SUPPLEMENTARY MATERIALS

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

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

Key exclusion criteria were:[1-3] 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[4] and the Declaration of Helsinki.[5] 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.[1-3] The primary endpoint was the change in HbA_{1c} 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

1. 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;41:258–66. doi: 10.2337/dc17-0417 [published Online First: 15 December 2017].
2. 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;6:275–86. doi: 10.1016/s2213-8587(18)30024-x [published Online First: 6 February 2018].
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4. The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use. Guideline for Good Clinical Practice. Available: https://database.ich.org/sites/default/files/E6_R2_Addendum.pdf [Accessed: 28 Apr 2020].
5. World Medical Association. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. *JAMA* 2013;310:2191–94.

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

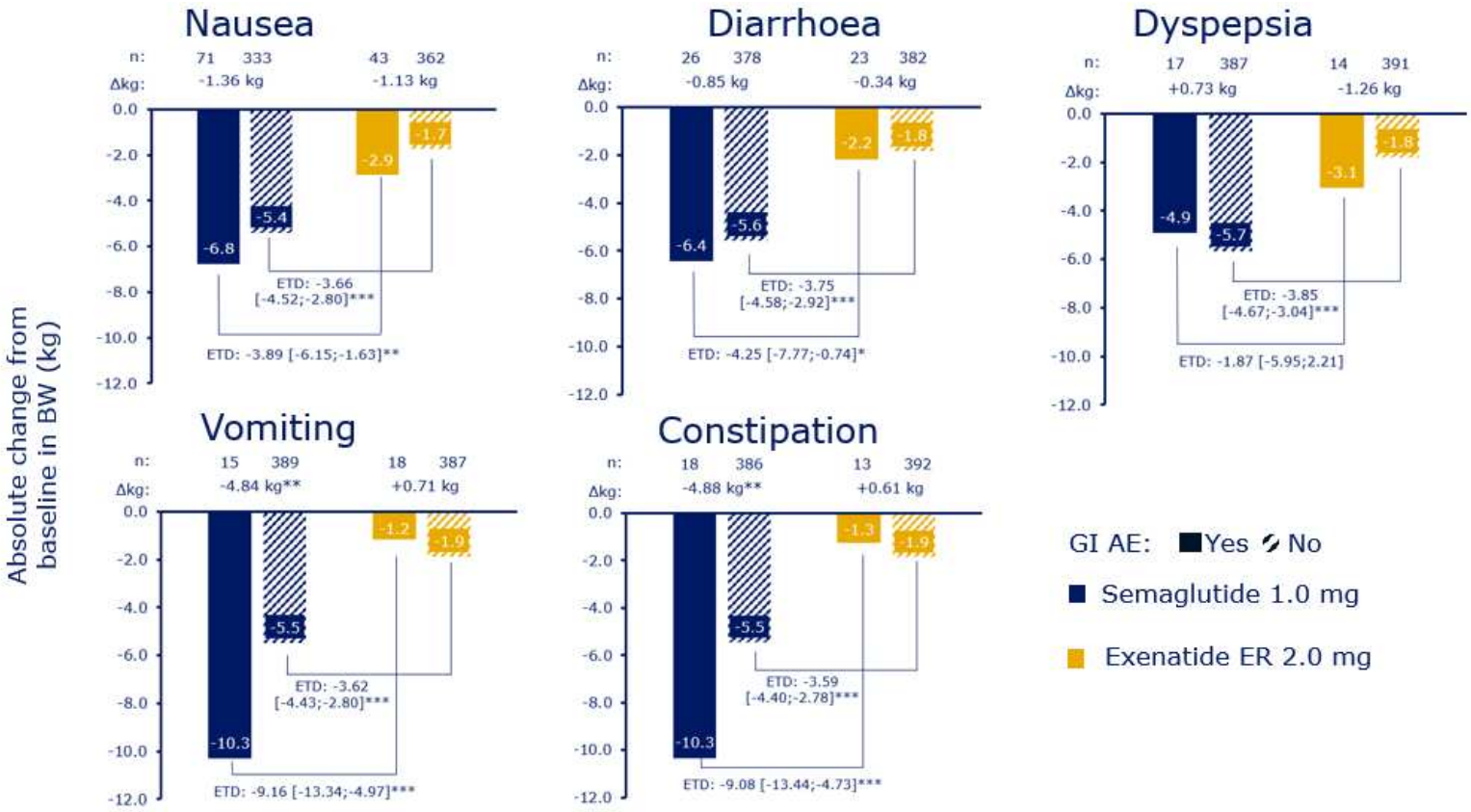
Treatment	Semaglutide 0.5 mg (SUSTAIN 7)		Semaglutide 1.0 mg (pooled)		Exenatide ER 2.0 mg (SUSTAIN 3)		Dulaglutide 0.75 mg (SUSTAIN 7)		Dulaglutide 1.5 mg (SUSTAIN 7)		Liraglutide 1.2 mg (SUSTAIN 10)	
N (total)	301		994		405		299		299		287	
GI AE Yes/No	Y	N	Y	N	Y	N	Y	N	Y	N	Y	N
Baseline to week 12												
N	112	189	362	632	102	303	85	214	123	176	92	195
Race, n (%)												
Asian	28 (25.0)	22 (11.6)	21 (5.8)	30 (4.7)	2 (2.0)	4 (1.3)	18 (21.2)	30 (14.0)	26 (21.1)	29 (16.5)	1 (1.1)	2 (1.0)
Black or African American	4 (3.6)	13 (6.9)	16 (4.4)	32 (5.1)	5 (4.9)	25 (8.3)	1 (1.2)	16 (7.5)	7 (5.7)	11 (6.3)	0 (0.0)	1 (0.5)
White	79 (70.5)	154 (81.5)	306 (84.5)	542 (85.8)	90 (88.2)	248 (81.8)	65 (76.5)	167 (78.0)	87 (70.7)	133 (75.6)	83 (90.2)	185 (94.9)
Other	1 (0.9)	0 (0.0)	19 (5.2)	28 (4.4)	5 (4.9)	26 (8.6)	1 (1.2)	1 (0.5)	3 (2.4)	3 (1.7)	8 (8.7)	7 (3.6)
Ethnic group, n (%)												
Hispanic or Latino	11 (9.8)	18 (9.5)	36 (9.9)	96 (15.2)	24 (23.5)	82 (27.1)	8 (9.4)	23 (10.7)	15 (12.2)	28 (15.9)	1 (1.1)	2 (1.0)
Not Hispanic or Latino	101 (90.2)	171 (90.5)	319 (88.1)	527 (83.4)	78 (76.5)	221 (72.9)	77 (90.6)	191 (89.3)	108 (87.8)	148 (84.1)	83 (90.2)	186 (95.4)
Other	0 (0.0)	0 (0.0)	7 (1.9)	9 (1.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	8 (8.7)	7 (3.6)
Baseline HbA_{1c}, %	8.3 (1.0)	8.3 (0.9)	8.2 (0.9)	8.3 (1.0)	8.4 (1.0)	8.3 (0.9)	8.1 (0.9)	8.2 (0.9)	8.1 (0.8)	8.3 (0.9)	8.1 (1.0)	8.3 (1.0)
Baseline BMI, kg/m^2	33.1(7.4)	34.0 (6.9)	33.1 (6.4)	34.2 (7.1)	33.2 (5.9)	33.7 (6.4)	33.7 (6.7)	33.6 (7.0)	31.9 (6.7)	33.9 (6.3)	32.8 (7.1)	34.0 (6.9)
Baseline BW, kg	94.3 (27.4)	97.6 (22.4)	94.0 (20.6)	97.3 (22.0)	92.3 (17.4)	96.4 (21.3)	95.6 (23.1)	95.7 (23.0)	89.6 (21.1)	96.0 (22.0)	94.9 (23.5)	98.3 (20.8)
Exposure time, years	0.7 (0.3)	0.8 (0.2)	0.8 (0.3)	0.9 (0.3)	1.0 (0.4)	1.0 (0.3)	0.8 (0.2)	0.8 (0.1)	0.7 (0.2)	0.8 (0.1)	0.6 (0.2)	0.7 (0.1)
Duration of diabetes, years	7.3 (5.4)	8.0 (6.2)	9.0 (6.4)	8.5 (5.7)	9.6 (6.2)	9.3 (6.9)	7.0 (5.1)	7.0 (5.6)	7.4 (5.7)	7.8 (5.6)	8.3 (5.4)	9.2 (5.8)
Onset of rescue, n (%)	1 (0.9)	2 (1.1)	8 (2.2)	31 (4.9)	6 (5.9)	42 (13.9)	2 (2.4)	12 (5.6)	2 (1.6)	5 (2.8)	3 (3.3)	9 (4.6)
Discontinued treatment, n (%)	28 (25.0)	19 (10.1)	93 (25.7)	79 (12.5)	27 (26.5)	58 (19.1)	14 (16.5)	13 (6.1)	25 (20.3)	11 (6.3)	15 (16.3)	11 (5.6)
Withdrawal from trial, n (%)	9 (8.0)	13 (6.9)	23 (6.4)	31 (4.9)	9 (8.8)	27 (8.9)	6 (7.1)	7 (3.3)	7 (5.7)	8 (4.5)	3 (3.3)	2 (1.0)
Lost to follow-up, n (%)	5 (4.5)	4 (2.1)	11 (3.0)	11 (1.7)	4 (3.9)	6 (2.0)	3 (3.5)	5 (2.3)	4 (3.3)	4 (2.3)	2 (2.2)	1 (0.5)
At any time from baseline to EOT												
N	127	174	420	574	132	273	100	199	142	157	107	180
Race, n (%)												
Asian	30 (23.6)	20 (11.5)	24 (5.7)	27 (4.7)	2 (1.5)	4 (1.5)	19 (19.0)	29 (14.6)	26 (18.3)	29 (18.5)	1 (0.9)	2 (1.1)
Black or African American	7 (5.5)	10 (5.7)	20 (4.8)	28 (4.9)	6 (4.5)	24 (8.8)	3 (3.0)	14 (7.0)	10 (7.0)	8 (5.1)	0 (0.0)	1 (0.6)
White	89 (70.1)	144 (82.8)	354 (84.3)	494 (86.1)	117 (88.6)	221 (81.0)	77 (77.0)	155 (77.9)	103 (72.5)	117 (74.5)	95 (88.8)	173 (96.1)
Other	1 (0.8)	0 (0.0)	22 (5.2)	25 (4.4)	7 (5.3)	24 (8.8)	1 (1.0)	1 (0.5)	3 (2.1)	3 (1.9)	11 (10.3)	4 (2.2)
Ethnic group, n (%)												
Hispanic or Latino	11 (8.7)	18 (10.3)	44 (10.5)	88 (15.3)	25 (18.9)	81 (29.7)	8 (8.0)	23 (11.6)	17 (12.0)	26 (16.6)	1 (0.9)	2 (1.1)
Not Hispanic or	116 (91.3)	156 (89.7)	369 (87.9)	477 (83.1)	107 (81.1)	192 (70.3)	92 (92.0)	176 (88.4)	125 (88.0)	131 (83.4)	95 (88.8)	174 (96.7)

Latino Other	0 (0.0)	0 (0.0)	7 (1.7)	9 (1.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	11 (10.3)	4 (2.2)
Baseline HbA_{1c}, %	8.3 (1.0)	8.3 (0.9)	8.2 (0.9)	8.3 (1.0)	8.3 (1.0)	8.3 (0.9)	8.1 (0.9)	8.2 (0.9)	8.0 (0.8)	8.3 (0.9)	8.1 (1.0)	8.4 (1.0)
Baseline BMI, kg/m^2	33.2 (7.5)	34.0 (6.8)	33.2 (6.5)	34.2 (7.0)	33.3 (6.0)	33.7 (6.3)	33.7 (6.7)	33.6 (7.0)	32.1 (6.4)	33.9 (6.6)	33.0 (6.9)	34.0 (7.0)
Baseline BW, kg	94.6 (27.0)	97.7 (22.3)	94.4 (21.1)	97.3 (21.8)	94.8 (18.9)	95.7 (21.2)	95.9 (23.5)	95.5 (22.8)	90.1 (20.2)	96.3 (22.8)	95.7 (22.4)	98.0 (21.3)
Exposure time, years	0.7 (0.2)	0.8 (0.2)	0.8 (0.3)	0.9 (0.3)	1.0 (0.4)	1.0 (0.3)	0.8 (0.2)	0.8 (0.1)	0.8 (0.2)	0.8 (0.1)	0.6 (0.2)	0.7 (0.1)
Duration of diabetes, years	7.2 (5.5)	8.1 (6.2)	8.9 (6.2)	8.5 (5.8)	9.6 (6.0)	9.3 (7.0)	6.9 (5.1)	7.1 (5.7)	7.6 (5.7)	7.7 (5.6)	8.3 (5.3)	9.2 (5.9)
Onset of rescue, n (%)	1 (0.8)	2 (1.1)	10 (2.4)	29 (5.1)	8 (6.1)	40 (14.7)	2 (2.0)	12 (6.0)	3 (2.1)	4 (2.5)	3 (2.8)	9 (5.0)
Discontinued treatment, n (%)	28 (22.0)	19 (10.9)	100 (23.8)	72 (12.5)	30 (22.7)	55 (20.1)	16 (16.0)	11 (5.5)	25 (17.6)	11 (7.0)	18 (16.8)	8 (4.4)
Withdrawal from trial, n (%)	9 (7.1)	13 (7.5)	25 (6.0)	29 (5.1)	10 (7.6)	26 (9.5)	7 (7.0)	6 (3.0)	7 (4.9)	8 (5.1)	3 (2.8)	2 (1.1)
Lost to follow-up, n (%)	5 (3.9)	4 (2.3)	12 (2.9)	10 (1.7)	5 (3.8)	5 (1.8)	4 (4.0)	4 (2.0)	4 (2.8)	4 (2.5)	2 (1.9)	1 (0.6)

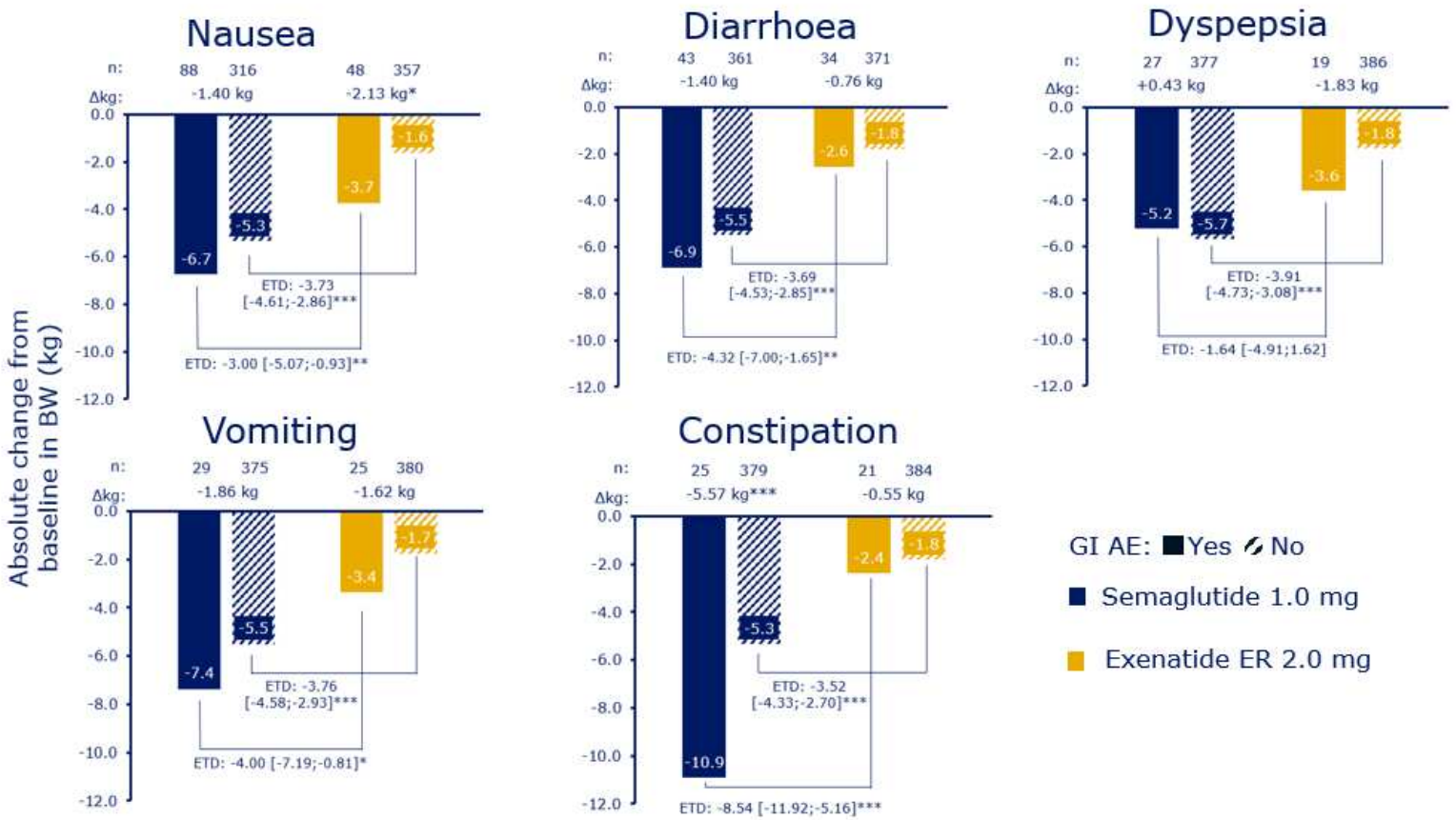
Data are mean (standard deviation) unless otherwise specified. Only subjects with non-missing subgroup information were selected.
AE, adverse event; BMI, body mass index; BW, body weight; EOT, end of treatment; exenatide ER, exenatide extended release; GI, gastrointestinal; HbA_{1c}, glycated haemoglobin.

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)



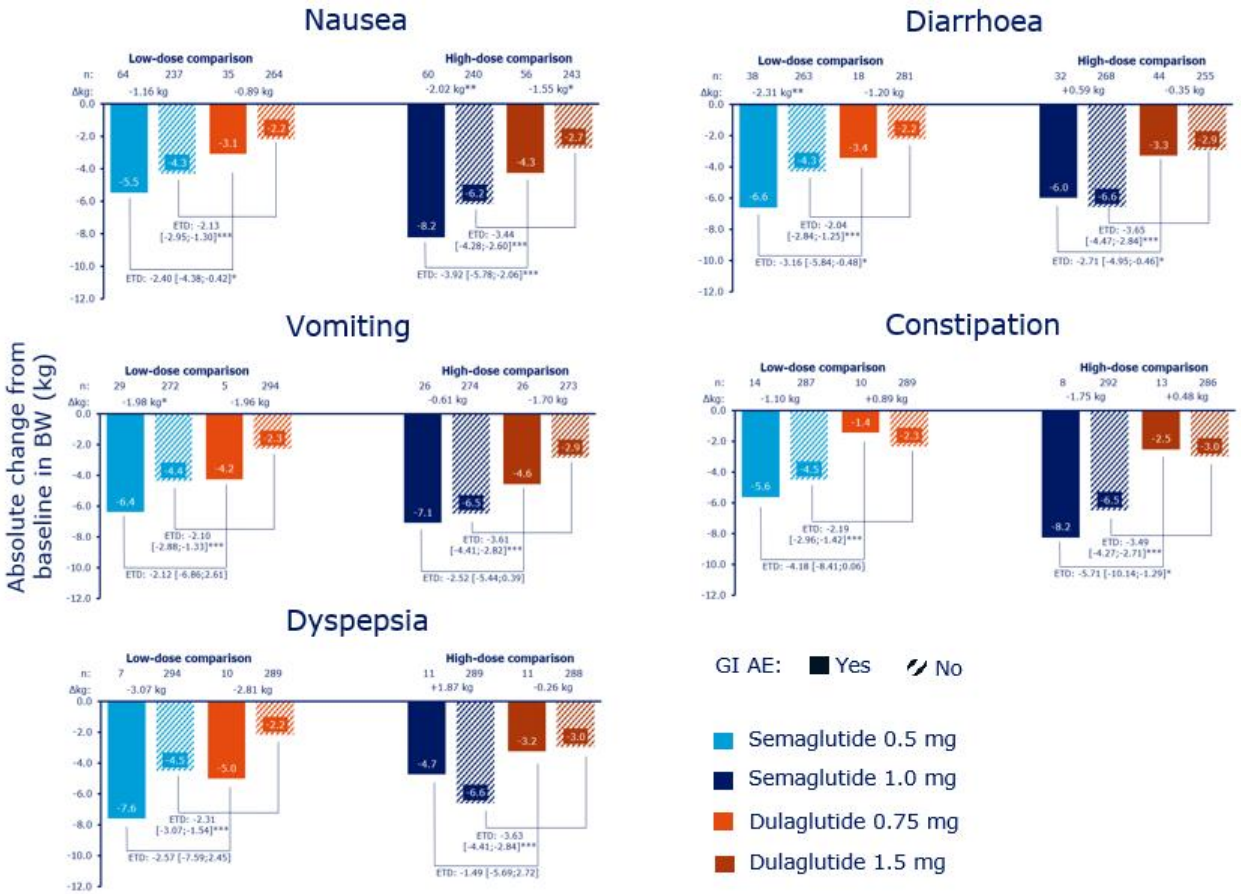
(B)



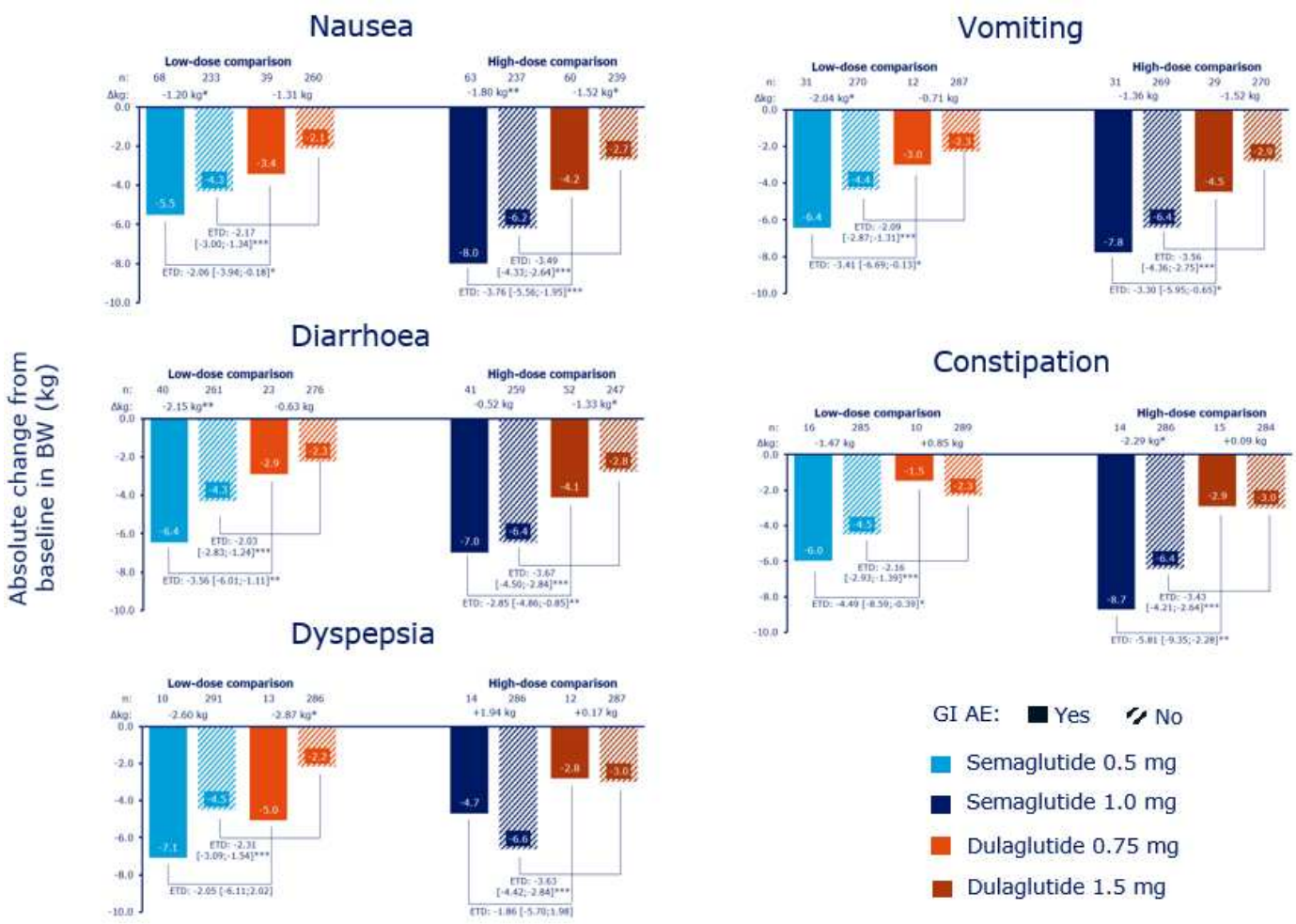
*p<0.05; **p<0.01; ***p<0.0001. Values are estimated means from a mixed model for repeated measurements analysis using 'on-treatment without rescue medication' data from subjects in the full analysis set. Values in square brackets indicate 95% confidence intervals. Δkg, differences in body weight within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



(B)

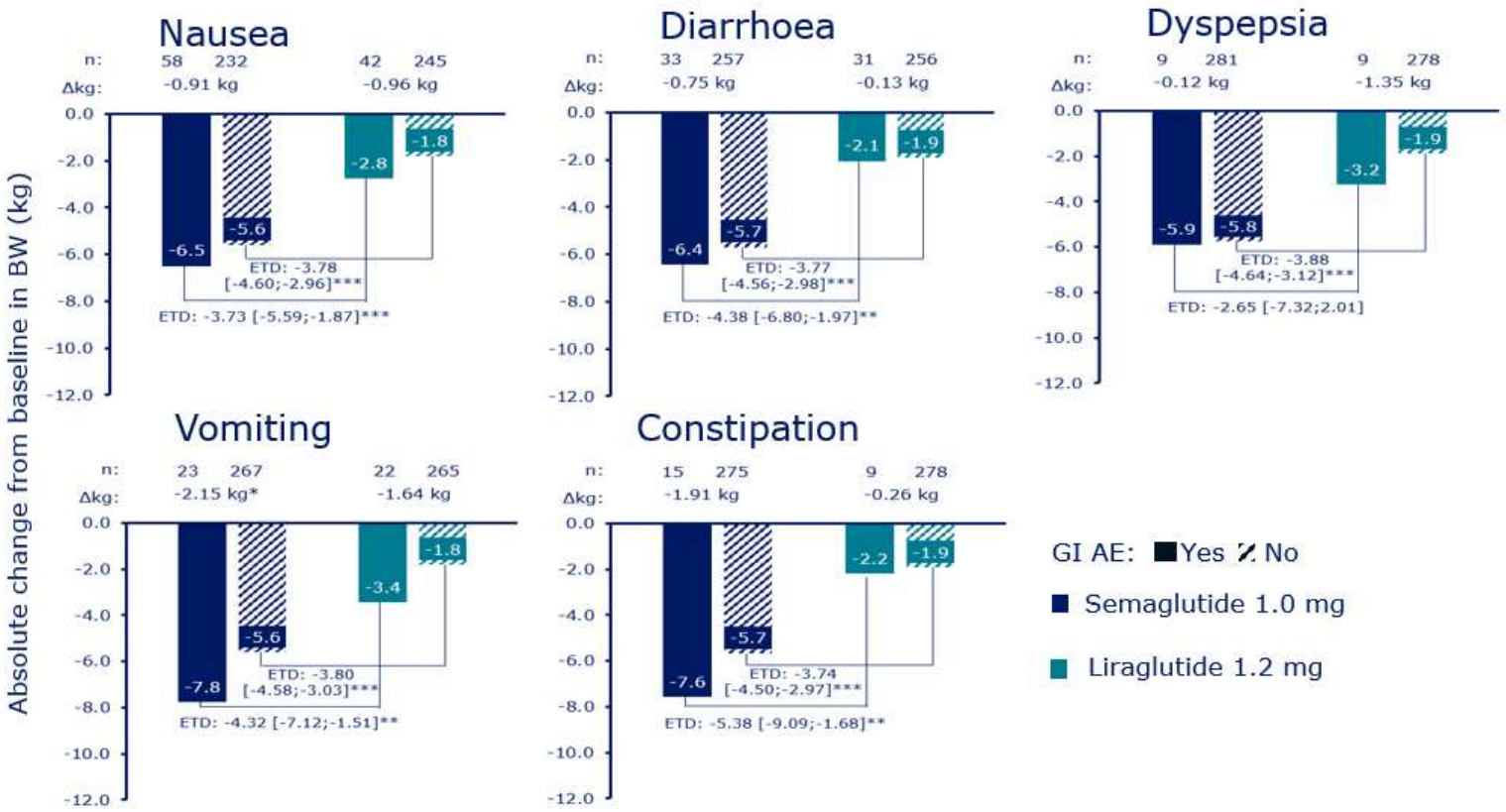

Nausea
Vomiting
Diarrhoea
Constipation
Dyspepsia
Low-dose comparison
High-dose comparison
Absolute change from baseline in BW (kg)
GI AE: Yes No
Semaglutide 0.5 mg
Semaglutide 1.0 mg
Dulaglutide 0.75 mg
Dulaglutide 1.5 mg

*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.

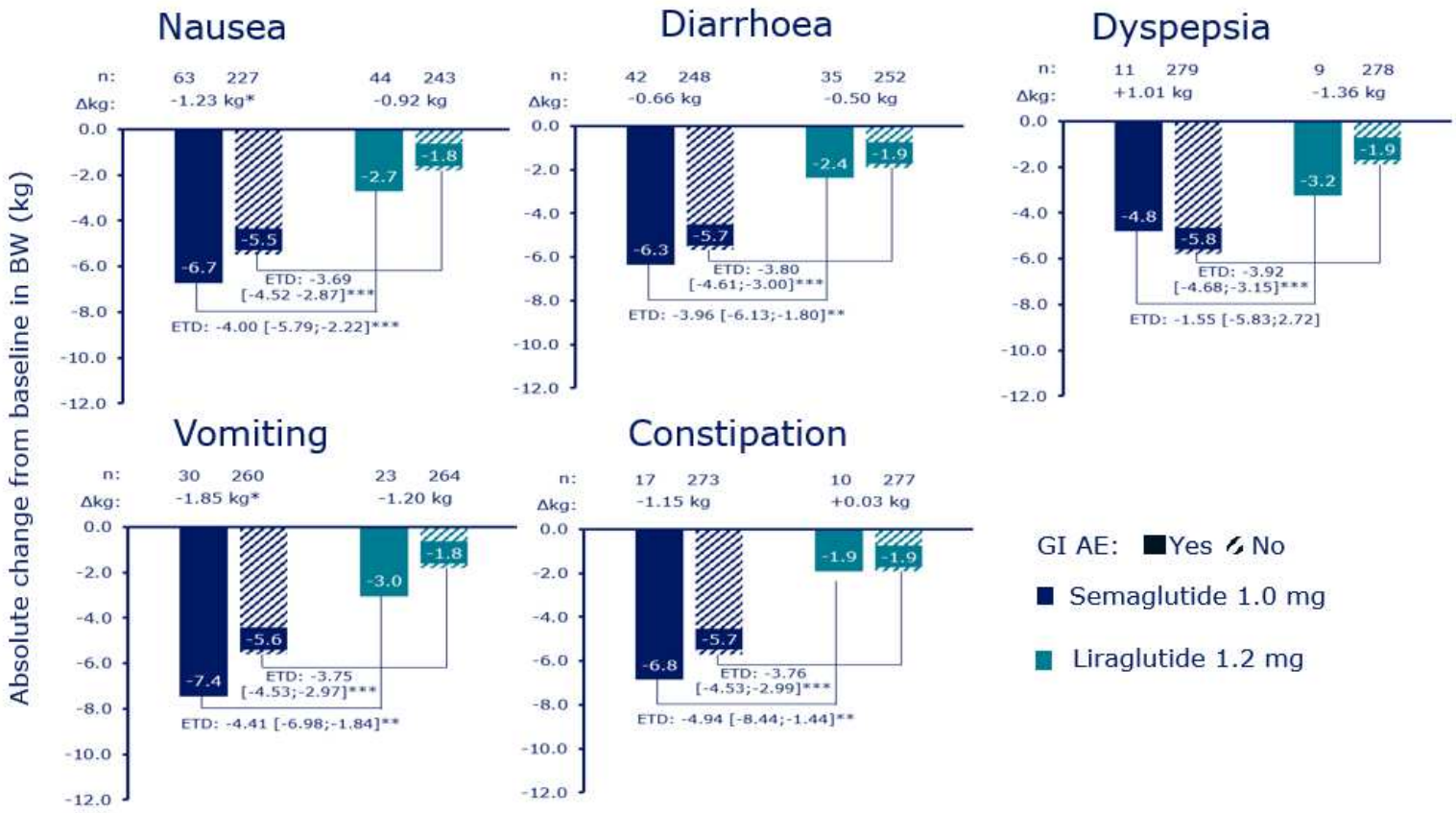
Δkg, differences in body weight within treatment arms; AE, adverse event; BW, body weight; ETD, estimated treatment difference; GI, gastrointestinal.

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)



(B)

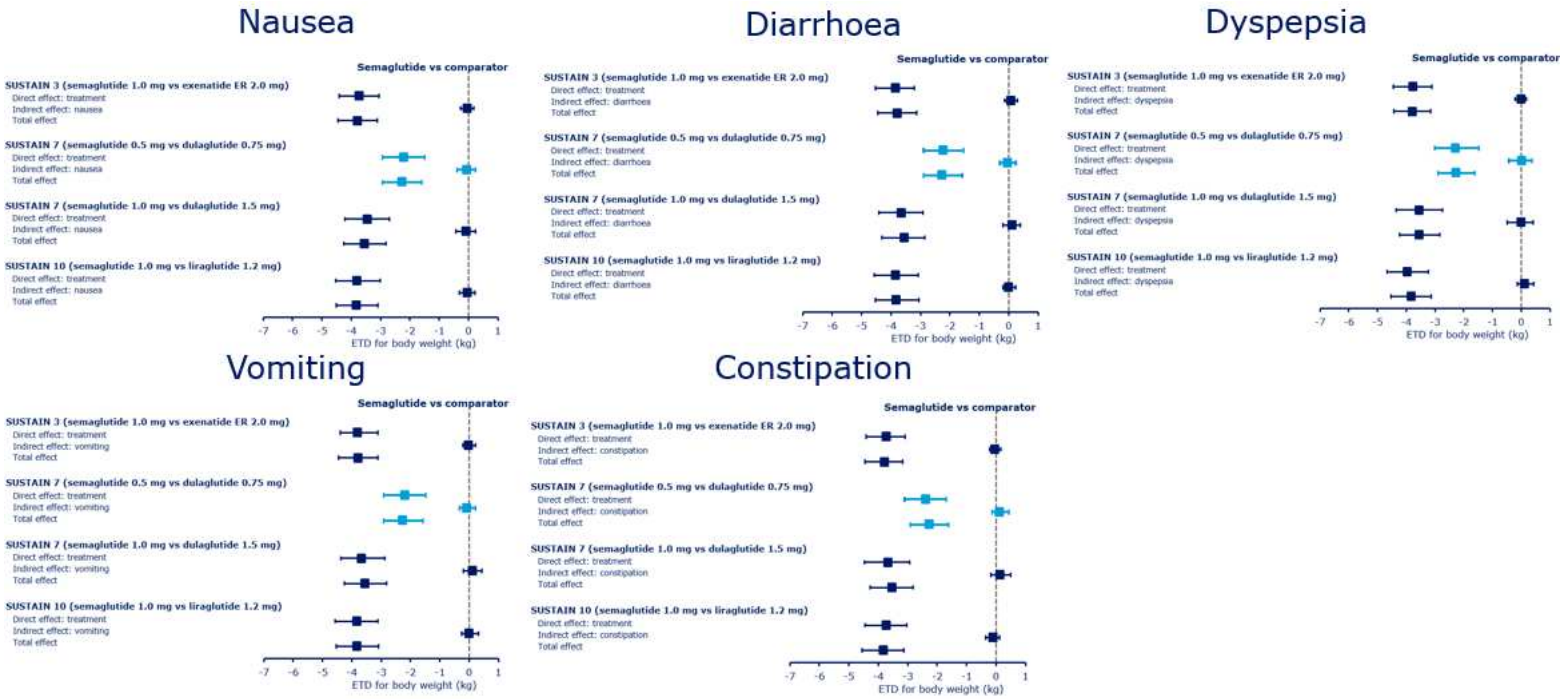


*p<0.05; **p<0.01; ***p<0.0001. Values are estimated means from a mixed model for repeated measurements analysis using 'on-treatment without rescue medication' data from subjects in the full analysis set. Values in square brackets indicate 95% confidence intervals.

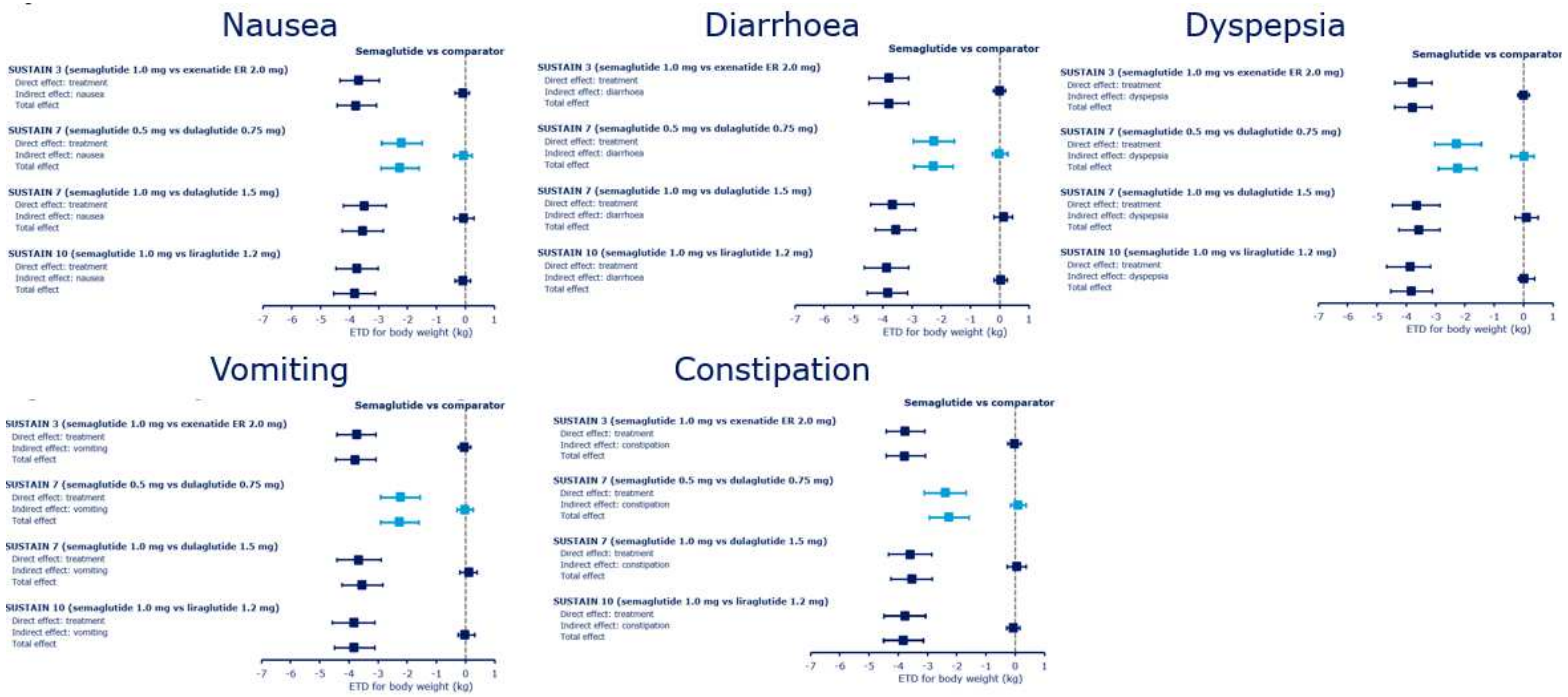
Δkg, differences in body weight within treatment arms; AE, adverse event; BW, body weight; ETD, estimated treatment difference; GI, gastrointestinal.

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)



(B)



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.