SUPPLEMENTARY DATA

Part A. Supplemental results

Other secondary efficacy endpoints

7-point SMBG

At week 26, dose-dependent reductions in mean 7-point SMBG levels were observed in all treatment groups. Reductions in mean 7-point SMBG levels were significantly greater in the semaglutide groups than in the liraglutide or pooled placebo groups ($p<0.001$ for all), except for semaglutide 0.1 mg versus liraglutide 0.6 mg(**Supplemental Figure S7**). The 7-point SMBG increment was comparable between treatment groups at baseline (mean 2.2 mmol/L), with reductions in all groups observed at week 26. Reductions were greater with semaglutide than with liraglutide or pooled placebo, but not all between-group differences were statistically significant (**Supplemental Figure S7**).

BMI

At week 26, reductions in BMI were observed in all groups, with a generally dose-dependent estimated mean change observed with semaglutide (range –1.0 to –2.9 kg/m^2) and with liraglutide (range –0.5 to –1.3 kg/m^2, although changes were similar between the 0.6 and 1.2 mg doses). Change in BMI in the pooled placebo group was –0.4 kg/m^2. Treatment differences were significant between all semaglutide doses and liraglutide (all $p\leq0.0001$) except for semaglutide 0.05 mg versus liraglutide 0.3 mg and all semaglutide doses versus placebo (all $p<0.02$).

Waist circumference

At week 26, reductions in waist circumference were observed all groups, with a dose-dependent estimated mean change observed with semaglutide (range –3.1 to –7.5 cm) and with liraglutide (range –2.2 to –4.6 cm, although changes were similar between the 0.6 and 1.2 mg doses). Change in waist circumference in the pooled placebo group was –2.0 cm**(Figure 2E)**.Treatment differences were significant between semaglutide 0.2 mg and liraglutide 1.2 mg ($p<0.0001$), between semaglutide 0.3 mg and liraglutide 1.8 mg ($p=0.0024$) and with all semaglutide doses versus placebo except for the 0.05 mg dose (all $p<0.002$).

Lipids

Overall, between baseline and week 26, lipid profiles showed modest improvements with semaglutide compared with either liraglutide or placebo.

Compared with liraglutide 0.6 and 1.2 mg, semaglutide 0.1 and 0.2 mg, respectively, resulted in significant improvements in total cholesterol (both $p<0.05$), VLDL-cholesterol (both $p<0.004$) and triglycerides ($p<0.002$). FFA were significantly improved with semaglutide 0.2 mg versus liraglutide 1.2 mg ($p=0.04$). Compared with placebo, semaglutide treatment generally resulted in significant, dose-dependent improvements in FFA, VLDL-cholesterol and triglycerides (all $p<0.02$, except 0.05 mg dose [p=not significant]). Semaglutide 0.2 and 0.3 mg treatment resulted in significant improvements in total cholesterol (both $p<0.02$), while the 0.2 mg dose also led to significant improvements in LDL-cholesterol ($p=0.04$).

DTSQ

SUPPLEMENTARY DATA

During treatment, an improvement was seen in 7 of 8 DTSQ components in all treatment groups. There was no dose–response effect with semaglutide or liraglutide, and no statistically significant difference between treatment groups in the improvements observed.

The mean change in the ‘treatment satisfaction’ score (from a mean baseline score of 28.3) with semaglutide ranged from 3.9 (0.05 mg dose) to 5.1 (0.2 mg) and with liraglutide ranged from 2.9 (0.3 mg) to 3.9 (0.6 mg). Mean change for the placebo group was 3.2. The estimated treatment difference was significant for semaglutide 0.2 mg versus placebo (p=0.01) and for semaglutide 0.2 mg versus liraglutide 1.2 mg (p=0.02).The change from baseline (95% CI) between semaglutide and placebo for perceived frequency of hyperglycemia and of hypoglycemia ranged from –0.89 (–1.40, –0.38) to –1.61 (–2.12,–1.10) and –0.07 (–0.50, 0.35) to 0.01 (–0.40, 0.43), respectively.Patient perception of improvement in the frequency of hyperglycemia was statistically significant at all doses between semaglutide and placebo (p<0.001), but was not significant for improvement in hypoglycemia.

Additional safety in the semaglutide flexible-dosing arm

Two episodes of severe or BG-confirmed symptomatic hypoglycemia were reported in two patients (3.1%). There was one EAC-confirmed neoplasm, which was malignant (clear cell renal cell carcinoma) and judged unlikely related to semaglutide treatment. There were no EAC-confirmed events of pancreatitis, one EAC-confirmed CV event, and one patient reported a diabetic retinopathy event.

SUPPLEMENTARY DATA

PART B. Supplemental tables

Supplementary Table S1. Inclusion and exclusion criteria

Inclusion
1. Informed consent obtained before any trial-related activities (i.e. any procedures that are carried out as part of the trial, including activities to determine suitability for the trial) 2. Male or female, age ≥18 years at the time of signing informed consent. 3. Diagnosed with type 2 diabetes at least ≥90 days prior to screening 4. On stable diabetes treatment consisting of diet and exercise with or without metformin (≥1,500 mg daily or maximum tolerated dose documented in the patient medical record) for at least 90 days prior to screening 5. HbA_{1c} 53–86 mmol/mol (7.0–10.0%) (both inclusive) 6. Body mass index 25.0–40.0 kg/m^2 (both inclusive)
Exclusion
1. Known or suspected hypersensitivity to trial products or related products; previous participation in the trial 2. Receipt of any investigational medicinal product within 90 days or five-times the half-life of the previous investigational medicinal product, whichever is longer, before screening 3. Simultaneous participation in any other clinical trial of an investigational medicinal product 4. Females who were pregnant, breast-feeding or intending to become pregnant, or of child-bearing potential and not using adequate contraceptive methods throughout the trial 5. Any condition which might jeopardize patient safety or compliance with the protocol 6. Treatment with any medication for diabetes or obesity other than stated in the inclusion criteria during the 90 days prior to screening (except for insulin treatment for acute illnesses

for ≤14 days)

7. Anticipated initiation or change in concomitant medications (for >14 consecutive days or on a frequent basis) known to affect weight or glucose metabolism
8. History of chronic or idiopathic acute pancreatitis
9. Screening calcitonin value ≥50 ng/L (≥50 pg/mL)
10. Family or personal history of multiple endocrine neoplasia type 2 or medullary thyroid carcinoma
11. Systolic blood pressure ≥160 mmHg and/or diastolic blood pressure ≥100 mmHg at screening
12. Moderate-to-severe renal impairment (estimated glomerular filtration rate <60 mL/min/1.73 m^2)
13. Myocardial infarction, stroke or hospitalization for unstable angina or transient ischemic attack within 180 days prior to screening
14. Planned coronary, carotid or peripheral artery revascularization
15. New York Heart Association Class III or IV
16. Proliferative retinopathy or maculopathy requiring acute treatment (as verified by fundoscopy/fundus photography), performed within 90 days prior to randomization
17. Diagnosis of malignant neoplasm within the last 5 years (except basal and squamous cell skin cancer, polyps and carcinomas *in situ*)

SUPPLEMENTARY DATA

Supplementary Table S2. Key supportive secondary endpoints

Efficacy

• Change from baseline to week 26 in:
  ○ FPG (key supportive secondary endpoint)
  ○ SMBG 7-point profile (mean 7-point profile and mean postprandial increment over all meals)
  ○ Fasting blood lipids (total cholesterol, low density lipoprotein [LDL]-cholesterol, very low-density lipoprotein [VLDL]-cholesterol, high density lipoprotein [HDL]-cholesterol, triglycerides, free fatty acids [FFA])
  ○ Body weight (key supportive secondary endpoint)
  ○ BMI and waist circumference
  ○ SBP and DBP (key supportive secondary endpoints)
• Patient-reported outcomes using the Diabetes Treatment Satisfaction Questionnaire (DTSQ)
• Patients who, after 26 weeks of treatment, achieved:
  ○ HbA_{1c}<7.0% (53 mmol/mol) [ADA target] (1) and ≤6.5% (48 mmol/mol) [American Association of Clinical Endocrinologists (AACE) target] (2)
  ○ Weight loss ≥5% and ≥10%

Safety
• Number of AEs and number of treatment-emergent AEs • Severe hypoglycemic episodes classified according to the American Diabetes Association definition(3) • Number of and occurrence of treatment-emergent severe or blood glucose-confirmed

symptomatic hypoglycemic episodes

- Change from baseline to week 26 in hematology, amylase and lipase levels, calcitonin, urinalysis, urinary albumin to creatinine ratio,pulse, electrocardiogram evaluation and physical examination
- Development of anti-semaglutide antibodies, either cross-reacting with endogenous glucagon-like peptide-1 or with an *in vitro* neutralizing effect.
- An independent external event adjudication committee was established to perform qualitative and quantitative validation of selected AEs according to pre-defined diagnostic criteria
    - Events were adjudicated according to the relevant and current US Food and Drug Administration requirements

AE, adverse event.

SUPPLEMENTARY DATA

Supplementary Table S3. Rescue medication on treatment, full analysis set

	Semaglutide 0.05 mg n (%)	**Semaglutide 0.1 mg** n (%)	**Semaglutide 0.2 mg** n (%)	**Semaglutide 0.3 mg** n (%)	**Semaglutide flexible dose** n (%)
Number of patients	64	63	65	63	64
Events	4 (6.3)	0	0	0	1 (1.6)
Sulfonylureas	1 (1.6)	0	0	0	0
Biguanides	1 (1.6)	0	0	0	1 (1.6)
Insulins and analogs for injection	2 (3.1)	0	0	0	0
Other*	1 (1.6)	0	0	0	0

SUPPLEMENTARY DATA

	Liraglutide 0.3 mg n (%)	**Liraglutide 0.6 mg** n (%)	**Liraglutide 1.2 mg** n (%)	**Liraglutide 1.8 mg** n (%)	**Pooled placebo** n (%)
Number of patients	64	64	64	65	129
Events	9 (14.1)	2 (3.1)	6 (9.4)	0	22 (17.1)
Sulfonylureas	4 (6.3)	1 (1.6)	1 (1.6)	0	9 (7.0)
Biguanides	0	0	1 (1.6)	0	3 (2.3)
Insulins and analogs for injection	4 (6.3)	0	2 (3.1)	0	1 (0.8)
Other†	3 (4.7)	1 (1.6)	2 (3.1)	0	13 (10.1)

n: number of patients with at least one medical history record, %: percentage of patients with at least one medical history record. Data are based on the total percentage of patients experiencing at least one event. *Other blood-glucose-lowering drugs, excluding insulins; †Other blood-glucose-lowering drugs, excluding insulins; dipeptidyl peptidase-4 inhibitors; and combinations of oral blood-glucose-lowering drugs.

SUPPLEMENTARY DATA

Supplementary Table S4. Change from baseline at week 26 in HbA_{1c} and body weight

Treatment arm	Estimated change from baseline	Estimated treatment difference (95% CI)
HbA_{1c} (%)		
Semaglutide 0.05 mg	–1.1	
Semaglutide 0.1 mg	–1.4	
Semaglutide 0.2 mg	–1.7	
Semaglutide 0.3 mg	–1.9	
Liraglutide 0.3 mg	–0.5	
Liraglutide 0.6 mg	–0.9	
Liraglutide 1.2 mg	–0.8	
Liraglutide 1.8 mg	–1.3	
Semaglutide 0.05 mg vs liraglutide 0.3 mg		–0.55 [–0.85;–0.25]
Semaglutide 0.1 mg vs liraglutide 0.6 mg		–0.51 [–0.81;–0.21]
Semaglutide 0.2 mg vs liraglutide 1.2 mg		–0.88 [–1.18;–0.58]
Semaglutide 0.3 mg vs liraglutide 1.8 mg		–0.57 [–0.87;–0.27]
Body weight (kg)		
Semaglutide 0.05 mg	–2.8	
Semaglutide 0.1 mg	–4.3	
Semaglutide 0.2 mg	–6.7	
Semaglutide 0.3 mg	–8.2	
Liraglutide 0.3 mg	–1.5	
Liraglutide 0.6 mg	–1.7	
Liraglutide 1.2 mg	–1.7	
Liraglutide 1.8 mg	–3.7	
Semaglutide 0.05 mg vs liraglutide 0.3 mg		–1.26 [–2.67;0.14]

Semaglutide 0.1 mg vs liraglutide 0.6 mg		–2.61 [–4.01;–1.20]
Semaglutide 0.2 mg vs liraglutide 1.2 mg		–4.94 [–6.35;–3.53]
Semaglutide 0.3 mg vs liraglutide 1.8 mg		–4.48 [–5.89;–3.08]

CI: confidence interval. Observed ‘on-treatment until rescue medication’ data. The post-baseline responses areanalyzed using a mixed model for repeated measurements with treatment, region and stratum as fixedfactors and baseline value as covariate, all nested within visit. Mean estimates are adjustedaccording to observed baseline distribution.

Supplementary Table S5. Overview of adverse events (on-treatment)

	Semaglutide 0.05 mg (n=64)				**Semaglutide 0.1 mg (n=63)**				**Semaglutide 0.2 mg (n=65)**				**Semaglutide 0.3 mg (n=63)**				**Semaglutide flexible dose (n=64)**			
	N	**%**	**E**	**R**	**N**	**%**	**E**	**R**	**N**	**%**	**E**	**R**	**N**	**%**	**E**	**R**	**N**	**%**	**E**	**R**
AEs	40	62.5	203	538	44	69.8	225	590	48	73.8	221	590	46	73.0	242	642	53	82.8	286	719
Serious AEs	6	9.4	9	24	3	4.8	3	8	2	3.1	2	5	2	3.2	2	5	4	6.3	4	10
Severity																				
Severe	4	6.3	13	34	4	6.3	5	13	4	6.2	4	11	2	3.2	2	5	7	10.9	18	45
Moderate	20	31.3	40	106	19	30.2	41	107	25	38.5	51	136	22	34.9	68	180	34	53.1	84	211
Mild	35	54.7	150	397	41	65.1	179	469	41	63.1	166	443	44	69.8	172	456	43	67.2	184	462
Discontinued treatment	4	6.3	6	16	5	7.9	8	21	6	9.2	6	16	5	7.9	12	32	3	4.7	4	10
	Liraglutide 0.3 mg (n=64)				**Liraglutide 0.6 mg (n=64)**				**Liraglutide 1.2 mg (n=64)**				**Liraglutide 1.8 mg (n=65)**				**Pooled placebo (n=129)**			
	N	**%**	**E**	**R**	**N**	**%**	**E**	**R**	**N**	**%**	**E**	**R**	**N**	**%**	**E**	**R**	**N**	**%**	**E**	**R**

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AEs	49	76.6	155	402	43	67.2	198	515	45	70.3	159	420	50	76.9	204	521	94	72.9	278	375
Serious AEs	1	1.6	1	3	2	3.1	2	5	1	1.6	4	11	7	10.8	11	28	4	3.1	6	8
Severity																				
Severe	1	1.6	1	3	3	4.7	7	18	4	6.3	8	21	8	12.3	13	33	4	3.1	8	11
Moderate	19	29.7	49	127	21	32.8	63	164	16	25.0	35	92	20	30.8	49	125	44	34.1	73	99
Mild	40	62.5	105	273	38	59.4	128	333	42	65.6	116	307	38	58.5	142	363	80	62.0	197	266
Discontinued treatment	2	3.1	2	5	4	6.3	5	13	5	7.8	7	18	5	7.7	8	20	14	10.9	18	24

AE: adverse event, E: number of events, N: number of patients experiencing at least one event, R: event rate per 100 years of exposure, %: percentage of patients experiencing at least one event. The 'on-treatment' overview includes treatment-emergent AEs with onset at or after the date of the first trial product dose and before or at the date of the last trial product dose plus 7 weeks, plus the 7 days' visit window for the end-of-treatment follow-up visit (=56 days).

SUPPLEMENTARY DATA

Supplementary Table S6. Most commonly reportedadverse events by system organ class (on-treatment)

	Semaglutide 0.05 mg				**Semaglutide 0.1 mg**				**Semaglutide 0.2 mg**				**Semaglutide 0.3 mg**				**Semaglutide flexible dose**			
	N	**%**	**E**	**R**	**N**	**%**	**E**	**R**	**N**	**%**	**E**	**R**	**N**	**%**	**E**	**R**	**N**	**%**	**E**	**R**
Number of patients	64				63				65				63				64			
Adverse events	40	62.5	203	538	44	69.8	225	590	48	73.8	221	590	46	73.0	242	642	53	82.8	286	719
Gastro-intestinal disorders	21	32.8	61	162	28	44.4	90	236	30	46.2	106	283	34	54.0	101	268	36	56.3	128	322
Infections and infestations	18	28.1	31	82	19	30.2	25	66	17	26.2	24	64	23	36.5	28	74	25	39.1	36	90
Nervous system disorders	11	17.2	26	69	13	0.6	41	107	9	13.8	19	51	16	25.4	27	72	14	21.9	30	75
Musculo-skeletal and connective tissue disorders	12	18.8	15	40	10	15.9	12	31	8	12.3	9	24	6	9.5	14	37	14	21.9	19	48

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Metabolism and nutrition disorders	7	10.9	8	21	9	14.3	9	24	9	13.8	9	24	9	14.3	12	32	16	25.0	16	40
Investigations	7	10.9	10	26	7	11.1	11	29	8	12.3	9	24	8	12.7	10	27	5	7.8	6	15
General disorders and administration site conditions	3	4.7	3	8	8	12.7	8	21	9	13.8	10	27	10	15.9	14	37	9	14.1	13	33
Respiratory, thoracic and mediastinal disorders	4	6.3	5	13	2	3.2	3	8	2	3.1	2	5	5	7.9	5	13	4	6.3	6	15
Injury, poisoning and procedural complication	6	9.4	15	40	3	4.8	4	10	6	9.2	6	16	3	4.8	4	11	2	3.1	2	5
Skin and subcutaneous tissue disorders	1	1.6	1	3	6	9.5	6	16	4	6.2	4	11	3	4.8	5	13	5	7.8	5	13
	Liraglutide 0.3 mg				**Liraglutide 0.6 mg**				**Liraglutide 1.2 mg**				**Liraglutide 1.8 mg**				**Pooled placebo**			
	N	**%**	**E**	**R**	**N**	**%**	**E**	**R**	**N**	**%**	**E**	**R**	**N**	**%**	**E**	**R**	**N**	**%**	**E**	**R**

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Number of patients	64				64				64				65				129			
Adverse events	49	76.6	155	402	43	67.2	198	515	45	70.3	159	420	50	76.9	204	521	94	72.9	278	375
Gastro-intestinal disorders	14	21.9	25	65	19	29.7	62	161	20	31.3	40	106	27	41.5	81	207	29	22.5	54	73
Infections and infestations	25	39.1	41	106	13	20.3	20	52	17	26.6	28	74	19	29.2	26	66	41	31.8	63	85
Nervous system disorders	7	10.9	9	23	10	15.6	22	57	14	21.9	23	61	6	9.2	15	38	14	10.9	14	19
Musculo-skeletal and connective tissue disorders	9	14.1	10	26	9	14.1	15	39	6	9.4	7	18	11	16.9	17	43	22	17.1	31	42
Metabolism and nutrition disorders	8	12.5	10	26	6	9.4	11	29	7	10.9	7	18	5	7.7	6	15	19	14.7	20	27
Investigations	5	7.8	7	18	10	15.6	15	39	6	9.4	8	21	9	13.8	14	36	10	7.8	11	15
General disorders and	3	4.7	4	10	6	9.4	18	47	6	9.4	7	18	7	10.8	7	18	11	8.5	13	18

administration site conditions																			
Respiratory, thoracic and mediastinal disorders	9	14.1	17	44	7	10.9	12	31	7	10.9	11	29	5	7.7	5	13	11	8.5	16	22
Injury, poisoning and procedural complications	4	6.3	4	10	3	4.7	4	10	5	7.8	6	16	3	4.6	3	8	10	7.8	12	16
Skin and subcutaneous tissue disorders	2	3.1	2	5	5	7.8	5	13	2	3.1	2	5	3	4.6	3	8	7	5.4	7	9

E: number of events, N: number of patients experiencing at least one event, R: event rate per 100 years of exposure. %: percentage of patients experiencing at least one event. The ‘on-treatment’ summary includes treatment-emergent adverse events with onset at/after the date of the first trial product dose and before/at the date of the last trial product dose plus 7 weeks, plus the 7 days’ visit window for the end-of-treatment follow-up visit (56 days). The exposure time is the duration of this period. The ten most-reported adverse events are shown.

Supplementary Table S7. Severe or BG-confirmed symptomatic hypoglycemic episodes (on-treatment)

	Semaglutide 0.05 mg (n=64)				**Semaglutide 0.1 mg (n=63)**				**Semaglutide 0.2 mg (n=65)**				**Semaglutide 0.3 mg (n=63)**				**Semaglutide flexible dose (n=64)**			
	N	%	E	R	N	%	E	R	N	%	E	R	N	%	E	R	N	%	E	R
Severe or BG-confirmed symptomatic	2	3.1	2	5.3	2	3.2	2	5.2	3	4.6	4	10.7	2	3.2	3	8.0	2	3.1	2	5.0
	Liraglutide 0.3 mg (n=64)				**Liraglutide 0.6 mg (n=65)**				**Liraglutide 1.2 mg (n=64)**				**Liraglutide 1.8 mg (n=65)**				**Pooled placebo (n=129)**			
Severe or BG-confirmed symptomatic	0	-	-	-	2	3.1	6	15.6	1	1.6	1	2.6	3	4.6	3	7.7	4	3.1	6	8.1

BG: blood glucose, E: number of events, N: number of patients experiencing at least one event, R: event rate per 100 years of exposure, %: percentage of patients experiencing at least one event. BG confirmed: BG <3.1 mmol/L (56 mg/dL). The on-treatment summary of hypoglycemic episodes comprises treatment-emergent events with onset on or after the day of first randomized dose to date of last dose plus 56 days.

Supplementary Table S8. Lipase and amylase estimates at week 26 (on-treatment)

	N	Estimate (SE)	95% CI	p value
Lipase (U/L)				
Ratio to baseline				
Semaglutide 0.05 mg	52	1.18 (0.07)		
Semaglutide 0.1 mg	56	1.36 (0.08)		
Semaglutide 0.2 mg	50	1.53 (0.09)		
Semaglutide 0.3 mg	53	1.52 (0.09)		
Liraglutide 0.3 mg	50	1.32 (0.08)		
Liraglutide 0.6 mg	53	1.44 (0.09)		
Liraglutide 1.2 mg	50	1.32 (0.08)		
Liraglutide 1.8 mg	55	1.39 (0.08)		
Placebo	92	0.93 (0.04)		
Treatment ratio				
Semaglutide 0.05 mg/Liraglutide 0.3 mg		0.90 (0.08)	0.76; 1.06	0.2162
Semaglutide 0.1 mg/ Liraglutide 0.6 mg		0.94 (0.08)	0.80; 1.12	0.5005
Semaglutide 0.2 mg/ Liraglutide 1.2 mg		1.17 (0.10)	0.98; 1.38	0.0805
Semaglutide 0.3 mg/ Liraglutide 1.8 mg		1.09 (0.09)	0.93; 1.29	0.2941
Semaglutide 0.05 mg/Placebo		1.28 (0.10)	1.10; 1.48	0.0013
Semaglutide 0.1 mg/Placebo		1.47 (0.11)	1.27; 1.70	<0.0001
Semaglutide 0.2 mg/Placebo		1.65 (0.13)	1.42; 1.92	<0.0001
Semaglutide 0.3 mg/Placebo		1.64 (0.12)	1.41; 1.90	<0.0001

Liraglutide 0.3 mg/Placebo		1.42 (0.11)	1.22; 1.65	<0.0001
Liraglutide 0.6 mg/Placebo		1.56 (0.12)	1.34; 1.81	<0.0001
Liraglutide 1.2 mg/Placebo		1.42 (0.11)	1.22; 1.65	<0.0001
Liraglutide 1.8 mg/Placebo		1.50 (0.11)	1.29; 1.73	<0.0001
Amylase (U/L)				
Ratio to baseline				
Semaglutide 0.05 mg	52	1.13 (0.04)		
Semaglutide 0.1 mg	56	1.20 (0.04)		
Semaglutide 0.2 mg	50	1.28 (0.04)		
Semaglutide 0.3 mg	53	1.23 (0.04)		
Liraglutide 0.3 mg	51	1.15 (0.04)		
Liraglutide 0.6 mg	54	1.15 (0.04)		
Liraglutide 1.2 mg	50	1.13 (0.04)		
Liraglutide 1.8 mg	55	1.13 (0.04)		
Placebo	92	0.99 (0.02)		
Treatment ratio				
Semaglutide 0.05 mg/Liraglutide 0.3 mg		0.98 (0.04)	0.90; 1.07	0.6790
Semaglutide 0.1 mg/ Liraglutide 0.6 mg		1.05 (0.05)	0.96; 1.14	0.3006
Semaglutide 0.2 mg/ Liraglutide 1.2 mg		1.13 (0.05)	1.04; 1.24	0.0060
Semaglutide 0.3 mg/ Liraglutide 1.8 mg		1.09 (0.05)	1.00; 1.19	0.0549
Semaglutide 0.05 mg/Placebo		1.13 (0.04)	1.05; 1.22	0.0015
Semaglutide 0.1 mg/Placebo		1.21 (0.05)	1.12; 1.31	<0.0001

Semaglutide 0.2 mg/Placebo		1.29 (0.05)	1.20; 1.40	<0.0001
Semaglutide 0.3 mg/Placebo		1.24 (0.05)	1.15; 1.34	<0.0001
Liraglutide 0.3 mg/Placebo		1.15 (0.05)	1.07; 1.25	0.0003
Liraglutide 0.6 mg/Placebo		1.16 (0.05)	1.07; 1.25	0.0002
Liraglutide 1.2 mg/Placebo		1.14 (0.05)	1.05; 1.23	0.0010
Liraglutide 1.8 mg/Placebo		1.14 (0.04)	1.06; 1.23	0.0008

CI: Confidence interval,N: Number of subjects with an observation at the visit, SE: Standard error. The log-transformed post-baseline responses are analyzed using a mixed model for repeated measurements with treatment, region and stratum as fixed factors and baseline value as covariate, all nested within visit. Standard errors are 1*SEM calculated on log-scale and back-transformed to original scale.

Supplementary Table S9. Summary of pregnancy cases

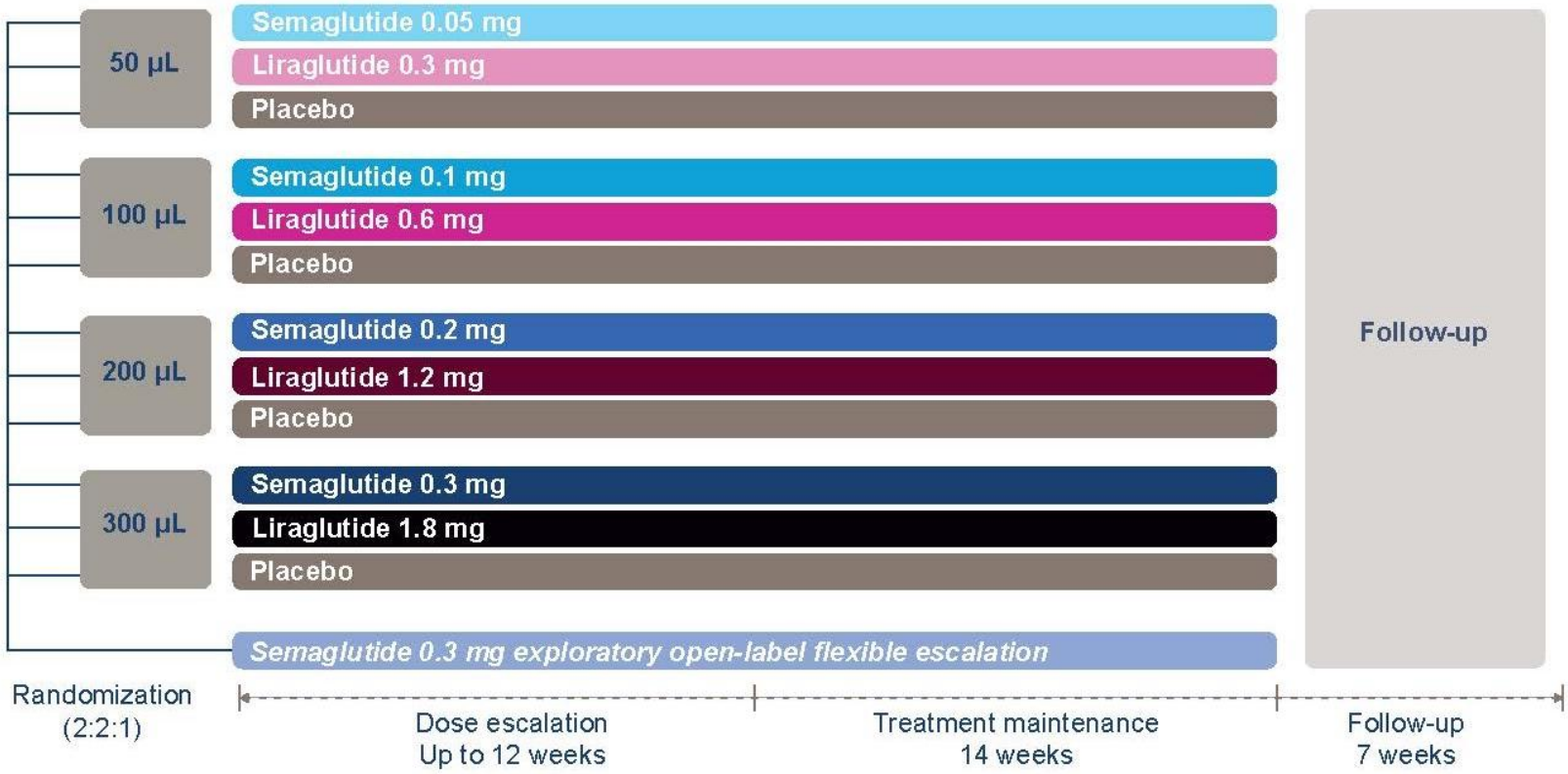
Treatment	Age	Trimester exposed	Exposure to fetus (weeks)*	Pregnancy details/action	Pregnancy outcome
Semaglutide 0.05 mg	39	First	~7	Pregnancy test at visit 2 (week 0) was negative. Patient tested positive at visit 4 (week 4). Treatment discontinued due to pregnancy on trial day 30.	Spontaneous abortion on trial day 48.
Liraglutide 1.8 mg	34	First	~4	Pregnancy test was negative at visits 1–13 and positive at visit 14 (end of treatment). Patient did not discontinue due to pregnancy. Patient completed trial.	No adverse events reported in connection to pregnancy. Delivery at gestational week 35 and 6 days to a healthy female child (birth weight 2500 g), with no health problems at delivery.

*Estimated fetal exposure includes exposure after endoftreatment.

SUPPLEMENTARY DATA

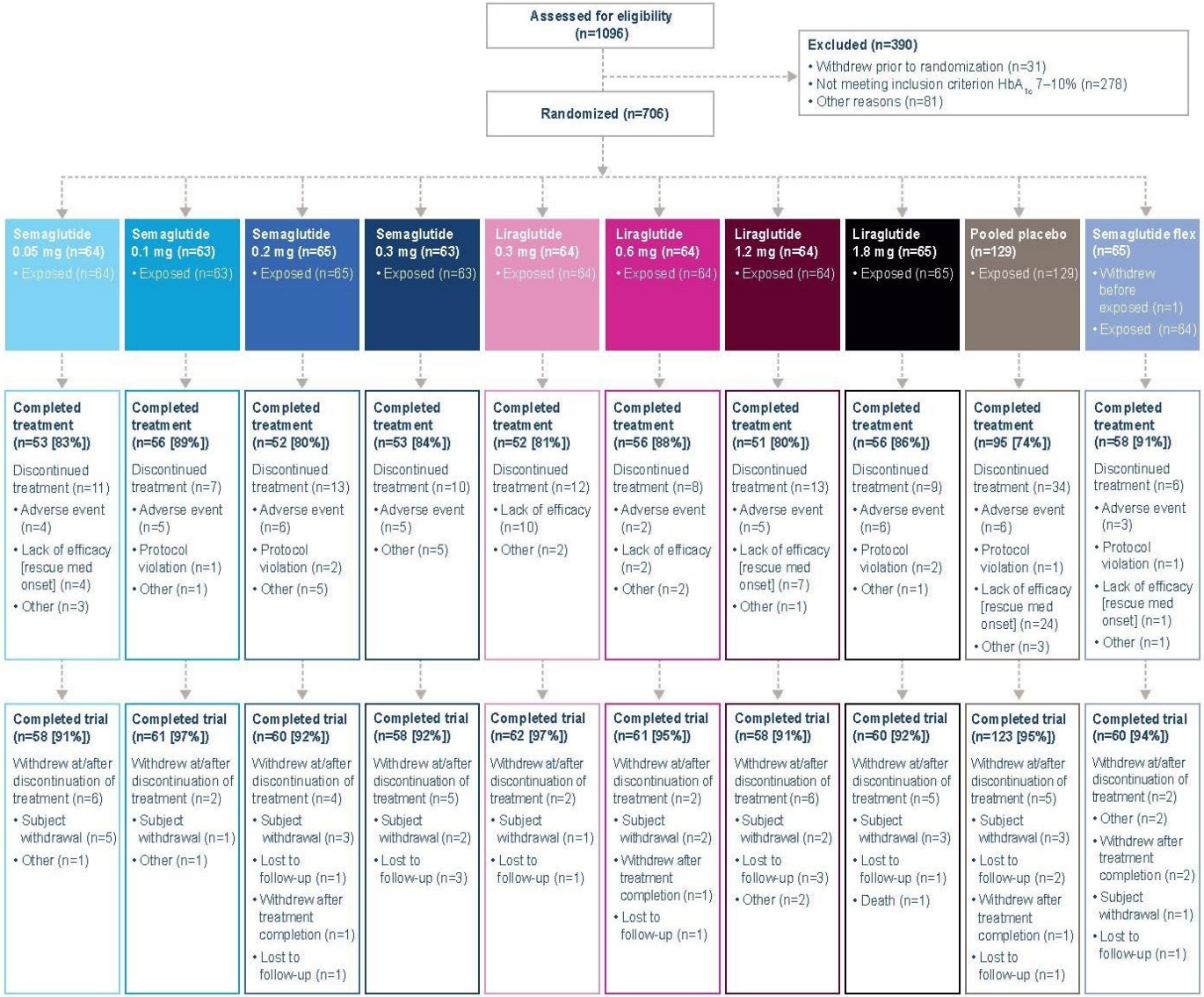
PART C. Supplemental figures

Supplementary Figure S1. Schematic overview of trial design



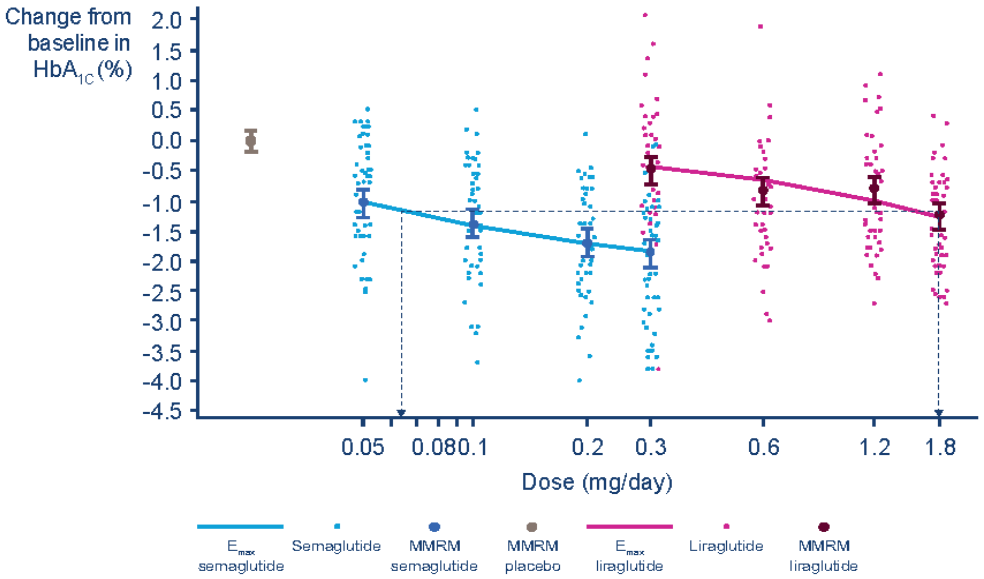
SUPPLEMENTARY DATA

Supplementary Figure S2. Trial flow chart



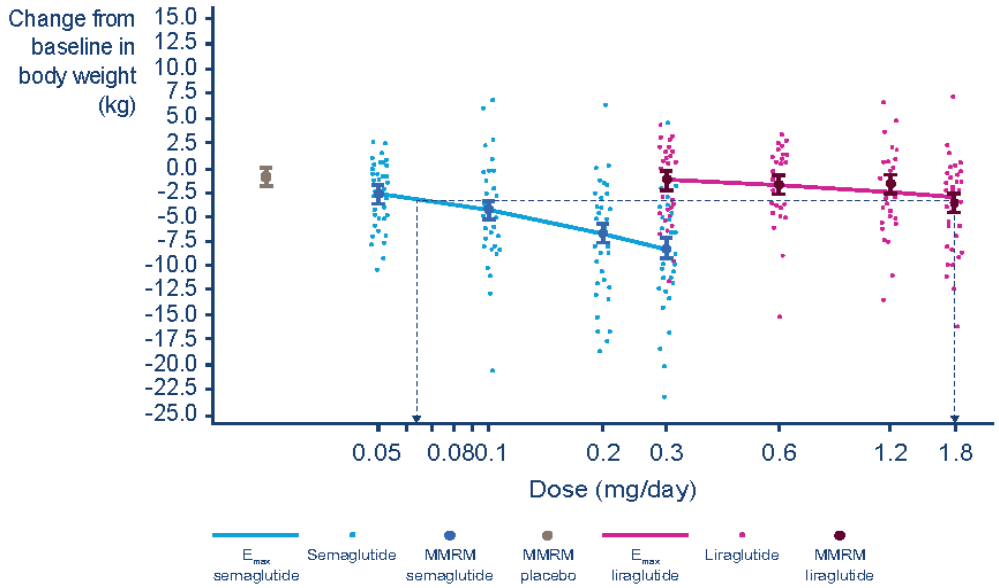
Supplementary Figure S3. Dose–response modeling of semaglutide and liraglutide: HbA_{1c} [%] (A), body weight [kg] (B) and equivalent semaglutide to liraglutide dose ratios for efficacy and safety parameters (C)

A



Parameter	Potency (95% CI)
HbA_{1c}	27.59 [18.52; 41.11]

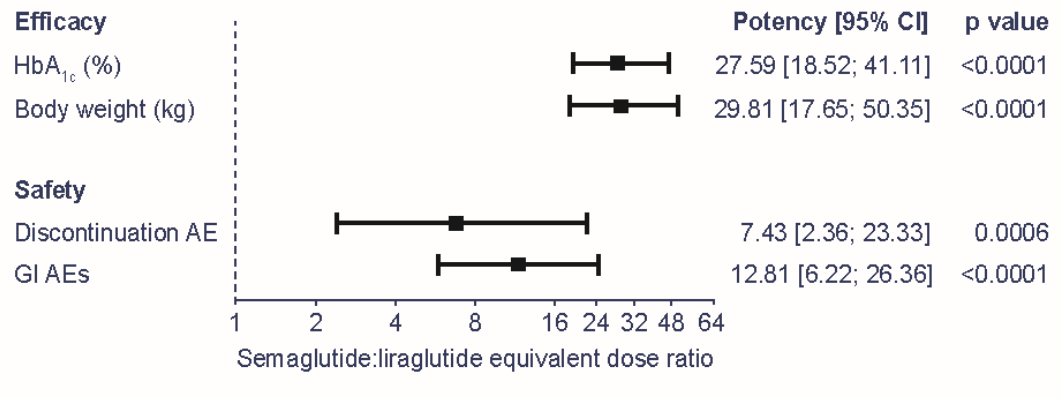
B



Parameter	Potency (95% CI)
Body weight	29.81 [17.65; 50.35]

SUPPLEMENTARY DATA

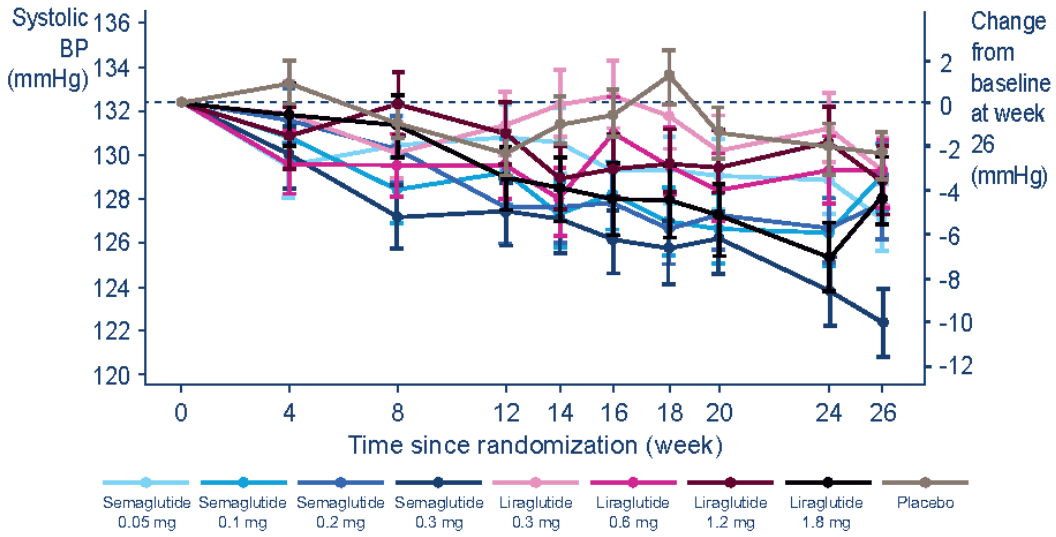
C



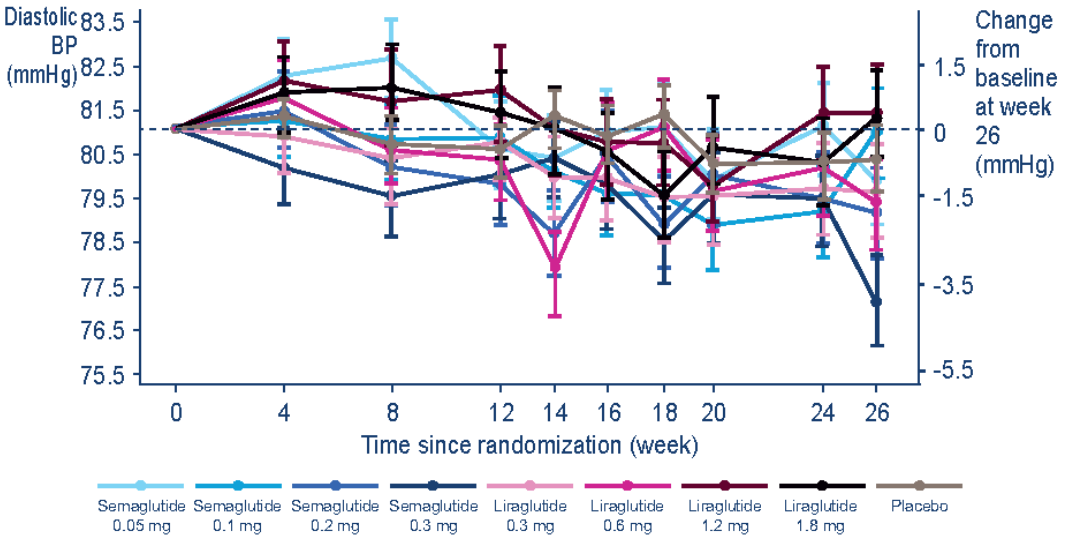
AE: adverse event, CI: confidence interval, GI: gastrointestinal, Lira: liraglutide, MMRM: mixed model for repeated measurements, Sema: semaglutide. 'On treatment until rescue medication' data. Part A shows results from 3-parameter E_{max} model together with MMRM estimates from primary model. Part B shows results from 3-parameter E_{max} model for a patient with baseline HbA_{1c} as the overall mean, together with MMRM estimates from primary model. Observed values have had their dose jittered to enhance interpretation. In part C, p-value potency is performed by testing log (potency) = 0. The 95% CI is calculated by exponentiating the CI limits for log (potency).

Supplementary Figure S4. Estimated mean systolic blood pressure (A) and diastolic blood pressure (B) by treatment week and by estimated treatment difference (C) at week 26

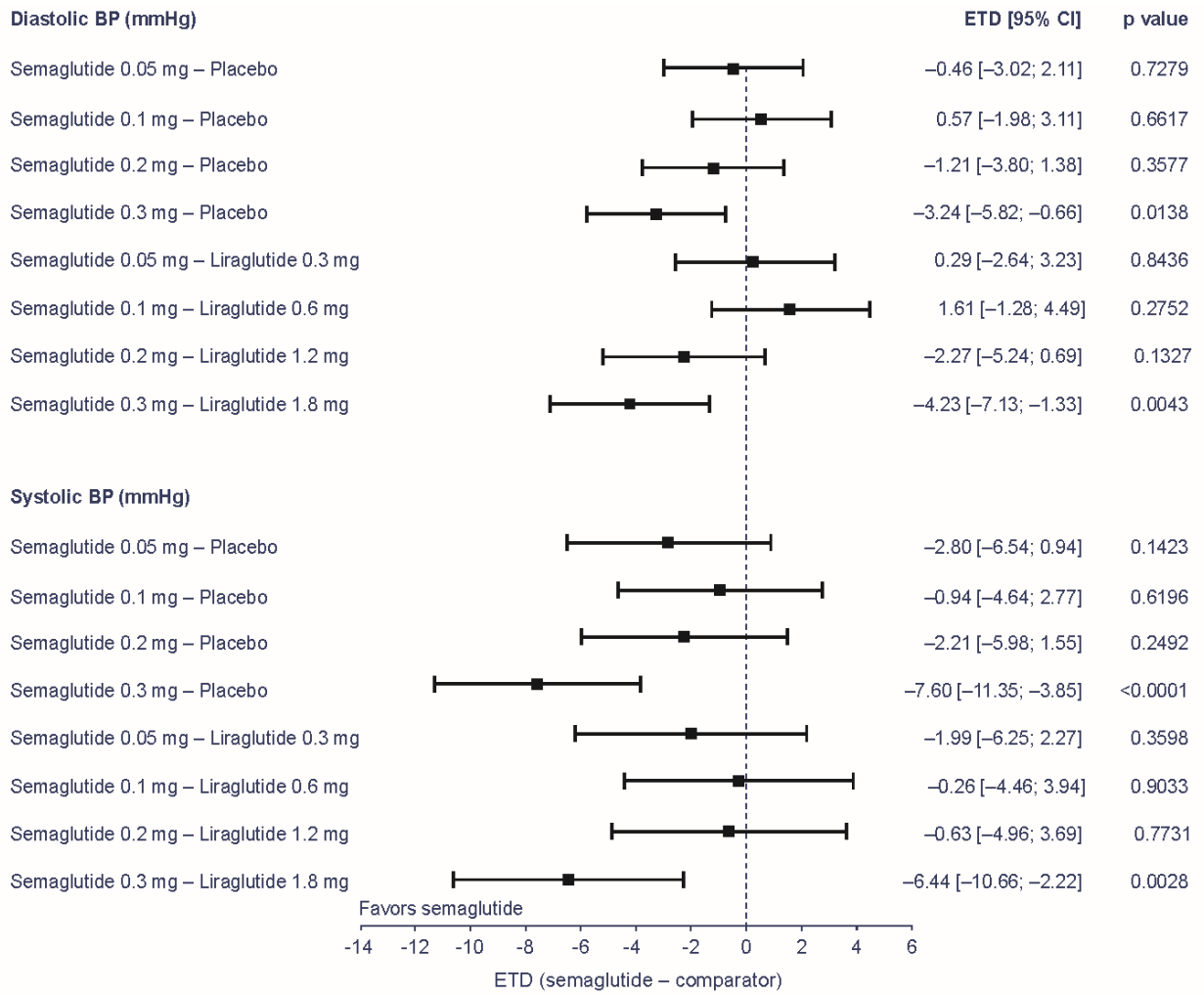
A



B

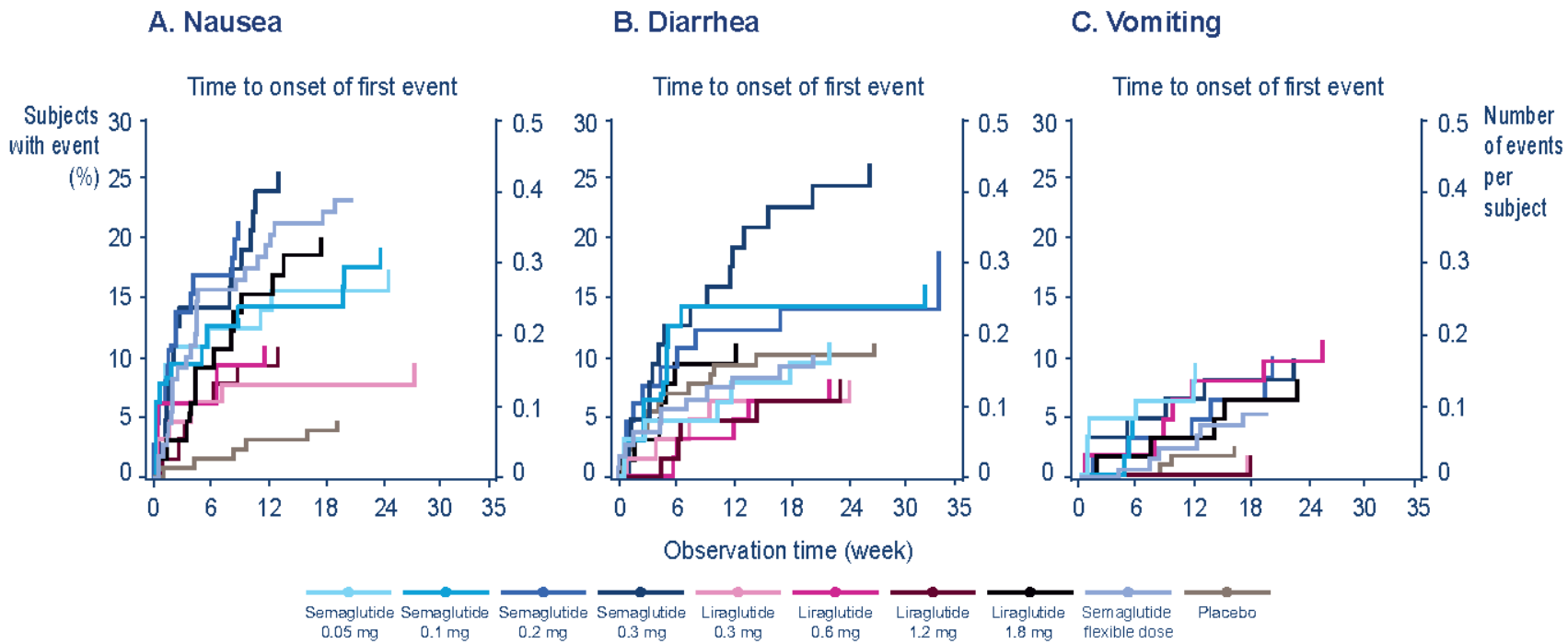


C



ETD: estimated treatment difference. Parts A and B are observed ‘on-treatment until rescue medication’ data. Mean estimates (+/- error bar) are from an MMRM analysis with treatment, region and stratum as fixed factors and baseline value as covariate, all nested within visit, and are adjusted according to observed baseline distribution. Error bars are ±1*SEM. Dotted line is the total average value at baseline. Part C is a summary of estimated treatment differences and associated confidence intervals from statistical analyses of the parameters at week 26 using the ‘on-treatment until rescue medication’ data. The mixed model for repeated measurements used for analysis include treatment, region, stratum and baseline value, all nested within visit.

Supplementary Figure S5. Kaplan–Meier estimator for time to onset of first event of nausea (A), diarrhea (B) and vomiting (C)

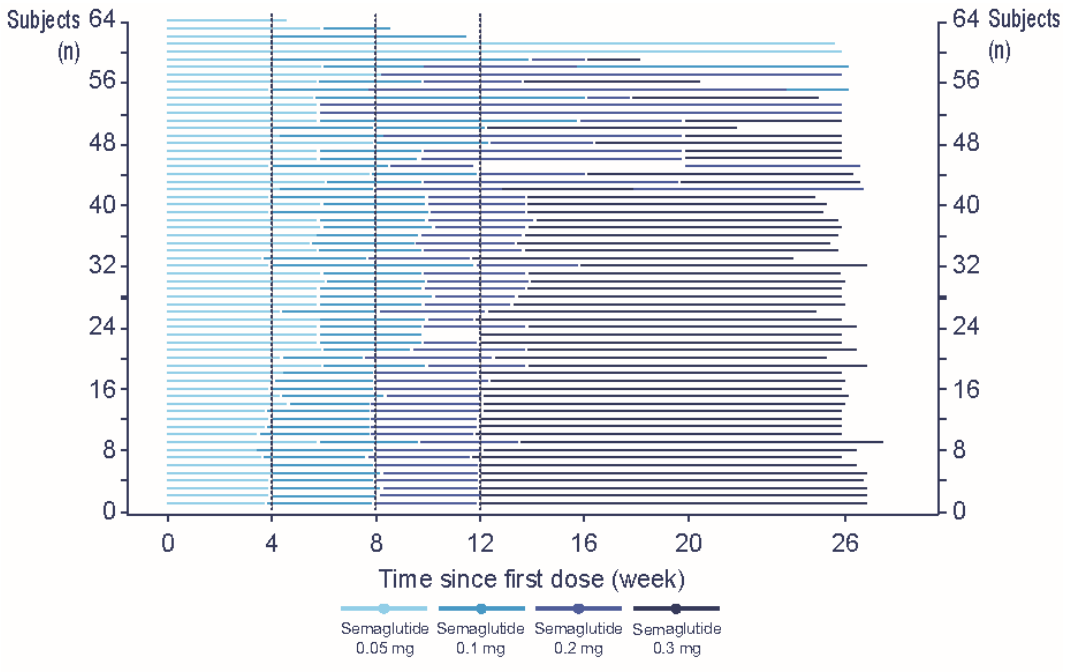


A patient is considered to have an event on-treatment if the event has onset on or after the day of first randomized dose and not after the follow-up visit scheduled 7 weeks after endoftreatment. Events are shown up until the scheduled follow-up visit. The 5% is calculated based on the total number of patients in the safety analysis set

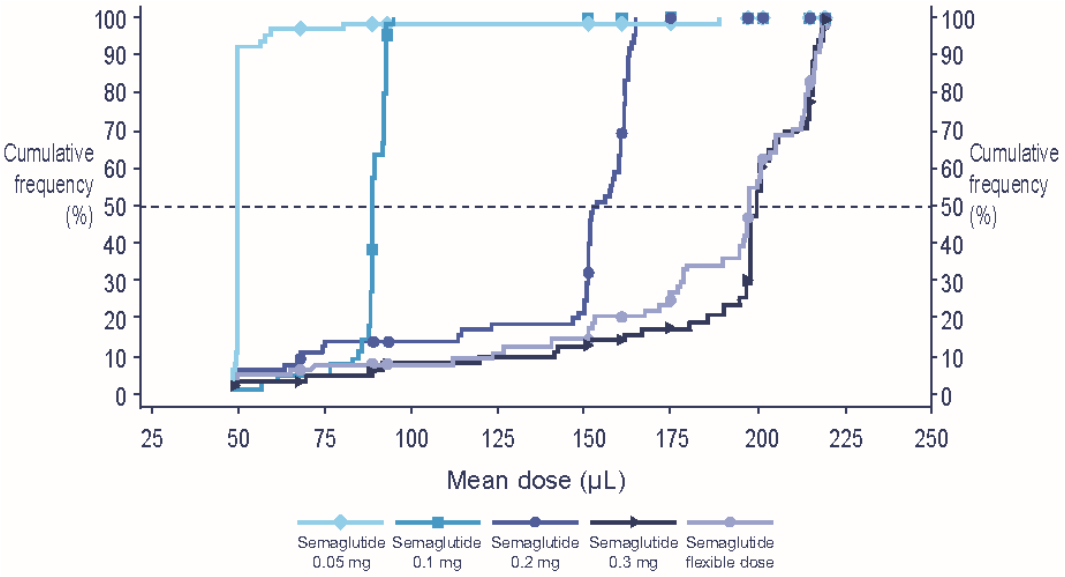
SUPPLEMENTARY DATA

Supplementary Figure S6. Dose history over time (A) and mean dose after 26 weeks of treatment – cumulative distribution function (B) in the semaglutide flexible-dosing arm

A



B

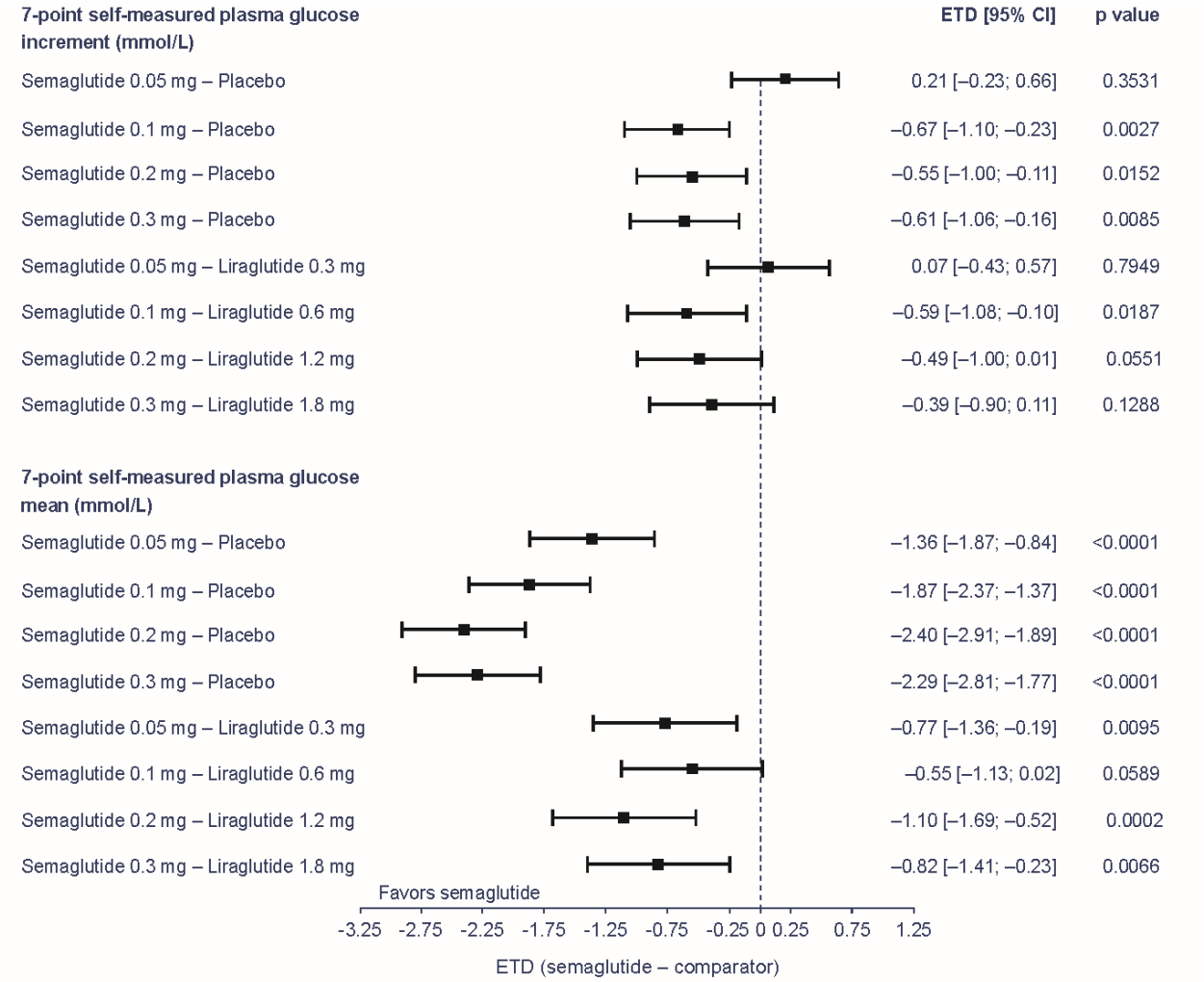


Dashed vertical lines in Part A indicate week of planned doseescalation in fixed-dose arms. In Part B, mean dose is calculated as the mean of each day's dose under the assumption that doses remain constant between consecutive recordings of (missed) doses. Missed doses are sat to 0 (zero) dose and observation stops at the date of last dose.

SUPPLEMENTARY DATA

Analysis of ‘on-treatment until rescue medication’ data. Mean estimates are from an mixed model for repeated measurements analysis with treatment, region and stratum as fixed factors and baseline value as covariate, all nested within visit, and are adjusted according to baseline distribution. Solid line is the total mean value at baseline.

Supplementary Figure S7. Estimated treatment differences for change in mean 7-point self-measured blood glucose (mmol/L) profileat week 26



CI: confidence interval,ETD: estimated treatment difference. Summary of ETDs and associated CIs from statistical analyses of the parameters at week 26 using the ‘on-treatment until rescue medication’ data. The mixed model for repeated measurements used for analysis includes treatment, region, stratum and baseline value, all nested within visit.

PART D. References

1. American Diabetes Association: Standards of Medical Care in Diabetes-2017. Diabetes Care 2017;40:S1-S135

2. Handelsman Y, Bloomgarden ZT, Grunberger G, et al: American Association of Clinical Endocrinologists and American College of Endocrinology - clinical practice guidelines for developing a diabetes mellitus comprehensive care plan - 2015. Endocrine Practice 2015;21 Suppl 1:1-87

3. Seaquist ER, Anderson J, Childs B, et al: Hypoglycemia and diabetes: a report of a workgroup of the American Diabetes Association and the Endocrine Society. Diabetes Care 2013;36:1384-1395