Electronic supplementary material (ESM)

ESM – Methods

Exclusion criteria

Participants were excluded if they had type 1 diabetes; had been exposed to semaglutide or another glucagon-like peptide-1 receptor agonist (including combination products), or to oral antihyperglycaemic medication other than metformin in the 3 months before screening; had received treatment with insulin during the 12 months before screening; had >1 episode of ketoacidosis or hyperosmolar state requiring hospitalisation, ≥1 episode of severe hypoglycaemia (requiring the assistance of another person) or any history of hypoglycaemia unawareness or poor recognition within the 6 months prior to screening; had resting heart rate ≥100 beats per minute (bpm), blood pressure ≥160/95 mmHg, renal artery stenosis or evidence of labile blood pressure (including symptomatic hypotension or a history of orthostatic hypotension, fainting spells or blackouts) at screening; had a marked prolongation of QT/QTc (Fridericia) interval >450 ms at screening or randomisation, or any other abnormal or clinically significant ECG finding at screening (e.g. Type II Mobitz II or third-degree atrioventricular [AV] block); had a heart rhythm disturbance (e.g. bradycardia with baseline heart rate <50 bpm in the absence of medications to lower the heart rate, supraventricular tachycardia or tachyarrhythmia) considered by the investigator as indicative of relevant cardiac disease, or with abnormalities that may interfere with the interpretation of ECG intervals at screening, or had a family history of long QT-syndrome, use of prescription or over-the-counter medications known to significantly prolong the QT or QTc interval at screening; had myocardial infarction, unstable angina, clinically relevant coronary artery disease, coronary artery bypass graft, urgent percutaneous coronary intervention, transient ischaemic attack, cerebrovascular accident (stroke) or decompensated heart failure within the last 6 months before screening; had a history of or were currently diagnosed with congestive

heart failure (New York Heart Association class III–IV), or had a history of symptomatic ventricular tachycardia, history of type 2 second degree AV block or third-degree AV block; had a bodyweight change of ± 5% or more in the past 3 months or on anti-obesity therapy at any time during the 6 months before screening; ongoing oral pharmacotherapy treatments or within 3 months before screening (e.g. antidepressants, central nervous system stimulants, antipsychotics, anticonvulsants [except gabapentin], diuretics); had major surgery within 12 weeks before randomisation or planned within 6 months after screening; had prior surgery of the gastrointestinal tract that could interfere with bodyweight (except appendectomy, simple hernia repair and simple cholecystectomy); had known significant autonomic neuropathy; had acute proliferative diabetic retinopathy or expected medical intervention/surgery during the trial; had a history of chronic or acute pancreatitis or elevation of serum lipase/amylase >2 × upper limit of normal (ULN) or serum triglyceride levels >500 mg/dl at screening (doses for lipid-lowering medication must be stable for 3 months before screening); had an eGFR of <45 ml/min/1.73 m^2, or had eGFR or a serum creatinine level that would contraindicate the use of metformin; had calcitonin ≥20 pg/ml at screening; had symptoms of liver disease, chronic or acute hepatitis or serum levels of alanine aminotransferase or aspartate aminotransferase >2.5 × ULN at screening; had a personal or familial history of medullary thyroid carcinoma or history of multiple endocrine neoplasia syndrome type 2, acromegaly, morbus Cushing, or pheochromocytoma, manifest hypo- or hyperthyroidism at screening; received continuous oral pharmacotherapy to treat any clinical condition during the trial (except metformin, antihypertensives, hormone replacement therapy, lipid-lowering, proton pump inhibitors, H2 blockers for gastroesophageal reflux disease, analgesics, sleep medications, antihistamines, selective alpha receptor blocker for benign prostatic hyperplasia); used drugs with narrow therapeutic index; had a disease of the central nervous system, or other relevant neurological or psychiatric disorder; had any suicidal behaviour in

the prior 2 years or any suicidal ideation of type 4 or 5 in the Columbia-Suicide Severity Rating Scale (C-SSRS) in the 3 months before screening; had a chronic or relevant acute infection; had a history of atopy or clinically significant multiple or severe drug allergies, or intolerance to topical corticosteroids, or severe post-treatment hypersensitivity reactions; had a history or organ transplant (other than corneal transplants); abused alcohol, drugs or liquorice within the 3 months before screening; had donated ≥450 ml of blood within 3 months before screening; had a blood transfusion or severe blood loss within 3 months before screening, or had known haemoglobinopathy, haemolytic anaemia, sickle cell anaemia, or a haemoglobin value <11 or <10 g/dl (for males and females, respectively); had confirmed active infection with SARS-CoV-2 within the 3 months before screening; or were women who were pregnant, nursing or planned to become pregnant during the trial.

Randomisation and blinding

Randomisation lists were generated using interactive response technology (IRT), which involved a pseudorandom number generator so that the resulting treatment was reproducible and nonpredictable. Patients, investigators and everyone involved in the trial conduct or analysis remained blinded to the randomised treatment assignments until after database lock. Emergency unblinding was available to the investigator via IRT and was to be used only when identity of the study drug had to be known by the investigator to provide appropriate medical treatment or ensure safety of the study participants.

Endpoints

Further efficacy endpoints included the change from baseline in: the control of eating behaviour and susceptibility to hunger as measured by the change in Three-Factor Eating Questionnaire (TFEQ-R18V2), the perception of hunger by the hunger visual analogue scale

(VAS), the Patient's Global Impression of Severity (PGI-S) for difficulty to control eating behaviours and the 7-point profile of self-monitoring of blood glucose (SMBG).

Procedures

At each study visit, participants were advised to adhere to the specific recommended diet and exercise plan provided to them during diet and exercise counselling throughout the study.

Survodutide was made available in vials (2 mg/ml, 1 ml fill volume per vial) for dose escalation in Weeks 1–6 and in pre-filled syringes (various concentrations, 0.5 ml fill volume) for maintenance dose in Weeks 7–16. The placebo solution (isotonic sodium chloride) was filled into identical vials or pre-filled syringes. In accordance with the doses recommended by the prescribing information [1], up to 1.0 mg of semaglutide was administered for dose escalation in an open-label fashion via a single-patient-use pen that delivered 0.25 or 0.5 mg per injection in Weeks 1–9, and by a single-patient-use pen that delivered 1.0 mg per injection for maintenance dose in Weeks 10–16. Survodutide or placebo were administered by subcutaneous injection in the abdomen. During the maintenance period, injections were administered at the study centre or self-administered by patients. Semaglutide was administered subcutaneously in the abdomen, thigh or upper arm. Patients who discontinued the study during the treatment period were encouraged to complete an end of treatment visit, and a follow-up visit was scheduled for 5 weeks after the last dose of study drug.

Safety and tolerability were assessed based on the general occurrence of treatment-emergent adverse events, safety laboratory parameters, physical examination, vital sign measurements and 12-lead ECG. ECG services were externally provided and recordings were evaluated centrally.

Statistical analyses

The study aimed to demonstrate proof of clinical concept (PoCC) regarding a non-flat dose–response curve for survodutide, and definition of a suitable dose-escalation scheme and dose range for survodutide in terms of efficacy, safety and tolerability. A multiple comparison procedure with modelling (MCPMod) approach was used [2], allowing for simultaneous evaluation of different potential dose–response patterns, while protecting against the overall probability of a type I error (one-sided $\alpha = 2.5\%$). For the contrast test (one-sided $\alpha = 2.5\%$), a sample size of 45 evaluable patients per dose group (DG) was needed to reach 94% average power for an assumed effect size of 0.6%. Calculations for the PoCC step were performed using the Dose Finding R-package with 1000 repetitions [3]. To account for the repeated nature of the data and covariates in the model, mixed model for repeated measures (MMRM) analysis was carried out and covariate-adjusted, least square means estimates of average response for each DG and the covariance matrix were extracted from the fit and used for MCPMod analysis. For the twice weekly dosing schemes, total dose per week was considered for the MCPMod analysis with a restricted maximum likelihood based approach using MMRM. Overall, the analyses included the fixed, categorical effects of treatment at each visit and the fixed continuous effects of baseline at each visit, with visit treated as the repeated measure and an unstructured covariance structure used to model within-subject measurements. The relative bodyweight change from baseline was evaluated using an MMRM model and MCP-Mod analysis in the same way as for the primary endpoint, and descriptive statistics. Absolute bodyweight change from baseline and change from baseline in waist circumference were assessed using an MMRM analysis as for the primary endpoint analysis, and descriptive statistics. The proportion of participants achieving ≥5% and ≥10% bodyweight reduction from baseline were analysed using a logistic regression and descriptive statistics. Patient reported outcomes (TFEQ-R18V2, VAS and PGI-S) were analysed by

MMRM, as for the primary endpoint, and descriptive statistics. All safety endpoints, NASH-related scores and SMBG were analysed descriptively.

ESM – Results

Patient-reported outcome questionnaires

No clear treatment effect was seen for the mean ± SD change from baseline in TFEQ-R18V2 parameters, with only minor changes observed in adjusted mean MMRM estimates for absolute change from baseline in cognitive restraint, emotional eating and uncontrolled eating (ESM Table 2). The changes observed in survodutide- and semaglutide-treated groups were not significant compared with placebo, except for the mean ± SE change from baseline in emotional eating score at Week 17 in DG5 (−6.98% ± 3.15; p=0.0274). The proportion of patients recording 'Not at all' for difficulty to control eating behaviours (via PGI-S) tended to increase in all DGs at Week 17 compared with baseline, including placebo (ESM Table 3). Hunger VAS score tended to decrease with survodutide treatment and semaglutide, although these changes were mostly minor, and scores were highly variable with marked discrepancies between the means and medians in all treatment groups (ESM Table 2). Changes from baseline were observed in DGs 4 and 6 at Week 17, with a median change of −8.0 observed in both groups.

References

1. Semaglutide (Ozempic) Prescribing Information. Novo Nordisk A/S. 2021.
2. Pinheiro J, Bornkamp B, Bretz F (2006) Design and analysis of dose-finding studies combining multiple comparisons and modeling procedures. J Biopharm Stat 16(5):639-656. https://doi.org/10.1080/10543400600860428
3. Bornkamp B, Pinheiro J, Bretz F, Sandig L (2023) Planning and analyzing dose finding experiments. Available from https://cran.r-project.org/web/packages/DoseFinding/DoseFinding.pdf. Accessed 26 January 2023

Tables

ESM Table 1 Absolute change from baseline in TFEQ-R18V2 parameters and Hunger VAS score at end of treatment

	Survodutide 0.3 mg qw (*n*=50)	Survodutide 0.9 mg qw (*n*=50)	Survodutide 1.8 mg qw (*n*=52)	Survodutide 2.7 mg qw (*n*=50)	Survodutide 1.2 mg biw (*n*=51)	Survodutide 1.8 mg biw (*n*=49)	Semaglutide 1.0 mg qw (*n*=50)	Placebo (*n*=59)
TFEQ-R18V2, mean ± SD								
Cognitive restraint score	1.06 ± 25.24	2.13 ± 28.90	−1.71 ± 24.78	5.39 ± 30.19	0.99 ± 21.95	4.20 ± 25.84	3.14 ± 23.50	−2.27 ± 30.60
Emotional eating score	−6.75 ± 17.76	−3.07 ± 18.49	−8.26 ± 13.95	−12.12 ± 16.87	−14.20 ± 19.16	−7.21 ± 22.29	−9.57 ± 18.96	−5.67 ± 24.68
Uncontrolled eating score	−9.70 ± 15.80	−8.67 ± 18.67	−11.11 ± 14.22	−11.0 ± 15.31	−11.77 ± 13.13	−10.19 ± 17.49	−9.20 ± 14.36	−8.24 ± 21.40
Hunger VAS, mean ± SD	0.4 ± 19.9	−2.7 ± 26.3	−8.9 ± 31.1	−5.1 ± 30.5	−8.4 ± 25.3	−9.4 ± 32.4	−3.4 ± 24.6	−1.5 ± 29.5
Comparison vs placebo								
TFEQ-R18V2, adjusted mean ± SE								
Cognitive restraint score	−0.71 ± 4.89	0.29 ± 4.82	−0.10 ± 4.95	2.51 ± 5.18	1.83 ± 4.84	−1.20 ± 5.07	1.59 ± 4.83	–
Emotional eating score	−3.43 ± 3.19	5.21 ± 3.14	−4.32 ± 3.22	−6.54 ± 3.35	−6.98 ± 3.15*	−2.04 ± 3.28	−3.05 ± 3.14	–
Uncontrolled eating score	−1.72 ± 2.84	1.78 ± 2.80	−1.89 ± 2.88	−2.44 ± 3.00	−1.35 ± 2.81	−1.77 ± 2.95	−1.23 ± 2.80	–

biw, twice weekly; qw, once weekly; VAS, visual analogue scale.

*p=0.0274

ESM Table 2 Change from baseline in PGI-S for difficulty to control eating behaviours

		PGI-S				
		Not at all	Mild	Moderate	Severe	Very severe
Survodutide 0.3 mg qw (*n*=50)	Baseline	19 (38.0)	9 (18.0)	18 (36.0)	4 (8.0)	0
	EoT	19 (45.2)	11 (26.2)	10 (23.8)	2 (4.8)	0
Survodutide 0.9 mg qw (*n*=50)	Baseline	12 (24.0)	16 (32.0)	20 (40.0)	2 (4.0)	0
	EoT	20 (42.6)	12 (25.5)	15 (31.9)	0	0
Survodutide 1.8 mg qw (*n*=52)	Baseline	14 (26.9)	13 (25.0)	22 (42.3)	2 (3.8)	1 (1.9)
	EoT	21 (53.58)	9 (23.1)	9 (23.1)	0	0
Survodutide 2.7 mg qw (*n*=50)	Baseline	20 (40.0)	15 (30.0)	14 (28.0)	1 (2.0)	0
	EoT	20 (60.6)	9 (27.3)	3 (9.1)	1 (3.0)	0
Survodutide 1.2 mg biw (*n*=51)	Baseline	10 (19.6)	14 (27.5)	25 (49.0)	2 (3.9)	0
	EoT	22 (48.9)	15 (33.3)	8 (17.8)	0	0
Survodutide 1.8 mg biw (*n*=49)	Baseline	12 (24.5)	19 (38.8)	15 (30.6)	3 (6.1)	0
	EoT	19 (51.4)	15 (40.5)	3 (8.1)	0	0
Semaglutide 1.0 mg qw (*n*=50)	Baseline	20 (40.0)	10 (20.0)	17 (34.0)	3 (6.0)	0
	EoT	29 (63.0)	9 (19.6)	7 (15.2)	1 (2.2)	0
Placebo (*n*=59)	Baseline	17 (28.8)	11 (18.6)	29 (49.2)	2 (3.4)	0
	EoT	27 (55.1)	7 (14.3)	13 (26.5)	2 (4.1)	0

Data are presented as the frequency of patients reporting each category; *n* (%).

biw, twice weekly; EoT, end of treatment; PGI-S, Patient's Global Impression of Severity; qw, once weekly.

ESM Table 3 Summary of serious AEs

	Survodutide 0.3 mg qw (*n*=50)	Survodutide 0.9 mg qw (*n*=50)	Survodutide 1.8 mg qw (*n*=52)	Survodutide 2.7 mg qw (*n*=50)	Survodutide 1.2 mg biw (*n*=51)	Survodutide 1.8 mg biw (*n*=49)	Semaglutide 1.0 mg qw (*n*=50)	Placebo (*n*=59)	Total survodutide (*n*=302)
Total patients with serious AEs	1 (2.0)	4 (8.0)	3 (5.8)	2 (4.0)	1 (2.0)	0	0	3 (5.1)	11 (3.6)
Abdominal pain	1 (2.0)[a]	0	0	0	0	0	0	0	1 (0.3)
Diarrhoea	0	0	0	1 (2.0)[a]	0	0	0	0	1 (0.3)
Irritable bowel syndrome	0	1 (2.0)[b]	0	0	0	0	0	0	1 (0.3)
Mouth ulceration	0	1 (2.0)[a,b]	0	0	0	0	0	0	1 (0.3)
Vomiting	1 (2.0)[a]	0	0	0	0	0	0	0	1 (0.3)
Inguinal hernia	0	0	0	0	0	0	0	1 (1.7)	0
Cellulitis	0	2 (4.0)	0	0	0	0	0	0	2 (0.7)
Viraemia	0	0	0	1 (2.0)	0	0	0	0	1 (0.3)
IIIrd nerve paralysis	0	0	1 (1.9)	0	0	0	0	0	1 (0.3)
Paraparesis	0	0	1 (1.9)[b]	0	0	0	0	0	1 (0.3)
Autoimmune disorder	0	1 (2.0)[a,b]	0	0	0	0	0	0	1 (0.3)

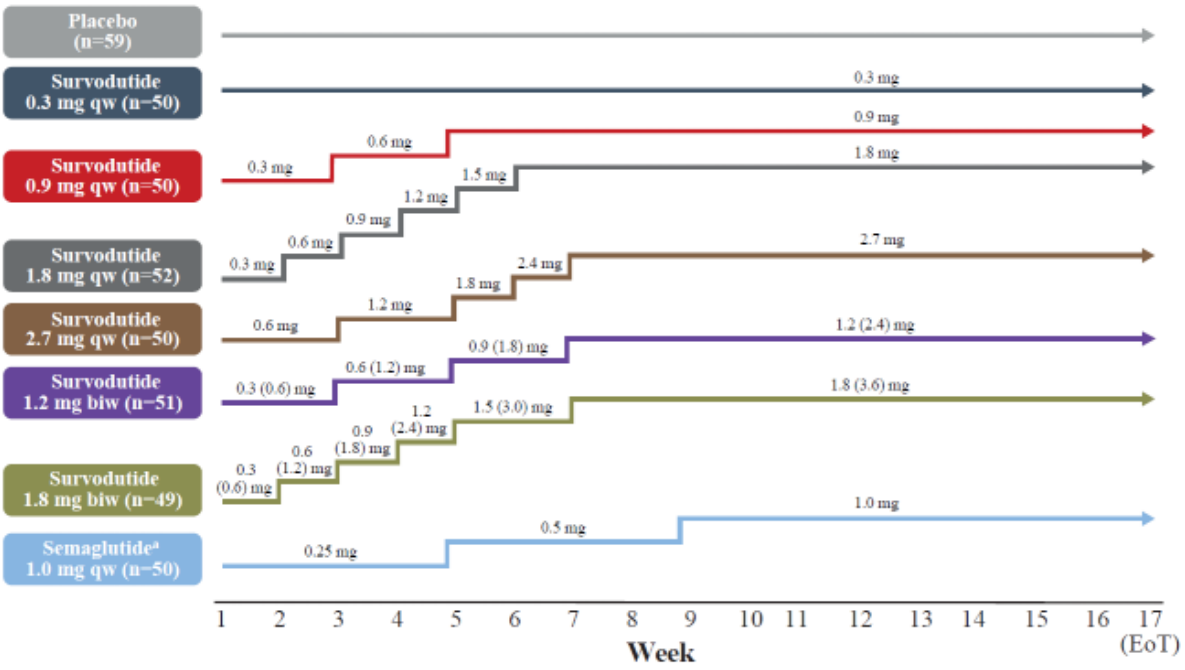
Dehydration	0	0	1 (1.9)[a]	0	0	0	0	0	1 (0.3)
Arthralgia	0	0	0	0	1 (2.0)	0	0	0	1 (0.3)
Back pain	0	0	0	0	1 (2.0)	0	0	0	1 (0.3)
Pharyngeal ulceration	0	1 (2.0)[a,b]	0	0	0	0	0	0	1 (0.3)
Cholecystitis	0	0	0	0	0	0	0	1 (1.7)	0
Hypotension	0	0	0	0	0	0	0	1 (1.7)	0

Data are presented as *n* (%).

[a]Assessed by investigator to be drug-related. [b]AE did not resolve until the completion of the trial.

AE, adverse event; biw, twice weekly; qw, once weekly.

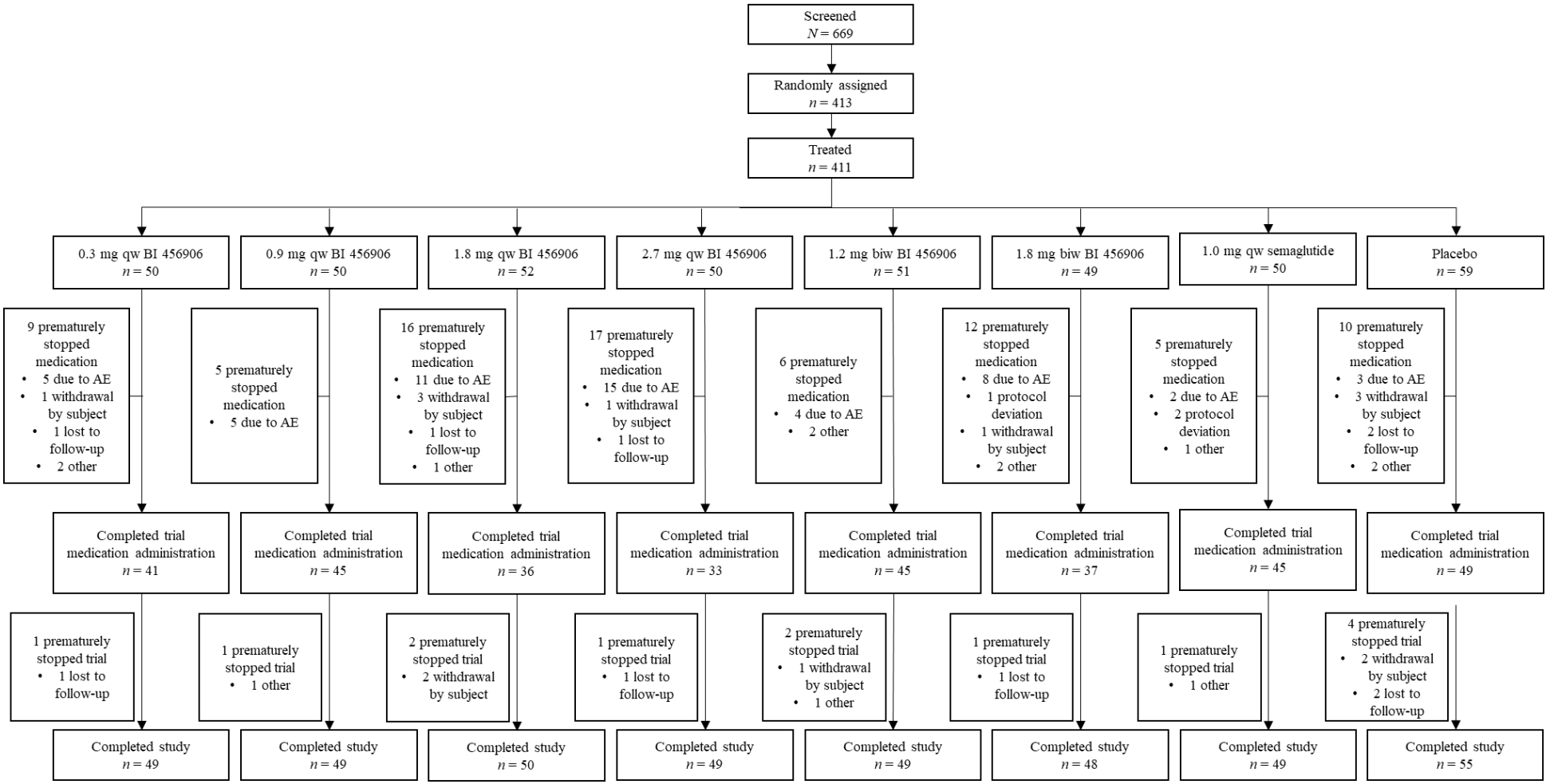
Figures



ESM Fig. 1 Dose-escalation schemes.

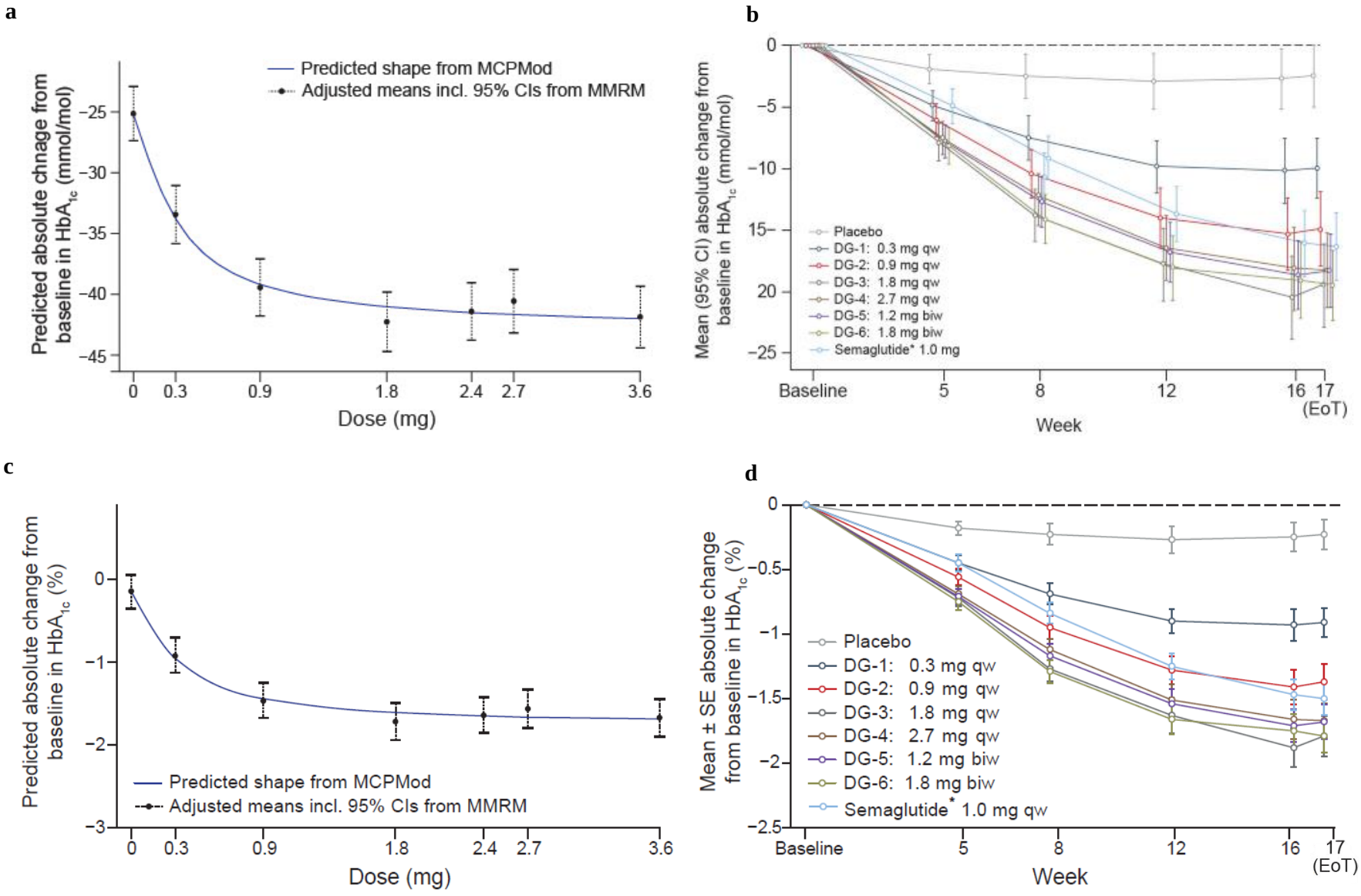
[a]Semaglutide arm is open label. Numbers in brackets signify total weekly dose.

biw, twice weekly; EoT, end of treatment; qw, once weekly.



ESM Fig. 2 Subject disposition flow diagram.

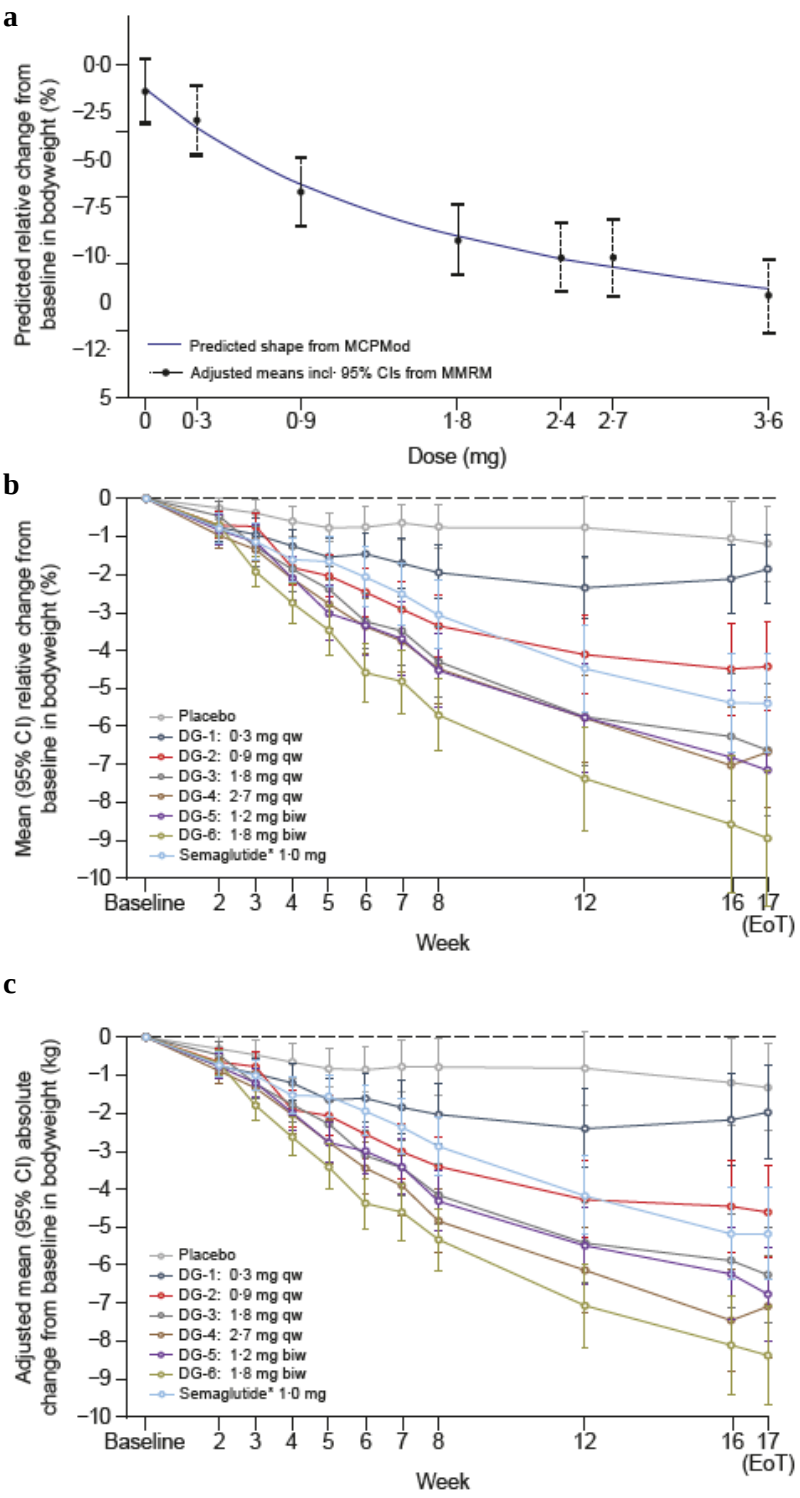
AE, adverse event; biw, twice weekly; qw, once weekly.


a
Predicted shape from MCPMod
Adjusted means incl. 95% CIs from MMRM
Predicted absolute chnage from baseline in HbA1c (mmol/mol)
−25
−30
−35
−40
−45
0
0.3
0.9
1.8
2.4
2.7
3.6
Dose (mg)
b
Mean (95% CI) absolute change from baseline in HbA1c (mmol/mol)
0
−5
−10
15−
20
−25
Placebo
DG-1: 0.3 mg qw
DG-2: 0.9 mg qw
DG-3: 1.8 mg qw
DG-4: 2.7 mg qw
DG-5: 1.2 mg biw
DG-6: 1.8 mg biw
Semaglutide* 1.0 mg
Baseline
5
8
12
16
17
(EoT)
Week
c
Predicted absolute change from baseline in HbA1c (%)
0
−1
−2
−3
Predicted shape from MCPMod
Adjusted means incl. 95% CIs from MMRM
0
0.3
0.9
1.8
2.4
2.7
3.6
Dose (mg)
d
Mean ± SE absolute change from baseline in HbA1c (%)
0
−0.5
−1
−1.5
−2
−2.5
Placebo
DG-1: 0.3 mg qw
DG-2: 0.9 mg qw
DG-3: 1.8 mg qw
DG-4: 2.7 mg qw
DG-5: 1.2 mg biw
DG-6: 1.8 mg biw
Semaglutide* 1.0 mg qw
Baseline
5
8
12
16
17
(EoT)
Week

ESM Fig. 3 Change from baseline in HbA_{1c}. (**a**) Predicted dose response of the change from baseline in HbA_{1c} (mmol/mol) after 16 weeks' treatment with survodutide, MCPMod averaging model. (**b**) Descriptive statistics for the absolute change from baseline in HbA_{1c} (mmol/mol) over time. (**c**) Predicted dose response of the change from baseline in HbA_{1c} (%) after 16 weeks' treatment with survodutide, MCPMod averaging model. (**d**) Descriptive statistics for the absolute change from baseline in HbA_{1c} (%) over time.

[a]Semaglutide arm is open label.

biw, twice weekly; DG, dose group; EoT, end of treatment; MCPMod, multiple comparison procedure with modelling techniques; MMRM, mixed model repeated measures; qw, once weekly.

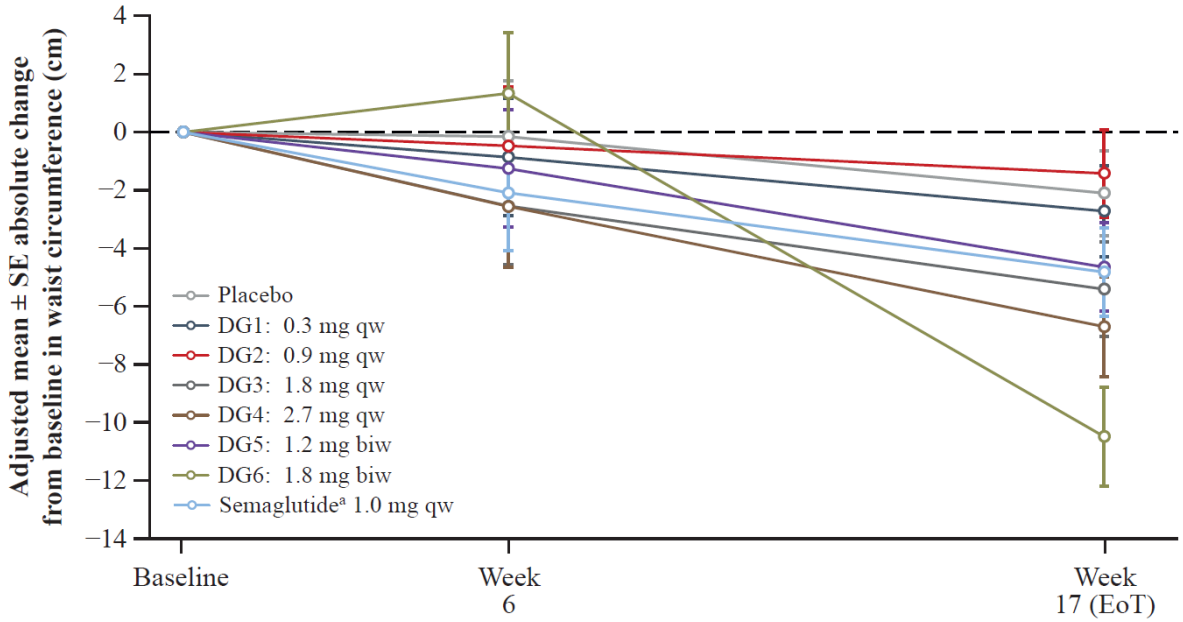


ESM Fig. 4 Change from baseline in bodyweight. (**a**) Predicted dose response of the relative change from baseline in bodyweight (%) after 16 weeks of treatment with survodutide, MCPMod averaging model. (**b**) Descriptive statistics for the relative change from baseline in

bodyweight (%) over time. (**c**) MMRM estimates for the absolute change from baseline in bodyweight (kg) over time.

[a]Semaglutide arm is open label.

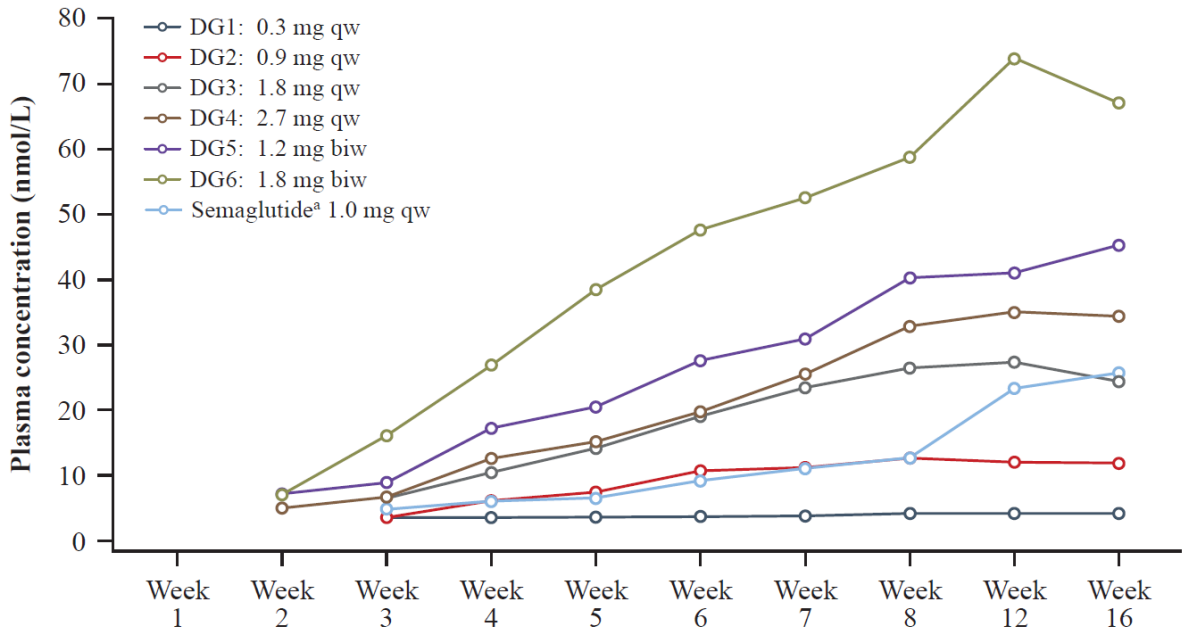
biw, twice weekly; DG, dose group; EoT, end of treatment; MCPMod, multiple comparison procedure with modelling techniques; MMRM, mixed model repeated measures; qw, once weekly.



ESM Fig. 5 Absolute change in waist circumference from baseline.

[a]Semaglutide arm is open label.

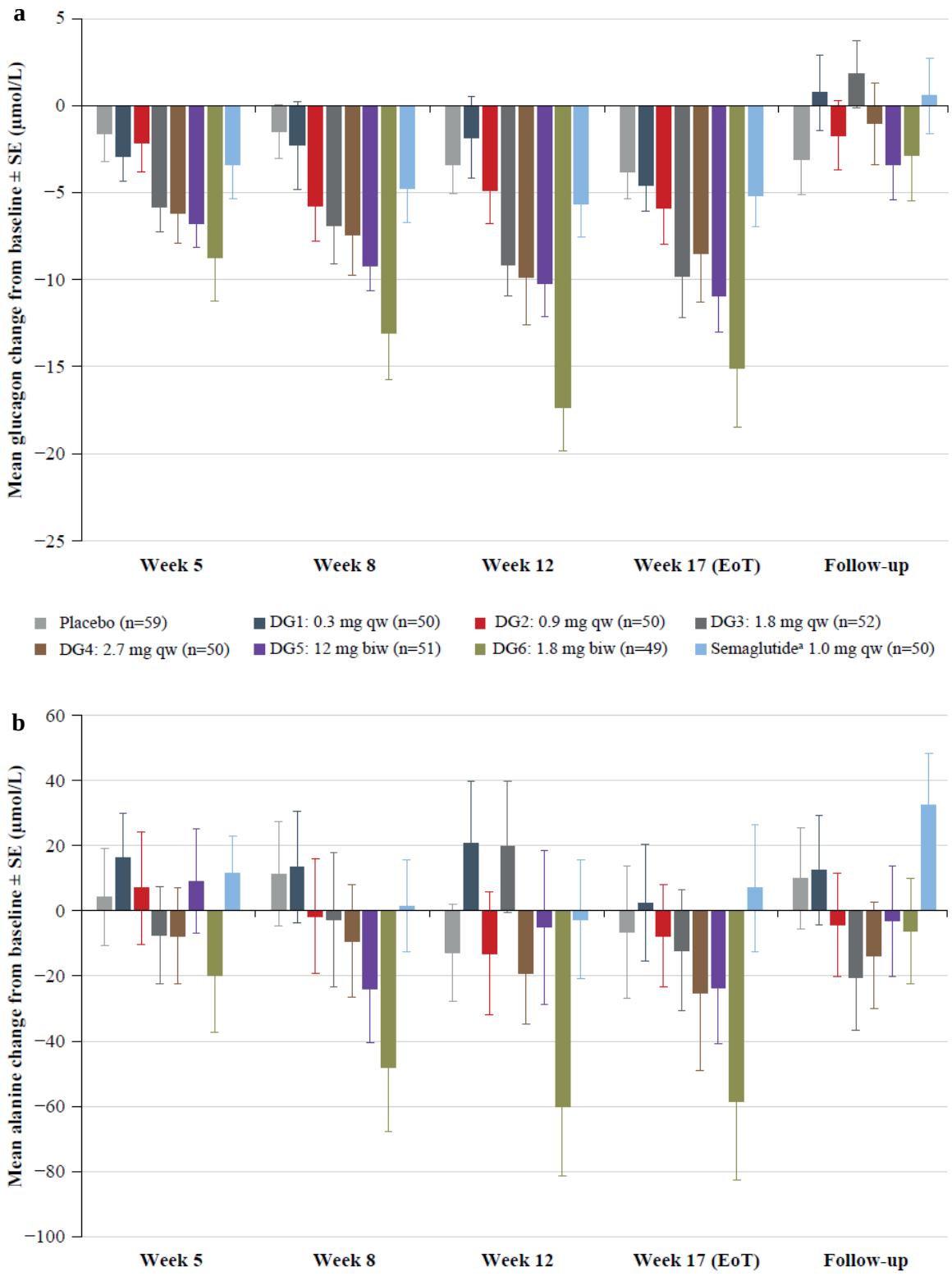
biw, twice weekly; DG, dose group; EoT, end of treatment; qw, once weekly.



ESM Fig. 6 Geometric mean plasma concentration–time profiles of survodutide and semaglutide.

[a]Semaglutide arm is open label.

biw, twice weekly; DG, dose group; qw, once weekly.



ESM Fig. 7 Mean absolute change from baseline in (**a**) plasma glucagon and (**b**) alanine.

[a]Semaglutide arm is open label.

biw, twice weekly; DG, dose group; EoT, end of treatment; qw, once weekly.

List of trial sites and investigators

Centre number	Investigator name and role	Address
Australia		
AUS1	Principal Investigator: Caterson Prof (BSc (Med)), Ian Sub-Investigator(s): Hocking Dr., Samantha Lau Dr., Namson Markovic, Tania	Boden Institute of Obesity, Nutrition, Exercise and Eating Disorders Charles Perkins Center D 17 John Hopkins Drive Camperdown New South Wales 2006 Australia
AUS2	Principal Investigator(s): Morbey Dr. (MBChB), Claire Sub Investigator(s): Diez Alvarez Dr., Sergio	Hunter Diabetes Centre Level 1, 41 Llewellyn St Merewether New South Wales 2291 Australia
AUS3	Principal Investigator(s): Cohen Dr. (MD), Neale Sub Investigator(s): Sharifi Dr., Amin	Baker Heart and Diabetes Institute 99 Commercial Rd Melbourne Victoria 3004 Australia
AUS5	Principal Investigator(s): Shirazi Dr. (MD), Mitra Sub Investigator(s): Montarello Dr., Nicholas Joseph	Royal Adelaide Hospital Clinical Trial Unit Level 3 1 Port Road Adelaide South Australia 5000 Australia
AUS8	Principal Investigator(s): Gilfillan Dr. (MBBS), Chris Sub Investigator(s): Simpson Dr., Richard McCarthy Dr., Josephine Yee Dr., Ming Li Gordon, Debra	Monash University Monash University Eastern Clinical Research Unit Level 2 5 Arnold Street Box Hill Victoria 3128 Australia
AUS7	Principal Investigator(s): Ekinci Dr. (MBBS), Elif Sub-Investigator(s): Nash Dr., Ben Neoh Dr., Sandra Seah Dr., Jas-mine Ali Dr., Aleena Price Dr., Sarah	Austin Health Metabolic Disorders Service Heidelberg Repatriation Hospital Level 1 Centaur Building, 198 Banksia St Heidelberg Victoria 3081 Australia
Austria		
AUT1	Principal Investigator(s): Kautzky-Willer Prof. Dr. (MD), Alexandra Sub-Investigator(s): Harreiter Dr., Juergen Leutner Dr., Michael	AKH - Medical University of Vienna Universitätsklinik für Innere Medizin III Abteilung für Endokrinologie und Stoffwechsel Waehringer Guertel 18-20 Vienna 1090 Austria
AUT6	Principal Investigator(s): Ludvik Dr. (MD), Bernhard	KH Rudolfstiftung, 1. Med. Abt., Wien Krankenanstalt Rudolfstiftung inkl. Semmelweis Frauenklinik 1.

	Sub-Investigator(s): Brix Dr., Johanna Maria Feder Dr., Astrid Hoellerl Dr., Florian Krzizek Dr., Eva-Christina Luger Dr., Philip Malek Dr., Sara Stoeckl, Alexander Gericke Dr., Greta Schrangl Dr., Christoph	Medizinische Abteilung 1. Medizinische Abteilung Juchgasse 25 Wien 1030 Austria
Canada		
CAN1	Principal Investigator(s): Akhras Dr. (MD), Ronald Sub-Investigator(s): Daginawala Dr., Khatija	Centre Medical Acadie Suite 101A 9825 boul de l'Acadie Montreal Quebec H4N 2W2 Canada
CAN3	Principal Investigator(s): Heaton Dr. (MD), Kenneth	Devonshire Clinical Research Inc. Devonshire Clinical Research Inc. Suite 301 423 Devonshire Avenue Woodstock Ontario N4S 5P5 Canada
CAN4	Principal Investigator(s): Garg Dr. (MD), Naveen Sub-Investigator(s): Breger Dr., Laurie Claveau Dr., Jessica	Manna Research (Montreal) Suite 145 175 Stillview Avenue Pointe-Claire Quebec H9R 4S3 Canada
CAN5	Principal Investigator(s): Wharton Dr. (MD), Sean Sub-Investigator(s): Greenspoon Dr., Allen Greenspoon Dr., Todd	The Wharton Medical Clinic Clinical Trials Inc. M14 414 Victoria Avenue North Hamilton Ontario L8L 5G8 Canada
CAN6	Principal Investigator(s): Goldenberg Dr. (MD), Ronald Sub-Investigator(s): D'Sylva Dr., Christopher Schlosser Dr., Robert Sionit Dr., David	LMC Clinical Research Inc. (Thornhill) Unit 5-10 1600 Steeles Avenue West Concord Ontario L4K 4M2 Canada
CAN7	Principal Investigator(s): Bajaj Dr.(MD), Harpreet Sub-Investigator(s): Aslam Dr., Nadeem Bahl Dr., Nupur Chandra Dr., Prakash Thobani Dr., Sanya	LMC Clinical Research Inc. (Brampton) 2979 Bovaird Drive East Brampton Ontario L6S 0C6 Canada
CAN8	Principal Investigator(s): Vallieres Dr. (MD), Gerald Sub-Investigator(s): Bissonnette Dr., Alain Blouin Dr., Francois	Manna Research (Quebec) Local 203 1190 A, Rue de Courchevel Levis Quebec G6W 0M5 Canada
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