-up, n (%)</td>
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<td><strong>At any time from baseline to EOT</strong></td>
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<tr>
<td>N</td>
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<td>225</td>
<td>245</td>
<td>749</td>
<td>57</td>
<td>348</td>
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<tr>
<td>Race, n (%)</td>
<td>Asian</td>
<td>16 (21.1)</td>
<td>34 (15.1)</td>
<td>14 (5.7)</td>
<td>37 (4.9)</td>
<td>1 (1.8)</td>
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<td>Black or African American</td>
<td>4 (5.3)</td>
<td>13 (5.8)</td>
<td>13 (5.3)</td>
<td>35 (4.7)</td>
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Continued
### Table 1  Continued

<table>
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<tr>
<th>Treatment</th>
<th>Semaglutide 0.5 mg (SUSTAIN 7)</th>
<th>Semaglutide 1.0 mg (pooled)</th>
<th>Exenatide ER 2.0 mg (SUSTAIN 3)</th>
<th>Dulaglutide 0.75 mg (SUSTAIN 7)</th>
<th>Dulaglutide 1.5 mg (SUSTAIN 7)</th>
<th>Liraglutide 1.2 mg (SUSTAIN 10)</th>
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<td>177 (78.7)</td>
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<td>Hispanic or Latino</td>
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<td>95 (27.3)</td>
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<tr>
<td>Not Hispanic or Latino</td>
<td>68 (89.5)</td>
<td>204 (90.7)</td>
<td>216 (88.2)</td>
<td>630 (84.1)</td>
<td>46 (80.7)</td>
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<td>Baseline HbA1c, %</td>
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<td>8.3 (1.0)</td>
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<td>Baseline BMI, kg/m²</td>
<td>32.9 (7.6)</td>
<td>33.9 (6.9)</td>
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<td>Baseline BW, kg</td>
<td>92.8 (28.2)</td>
<td>97.6 (22.9)</td>
<td>93.4 (20.4)</td>
<td>97.0 (21.9)</td>
<td>91.0 (16.1)</td>
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<td>Exposure time, years</td>
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<td>0.8 (0.2)</td>
<td>0.8 (0.3)</td>
<td>0.9 (0.3)</td>
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<td>1.0 (0.3)</td>
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<td>Duration of diabetes, years</td>
<td>7.3 (5.8)</td>
<td>7.9 (6.0)</td>
<td>8.9 (6.5)</td>
<td>8.6 (5.8)</td>
<td>9.5 (7.1)</td>
<td>9.4 (6.7)</td>
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<tr>
<td>Onset of rescue, n (%)</td>
<td>0 (0.0)</td>
<td>3 (1.3)</td>
<td>3 (1.2)</td>
<td>36 (4.8)</td>
<td>3 (5.3)</td>
<td>45 (12.9)</td>
</tr>
<tr>
<td>Discontinued treatment, n (%)</td>
<td>21 (27.6)</td>
<td>26 (11.6)</td>
<td>67 (27.3)</td>
<td>105 (14.0)</td>
<td>13 (22.8)</td>
<td>72 (20.7)</td>
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<td>Withdrawal from trial, n (%)</td>
<td>5 (6.6)</td>
<td>17 (7.6)</td>
<td>19 (7.8)</td>
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<td>Lost to follow-up, n (%)</td>
<td>3 (3.9)</td>
<td>6 (2.7)</td>
<td>9 (3.7)</td>
<td>13 (1.7)</td>
<td>2 (3.5)</td>
<td>8 (2.3)</td>
</tr>
</tbody>
</table>

Data are mean (standard deviation) unless otherwise specified. Only subjects with non-missing subgroup information were selected.

AE, adverse event; BMI, body mass index; BW, body weight; EOT, end of treatment; exenatide ER, exenatide extended release; GI, gastrointestinal; HbA1c, glycated hemoglobin.
kg vs −4.3 kg (p=0.0542) for semaglutide 0.5 mg and
−7.9 kg vs −6.2 kg (p=0.0074) for semaglutide 1.0 mg
(figure 1B,C). The corresponding values for dulaglutide 0.75 mg and dulaglutide 1.5 mg were −3.3 kg vs
−2.2 kg (p=0.1153) and −4.1 kg vs −2.7 kg (p=0.0340), respectively.

In subjects experiencing nausea/vomiting at any time
from baseline to EOT versus those who did not experience

Figure 1  Absolute change from baseline in BW at EOT by nausea/vomiting occurring at any time from baseline to week 12 and at any time from baseline to EOT in SUSTAIN 3 (A), SUSTAIN 7 (B,C) and SUSTAIN 10 (D). *P<0.05; **p<0.01; ***p<0.0001. EOT was at week 56 for SUSTAIN 3, week 40 for SUSTAIN 7 and week 30 for SUSTAIN 10. Values are estimated means from a mixed model for repeated measurements analysis using ‘on-treatment without rescue medication’ data from subjects in the full analysis set. Values in square brackets indicate 95% CIs. BW, body weight; Δkg, differences in body weight within treatment arms; EOT, end of treatment; ETD, estimated treatment difference; exenatide ER, exenatide extended release.

Figure 2  Mediation analysis of direct (due to treatment) and indirect (due to nausea or vomiting) effects on weight loss for subjects treated with semaglutide from baseline to week 12 (A) and from baseline to end of treatment (B) in the SUSTAIN 3, 7 and 10 trials. Data are ‘on-treatment without rescue medication’ ETDs (95% CIs) for the change from baseline at (A) at any time in the first 12 weeks and (B) week 56 (SUSTAIN 3), week 40 (SUSTAIN 7) or week 30 (SUSTAIN 10) from all randomized patients exposed to at least one dose of trial product (full analysis set). Post-baseline data were analyzed using a mixed model for repeated measurements that included the interaction of treatment and any nausea/vomiting. ETD, estimated treatment difference; exenatide ER, exenatide extended release.
these events, the weight change was –5.6 kg vs –4.2 kg at EOT (p=0.0236) for semaglutide 0.5 mg and –7.9 kg vs –6.2 kg for semaglutide 1.0 mg (p=0.0051; figure 1B,C). The corresponding values for dulaglutide 0.75 mg and dulaglutide 1.5 mg were –3.4 kg vs –2.1 kg (p=0.0375) and –4.0 kg vs –2.7 kg (p=0.226), respectively.

ETDs (95% CIs) favored semaglutide versus dulaglutide in all comparisons (figure 1B,C).

**SUSTAIN 10 (semaglutide versus liraglutide)**

At EOT, a weight change of –6.8 kg was observed in subjects treated with semaglutide 1.0 mg experiencing nausea/vomiting from randomization to week 12 vs –5.4 kg in those who did not experience these events (p=0.0071). The corresponding values for liraglutide were –2.9 vs –1.7 kg (p=0.0295; figure 1D).

In subjects treated with semaglutide 1.0 mg experiencing nausea/vomiting at any time from randomization to EOT, a weight change of –6.9 kg vs –5.4 kg at EOT was observed versus those who did not experience these events (p=0.0021). The corresponding values for liraglutide were –2.7 vs –1.8 kg (p=0.0528; figure 1D).

ETDs (95% CIs) favored semaglutide versus liraglutide in all comparisons (figure 1D).

**Mediation analyses of BW reduction by nausea/vomiting**

**SUSTAIN 3 (semaglutide versus exenatide ER)**

Mediation analyses showed that 0.05 kg of a total of 3.78 kg weight loss at EOT (week 56) observed with semaglutide versus exenatide ER in SUSTAIN 3 was mediated by nausea/vomiting from baseline to week 12 (p<0.0001; figure 2A). Similarly, only 0.09 kg of a total of 3.78 kg was mediated by nausea/vomiting at any time from baseline to EOT (p<0.0001; figure 2B).

**SUSTAIN 7 (semaglutide versus dulaglutide)**

In SUSTAIN 7, 0.06 kg of a total of 2.26 kg of the greater weight loss at EOT (week 40) observed with semaglutide 0.5 mg vs dulaglutide 0.75 mg and 0.08 kg of a total of 3.55 kg for semaglutide 1.0 mg vs dulaglutide 1.5 mg was mediated by nausea/vomiting from baseline to week 12 (both p<0.0001; figure 2A). In SUSTAIN 7, 0.03 kg of 2.26 kg of the greater weight loss at EOT observed with semaglutide 0.5 mg vs dulaglutide 0.75 mg and 0.04 kg of a total of 3.55 kg for semaglutide 1.0 mg vs dulaglutide 1.5 mg was mediated by nausea/vomiting at any time up to the EOT (both p<0.0001; figure 2B).

**SUSTAIN 10 (semaglutide versus liraglutide)**

Mediation analysis showed that 0.05 kg of a total of 3.82 kg weight loss at EOT (week 30) observed with semaglutide 1.0 mg vs liraglutide 1.2 mg in SUSTAIN 10 was mediated by nausea/vomiting from baseline to week 12 (p<0.0001; figure 2A). Similarly, only 0.09 kg of the total of 3.82 kg weight loss observed with semaglutide versus liraglutide at EOT was mediated by nausea/vomiting at any time up to the EOT (p<0.0001; figure 2B).

**DISCUSSION**

The rationale for conducting this posthoc analysis of SUSTAIN 3, 7 and 10 trials was to investigate whether GI AEs contributed to the superior weight loss observed with semaglutide versus the other GLP-1RAs, exenatide ER, dulaglutide or liraglutide. In this posthoc analysis, we found that in SUSTAIN 3, 7 and 10, subjects who experienced nausea/vomiting, or any of the five evaluated commonly reported GI AEs, generally had slightly greater weight loss compared with subjects who did not experience these symptoms (with some exceptions). In addition, treatment with semaglutide resulted in a significantly greater weight loss than with exenatide ER, dulaglutide or liraglutide, also in subjects who did not experience nausea/vomiting, suggesting that the superior weight loss observed with semaglutide was not related to the occurrence of these events. Mediation analyses support this observation and establish that the superior weight loss seen with semaglutide (2.26 to 3.82 kg) versus exenatide ER, dulaglutide or liraglutide was independent of GI AEs (only 0.03 to 0.09 kg due to nausea/vomiting). This is consistent with the previous analysis of the SUSTAIN 1–5 trials, which showed that a small amount (0.07 to 0.5 kg) of the total ETD (2.3 to 6.3 kg) in weight loss at EOT versus mixed-class comparators was due to nausea/vomiting—thus, the majority of the weight-loss effect for semaglutide was not mediated by GI AEs such as nausea/vomiting.

Furthermore, in this analysis, there was no evidence of a temporal association between the incidence of GI AEs and weight loss at EOT. The prevalence of GI AEs with GLP-1RA treatment was previously found to peak within the initial 12 weeks of treatment and decline thereafter. However, subjects in all treatment arms experienced weight loss between baseline and week 12, and from baseline to EOT (SUSTAIN 3, week 56; SUSTAIN 7, week 40; SUSTAIN 10, week 30).

Excess weight is an important contributing factor in the complex etiology of T2D, and BW control is an important factor in the individualized management of T2D. GLP-1RAs are established and effective therapies for T2D and can be prescribed at all stages of T2D. In addition to managing glucose levels, GLP-1RAs also reduce BW and this potential for weight loss has been reflected by the GLP-1RA liraglutide (3.0 mg once daily) gaining approval as a treatment for obesity. Because GI AEs including nausea, vomiting or diarrhoea are the most common type of AE with GLP-1RAs, it is important to establish whether the weight loss difference between treatment is mediated through the occurrence of GI AEs.

The previous mediation analysis of the SUSTAIN 1–5 trials showed that only a small component of the superior weight loss with semaglutide was associated with GI AEs. Although GI AEs tend to be more common with semaglutide versus GLP-1RA comparators, they are usually reported during the dose-escalation phase of the trial and, consistent with the GLP-1RA class, are generally mild to moderate in severity and transient in nature.

In this analysis, the fact that greater weight loss with semaglutide versus class comparators was minimally affected by...
GI AEs indicates involvement of alternative mechanisms. The unique physicochemical properties of semaglutide may contribute to the greater weight loss observed versus exenatide ER, dulaglutide or liraglutide. In a randomized controlled trial, semaglutide was associated with lower energy intake and higher BW loss versus placebo, the mechanisms likely being less appetite and food cravings, better control of eating and lower preference for fat-rich foods.39 Other GLP-1RAs promote weight loss through a similar mechanism of action,40 hence, the difference between semaglutide and other GLP-1RAs may just be quantitative. Although current evidence is limited to animal studies, the data suggest that semaglutide-associated weight loss is centrally mediated through the activation of areas of the brain involved in appetite control and reward, including the hypothalamus neural circuits, the arcuate nucleus, the pro-opiomelanocortin neurons and the nucleus of the tractus solitarius.11–43

Subjects experiencing nausea/vomiting had a lower baseline BW and were more likely to discontinue treatment compared with subjects not experiencing them. Of note, despite the lower baseline BW, these subjects still experienced greater weight loss with semaglutide; this could be because semaglutide produces weight loss, irrespective of baseline BW, across a range of exposures.38

The strengths of this study are: GI AEs were analyzed in week 12, which is the time-point when they peak, as well as any time from baseline to EOT; it is an intention-to-treat analysis; mediation analysis of BW reduction was used to calculate differences between groups (not only for nausea/vomiting but also for other GI AEs); semaglutide treatment resulted in significantly greater weight loss than comparators even in subjects who did not experience GI AEs which supports the hypothesis; similar results from SUSTAIN 1–5 trials also support the hypothesis.

Potential limitations of this post hoc analysis include its inherent retrospective nature and that it was not sufficiently powered to detect the effects assessed. For example, the small number of subjects per treatment arm in the groups that experienced GI AE; therefore, results should be interpreted in this context. Another possible limitation is the different durations of follow-up for subjects with GI AE in all three trials. In addition, the results should be viewed in the context that SUSTAIN 3, 7 and 10 were open-label trials and nausea is a subjective symptom. Furthermore, in the mediation analysis, the effect of ‘one unit’ mediator was assumed to be the same in the treatment arms being compared. Mediation analyses rely on strong, unverifiable assumptions, and the results of the analysis may be biased in case of potential unknown confounders that affect the risk of experiencing GI AEs as well as change in BW.

CONCLUSION

In this post hoc analysis of SUSTAIN 3, 7 and 10, nausea/vomiting contributed minimally to the significantly greater BW reductions with semaglutide versus exenatide ER, dulaglutide or liraglutide. These reductions were independent of the individual GI AEs of nausea, vomiting, diarrhea, dyspepsia and constipation in a subset of GLP-1RA class comparators with which GI AEs are the most commonly observed AEs.

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Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All data relevant to the study are included in the article or uploaded as supplemental information. SUSTAIN 3: https://clinicaltrials.gov/ct2/show/NCT01855208SUSTAIN 7: https://clinicaltrials.gov/ct2/show/NCT02648204 SUSTAIN 10: https://clinicaltrials.gov/ct2/show/NCT03191396

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Emerging technologies, pharmacology and therapeutics

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SUPPLEMENTARY MATERIALS

Title: Superior weight loss with once-weekly semaglutide versus other glucagon-like peptide-1 receptor agonists is independent of gastrointestinal adverse events

Authors: Ildiko Lingvay, Thomas Hansen, Stanislava Macura, Michel Marre, Michael Nauck, Raymond de la Rosa, Vincent Woo, Emre Yildirim, John Wilding

Trial Registration

SUSTAIN 3: https://clinicaltrials.gov/ct2/show/NCT01885208
SUSTAIN 7: https://clinicaltrials.gov/ct2/show/NCT02648204
SUSTAIN 10: https://clinicaltrials.gov/ct2/show/NCT03191396
Subject population in SUSTAIN 3, 7 and 10 trials

The inclusion and exclusion criteria were similar in the SUSTAIN 3, 7 and 10 trials. Key inclusion criteria were: diagnosis of type 2 diabetes (T2D); age ≥18 years; HbA1c ≥53.0–91.3 mmol/mol (7.0–10.5%; SUSTAIN 3), HbA1c ≥53.0–91.0 mmol/mol (7.0–10.5%; SUSTAIN 7) or HbA1c ≥53.0–96.7 mmol/mol (7.0–11.0%; SUSTAIN 10); and estimated glomerular filtration rate ≥60 mL/min/1.73 m² (SUSTAIN 3 and SUSTAIN 7) or >30 mL/min/1.73 m² (SUSTAIN 10). Study medication was added onto background treatment with: metformin in SUSTAIN 7; or 1–2 oral antidiabetic drugs (metformin, thiazolidinedione or sulphonylurea [SU]) in SUSTAIN 3; or metformin with or without SU or sodium–glucose co-transporter-2 inhibitors in SUSTAIN 10.

Key exclusion criteria were: renal impairment; history of chronic or acute pancreatitis; known proliferative retinopathy or maculopathy requiring acute treatment; screening calcitonin value ≥50 ng/L (SUSTAIN 3, SUSTAIN 7) or ≥100 ng/L (SUSTAIN 10); personal/family history of medullary thyroid carcinoma or multiple endocrine neoplasia syndrome type 2; acute coronary or cerebrovascular event within 90 days (SUSTAIN 3, SUSTAIN 7) or 180 days (SUSTAIN 10) before randomisation; and severe heart failure (New York Heart Association Class IV).

Trials were conducted in compliance with the International Conference on Harmonisation Good Clinical Practice guidelines and the Declaration of Helsinki. The protocol was approved by local ethics committees and institutional review boards. Written informed consent was obtained from all subjects before trial commencement. The trials are registered at ClinicalTrials.gov (NCT01885208, NCT02648204 and NCT03191396).

Study endpoints and assessments

In the pre-planned analysis, the key endpoints were similar in the SUSTAIN 3, 7 and 10 trials. The primary endpoint was the change in HbA1c from baseline to end of treatment (EOT; 56 weeks for SUSTAIN 3, 40 weeks for SUSTAIN 7 and 30 weeks for SUSTAIN 10). The confirmatory secondary endpoint was the change in body weight (BW) from baseline to EOT. Safety outcomes were also assessed.
Efficacy endpoints were based on the full analysis set from the ‘on-treatment without rescue medication’ observation period. Analysed data were based on results from the subjects who stayed on treatment and did not discontinue or receive any non-investigational antidiabetic treatment (rescue medication), and hence the analysed data were not confounded by antidiabetic medications not present at randomisation.

**Subject disposition and baseline characteristics by commonly experienced GI AEs**

More subjects with gastrointestinal (GI) adverse events (AEs) of nausea, vomiting, diarrhoea, constipation or dyspepsia (occurring from baseline to week 12 and from baseline to end of treatment) discontinued treatment than subjects without; subjects with GI AEs also had lower baseline BW than subjects without. There were no other notable differences in baseline characteristics for subjects with or without these GI AEs (**Supplementary Table 1**).

**Change from baseline in body weight in subjects with and without GI AEs**

Overall, BW reductions at end of treatment, by commonly experienced GI AEs (nausea, vomiting, diarrhoea, constipation or dyspepsia) from baseline to week 12, and at any time up to EOT, were greater with semaglutide vs comparators (**Supplementary Figures 1–3**). In general, there was greater weight loss in subjects who reported vs those who did not report the five common GI AEs.

**SUSTAIN 3 (semaglutide vs exenatide ER)**

In subjects treated with semaglutide, weight loss was greater in subjects reporting vs not reporting a GI AE of nausea (–6.8 kg vs –5.4 kg; p=0.0799), diarrhoea (–6.4 kg vs –5.6 kg; p=0.5398), vomiting (–10.3 kg vs –5.5 kg; p=0.0192) and constipation (–10.3 kg vs –5.5 kg; p=0.0049) from baseline to week 12. An exception was with dyspepsia, although the difference was not significant (–4.9 kg vs –5.7 kg; p=0.6073; **Supplementary Figure 1A**).

In subjects treated with exenatide extended release (exenatide ER), weight loss was also greater in subjects reporting vs not reporting a GI AE of nausea (–2.9 kg vs –1.7 kg; p=0.2711), diarrhoea (–2.2 kg vs –1.8 kg; p=0.8480), dyspepsia (–3.1 kg vs
-1.8 kg; p=0.4180) from baseline to week 12, except for vomiting (−1.2 kg vs −1.9 kg; p=0.7646) and constipation (−1.3 kg vs −1.9 kg; p=0.5482). None of the differences were significant (Supplementary Figure 1A).

The pattern of greater weight loss in subjects reporting vs not reporting common GI AEs was also consistent for the time frame of GI AEs at any time up to EOT (week 56) for semaglutide; however, for exenatide ER, at week 56, the number of subjects reporting vs not reporting vomiting and constipation was greater than at week 12 (Supplementary Figure 1B).

SUSTAIN 7 (semaglutide vs dulaglutide)

In both the low-dose (0.5 mg) and high-dose (1.0 mg) semaglutide treatment arms, in general there was greater weight loss in subjects reporting vs those not reporting common GI AEs in the first 12 weeks (Supplementary Figure 2A) and at any time from baseline to EOT (week 40; Supplementary Figure 2B). The exceptions were in the first 12 weeks of the high-dose arm of semaglutide treatment for diarrhoea (−6.0 kg vs −6.6 kg; p=0.7368) and dyspepsia (−4.7 kg vs −6.6 kg; p=0.2007; Supplementary Figure 2A), and at any time up to EOT for dyspepsia (−4.7 kg vs −6.6 kg; p=0.1547; Supplementary Figure 2B); however, none of these differences were significant.

In subjects treated with dulaglutide, for both the low dose (0.75 mg) and high dose (1.5 mg), weight loss was also greater in subjects reporting vs not reporting a GI AE of nausea (−3.1 kg vs −2.2 kg; p=0.2094 and −4.3 kg vs −2.7 kg; p=0.0214), diarrhoea (−3.4 kg vs −2.2 kg; p=0.1983 and −3.3 kg vs −2.9 kg; p=0.4441), vomiting (−4.2 kg vs −2.3 kg; p=0.2988 and −4.6 kg vs −2.9 kg; p=0.0546) and dyspepsia (−5.0 kg vs −2.2 kg; p=0.0700 and −3.2 kg vs −3.0 kg; p=0.9073) from baseline to week 12. The exceptions were in the first 12 weeks for constipation (−1.4 kg vs −2.3 kg; p=0.8065 and −2.5 kg vs −3.0 kg; p=0.9913; Supplementary Figure 2A), and at any time up to EOT for dyspepsia (dulaglutide 1.5 mg: −2.8 kg vs −3.0 kg; p=0.9164) and constipation (dulaglutide 0.75 mg: −1.5 kg vs −2.3 kg; p=0.8230 and dulaglutide 1.5 mg: −2.9 kg vs −3.0 kg; p=0.7730; Supplementary Figure 2B); however, none of these differences were significant.

SUSTAIN 10 (semaglutide vs liraglutide)
Weight loss between semaglutide-treated subjects reporting vs not reporting a GI AE was: nausea (−6.5 kg vs −5.6 kg; p=0.0743), diarrhoea (−6.4 kg vs −5.7 kg; p=0.3748), vomiting (−7.8 kg vs −5.6 kg; p=0.0246) and constipation (−7.6 kg vs −5.7 kg; p=0.0813) from baseline to week 12. An exception to this weight-loss pattern was with dyspepsia, in which weight loss was similar between groups (−5.9 kg vs −5.8 kg; p=0.8773; Supplementary Figure 3A).

In subjects treated with liraglutide, weight loss was also greater in subjects reporting vs not reporting a GI AE of nausea (−2.8 kg vs −1.8 kg; p=0.0911), diarrhoea (−2.1 kg vs −1.9 kg; p=0.7983), vomiting (−3.4 kg vs −1.8 kg; p=0.0719), dyspepsia (−3.2 kg vs −1.9 kg; p=0.3334) and constipation (−2.2 kg vs −1.9 kg; p=0.7618) from randomisation to week 12 (Supplementary Figure 3A). The pattern of greater weight loss in subjects reporting vs not reporting common GI AEs was also consistent for the time frame of GI AEs at any time up to the end of treatment (week 30; Supplementary Figure 3B).

Mediation analyses of ETDs in BW reductions by individual GI AEs

The ETDs favoured semaglutide vs exenatide, vs dulaglutide and vs liraglutide for subjects reporting any of the five commonly reported GI AEs (nausea, vomiting, diarrhoea, dyspepsia, constipation) either during the dose escalation phase (from baseline to week 12; Supplementary Figure 4A) or from baseline to EOT (Supplementary Figure 4B). The mediation analyses indicate that the additional weight reduction observed with semaglutide vs exenatide ER in SUSTAIN 3, dulaglutide in SUSTAIN 7 or liraglutide in SUSTAIN 10 was not individually mediated by any of the five commonly reported GI AEs (nausea, vomiting, diarrhoea, dyspepsia, constipation) either during the dose escalation phase or from baseline to EOT (Supplementary Figure 4). Mediation analysis of ‘direct’ vs ‘indirect’ effects of treatment showed that a very small amount of the greater weight loss at EOT observed with semaglutide vs comparators was mediated by the analysed GI AEs (Supplementary Figure 4).
REFERENCES


### Supplementary Table 1. Baseline characteristics and disposition of subjects with onset of any GI AE from baseline to week 12 and at any time from baseline to end of treatment (yes/no) in the SUSTAIN 3, 7 and 10 trials

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<th>Treatment</th>
<th>Baseline to week 12</th>
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<tr>
<td></td>
<td>N (total)</td>
<td>Y</td>
</tr>
<tr>
<td></td>
<td>N</td>
<td>Y</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>28 (25.0)</td>
<td>22 (11.6)</td>
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<tr>
<td>Black or African American</td>
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<td></td>
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<tr>
<td>White</td>
<td>4 (3.6)</td>
<td>13 (6.9)</td>
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<tr>
<td>Other</td>
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<td>154 (81.5)</td>
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<tr>
<td></td>
<td>1 (0.9)</td>
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<td>Ethnic group, n (%)</td>
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<tr>
<td>Baseline HbA1c, %</td>
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<td>8.3 (0.9)</td>
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<tr>
<td>Baseline BMI, kg/m²</td>
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<td>Baseline BW, kg</td>
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<td>97.6 (22.4)</td>
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<tr>
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<td>0.8 (0.2)</td>
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<tr>
<td>Duration of diabetes, years</td>
<td>7.3 (5.4)</td>
<td>8.0 (6.2)</td>
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<tr>
<td>Onset of rescue, n (%)</td>
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<td>2 (1.1)</td>
</tr>
<tr>
<td>Discontinued treatment, n (%)</td>
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<tr>
<td>Withdrawal from trial, n (%)</td>
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<td>13 (6.9)</td>
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<tr>
<td>Lost to follow-up, n (%)</td>
<td>5 (4.5)</td>
<td>4 (2.1)</td>
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Supplemental material placed on this supplemental material which has been supplied by the author(s).
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<th>Other</th>
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<tr>
<td>Baseline HbA1c, %</td>
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<tr>
<td>Baseline BMI, kg/m²</td>
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<td>Baseline BW, kg</td>
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<td>Exposure time, years</td>
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<td>Discontinued treatment, n (%)</td>
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<tr>
<td>Withdrawal from trial, n (%)</td>
<td>9 (7.1)</td>
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<tr>
<td>Lost to follow-up, n (%)</td>
<td>5 (3.9)</td>
</tr>
</tbody>
</table>

Data are mean (standard deviation) unless otherwise specified. Only subjects with non-missing subgroup information were selected.

AE, adverse event; BMI, body mass index; BW, body weight; EOT, end of treatment; exenatide ER, exenatide extended release; GI, gastrointestinal; HbA1c, glycated haemoglobin.
Supplementary Figure 1. Absolute change from baseline in body weight at end of treatment by commonly experienced GI AEs occurring at any time from baseline to week 12 (A) and at any time from baseline to week 56 (B) in SUSTAIN 3

(A)

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GI AE:  ■ Yes ☑ No
■ Semaglutide 1.0 mg
☑ Exenatide ER 2.0 mg
*p<0.05; **p<0.01; ***p<0.0001. Values are estimated means from a mixed model for repeated measurements analysis using 'on-treatment without rescue medication' data from subjects in the full analysis set. Values in square brackets indicate 95% confidence intervals. Δkg, differences in body weight within treatment arms; AE, adverse event; BW, body weight; ETD, estimated treatment difference; exenatide ER, exenatide extended release; GI, gastrointestinal.
**Supplementary Figure 2.** Absolute change from baseline in body weight at end of treatment by commonly experienced GI AEs occurring at any time from baseline to week 12 (A) and at any time from baseline to week 40 (B) in SUSTAIN 7

(A)
*p<0.05; **p<0.01; ***p<0.0001. Values are estimated means from a mixed model for repeated measurements analysis using 'on-treatment without rescue medication' data from subjects in the full analysis set. Values in square brackets indicate 95% confidence intervals.

Δkg, differences in body weight within treatment arms; AE, adverse event; BW, body weight; ETD, estimated treatment difference; GI, gastrointestinal.
**Supplementary Figure 3.** Absolute change from baseline in body weight at end of treatment by commonly experienced GI AEs occurring at any time from baseline to week 12 (A) and at any time from baseline to week 30 (B) in SUSTAIN 10.

(A)
*p<0.05; **p<0.01; ***p<0.0001. Values are estimated means from a mixed model for repeated measurements analysis using 'on-treatment without rescue medication' data from subjects in the full analysis set. Values in square brackets indicate 95% confidence intervals.

Δkg, differences in body weight within treatment arms; AE, adverse event; BW, body weight; ETD, estimated treatment difference; GI, gastrointestinal.
Supplementary Figure 4. Mediation analysis of direct (due to treatment) and indirect (due to commonly experienced GI AEs) effects on weight loss for subjects treated with semaglutide from baseline to week 12 (A) and from baseline to end of treatment (B) in the SUSTAIN 3, 7 and 10 trials.

(A)
Data are 'on-treatment without rescue medication' ETDs [95% confidence intervals] for the change from baseline (A) at any time in the first 12 weeks (all trials) and (B) at week 56 (SUSTAIN 3), week 40 (SUSTAIN 7) or week 30 (SUSTAIN 10) from all randomised patients exposed to at least one dose of trial product (full analysis set). Post-baseline data were analysed using a mixed model for repeated measurements that included the interaction of treatment and any nausea/vomiting.

AE, adverse event; ETD, estimated treatment difference; exenatide ER, exenatide extended release; GI, gastrointestinal.