11 November 2021
EMA/112307/2022
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Wegovy

International non-proprietary name: semaglutide

Procedure No. EMEA/H/C/005422/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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Administrative information

Name of the medicinal product:	Wegovy
Applicant:	Novo Nordisk A/S Novo Alle 1 2880 Bagsvaerd DENMARK
Active substance:	Semaglutide
International Non-proprietary Name:	Semaglutide
Pharmaco-therapeutic group (ATC Code):	Drugs used in diabetes, glucagon-like peptide-1 (GLP-1) analogues (A10BJ06)
Therapeutic indication(s):	Wegovy is indicated as an adjunct to a reduced-calorie diet and increased physical activity for weight management, including weight loss and weight maintenance, in adults with an initial Body Mass Index (BMI) of • ≥30 kg/m^2 (obesity), or • ≥27 kg/m^2 to <30 kg/m^2 (overweight) in the presence of at least one weight-related comorbidity e.g. dysglycaemia (prediabetes or type 2 diabetes mellitus), hypertension, dyslipidaemia, obstructive sleep apnoea or cardiovascular disease.
Pharmaceutical form(s):	Solution for injection
Strength(s):	0.25 mg, 0.5 mg, 1 mg, 1.7 mg and 2.4 mg
Route(s) of administration:	Subcutaneous use
Packaging:	pre-filled syringe (glass) in pre-filled pen
Package size(s):	4 pre-filled pens

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List of abbreviations

ACB	Nucleus accumbens
ADA	American diabetes association
Ado	8-amino-3,6-dioxaoctanic acid
ADR	adverse drug reaction
AE	adverse event
AGRP	Agouti-related peptide
Aib	2-aminoisobutyric acid
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AP	Area postrema
ApoE	Apoprotein E
ARH	Arcuate hypothalamic nucleus
AST	aspartate aminotransferase
AUC	Area under the plasma drug concentration-time curve
BBB	Blood-brain-barrier
BMI	body mass index
BST	Bed nucleus of stria terminalis
cAMP	Cyclic adenosine monophosphate
CART	Cocaine- and amphetamine-regulated transcript
Cavg	Average plasma concentration
CeA	Central amygdala
CFR	US Code of Federal Regulations
CGRP	calcitonin gene-related peptide
CHMP	Committee for Medicinal Products for Human Use (European Medicines Agency)
chpl	Choroid plexus
CI	confidence interval
Cmax	Maximum drug concentration observed in plasma
Cmax	maximum concentration
CNS	Central nervous system
COPD	chronic obstructive pulmonary disease
COVID-19	coronavirus disease 2019
CRF	case report form
CRP	c-reactive protein
CS	clinically significant
C-SSRS	Columbia–Suicide Severity Rating Scale
CT	computerised tomography
CTR	clinical trial report

CV	coefficient of variation
CVO	Circumventricular organ
CVOT	cardiovascular outcomes trial
CYP	Cytochrome P450
CYP	cytochrome P450
DBL	database lock
DBP	diastolic blood pressure
DDI	Drug-drug interaction
DEXA	dual-energy x-ray absorptiometry
DIO	Diet induced obesity
DMX	Dorsal motor nucleus of the vagus nerve
DPP-4	Dipeptidyl peptidase 4
EAC	event adjudication committee
EC50	Effective concentration 50%
ECG	Electrocardiogram
ECG	electrocardiogram
ED50	Effective dose 50%
eGFR	estimated glomerular filtration rate
ELISA	Enzyme-linked immunosorbent assay
EMA	European Medicines Agency
EOT	end of text
ETD	estimated treatment difference
EU	European Union
FAS	full analysis set
FDA	Food and Drug Administration (United States)
FFA	free fatty acids
FPG	fasting plasma glucose
GD	Gestational day
GGT	gamma-glutamyltransferase
GLP	Good laboratory practice
GLP-1	glucagon-like peptide-1
GLP-1 RA	glucagon-like peptide-1 receptor agonist
GLP-1R	Glucagon like peptide -1 receptor
HbA1c	Hemoglobin A1c (glycolated hemoglobin)
HDL	high density lipoprotein
hERG	Human ether-a-go-go related gene
HLGT	high-level group term
HRQOL	health-related quality of life
i.v.	Intravenous
IBT	intensive behavioural therapy

ICH International conference on harmonisation
IHSG international hypoglycaemia study group
IND investigational new drug
INR international normalized ratio
IRB institutional review board
ISO International Organization for Standardization
IT in-trial
IWQOL-Lite-C Impact of Weight on Quality of Life-Lite for Clinical Trials
LCD low calory diet
LC-MS Liquid chromatography-mass spectrometry
LDL low density lipoprotein
LLT lower level term
LOCI Luminescent oxygen channeling immunoassay
LS Caudal part of the lateral septal nucleus
MAA marketing authorisation application
MACE Major adverse cardiovascular event
ME Median eminence
MEB Medicines Evaluation Board
MedDRA Medical Dictionary for Regulatory Activities
MPA Medical Products Agency
MRHD Maximum recommended human dose
mRNA Messenger ribonucleic acid
MTN Midline group of the dorsal thalamus
NAFLD non-alcoholic fatty liver disease
NASH non-alcoholic steatohepatitis
NDA new drug application
NEP Neutral endopeptidase (neprilysin)
NOAEL No observed adverse effect level
NPY Neuropeptide Y
NTS Nucleus of the solitary tract
OAD oral anti-diabetic drug
OECD Organisation for Economic Co-operation and Development
OR odds ratio
OV Organum vasculosum of lamina terminalis
PCOS polycystic ovary syndrome
PD protocol deviation
PDCO Paediatric Committee
(European Medicines Agency)
PHQ-9 Patient Health Questionnaire-9
PK pharmacokinetic

PMDA	Pharmaceuticals and Medical Devices Agency (Japan)
POMC	Pro-opiomelanocortin
PRO	patient-reported outcome
PT	preferred term
PVT	Paraventricular nucleus of the thalamus
PYE	patient years of exposure
PYO	patient years of observation
RET	Rearranged during transfection
s.c.	Subcutaneous
SAE	serious adverse event
SBP	systolic blood pressure
SD	standard deviation
SF	Septofimbrial nucleus
SF-36	Short Form 36 v2.0 acute
SFO	Subfornical area
SGLT2i	sodium/glucose cotransporter-2
SOC	system organ class
STEP	Semaglutide Treatment Effect in People with obesity
STEP 1	NN9536-4373 (weight management)
STEP 2	NN9536-4374 (weight management)
STEP 3	NN9536-4375 (weight management)
STEP 4	NN9536-4376 (sustained weight management)
SUSAR	suspected unexpected serious adverse reaction
t1/2	Terminal plasma half-life
T2D	Type 2 diabetes mellitus
tau	Dosing interval
TBL	total bilirubin
tmax	Time at which Cmax occurs
TRS	Triangular nucleus of septum
UACR	urine albumin-to-creatinine ratio
UK	United Kingdom
ULN	upper limit of normal range
US	United States of America
VAS	visual analogue scale
VLDL	very-low-density lipoprotein
VTA	Ventral tegmental area
WHO	World Health Organization

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Novo Nordisk A/S submitted on 17 December 2020 an application for marketing authorisation to the European Medicines Agency (EMA) for Wegovy, through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 25 July 2019.

The applicant applied for the following indication

Wegovy is indicated as an adjunct to a reduced-calorie diet and increased physical activity for weight management, including weight loss and weight maintenance, in adults with an initial Body Mass Index (BMI) of

- *⩾30 kg/m2 (obesity), or*
- *⩾27 kg/m2 to <30 kg/m2 (overweight) in the presence of at least one weight-related comorbidity e.g. dysglycaemia (prediabetes or type 2 diabetes mellitus), hypertension, dyslipidaemia, obstructive sleep apnoea or cardiovascular disease.*

1.2. Legal basis, dossier content

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

1.3. Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0007/2019 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP EMEA-001441-PIP03-17 was not yet completed as some measures were deferred.

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

1.5. Scientific advice

The applicant received the following Scientific advice on the development of semaglutide relevant for the weight management indication subject to the present application:

Date	Reference	SAWP co-ordinators
9 November 2017	EMEA/H/SA/3657/1/2017/III	Dr Elmer Schabel, Dr Kolbeinn Gudmundsson

The Scientific Advice pertained to the following Pre-Clinical and Clinical aspects:

- Acceptability to cross-reference for non-clinical evidence from T2DM indication
- Phase 3 programme to support weight management indication: number of clinical studies, study populations, efficacy endpoints, subject exposure/safety database, cardiovascular safety to rely on cardiovascular outcome trial performed in T2DM, use of DEXA scans in subpopulation to characterise change in body composition, dose justification and escalation regimen, statistical analysis plan, handling of missing data
- Plans to characterise clinical pharmacology properties using population PK and exposure response analyses of Phase 3a data and cross-referencing to clinical pharmacology characterisation from T2DM programme
- Bioequivalence between Phase 3a drug product and intended-to be marketed drug product
- Randomised-withdrawal design to demonstrate maintenance of activity, tolerability and safety
- Clinical outcome assessments (Quality of life, physical performance)
- Immunogenicity characterisation

1.6. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Johann Lodewijk Hillege Co-Rapporteur: Sinan B. Sarac

The application was received by the EMA on	17 December 2020
The procedure started on	21 January 2021
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	12 April 2021
The CHMP Co-Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	13 April 2021
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	23 April 2021
The CHMP agreed on the consolidated List of Questions to be sent to the	20 May 2021

applicant during the meeting on	
The applicant submitted the responses to the CHMP consolidated List of Questions on	16 July 2021
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	21 September 2021
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	30 September 2021
The CHMP agreed on a list of outstanding issues to be sent to the applicant on	14 October 2021
The applicant submitted the responses to the CHMP List of Outstanding Issues on	19 October 2021
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	8 October 2021
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Wegovy on	11 November 2021

2. Scientific discussion

2.1. Problem statement

In this application, data collected by Novo Nordisk (sponsor, applicant) are presented to support the use of semaglutide s.c. 2.4 mg once weekly (hereafter referred to as semaglutide 2.4 mg) as an adjunct to a reduced-calorie diet and increased physical activity for weight management, including weight loss and weight maintenance, in adults with an initial body mass index (BMI) of

- ≥30 kg/m^2 (obesity), *or*
- ≥27 kg/m^2 to <30 kg/m^2 (overweight) in the presence of at least one weight-related comorbidity.

2.1.1. Disease or condition

Overweight and obesity are defined as abnormal or excessive fat accumulation. Obesity is a medical condition in which excess body fat has accumulated to the extent that it may have a negative effect on health. A body mass index (BMI) over 25 is considered overweight, and over 30 is obese.

2.1.2. Epidemiology and Biologic features

The prevalence of obesity has reached epidemic proportions and continues to increase. Obesity is currently considered one of the most significant public health challenges worldwide due to its substantial medical, societal and economic impact. Obesity is associated with several health-related complications. Most concerning, obesity increases the risk of developing cardiovascular disease and certain types of cancers, which are some of the leading causes of early death in these patients. In addition, obesity is a well-established risk factor for other serious conditions including, but not limited to, T2D, hypertension, dyslipidaemia, obstructive sleep apnoea, osteoarthritis, urinary incontinence, asthma and non-alcoholic steatohepatitis. Obesity also significantly impacts health-related quality of life by impairing physical health status and imposing limitations on daily activities. Furthermore, stigmatization and discrimination associated with obesity can contribute to impaired mental well-being.

The risk of obesity-related complications and comorbidities increases with increasing BMI, and a weight loss of 5−10% has significant health benefits by improving obesity-related comorbidities, including slowing progression to T2D, and improving physical symptoms and quality of life. Studies suggest a beneficial impact of weight loss on cardiovascular risk and mortality in people with obesity, with or without T2D.

2.1.3. Management

Lifestyle intervention in the form of diet and exercise is first-line treatment for obesity, but most people with obesity struggle to achieve and maintain their weight loss, most likely due in large part to a homeostatic mechanism involving counteractive biological responses.

Bariatric surgery offers an effective alternative for some people with severe obesity, but surgery carries a risk in connection with the procedure and for complications afterwards, and requires close follow-up, which can be cumbersome and costly. For people with obesity, there is a lack of safe and efficacious treatment options that can provide a reduction in body weight approaching what can be obtained by surgical procedures, and at the

same time enables the patient to maintain the weight loss. Pharmacotherapy may serve as a valuable alternative to bariatric surgery as a supplement to lifestyle intervention to achieve and sustain a clinically relevant weight loss. Currently, only a very limited number of pharmacological options are approved for weight management.

Collectively, the Applicant describes an unmet medical need for a convenient, efficacious and safe weight lowering drug with beneficial effects on obesity-related comorbidities. The GLP-1 RA drug class is associated with multiple benefits; they have a well-documented safety profile, reduce body weight, improve blood pressure, lipid profile and other cardiovascular risk factors as well as glucose metabolism.

2.2. About the product

Semaglutide is a glucagon-like peptide-1 (GLP-1) analogue and classified as a GLP-1 receptor agonist (GLP-1 RA). It has a 94% homology to human GLP-1 and a long half-life suitable for once-weekly dosing.

Semaglutide 0.5 mg and 1.0 mg for once-weekly s.c. injection is approved worldwide under the tradename (Ozempic) for treatment of type 2 diabetes (T2D), and in the US and Russia also for cardiovascular risk reduction in people with T2D and established cardiovascular disease. Oral semaglutide (7 mg and 14 mg) is approved in the US, Canada, the EU and Japan for the treatment of T2D (Rybelsus). In addition, another GLP-1 analogue, the once-daily GLP-1 analogue liraglutide, is approved worldwide for weight management (Saxenda). Clinical experience exists from semaglutide for the treatment of T2D and the use of liraglutide for weight management.

2.3. Type of Application and aspects on development

Development programme

The global clinical development programme for semaglutide s.c. 2.4 mg for weight management, forming the basis for this application, comprises 8 completed clinical trials:

- clinical pharmacology trials (of which two are bioequivalence trials)
- 1 phase 2 dose-finding trial
- 4 phase 3a therapeutic confirmatory trials (referred to as the STEP trials)

The cut-off date for inclusion of completed trials was 28 October 2020 (DBL for the last bioequivalence trial, trial 4590).

The application includes blinded safety data from 1 extension trial (extension phase of STEP 1) and 5 other ongoing trials. For data from these trials, a cut-off date of 01 September 2020 has been used.

An overview of the clinical trials included in the application is provided in **Table 1** (completed trials) and **Table 2** (ongoing trials).

All trials in the clinical development programme followed accepted industry and regulatory requirements for developing weight management products, and were conducted in accordance with ICH Good Clinical Practice and FDA 21 CFR 312.120.

Clinical trials conducted with semaglutide s.c. 2.4 mg for weight management are identified by the project name (NN9536) followed by a unique 4-digit number, e.g., NN9536-4373. In this application, the trials are

referred to as 'trial xxxx', where 'xxxx' is the unique 4-digit number (e.g. trial 4373). Trials from other development programmes are referred to by their project number (NNXXXX) followed by the unique 4-digit number (e.g. semaglutide s.c. for T2D [Ozempic]: trial NN9535-3744).

The nonclinical and clinical pharmacology data generated with semaglutide as part of the Ozempic programme support the weight management indication.

Table 1 Completed clinical trials in the semaglutide s.c. 2.4 mg weight management development programme (NN9536) included in the application

Trial	Subjects	Brief description
Phase 3a		
Trial 4373 (STEP 1) weight management	N=1961	68-week, randomised, double-blind trial comparing the efficacy and safety of semaglutide s.c. 2.4 mg once weekly vs placebo, as an adjunct to lifestyle intervention, in adults with overweight or obesity.
Trial 4374 (STEP 2) weight management in T2D	N=1210	68-week, randomised, double-blind trial comparing the efficacy and safety of semaglutide s.c. 1.0 mg and 2.4 mg once weekly vs placebo, as an adjunct to lifestyle intervention, in adults with overweight or obesity and T2D.
Trial 4375 (STEP 3) weight management with IBT	N=611	68-week, randomised, double-blind trial comparing the efficacy and safety of semaglutide s.c. 2.4 mg once weekly vs placebo, as an add-on to intensive behavioural therapy (IBT), in adults with overweight or obesity.
Trial 4376 (STEP 4) sustained weight management	N=902	68-week, randomised, double-blind, placebo-controlled trial comparing the efficacy and safety of semaglutide s.c. 2.4 mg once weekly vs placebo in adults with overweight or obesity who had reached the maintenance dose of semaglutide (2.4 mg) during a 20-week run-in period.
Phase 2		
Trial 4153 dose-finding	N=957	52-week, randomised, double-blind, placebo-controlled, 16-armed trial with liraglutide 3.0 mg as active comparator evaluating different doses of semaglutide administered once daily at doses from 0.05 mg/day to 0.4 mg/day in adults with obesity, following two different escalation schemes.
Clinical pharmacology		
Trial 4455 pharmacodynamics	N=72	21-week, randomised, double-blind, placebo-controlled trial investigating the effect of semaglutide 2.4 mg once-weekly on gastric emptying in adults with obesity.
Trial 4590 bioequivalence 1.0 mg and 2.4 mg	N=68	21-week, randomised, open-label trial to demonstrate bioequivalence between semaglutide formulation D with the single-dose pen-injector (DV3396) and semaglutide formulation B with the PDS290 pen-injector in adults with overweight or obesity.
Trial NN9535-4588[a] bioequivalence 0.25 mg	N=68	7-week, randomised, open-label trial to demonstrate bioequivalence between semaglutide formulations D for the single-dose pen-injector and semaglutide B formulation for the PDS290 pen-injector in adults with overweight or obesity.

[a] In trial NN9535-4588 (conducted as part of the Ozempic programme), bioequivalence was assessed at doses of 0.25 and 1.0 mg, however only the 0.25 mg dose is relevant for the weight management indication. IBT: Intensive Behavioural Therapy; T2D: type 2 diabetes. N: number of randomised subjects.

Table 2 Ongoing clinical trials in the semaglutide s.c. 2.4 mg weight management development programme (NN9536) included in the application

Trial	Subjects	Brief description
Phase 3a		
Trial 4373 (STEP 1) ext Off-treatment extension phase	N=300	45-week extension period off all treatments, including trial product and lifestyle interventions, to explore sustained efficacy after treatment discontinuation in a subset of subjects participating in the main phase of STEP 1.
Trial 4382 (STEP 6) East Asian trial	N=400	68-week, randomised, double-blind, placebo-controlled trial investigating the effect and safety of semaglutide s.c. once weekly in East Asian adults with overweight or obesity.
Trial 4451 (STEP TEENS) Adolescents (12-17 years)	N=192	68-week, randomised, double-blind, placebo-controlled trial investigating the effect and safety of semaglutide 2.4 mg once weekly on weight management in adolescents with overweight or obesity.
Phase 3b		
Trial 4378 (STEP 5) Long-term weight management	N=300	104-week, randomised, double-blind, placebo-controlled trial investigating the two-year effect and safety of semaglutide s.c. 2.4 mg once weekly in adults with overweight or obesity.
Trial 4576 (STEP 8) Sema 2.4 mg vs lira 3.0 mg	N=336	68-week, randomised, open label, pairwise placebo-controlled, US trial comparing effect and safety of semaglutide s.c. 2.4 mg once weekly vs liraglutide 3.0 mg once daily in adults with overweight or obesity.
Trial 4388 (SELECT) CVOT	N=17500	Event-driven, randomised, double-blind, placebo-controlled trial investigating semaglutide effects on cardiovascular outcomes in adults with overweight or obesity. Estimated trial duration for an individual subject is from 31 to 59 months.

Ongoing is defined as a trial that had first patient first visit but not yet database lock at the time of the MAA cut-off date.
Ext: extension; sema: semaglutide; lira: liraglutide; CVOT: cardiovascular outcome trials; N: planned number of randomised subjects.

Impact of COVID-19 on the clinical programme

The COVID-19 public health emergency occurred when almost all subjects in the phase 3a trials had completed their last visits. Therefore, the impact of COVID-19 on STEP 1–4 was limited. Novo Nordisk followed the guidance provided by the FDA and EMA on handling changes to trials related to COVID-19.

No subjects discontinued treatment due to COVID-19, but 1 subject (placebo) in STEP 2 and 1 subject (semaglutide 2.4 mg) in STEP 3 were reported as withdrawn from the trial during the follow-up period due to COVID-19. These 2 subjects were treatment completers.

COVID-19-related AEs were reported for 3 subjects, 1 in each of the STEP 1–3 trials, all in the semaglutide 2.4 mg groups (PTs: corona virus infection [2 subjects] and coronavirus test positive [1 subject]). The AEs in STEP 1 and 3 were non-serious and of mild severity. The AE in STEP 2 was an SAE reported as 'severe' and requiring hospitalisation (in-trial period, after the last dosing); the outcome was reported as recovered.

To mitigate the risk of exposure to COVID-19 for subjects and trial staff, site visits could be converted to phone visits, thus ensuring reporting of AEs and other safety follow-up information. Visit conversions due to COVID-19 were categorised as important PDs, marked as being related to COVID-19.

Based on information from important PDs, very few subjects (1 in each of the STEP 1–3 trials) had missing assessments at the end-of-treatment visit (week 68) for reasons related to COVID-19. As a result, the impact of COVID-19 on missing data for the primary and confirmatory secondary endpoints was minimal, and no changes were made to the statistical analysis plans due to COVID-19.

A larger number of subjects (181 in STEP 1, 230 in STEP 2, 135 in STEP 3, and 12 in STEP 4) had missing assessments due to COVID-19 at the end-of-trial follow-up visit (week 75) due to visit conversion. The assessments to be done at this visit were mainly related to safety follow-up. In STEP 1 and 2, blood sampling for PK and antibodies were to be done at week 75, and these samples were not taken for subjects who had the follow-up visit done by phone due to COVID-19. In the context of the previous experience with semaglutide, the missing data from the follow-up visits did not give rise to any concerns. The missing PK and antibody samples did not have any impact on the immunogenicity assessment of semaglutide 2.4 mg. Although subjects were allowed to perform some assessments themselves at home (e.g. body weight, pulse, blood pressure), the results of these assessments were treated as missing data and were not included in any descriptive summaries or statistical analyses. Home pregnancy testing in women of childbearing potential was allowed at week 75 (follow-up visit) in order to ensure the safety of the subjects. A total of 20 subjects (18 in STEP 1, 1 in STEP 3, and 1 in STEP 4) performed a home pregnancy test at week 75 because the clinic visit had been converted to a phone visit due to COVID-19.

The impact of COVID-19 on the two bioequivalence trials was limited. In trial 4590, some doses were changed from being self-administered at the trial site to being self-administered at home, and in trial NN9535-4588, 1 PK visit was affected due to a subject with a possible COVID-19 infection.

Compliance with guidances

Compliance to CHMP guidelines is discussed in the respective paragraphs, no issues were identified.

2.4. Quality aspects

2.4.1. Introduction

Semaglutide, the active substance contained in Wegovy, is a glucagon-like peptide-1 (GLP-1) analogue substituted with a linker and a fatty acid side chain. It is produced using recombinant DNA technology in *Saccharomyces cerevisiae* followed by chemical modifications. Semaglutide is the same active substance contained in the currently authorised product Ozempic (EMEA/H/C/4174).

Wegovy is presented as a clear and colourless solution for subcutaneous injection in a 1 mL prefilled Type I glass syringe (PFS) attached with stainless steel needle, rigid needle shield (type II/polyisoprene) and a rubber plunger (type I/chlorobutyl).The PFS is assembled into a single-use prefilled pen (PFP).

The following presentations are proposed with packs of 4 PFPs each:

- 0.25 mg semaglutide in 0.5 mL (strength 0.25 mg);

- 0.5 mg semaglutide in 0.5 mL (strength 0.5 mg);

- 1 mg semaglutide in 0.5 mL (strength 1 mg);

- 1.7 mg semaglutide in 0.75 mL (strength 1.7 mg);

- 2.4 mg semgaglutide in 0.75 mL (strength 2.4 mg).

2.4.2. Active Substance

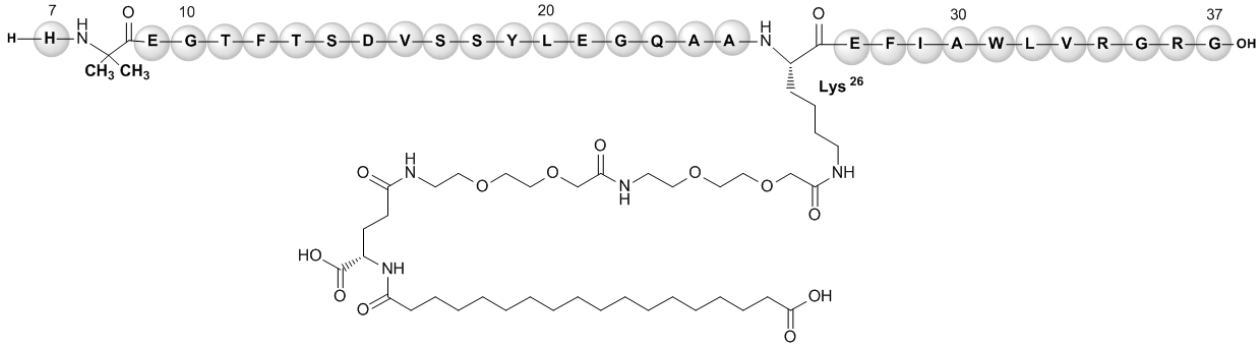
The information on semaglutide as described in Module 3.2.S. of this marketing authorisation application (MAA) is identical to Module 3.2.S of the Ozempic dossier. Minor updates have been implemented to the Wegovy dossier. No issue was identified during the procedure.

General Information

Semaglutide is a long-acting analogue of human glucagon like-1 peptide i.e. an Aib^{8}, Arg^{34}-GLP-1(7-37) analogue substituted on the ε-amino group of the lysine residue in position 26 with an (S)-22,40-dicarboxy-10,19,24-trioxo-3,6,12,15-tetraoxa-9,18,23-triazatetracontan-1-oyl side chain. The side chain consists of two 8-amino-3,6-dioxaoctanoic acid (ADO) spacers, one γ-glutamic acid (Glu) spacer, and a fatty diacid (1,18-octadecanedioic acid). Semaglutide is produced using recombinant DNA technology in yeast (*Saccharomyces cerevisiae*) and chemical modification.

The structural formula of semaglutide is given in Figure 1.

Figure 1 – Structural formula of semaglutide



Manufacture, process controls and characterisation

Manufacturing process

Semaglutide is manufactured at Novo Nordisk A/S, Hallas Allé, DK-4400 Kalundborg, Denmark (site currently authorised for Ozempic). EU GMP compliance for all the sites involved in active substance manufacture and control was confirmed.

The manufacturing process for semaglutide active substance consists of a fermentation process in yeast cells, recovery and purification of semaglutide precursor. The semaglutide precursor is subject to a synthetic modification process and purified. All steps have been described and explained.

The harvested culture broth is split into several batches at delivery to recovery. The subsequent steps in recovery and purification (including modification) are all performed as batch processes, and unique batch numbers are assigned at designated steps.

In addition to the active substance itself, three other intermediates are isolated and storage conditions and shelf life are defined.

Control of materials

The construction of the expression plasmid and the source and history of *S. cerevisiae* strain Arg34]GLP-1-(9-37)) producing semaglutide precursor is described in detail. The cell banking system of master cell bank (MCB) and working cell bank (WCB) is explained and characterisation of MCB and WCB is reported. Stability results of MCB and WCB are available and the results comply with the specification acceptance criteria for the MCB and WCB.

No animal-derived substances are used in the production of semaglutide.

Reference is made to the CHMP assessment report for Ozempic regarding the definition of stating materials and critical intermediates.

Control of critical steps and intermediates

Critical operational parameters and critical in-process tests are defined for process steps. Critical in-process tests focus on microbial contamination and product purity. A set of critical operational parameters has been defined for the multistep process supported by the evaluation studies in manufacturing process development.

Process validation

The manufacturing process design consists of process characterisation and process justification. This is followed by process verification (also referred to as process performance qualification (PPQ)), confirming that the semaglutide manufacturing process can consistently produce semaglutide active substance of the required quality in a manufacturing scale. To ensure that the semaglutide active substance manufacturing process remains in a state of control during commercial manufacture and that the validated state following PPQ is maintained, ongoing process verification was initiated.

Based on the totality of the experiments performed during process justification, ranges of both critical and non-critical operational parameters and the acceptance criteria for the critical in-process tests have been supported. Steps having one or more critical operational parameters have been defined as critical steps.

The PPQ results of the critical operational parameters, critical in-process tests, and the results of the semaglutide active substance specification tests were all consistent for the fermentation, recovery, and purification batches and all acceptance criteria were fulfilled. Based on these results, the applicant concludes that the semaglutide manufacturing process consistently produces semaglutide active substance of reproducible quality in accordance with the predetermined specifications; the process is considered validated and ready for commercial production.

The evaluation of impurity reduction was carried out at a manufacturing scale, covering representative production batches from the PPQ. Selected product-related impurities analysed during the PPQ. Process steps are monitored, reduction factors calculated, and in-process acceptance criteria set.

Manufacturing process development

Description and explanation of every change during product and process development is presented, batch analysis data and the use of the batch is indicated.

Comparability and stability data demonstrate that the process has been improved during development with respect to impurity levels and robustness of the manufacturing process. The changes made during development have not adversely affected the product with respect to quality, safety, or efficacy.

Characterisation

Structural characterisation and elucidation of the physico-chemical properties of semaglutide has been performed using active substance batches representative for the manufacturing process used for phase 3 clinical trials and intended for the commercial product. The results of the structural characterisation of semaglutide have confirmed the expected and theoretical structure.

The bioactivity of semaglutide is determined by a cell-based bioactivity assay, which indirectly measures adenylate cyclase activation of the cloned human GLP-1 receptor. The bioactivity of isolated semaglutide related impurities has been investigated by isolation of the semaglutide main peak and major semaglutide related impurities from semaglutide active substance, followed by testing for content and purity of each peak by reverse phase high performance liquid chromatography (RP-HPLC) and bioactivity. An evaluation of the correlation between the bioactivity and the content determined by RP-HPLC of semaglutide in active substance and finished product, including forced degraded samples, is provided. It is concluded that the RP-HPLC analytical procedure established for the determination of the main peak content in the semaglutide active substance and finished product specifications offers a reliable measure of the bioactivity of semaglutide in both active substance and finished product.

Product-related impurities are structurally related to semaglutide. They are generated as by-products in fermentation by the host organism as well as in the recovery and purification process of semaglutide precursor, in the modification steps and in the purification process of semaglutide.

The major impurity peaks from semaglutide active substance have been isolated and the identity of the components present in each peak has been determined by high-resolution liquid chromatography mass spectrometry (LC/MS).

Specification, analytical procedures, reference standards, batch analysis, and container closure

Specification

The specification for semaglutide active substance include control of identity, purity, bioactivity and other general tests.

Justification of individual specification parameters and acceptance criteria is provided. Specification limits are based on process capability.

A systematic and risk-based approach has been used to establish the control strategy of semaglutide active substance.

The resulting control strategy for semaglutide active substance is a planned set of controls which are derived from accumulated product and process understanding and hereby ensures process performance and product quality.

Analytical procedures

Method descriptions and validation of test methods are provided.

The analytical procedures are described, and validation reports have been provided.

Batch analyses

The analytical results for relevant semaglutide active substance batches are presented. The batches have been used for non-clinical studies, clinical trials (early phase 1 and 2 trials), clinical pharmacology and phase 3 trials, stability studies, reference material, process performance qualification, and setting of specifications. Data is presented as ranges obtained within the given campaign. All batch release data shown comply with the active substance specification for semaglutide, which was in force at the time for releasing the batches.

Reference standards

A Novo Nordisk A/S reference material hierarchy has been established for semaglutide, consisting of a semaglutide primary reference material (PRM) and a semaglutide secondary reference material (SRM).

The content of the semaglutide PRM was assigned upon an analytical determination of nitrogen content, related to the theoretical content of nitrogen in semaglutide, and corrected for sum of impurities by RP-HPLC. The semaglutide PRM serves as reference for identification and calibrator for assignment of Content to semaglutide SRM, as well as to confirm bioactivity expressed as Specific bioactivity to semaglutide SRMs.

Semaglutide SRM is used for quality control of semaglutide active substance and finished product for identification and determination of Content, as well as to determine the biological activity expressed as Specific bioactivity of semaglutide active substance.

Container closure system

The active substance is stored in 5 L or 10 L high density polyethylene (HDPE) containers equipped with a sealing ring and a handgrip. The container closure system is considered suitable and qualified for its intended use.

Stability

The semaglutide active substance is stored frozen below or at -20°C, a shelf-life of 60 months is approved.

All data for each test parameter from both supportive, primary and PPQ studies, when stored at -20°C ± 5°C, are within the acceptance criteria and shows no change over time. Furthermore, the batches have comparable trends. In addition, all data for each test parameter from both supportive, primary, and PPQ studies, when stored at accelerated condition at +5°C ± 3°C, shows no change over time. The batches have comparable trends.

2.4.3. Finished Medicinal Product

Description of the product and pharmaceutical development

Description of the product

Semaglutide 0.25 mg, 0.5 mg, 1.0 mg, 1.7 mg and 2.4 mg solution for injection (hereafter referred to as semaglutide finished products) are clear and colourless solutions filled in a pre-fillable syringe, with a filling volume of 0.5 mL (0.25 mg, 0.5 mg and 1 mg) or 0.75 ml (1.7 mg and 2.4 mg), assembled in a pen-injector.

The semaglutide finished products comprise the following commonly used excipients: disodium phosphate dihydrate (buffering agent), sodium chloride (tonicity agent), hydrochloric acid (pH adjustment), sodium hydroxide (pH adjustment), and water for injections (solvent).

The primary packaging is a 1 mL glass syringe barrel with a staked needle, rigid needle shield and a rubber plunger. The prefilled syringe is assembled in a DV3396 single dose pen-injector.

Pharmaceutical development

Finished product understanding has been achieved based on the Quality Target Product Profile (QTPP), prior knowledge gained during the development of Ozempic, formulation development studies, and risk assessment of the manufacturing process.

There were several changes to the formulation and drug-device combination (DDC) during clinical development. The semaglutide finished products for clinical trials contained slightly different semaglutide concentrations and were used with the multi-dose pen-injector known from Ozempic (PDS290). The primary packaging and excipients were also identical to Ozempic. Comparability of the different finished product formulations is demonstrated at the level of semaglutide related impurities and stability.

The manufacturing process development is based on the manufacturing process of Ozempic. The manufacturing process has remained essentially the same from the manufacture of finished products for the clinical trials to the manufacturing process intended for the market.

Extractable and leachable studies have been performed with the syringe components.

The Applicant’s proposal for 36 months container closure integrity is supported by data. The semaglutide finished products are found to be compatible with the 1 mL syringe container closure system and the single-dose pen-injector.

Manufacture of the product and process controls

Manufacture

GMP compliance for all the sites involved in finished product manufacture and control was confirmed.

Briefly, semaglutide active substance is dissolved in a solution containing all excipients and diluted with water for injections to obtain the desired weight. The pH is adjusted by adding diluted sodium hydroxide or diluted hydrochloric acid. The final solution is sterile filtered and filled aseptically into sterilised and depyrogenated syringes.

Assembly of the single dose pen-injector is achieved by inserting the prefilled syringe into the pen-injector's front assembly, followed by insertion of the rear assembly. After final assembly, the single-dose pen-injector is labelled and packed before final release. The descriptions are sufficiently detailed.

Process controls

Critical steps and in-process controls (IPCs) have been assigned for the semaglutide finished products. The proposed actions for failing to meet acceptance criteria are considered acceptable. Adequate process controls are in place for the front and rear assembly and the final assembly. The dose accuracy of the finished products is controlled routinely.

Process validation

Validation activities have been performed to confirm that the manufacturing process for the semaglutide finished products is capable of consistently and reproducibly producing finished product of the required quality on a commercial manufacturing scale. The process validation activities encompass: a) Process justification, b) Process validation programme, and c) Ongoing process verification.

The process justification was performed with scalable process parameters (batch size-independent) and non-scalable process parameters (batch size-dependent and/or equipment specific).

Based on the results from process validation it can be concluded that the manufacturing process for semaglutide finished product is in a validated state and suited for commercial production.

The drug-device combination is assembled on a high volume, fully automatic assembly line. The assembly line is adequately validated.

Product specification, analytical procedures, batch analysis

Specifications

The specification for semaglutide finished products include control of identity, purity, bioactivity and other general tests.

Analytical procedures

Analytical procedures are described and validated according to relevant ICH guidelines or reference is made to compendial requirements (Ph. Eur.).

Batch analyses

Analyses of all relevant finished product batches are provided. The results are not reproduced in this report.

Characterisation of impurities

A characterisation study was conducted to characterise the semaglutide related impurities generated during the manufacture and storage of the semaglutide finished products.

The risk assessment for elemental impurities in accordance with ICH Q3D guideline is considered approvable and the levels found were consistently below the permissible daily exposure (PDE) value based on the worst case finished product dosing.

A risk evaluation concerning the potential presence of nitrosamine impurities in the finished product is provided and considered approvable. No additional testing is considered necessary.

Reference standards

Reference is made to the active substance part.

Container closure system

The container closure system for the semaglutide finished products comprises the primary packaging and the DV3396 single dose pen-injector.

The primary packaging is a 1 mL pre-fillable syringe with a syringe barrel made of type I borosilicate glass (Ph. Eur.), a stainless steel staked needle, a rigid needle shield where the rubber part is made of polyisoprene rubber-type II (Ph. Eur.), and a plunger made of chlorobutyl rubber-type I (Ph. Eur.). All of the above components have direct contact with the finished product. Extractable and leachable studies and container closure integrity testing were part of the finished product development studies. The syringe components are supplied sterile and ready-to-use. Sufficient documentation is provided.

The PFSs are assembled with sub-assembled device components at the site. The device secondary functional packaging are not in direct contact with the semaglutide solution. Device operations are described in detail. The device components are identical for all to-be-marketed semaglutide finished products; there is, however a difference in the placement of the plunger rod to accommodate the dose volumes 0.5 mL and 0.75 mL.

The DDCs have been tested in a usability study and are found to be safe and effective for intended users, intended use and use environments with regards to handling and differentiation. In addition, a Notified Body Opinion according to Article 117, Regulation (EU) 2017/745 on Medical Devices, confirming full compliance with the relevant general safety and performance requirements (GSPRs).

Stability of the product

The stability test programme for the semaglutide finished products is provided, also listing what data is available at the time of submission. The studies were performed according to current ICH guidelines.

Thirty six months stability data is available for Ozempic (1.34 mg/ml semaglutide) and Wegovy finished products used in phase 2 and phase 3 clinical trials, but with a slightly different formulation.

All long term and accelerated stability studies were performed on semaglutide finished products in primary containers (1 mL syringe). A separate study is included in which 1 mL syringes from the primary stability batches are assembled in the DV3396 single dose pen-injector. The currently available stability data indicate that the assembly has no impact on the stability of the finished products. Long-term testing will continue up to 36 months.

The proposed shelf-life for semaglutide finished products in the single-dose pen-injector is 24 months when stored refrigerated (2° to 8°C) in carton. This is supported by stability data and therefore approvable. The Applicant has provided results from ongoing studies of the to-be-marketed formulation in the proposed device as part of stability studies. The results so far support stable performance of dose accuracy of the combination product. The study will continue up to 36 months.

An in-use stability time of 28 days below 30°C to allow storage outside the refrigerator before use is proposed. The Applicant has presented in-use stability data for the 1 mL PFS assembled in the single dose pen-injector. The results raise no issues. The study was performed at the end of the currently proposed shelf life of 24 months. The Applicant confirms that the study will continue until 36 months.

Post approval change management protocol(s)

A post-approval change management protocol (PACMP) is included to add a second manufacturing site for the finished product. The contents of the PACMP are well aligned with those recently accepted for additional finished product facilities for Ozempic and are considered acceptable.

Adventitious agents

The semaglutide precursor peptide is produced from a yeast strain. Yeast is not a host for mammalian viruses. The cell line has been tested for microbial purity. As no further raw materials or excipients of human or animal origin are used for the manufacture of semaglutide, the finished products are evaluated to be safe regarding TSE agents and there is no risk of contaminating the product with mammalian viruses.

2.4.4. Discussion on chemical, pharmaceutical and biological aspects

The active substance section of the dossier is identical to the approved Ozempic dossier (with the exception of minor updates) and is therefore considered approvable.

Finished products used in clinical trials were similar to Ozempic regarding the excipients, container closure system and DDC, but the to-be-marketed products are used with a single dose pen-injector and a formulation optimised for single use.

The finished product manufacturing process is straightforward and sufficiently described. Process characterisation/justification studies and PPQ studies generally support the process ranges/limits and product intermediate holding times.

The proposed specifications and acceptance criteria have been adequately justified.

The primary container closure system is a 1 mL pre-fillable syringe that is supplied sterile and ready-to-use. Descriptions are concise but contain all relevant details. PFSs are assembled into single-dose pen-injectors, for which extensive documentation is provided. The performance of the pen-injector is demonstrated to be consistent and robust.

Stability studies are performed using primary stability batches that are representative of the to-be-marketed finished products.

As requested during the procedure (major objection), the Applicant provided a risk evaluation on the potential presence of nitrosamines in the finished product. The outcome is satisfactory and no additional controls are necessary.

2.4.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of Wegovy is considered acceptable when used in accordance with the conditions defined in the SmPC. Physico-chemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

In conclusion, based on the review of the data provided, the marketing authorisation application for Wegovy is considered approvable from the quality point of view.

2.4.6. Recommendation(s) for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends a point for investigation.

2.5. Non-clinical aspects

2.5.1. Pharmacology

Semaglutide is a long-acting human glucagon-like peptide-1 (GLP-1) receptor agonist, which specifically activates the GLP-1 receptor (GLP-1R). Semaglutide is an Aib8, Arg34-GLP-1(7-37) analogue substituted with a side chain on the lysine residue in position 26. The side chain consists of two ADO (8-amino-3,6-dioxaoctanoic acid) spacers, one γ-glutamic acid (Glu) spacer, and a fatty diacid (1,18-octadecanedioic acid). Semaglutide is produced using recombinant DNA technology in yeast (Saccharomyces cerevisiae) and chemical modification. Semaglutide has a 94% structural homology to native GLP-1, a molecular weight of 4113,58 g/mol and is good soluble in an aqueous solution. Semaglutide is suitable for once-weekly administration in humans.

The pharmacological mechanism of GLP-1R agonists is well described in the literature, with blood glucose-lowering and body fat loss mediated by lowered intake of calories. The primary pharmacological target tissues for GLP-1R agonists are the pancreas (beta-cells), the gastrointestinal system and the brain. The amino acid sequence of GLP-1 is preserved in mammals, and only one receptor, the GLP-1R, has been identified. Rat and human GLP-1R have 90% homology, and monkey and human 99%. The GLP-1R is a G-protein coupled receptor, and the cellular action of GLP-1 is mediated through the G-protein and subsequent activation of adenylate cyclase, leading to increased cAMP accumulation.

2.5.1.1. Primary pharmacodynamic studies

Baby hamster kidney (BHK) cell membranes, stably expressing the human GLP-1 receptor, were used to characterize the in vitro pharmacological receptor effect of semaglutide using binding and functional studies on the human GLP-1 receptor. The binding affinity of semaglutide to the GLP-1 receptor in the membrane preparation, was found to be influenced by albumin concentrations.

The results of the functional, receptor activating, studies, measuring cAMP production, showed that semaglutide is a GLP-1 receptor agonist with a potency of 0.15 nM, which is comparable to liraglutide and 8-fold less potent than GLP-1 itself.

In an ex vivo study using rat isolated perfused pancreas, semaglutide stimulated insulin secretion dose-dependently. Two pancreas preparations were studied with increasing concentration of semaglutide, and the EC50 of insulin secretion was estimated to be ~14 nM.

The primary pharmacodynamic effect was evaluated in a number of animal models.

In normal male rats, the in vivo potency was estimated by dosing semaglutide subcutaneously (sc) followed by an i.v. glucose infusion 3 hrs later. Semaglutide stimulated plasma insulin secretion and lowered blood glucose at a dose of 123 µg/kg (~6 nM plasma exposure), and a trend towards stimulation was observed at 41 µg/kg.

In male diabetic db/db mice, upon single or repeated 4-week sc dosing, semaglutide lowered blood glucose dose-dependently and had a long duration of action. The ED50 for lowering of blood glucose (6 hours post-dosing) was estimated to be 1.2 µg/kg for semaglutide, whereas it was about 20-fold higher for liraglutide, indicating that semaglutide was more potent in vivo than liraglutide. The maximal effect on blood glucose-lowering was comparable for semaglutide and liraglutide, and was obtained at 4 - 8 µg/kg for semaglutide in the 4-week study. The effect on body weight was maximal at a dose of 21 µg/kg.

The beta-cell-reduced Göttingen minipig is a model in which the human conditions of impaired glucose tolerance are mimicked and resembles humans than rodent models. This model was used for the evaluation of the duration of action of GLP-1R agonists. In a hyperglycaemic clamp study in beta-cell-reduced minipigs, semaglutide stimulated insulin secretion for up to 7 days after the last dose (8.2 µg/kg) was administered.

GLP-1 and its analogues are, among other effects, able to reduce food intake, which is an important aspect in the treatment of obesity and diabetes. The subchronic efficacy of semaglutide on body weight reduction was evaluated in diet-induced obese (DIO) aged female rats, which were given chocolate in addition to normal chow for 9 months. Subcutaneous doses of 1.2 and 4.1 µg/kg once-daily for 77 days led to a dose-dependent, significant decrease in body weight, primarily from fat. Furthermore, semaglutide dose-dependently decreased overall food intake, which mainly consisted of chocolate. Leptin, total cholesterol, and free fatty acids were significantly decreased after treatment with semaglutide, while plasma glucose, HbA1c, insulin, glucagon and triglycerides were not changed.

The effects of semaglutide on hypothalamic appetite signals were evaluated in high-fat diet obese (DIO) mice. Dosing of semaglutide for 18 days (0.15 mg/kg, s.c., daily) significantly lowered body weight. This was associated with increased mRNA expression of the satiety peptide cocaine- and amphetamine-regulated transcript (CART) in the arcuate nucleus (ARC) in the hypothalamus. Expression levels of the hunger peptides neuropeptide Y (NPY) and Agouti-related peptide (AGRP) in the ARC in the hypothalamus were not different between semaglutide and vehicle but were lower than in the weight-matched vehicle group.

The effect and duration of semaglutide on lowering food intake were also studied in young, growing pigs. Steady-state plasma levels of semaglutide were achieved by dosing every other day at 21 µg/kg. When steady-state had been reached, dosing was stopped, and daily food intake was assessed. Semaglutide decreased food intake in pigs for at least 2 days after cessation of dosing. The potency of semaglutide for decreasing food intake was in magnitude comparable to liraglutide in pigs, but with a longer duration of action.

The access and neuronal interaction of semaglutide in the rodent (SD rat, C57BL mice) brain were investigated using peripherally administered fluorescently labelled semaglutide. Semaglutide was shown to have access to discrete brain regions expressing the GLP-1R, including some well-defined circumventricular organs. Fluorescently labelled semaglutide also gained access to brain regions protected by the blood-brain barrier (BBB), such as NTS (nucleus tractus solitarus) in the brain stem and in the hypothalamus, where it was present in CART positive neurons in the ARC. The fluorescent signal was lost in the GLP-1R Knock-Out (KO) mouse, suggesting dependence upon binding to the GLP-1 receptor. Electrophysiological measurements of mouse brain slices revealed that semaglutide (100 nM) directly stimulated Pro-opiomelanocortin (POMC)/CART neurons and indirectly inhibited neural activity in neurons expressing NPY.

The effect of semaglutide on the development of atherosclerosis was investigated in two hypercholesterolemic mouse models, the ApoE- and LDL-receptor KO mouse models, at sc doses of 4, 12 and 60 µg/kg administered once-daily for 13 or 17 weeks, respectively. These models are widely used to study

plaque formation when on a western diet (WD) consisting of high fat and carbohydrate content and 0.2% cholesterol.

In the LDLr KO mouse model, semaglutide showed a significant, about two-third, reduction of aortic plaque area at all three dose levels tested. This effect was accompanied by a significantly reduced body weight gain and a reduction in plasma TG levels with the highest dose, while plasma cholesterol and cholesterol lipoprotein levels were not changed by semaglutide treatment.

In the ApoE KO mouse, semaglutide treatment showed a significant attenuation of aortic plaque area at all three dose levels tested after 13 weeks of daily treatment. This effect was accompanied by a significantly reduced body weight gain with all doses.
In conclusion, the development of WD-induced aortic plaque lesion areas was attenuated by semaglutide in both KO models at all dose levels. The effect was partially independent of reduced body weight gain.

In conclusion, the efficacy pharmacodynamic studies have been conducted in vitro, ex vivo, and in vivo in normal, diabetic and obese rodent models and normal pigs and minipigs. The studies have shown that semaglutide has pharmacological properties consistent with a GLP-1R agonist showing increases in insulin secretion, plasma glucose-lowering and weight lowering due to reduced food intake.

Semaglutide for weight management

In support of the present indication for weight management, two new studies were performed to evaluate the mechanism of action of semaglutide in the brain concerning weight loss.

Semaglutide had access to distinct brain regions expressing the GLP-1R, including the circumventricular organs not protected by the blood-brain barrier (BBB). Semaglutide also reached select GLP-1R populations in brain regions protected by the BBB. These included several nuclei in the brain stem (in the NTS and the dorsal motor nucleus of the vagus nerve (DMX)) and in the hypothalamus (in the arcuate nucleus (ARH), among others). The access of fluorescent semaglutide to these sites contributes to the idea that the brain stem and hypothalamus are important regions for GLP-1R agonists central effects to regulate homeostatic food intake. In addition, fluorescent semaglutide was observed in the septum, including the lateral septal nucleus (LS).

The administration of semaglutide resulted in the activation of some brain regions as measured by increased expression of immediate early gene cFos. It should be noted that cFos expression does not specifically means GLP-1R activation, but rather general neuronal activation. cFos expression was seen in the circumventricular organs and the area postrema (AP) and the nucleus of the solitary tract (NTS) in the brain stem, areas known to be involved in regulating body weight. Further, deeper brain regions that were not directly targeted by semaglutide were positive for cFos, which included the parabrachial nucleus (PB), the midline group of the dorsal thalamus (MTN), bed nuclei of the stria terminalis (BST), and the central amygdala nucleus (CeA). These are areas associated with energy homeostasis and reward, and are potentially indirectly activated via projections from the brain stem, septum or hypothalamus. However, activation of these areas seems not solely mediated by semaglutide since the access of semaglutide or direct GLP-1R activation in these areas was not confirmed in these studies. Hence, the role of semaglutide for the proposed projections remains a theoretical possibility. In the cFos positive PB, a population of cells in the dorsal lateral nuclei was positive for neuropeptide calcitonin gene-related peptide (CGRP). As CGRP acts as an appetite suppressant in mice, this area might play a role in regulating food intake. However, the potential relevance for humans seems limited.

Overall, it was confirmed that semaglutide crosses the BBB and that its effects include central homeostatic mechanisms involving the hypothalamus and brain stem. Evidence for the direct involvement of the hedonic

system is limited, yet supported by semaglutide access to the septum. More evidence suggestive of the involvement of reward-related brain regions in the hedonic regulation of food intake included activation of deeper brain regions, possibly indirectly via projections from the homeostatic system that were directly accessible for semaglutide.

2.5.1.2. Secondary pharmacodynamic studies

A broad profiling screening panel using 68 biochemical receptors, ion-channels and neurotransmitter transporters did not show a competitive interaction with semaglutide. Also, semaglutide, up to 10 µM, did not activate the glucagon receptor. No secondary pharmacology effects are expected from semaglutide.

2.5.1.3. Safety pharmacology programme

The safety pharmacology studies were designed to investigate the effect of semaglutide on major organ function (central nervous system, respiratory system and cardiovascular system). Exposure measurements in both the rat CNS study and the cynomolgus monkey cardiovascular study exposure of treated animals confirmed exposure of treated animals could correlate to exposure. Due to differences in dosing frequency between humans (once weekly) and animals (daily/biweekly), the mean maximal plasma concentration (Cmax) at the maximum recommended human dose (MRHD) of 2.4 mg/week has been used for exposure comparison in the safety pharmacology section. A value of ~75 nM has been taken as the mean Cmax in humans at MRHD.

The effect of semaglutide on the central nervous system was studied in the rat CNS (Irwin) study. In this study, no significant gross behavioural or physiological changes were observed during the 24 h post-dose period in rats receiving subcutaneous treatment with semaglutide. Abnormal gait (walking on toes), passivity, decreased touch response, increased urination, lethargy and piloerection were observed in animals administered 95 µg/kg semaglutide, which corresponds to ~0.6 fold the maximal plasma (Cmax) exposure at the maximum recommended human dose (MRHD). The observed effects are considered pharmacology-related and likely due to the activity at GLP-1 receptors in the CNS. The No Observed Adverse Effect Level (NOAEL) was determined to be 22 µg/kg.

Semaglutide, given subcutaneously at doses up to 84 µg/kg, had no statistically significant effects on respiratory rate, tidal volume or minute volume up to 24 hours after dosing in male SD rats.

Treatment with semaglutide (>100-fold higher concentration than the mean maximal plasma concentration at the MRHD) produced no inhibition of hERG channel tail current recorded in HEK293 cells stably transfected with hERG cDNA, nor an effect on action potential parameters in isolated female rabbit Purkinje fibres. This indicates that semaglutide has a low potential for QT prolongation.

The acute effect of semaglutide on cardiovascular function was studied in male conscious unrestrained cynomolgus monkeys equipped with telemetry transmitters and dosed subcutaneously with ascending doses of semaglutide. No effects related to semaglutide were observed on arterial blood pressure (systolic, diastolic and mean) or the lead II ECG variables examined (RR, PR, QR, QTcF and QTcQ intervals or QRS duration). In conclusion, it was found that there were no clinically relevant findings in cynomolgus monkeys in single doses up to 470 µg/kg (about 6-fold above MRHD based on Cmax).

In addition, in the repeat dose toxicology study at week 13, 26 and 52, the cardiac electrophysiology was monitored by ECG in male and female telemetered cynomolgus monkeys (10, 60 and 360 µg/kg twice-weekly

sc). In this 52-week toxicity monkey study, a left-bundle-branch-block was observed in one female animal at high dose of 360 µg/kg (~10-fold above MRHD). The animal exhibited no clinical signs attributable to the ECG finding and histopathology revealed no correlating changes. Cardiac bundle-branch blocks are an occasional finding in monkeys and humans, and are in most cases a consequence of other underlying cardiac diseases. Although histopathology revealed no changes in the heart, the ECG finding was considered adverse. When heart rate was analysed as a change from baseline, it was shown that there seems to be a transient increase in heart rate at week 26, which returns to baseline values at week 52 in males but remains elevated at week 52 in high dose females. This finding supports the increase in heart rate seen in patients in the clinical trials.

A renal function study was performed to evaluate the acute effects of semaglutide on the renal system in the rat. Semaglutide caused an acute transient increase in diuresis during the first 8 hours after dosing at the highest doses (23 and 89 µg/kg) and a decrease in the diuresis parameters thereafter. These observations are well-known effects of GLP-1R agonists in the rat. Acute effects on diuresis have also been shown in humans with native GLP-1, but not following chronic administration of GLP-1R agonists. The NOAEL was determined to be 5 µg/kg.

2.5.1.4. Pharmacodynamic drug interactions

Nonclinical pharmacodynamic drug interaction studies have not been conducted with semaglutide, which is agreed upon. GLP-1R agonists have been reported to delay gastric emptying but this was evaluated in clinical trials.

2.5.2. Pharmacokinetics

Methods of analysis

The methods developed for the analysis of semaglutide in plasma with LC-MS/MS (mouse, rat, monkey) and ELISA (mouse, rabbit, monkey) were sufficiently validated with satisfactory assay performance.

The LOCI assay was affected by interference from the plasma matrix and dilution linearity issues with a larger impact on low concentrations, leading to underestimating semaglutide exposures (rat, rabbit, monkey). For this reason, the plasma assay in rat and monkey was replaced by LC-MS/MS and ELISA. In the rabbit embryo-foetal development study (207360), the measured concentration was below 200 nM, where Hook effect occurred, and the values for dose-normalized average concentrations (Cavg) did not deviate from the other tests.

Absorption

Single dose absorption and plasma pharmacokinetics

The pharmacokinetics were dose-proportional, and there was no gender dependency. The absorption of Semaglutide from the subcutaneous injection site was rapid in mouse and rat, but slower in rabbit, monkey and minipig. The time to maximum concentration (tmax) was 2 to 3 hours in mouse and rat, and about 24 hours in rabbit, monkey and minipig. The bioavailability ranged from 86% (monkey) to 94% (minipig). In human, the bioavailability was equally high (89%), but the absorption was slower (tmax 60 h).

The mean dose-normalized concentration was comparable in monkey and human, while it was lower in mouse, rabbit and rat due to faster clearance. The terminal half-life was estimated to be 8 h in the mouse, 11 hr in the rat, 28 h in the rabbit, 51 h in the monkey and 148 h in human.

The distribution volume was low (0.2 L/kg) following i.v. administration in the monkey, which corresponds approximately to the volume of extracellular water, indicates that a high fraction of semaglutide is circulating in plasma and extracellular fluid.

Comparing single-dose pharmacokinetics in monkeys after subcutaneous and intravenous dosing indicated that the absorption rate from subcutis does not limit elimination.

Distribution

Plasma protein binding

In-vitro binding studies showed that the plasma protein binding was high, >99%, and that albumin was the primary protein responsible for binding of semaglutide in plasma. The potential binding to other plasma proteins has not been studied. The fraction unbound was somewhat lower in plasma from mouse, rat and rabbit (0.07-0.28%) as compared to plasma from monkey (0.46%) and human (0.36%).

Distribution to red blood cells

As determined in rats, whole blood concentrations of semaglutide-related material were approximately half of the values in plasma, suggesting no preferential uptake into red cells.

Tissue distribution

Distribution studies in rats showed the highest presence of semaglutide-related material in blood and in highly perfused tissues.

After subcutaneous administration of [3H]-Oct- or [3H]-Tyr-labelled semaglutide, the tissue-to-blood ratios of semaglutide related material were generally below 1. The highest levels were associated with lung, tooth pulp, kidney (cortex and medulla), bladder, adrenal medulla and uterus. The high levels in the bile ducts, up to and including 3 days after dosing, suggests that biliary secretion may have played an important role in elimination by contributing to faecal excretion. In addition, the moderate levels of radioactivity present in the kidneys and bladder also suggest that urinary elimination occurred. The lowest concentrations were present in the central nervous system (brain and spinal cord) and white fat.

The distribution and concentrations of [3H]-Oct-semaglutide related material in male pigmented rats were similar to that in male albino rats, suggesting that semaglutide related material does not bind to melanin or accumulate in pigmented tissues.

Placenta transfer

Semaglutide related material passed the placental barrier in rats and rabbits, but distributed to foetal tissue at levels lower than in dam plasma (<4%). This suggests limited distribution across the placenta. Nevertheless, a single dose of semaglutide to pregnant rats at GD18, led to low, but measurable levels in foetuses at 24h post-dose and effects on the foetus were observed.

Excretion into milk

Semaglutide and metabolites are excreted into rat milk. Mean concentrations were 3-12 times lower than in plasma up to 24 hours after a subcutaneous dose 0.3 mg/kg/day semaglutide. There are no data on the

excretion of semaglutide in human milk. A risk to the newborns/infants cannot be excluded. Semaglutide should not be used during breastfeeding.

Metabolism

The in-vitro metabolism of radiolabelled semaglutide was studied in hepatocytes from rats, monkeys and humans. Limited metabolism was observed in all species, and no unique human metabolites were formed. It was shown that semaglutide is metabolised by proteolytic cleavage of the peptide backbone by neutral endopeptidase (neprilysin) and sequential beta-oxidation of the fatty acid side chain.

The in-vivo metabolism of semaglutide was investigated by chromatographic metabolite profiling of plasma, urine and faeces from rat, monkey and human following administration of radiolabelled semaglutide. The metabolite profiles from plasma were similar across species. The peptide backbone of semaglutide was metabolised by proteolytic degradation, and the fatty acid moiety was degraded by sequential beta-oxidation.

Semaglutide was the most abundant component in plasma across animal species, accounting for 69-93% of the total amount of semaglutide related material and 4 to 12 metabolites, which constituted only a small part concerning the amount unchanged semaglutide.

In human plasma, there were 6 metabolites, each contributing 0.4-7.7% to the total amount of semaglutide-related material, whereas the contribution of unchanged semaglutide was 83%. The largest metabolite (P3) contained at least three components (P3A, P3B and P3C). P3C was characterised as a semaglutide isomer. P3B was identified as a peptide metabolite from semaglutide, following proteolytic cleavage and the loss of the first 13 amino acids. Neprilysin was capable of forming the metabolite P3B in vitro. No further structural information could be provided P3A and P3C, due to the limited amounts in plasma. All human metabolites are also present in rats, and P3, P5 and P7 are also present in monkeys.

The two primary metabolites in human (U6 and U7) were identified as the free Lys26 amino acid bound to the ADO-linker with butyric (C4) or hexanoic (C6) di-acid side chains attached. These metabolites are products formed from full proteolytic cleavage of the peptide backbone with sequential removal of C2-units by beta-oxidation of the di-fatty acid side chain. The urine metabolite U22 was identified as semaglutide. Only limited amounts of unchanged semaglutide were observed in urine of animals (1%) and humans (3%).

The pharmacological activity of the metabolites has not been evaluated. These metabolites, such as P3B and P3C, may be pharmacologically active since they have structural similarities with semaglutide. The possible contribution of these metabolites to the pharmacological activity of the final product will be minor, because in plasma they are only a small part in relation to the amount of unchanged semaglutide (< 7.7%).

Excretion

Semaglutide was extensively metabolised prior to elimination. In human, unchanged semaglutide were observed in small amounts in human urine (3.1%), but was not detected in faeces. In rat and monkey, both urine and faeces were equally important as excretion routes of semaglutide and related material. The contribution of urinary excretion was 37% in rats and 30% in monkey, whereas the contribution of faecal excretion was 35% and 21% in these species, respectively. In human, the urinary excretion was the predominant route of excretion (53%), followed by faeces (18.6%).

In bile-cannulated rats, bile was the primary route for excretion of semaglutide-related material into faeces (48%), of which approximately 14% was unchanged semaglutide. Other components in bile were

metabolites, each accounting for less than 5% of the administered dose.

Pharmacokinetic drug interactions

The results of the in-vitro and in-vivo studies on the drug interaction potential of semaglutide have been evaluated in the clinical assessment report.

2.5.3. Toxicology

2.5.3.1. Single dose toxicity

A single dose up to 12mg/kg (mouse) or 7.532 mg/kg (rat) was generally well tolerated. Observed major findings such as reduced body weight and food intake showed quick recovery and can be related to the pharmacological action of semaglutide.

2.5.3.2. Repeat dose toxicity

Repeated dose studies in mice, rats and cynomolgus monkeys revealed mainly effects related to the pharmacological action of semaglutide. Reduction in food intake and body weight gain were dose-limiting, as exceeding the maximum tolerated dose in monkeys led to dehydration, consequently followed by euthanization. However, dose escalation improves tolerability.

Hypertrophy of Brunner's glands of the duodenum was observed in rats after 26 weeks of treatment. This effect is likely due to the high expression of GLP-1R on Brunner's glands. However, there was no progression to hyper- or neoplasia in the rodent carcinogenicity studies, and no similar observations in cynomolgus monkeys dosed for 52 weeks. Therefore, this observation is not considered a safety concern in humans. Thyroid C-cell hyperplasia was only observed in mice at all dose levels. This is an expected result also seen with other GLP-1 agonists and can be considered a class effect.

The 52-week monkey study revealed a chronic left bundle-branch-block in one high dose female. Although the abnormal ECG was confined to a single animal, the observation was considered adverse.

An increase in uterus fluid distension and luminal dilatation is seen in rats after 26 weeks of dosing. These findings are likely due to differences in the stage of the sexual cycle which could be treatment-related, and likely secondary to a reduction in body weight. Daily subcutaneous administration to Sprague-Dawley rats over a treatment period of 13 weeks with 0.48 mg/kg/day and 0.45 mg/kg/day semaglutide, respectively, demonstrated generally similar observations between two formulations based on two different manufacturing processes. Although there were a few minor differences, none was considered of any toxicological significance.

2.5.3.3. Genotoxicity

Semaglutide is not genotoxic *in vitro* or *in vivo*.

2.5.3.4. Carcinogenicity

In carcinogenicity studies in mice and rats, thyroid C-cell adenomas and carcinomas were observed at all

dose levels. This is an expected result also seen with other GLP-1 agonists and can be considered a class effect. No other tumours were found. Other non-neoplastic effects were secondary to the decreased body weight gain related to the pharmacological action of semaglutide. To determine whether the thyroid C-cell tumours are indeed caused by the same mechanism as is responsible for C-cell tumours observed after treatment with GLP-1 agonists, the applicant performed some mechanistic studies. The activation of the GLP-1R was tested in vitro on a thyroid C-cell tumour cell line and compared to GLP-1, exenatide and liraglutide. It was shown that the potency of semaglutide to activate the receptor was similar to liraglutide, and less potent than GLP-1 and exenatide.

Increased plasma calcitonin concentration is considered a marker for increased activation of GLP-1R on the thyroid C-cells. Upon chronic activation, this leads to up-regulation of calcitonin synthesis and further to C-cell proliferation and tumour formation. Therefore, the applicant performed in vivo studies in mice and rats, which show that even after a single 1 mg/kg dose of semaglutide in mice, plasma calcitonin levels were increased 12 and 24 hours after injection. However, in rats, an increased calcitonin level was not seen in females and not very convincingly in males after 6 weeks of treatment. This could be due to the very short half-life of calcitonin in rats of 4 minutes or a delayed effect which is still not apparent after 6 weeks. Further, an inconsistent effect on calcitonin levels in rats was also seen for liraglutide. Overall, the mechanism of formation of rodent thyroid C-cell tumours is well known and discussed in the public literature. There is no reason to suggest a different mechanism might be responsible for the C-cell tumours observed after treatment with semaglutide, and therefore the thyroid C-cell tumours are likely rodent specific. Since relevance for humans cannot be completely ruled out, thyroid C-cell tumours are listed in the RMP as potential risk.

2.5.3.5. Reproductive and developmental toxicity

Semaglutide caused embryotoxicity in the rat. The observed effects included embryo-foetal mortality, growth retardation, and skeletal and visceral abnormalities. The effects were observed at dose levels of 0.03 mg/kg/day and above, with AUC exposures below the clinical exposure at the MRHD of 2.4 mg/week. The applicant describes a mechanism of action for the embryotoxic effects observed in the rat reproduction study, which involves the presence of GLP-1R on the yolk sac. Semaglutide binds to the receptors on the yolk sac, leading to inhibition of transport of nutrients across the membrane. This mechanism is likely rat specific, since rat embryos are dependent on the yolk sac for their nutrient supply which is, e.g. less important in other species including humans and monkeys. Moreover, GLP-1R is not expressed on monkey yolk sacs.

It is agreed that the mechanism demonstrated is specific for rats, and could explain the malformations seen in the rat foetuses. Although undoubtedly this mechanism is responsible for most of the malformations observed, it cannot be excluded that other mechanisms that may not be rat specific are also involved. This is based on the fact that not only more and other malformations are present, but also foetal weight is much further reduced in embryos of dams treated up to GD17 as compared to GD13. This is after the period (GD12) in which embryos are solely dependent on the yolk sac for nutrition, but also rely on the developing chorioallantoic placenta. Although the additional skeletal abnormalities that occur between GD13 and GD17 could still be due to the impaired yolk sac, due to the presence of the GLP-1R on the rat embryo from GD13.5 and the presence of low levels of semaglutide in the foetus as measured on GD20, a direct effect of semaglutide on the foetus, of which the clinical relevance is unknown, cannot be excluded. It appears that a potential direct effect of semaglutide is only relevant in the later stages of pregnancy in rats, since the receptor is not present before GD13.5. Timing of receptor expression, if this is relevant for humans at all, is unknown, but a potential risk for humans is mitigated through the labelling in SmPC section 4.6, where it is

stated that semaglutide should not be used during pregnancy and women of childbearing potential should use contraception to avoid unplanned pregnancies. Any further risk mitigation measures are not warranted.

A second embryo-foetal toxicity study was performed in rabbits. Once-daily SC administration of semaglutide to pregnant New Zealand White rabbits markedly reduced maternal body weight and food consumption. This coincided with increased post-implantation losses, incomplete ossification of foetal metacarpals/phalanges, and increased incidences of minor skeletal and visceral foetal abnormalities. The increased post-implantation losses and the foetal pathology findings were possibly secondary to the marked maternal effects, but a direct effect of semaglutide could not be excluded. On the other hand, marked maternal toxicity could also mask a direct effect on the embryo or foetus. Although exposure in the high dose group at GD19 was above the human exposure, it was below human exposure at GD6. The Applicant attributes the observations in the rabbit as described above, primarily to the maternal effects on body weight and food consumption. Delayed ossification observed without concomitant decreases in foetal body weight may warrant increased attention (Carney and Kimmel 2007). However, as the mid and high-dose dams showed lower body weight gains on GD 6-19, and higher than control body weight gains on GD 20-29, any decreased foetal body weights in the mid and high dose groups may have been recovered at termination of the study when the foetal examinations were performed.

Cynomolgus monkeys were used as a third species for embryo-toxicity testing of semaglutide, since monkeys do not rely on a yolk sac for nutrition. In all dose groups, the pregnant females had an initial loss of body weight, and a lower body weight gain as compared to control animals. There were 2 cases of abortion in all dose groups as compared to 1 in the control group. The incidence of 2 out of 16 (12.5%) is close to the incidence of pregnancy loss in cynomolgus monkey controls reported in literature of 11.5% up to GD75 (Jarvis et al, Birth Defects Research (Part B) 89:175–187 (2010)).

Further, two major malformations were reported in the study. In the mid-dose group, a single foetus had a fused kidney, and in the high dose group, there was one foetus with a misshapen brain. These effects have not previously been reported in historical controls from the same testing site. However, a relevance for humans is unlikely due to the lack of a mechanistic relation to semaglutide and lack of similar findings in other studies. Moreover, any potential risk is mitigated through the labelling in SmPC section 4.6.

There was no effect on postnatal development in offspring of cynomolgus monkeys treated with semaglutide until GD140. Initial maternal body weight losses likely led to an increased incidence of early pregnancy loss and reduced foetal weight in the mid and high dose. No other effects were observed.

A juvenile study was performed where rats from the age of 21 days were dosed for 11 weeks. Apart from general signs of toxicity, sexual maturation and fertility were investigated. Sexual maturation was delayed for both sexes, but this did not coincide with effects on fertility or mating performance. No histopathological findings were noted, and therefore it is considered likely that the delay is due to the decreased body weight gain of the treated animals. No new findings were seen in these juvenile animals that were not seen in the adult animals. This study is of limited relevance in the current procedure, as the indication applied for is in adults only.

2.5.3.6. Toxicokinetic data

The pharmacokinetics following repeated dosing of subcutaneous semaglutide showed a linear relationship between doses and exposures. No gender differences were noted. The dose normalised exposure was generally lower for mice, rats, rabbits and minipigs compared to monkeys and humans due to faster clearance. To ensure continued exposure, and to mimic the once-weekly exposure profile in humans, once-

daily dosing was used in mice and rats, and twice-weekly dosing was used in monkeys. At these dose intervals, there was no apparent (i.e. < 2-fold) systemic accumulation.

No difference in exposure was observed between pregnant and non-pregnant animals following repeated administration of semaglutide to rats, rabbits and monkeys. However, rabbits showed some accumulation in the embryofoetal development study, but the wide range (1.3 up to 13-fold) and the few data do not permit a clear conclusion.

2.5.3.7. Local Tolerance

In a local toxicity study in pigs using the subcutaneous route of administration only mild effects related to the vehicle or injection procedure were seen. Further, in all pivotal toxicity studies the subcutaneous route of administration was applied, and therefore local toxicity is considered sufficiently investigated and no concerns for human safety were identified.

In clinical practise it is possible that the product will be administered by intravenous, intra-arterial or intramuscular routes by mistake. Therefore, possible adverse effects were investigated in rabbits using these routes of administration. No adverse effects were seen other than mild effects related to the vehicle or injection procedure.

2.5.4. Ecotoxicity/environmental risk assessment

The active substance is a peptide. Therefore, semaglutide is not expected to pose a risk to the environment.

2.5.5. Discussion on non-clinical aspects

In support of the present indication for weight management, two new studies were performed to evaluate the mechanism of action of semaglutide in the brain in relation to weight loss.

It was confirmed that semaglutide crosses the BBB, and that its effects include central homeostatic mechanisms involving the hypothalamus and brain stem. Evidence for the direct involvement of the hedonic system is limited, yet supported by semaglutide access to the septum. More evidence suggestive of the involvement of reward-related brain regions in the hedonic regulation of food intake included activation of deeper brain regions, possibly indirectly via projections from the homeostatic system that were directly accessible for semaglutide.

The active substance is a natural substance, the use of which will not alter the concentration or distribution of the substance in the environment. Therefore, semaglutide is not expected to pose a risk to the environment.

2.5.6. Conclusion on the non-clinical aspects

The pharmacology, safety pharmacology, pharmacokinetics and toxicology programs are considered sufficient.

2.6. Clinical aspects

2.6.1. Introduction

GCP aspects

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the Community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- **Tabular overview of clinical studies**

A total of eight studies with semaglutide S.C. have been executed to support the weight management indication, and six are ongoing. The trials from the weight management program are shown in **Table 10** and **11**.

Previous clinical studies that were submitted to support the application of Ozempic are listed in **Table 12** but only discussed in this report when relevant for the current application.

Table 3: Completed clinical trials in the semaglutide s.c. 2.4 mg weight management development programme (NN9536) included in the application

Trial	Subjects	Brief description
Phase 3a		
Trial 4373 (STEP 1) weight management	N=1961	68-week, randomised, double-blind trial comparing the efficacy and safety of semaglutide s.c. 2.4 mg once weekly vs placebo, as an adjunct to lifestyle intervention, in adults with overweight or obesity.
Trial 4374 (STEP 2) weight management in T2D	N=1210	68-week, randomised, double-blind trial comparing the efficacy and safety of semaglutide s.c. 1.0 mg and 2.4 mg once weekly vs placebo, as an adjunct to lifestyle intervention, in adults with overweight or obesity and T2D.
Trial 4375 (STEP 3) weight management with IBT	N=611	68-week, randomised, double-blind trial comparing the efficacy and safety of semaglutide s.c. 2.4 mg once weekly vs placebo, as an add-on to intensive behavioural therapy (IBT), in adults with overweight or obesity.
Trial 4376 (STEP 4) sustained weight management	N=902	68-week, randomised, double-blind, placebo-controlled trial comparing the efficacy and safety of semaglutide s.c. 2.4 mg once weekly vs placebo in adults with overweight or obesity who had reached the maintenance dose of semaglutide (2.4 mg) during a 20-week run-in period.
Phase 2		
Trial 4153 dose-finding	N=957	52-week, randomised, double-blind, placebo-controlled, 16-armed trial with liraglutide 3.0 mg as active comparator evaluating different doses of semaglutide administered once daily at doses from 0.05 mg/day to 0.4 mg/day in adults with obesity, following two different escalation schemes.
Clinical pharmacology		
Trial 4455 pharmacodynamics	N=72	21-week, randomised, double-blind, placebo-controlled trial investigating the effect of semaglutide 2.4 mg once-weekly on gastric emptying in adults with obesity.
Trial 4590 bioequivalence 1.0 mg and 2.4 mg	N=68	21-week, randomised, open-label trial to demonstrate bioequivalence between semaglutide formulation D with the single-dose pen-injector (DV3396) and semaglutide formulation B with the PDS290 pen-injector in adults with overweight or obesity.
Trial NN9535-4588[a] bioequivalence 0.25 mg	N=68	7-week, randomised, open-label trial to demonstrate bioequivalence between semaglutide formulations D for the single-dose pen-injector and semaglutide B formulation for the PDS290 pen-injector in adults with overweight or obesity.

[a] In trial NN9535-4588 (conducted as part of the Ozempic programme), bioequivalence was assessed at doses of 0.25 and 1.0 mg, however only the 0.25 mg dose is relevant for the weight management indication. IBT: Intensive Behavioural Therapy; T2D: type 2 diabetes. N: number of randomised subjects.

- **Table 4 Ongoing clinical trials in the semaglutide s.c. 2.4 mg weight management development programme (NN9536) included in the application**

Trial	Subjects	Brief description
Phase 3a		
Trial 4373 (STEP 1) ext Off-treatment extension phase	N=300	45-week extension period off all treatments, including trial product and lifestyle interventions, to explore sustained efficacy after treatment discontinuation in a subset of subjects participating in the main phase of STEP 1.
Trial 4382 (STEP 6) East Asian trial	N=400	68-week, randomised, double-blind, placebo-controlled trial investigating the effect and safety of semaglutide s.c. once weekly in East Asian adults with overweight or obesity.
Trial 4451 (STEP TEENS) Adolescents (12-17 years)	N=192	68-week, randomised, double-blind, placebo-controlled trial investigating the effect and safety of semaglutide 2.4 mg once weekly on weight management in adolescents with overweight or obesity.
Phase 3b		
Trial 4378 (STEP 5) Long-term weight management	N=300	104-week, randomised, double-blind, placebo-controlled trial investigating the two-year effect and safety of semaglutide s.c. 2.4 mg once weekly in adults with overweight or obesity.
Trial 4576 (STEP 8) Sema 2.4 mg vs lira 3.0 mg	N=336	68-week, randomised, open label, pairwise placebo-controlled, US trial comparing effect and safety of semaglutide s.c. 2.4 mg once weekly vs liraglutide 3.0 mg once daily in adults with overweight or obesity.
Trial 4388 (SELECT) CVOT	N=17500	Event-driven, randomised, double-blind, placebo-controlled trial investigating semaglutide effects on cardiovascular outcomes in adults with overweight or obesity. Estimated trial duration for an individual subject is from 31 to 59 months.

Ongoing is defined as a trial that had first patient first visit but not yet database lock at the time of the MAA cut-off date. Ext: extension; sema: semaglutide; lira: liraglutide; CVOT: cardiovascular outcome trials; N: planned number of randomised subjects.

- **Table 5 Clinical studies with semaglutide, previously submitted to support the application of Ozempic**

Study	Population	Objectives of the study	Test product(s); Semaglutide dose	Number of subjects in full analysis set
Phase 1				
1820	Healthy	First in human, dose escalation safety, PK and PD	0.625, 1.25, 2.5, 5, 10, 20, 40 and 80 µg/kg; single s.c dose	56 (M: 56, F: 0)
3679	healthy	Equivalence -product strength	1.0 mg/mL, 3.0 mg/mL and 10.0 mg/mL; single s.c. dose of 0.8 mg	44 (M: 44, F: 0)
3687	healthy	Equivalence -product strength / Bioavailability	1.0 mg/mL, 3.0 mg/mL and 10.0 mg/mL; single s.c. dose of 1.0 mg single i.v. dose of 0.25 mg	42 (M: 25, F: 17)
4010	healthy	Bioequivalence two manufacturing processes	Single s.c. 0.5 mg dose (1.34 mg/mL)	28 (M: 12, F: 16)
3633	healthy Japanese and Caucasian	Multiple dose-Caucasian/Japanese dose escalation trial	Multiple s.c. 0.1 mg, 0.2 mg, 0.4 mg, 0.8 mg, 1.2mg dose	84 (M: 84, F: 0)
3634	healthy Japanese and Caucasian	PK/PD-Caucasian / Japanese	1.34 mg/mL; 0.5 and 1.0 mg, multiple s.c. doses	44 (M: 44, F: 0)

Study	Population	Objectives of the study	Test product(s); Semaglutide dose	Number of subjects in full analysis set
3789	healthy	ADME	Labelled 0.5 mg, single s.c. dose	7 (M: 7, F: 0)
3616	healthy, mild, moderate, severe, ESRD	Renal impairment	0.5 mg and 10 µg/kg, single s.c. dose	0.5 mg: 56 (M: 34, F: 22); 10 µg/kg: 6 (M: 5, F: 1)
3651	healthy, mild, moderate, severe	Hepatic impairment	1.34 mg/mL; 0.5 mg, single s.c. dose	44 (M: 21, F: 23)
3817	healthy	DDI metformin and warfarin	1.34 mg/mL; 1.0 mg, multiple s.c. doses. Warfarin 5 mg; single 25 mg oral dose. Metformin 500 mg; twice daily, multiple oral dose	23 (M: 13, F: 10)
3818	healthy	DDI atorvastatin and digoxin	1.34 mg/mL; 1.0 mg, multiple s.c. doses. Atorvastatin 40 mg; single oral dose. Digoxin 0.25 mg; 0.5 mg single oral dose	31 (M: 15, F: 16)
3819	T2D	DDI oral contraceptives1.0 mg, multiple s.c. doses; Microgynon (EE 0.03 mg/LNG 0.15 mg)	43 (M: 0, F: 43)	
3652	healthy	QTc	1.34 mg/mL; 1.5 mg, multiple s.c. doses. Moxifloxacin 400 mg; single oral dose	166 (M: 99, F: 67)
Phase 2				
3685	obese	Energy intake, appetite sensations, postprandial glucose and triglyceride metabolism, and gastric emptying	1.34 mg/mL; 1.0 mg, multiple s.c. doses	30 (M: 20, F: 10)
3635	T2D and healthy	Effects on β cell function	1.34 mg/mL; 1.0 mg, multiple s.c. doses	87 (M: 59, F: 28)
3684	T2D	Hypoglycaemia counter-regulation	1.34 mg/mL; 1.0 mg, multiple s.c. doses	37 (M: 25, F: 12)
1821	T2D	Dose finding + effect gastric emptying (paracetamol)	(1.0 mg/mL and 10 mg/mL); 0.1, 0.2, 0.4, 0.8 and 1.6 mg once-weekly; s.c. doses	411 (M: 267, F: 144)
Phase 3				
3623	T2D drug-naïve	Efficacy and safety (vs placebo (SUSTAIN 1)	1.34 mg/mL or semaglutide-placebo solution; 0.5 and 1.0 mg once-weekly; s.c. doses	387 (M: 210, F: 177)
3626	T2D (on treatment with metformin and/or TZDs)	Efficacy and safety (vs sitagliptin (SUSTAIN 2)	1.34 mg/mL solution; 0.5 and 1.0 mg once weekly, s.c. doses. Sitagliptin, 100 mg once daily, oral doses	1225 (M: 620, F: 605)
3624	T2D (on treatment with 1-2 OADs)	Efficacy and safety (vs exenatide ER (SUSTAIN 3)	1.34 mg/mL solution; 1.0 mg once-weekly; s.c. doses. Exenatide ER; 2.0 mg once-weekly; s.c. doses	809 (M: 447, F: 362)
3625	T2D, (insulin-naïve, on treatment with metformin with or without SUs)	Efficacy and safety (vs insulin glargine (SUSTAIN 4)	1.34 mg/mL solution; 0.5 and 1.0 mg once-weekly; s.c. doses. Insulin glargine 100 IU/mL; initial dose of 10	1082 (M: 574, F: 508)

Study	Population	Objectives of the study	Test product(s); Semaglutide dose	Number of subjects in full analysis set
			IU, then treat-to-target once-daily; s.c. doses	
3627	T2D (on treatment with basal insulin with or without metformin)	Efficacy and safety (vs placebo(insulin)(SUSTAIN 5)	1.34 mg/mL or semaglutide-placebo solution; 0.5 and 1.0 mg once-weekly; s.c. doses	396 (M: 222, F: 174)
4092	T2D Efficacy and safety (vs sitagliptin)	1.34 mg/mL solution; 0.5 and 1.0 mg once-weekly; s.c. doses. Sitagliptin, 100 mg once daily, oral doses	308 (M: 235, F: 73)	
4091	T2D (on treatment with 1 OAD [SU, glinide, α-GI or TZD])	Efficacy and safety (vs OAD)	1.34 mg/mL solution; 0.5 and 1.0 mg once-weekly; s.c. administration. One OAD (SU, glinide, α-GI or TZD); dosing and administration as appropriate	600 (M: 429, F: 171)
3744	T2D (on treatment with 1-2 OADs or with insulin [basal, long-acting or premixed] with or without 1-2 OADs, or T2D drug-naïve)	Safety (vs placebo, CVOT (SUSTAIN 6)	1.34 mg/mL or semaglutide-placebo solution; 0.5 and 1.0 mg once-weekly; s.c. doses	3297 (M: 2002, F: 1295)

2.6.2. Clinical pharmacology

2.6.2.1. Pharmacokinetics

The pharmacokinetics of semaglutide up to a s.c. dose of 2.4 mg were extensively characterised during the weight management and T2D clinical pharmacology programme.

Semaglutide pharmacokinetics profile is suitable for once-weekly subcutaneous administration due to the prolonged-release characteristics (e.g. albumin binding, slow-release from subcutis and reduced degradation by enzymes).

Semaglutide should be carefully up-titrated due to the occurrence of GI-adverse effects. An exposure-response relationship was observed for gastrointestinal adverse events, but tolerance for gastrointestinal adverse events develops over time. Therefore, it is recommended to escalate the dose every 4 weeks.

Methods

During the weight management program, appropriately validated LC-MS/MS assays were used to analyse semaglutide in plasma. Assay interference was not detected in hyperlipidaemic matrix.

A multi-tiered approach has been used to assess the anti-semaglutide and neutralizing antibodies. In general, the assay validation was adequately performed, and no lipemic interference was detected in the immunogenicity assays. The employed four-tiered strategy, including a screening, confirmatory, cross reactivity to endogenous glucagon-like peptide-1 (GLP-1) and neutralization assay, agrees with the draft Guideline on Immunogenicity assessment of biotechnology-derived therapeutic proteins (EMEA/CHMP/BMWP/14327/2006 Rev. 1). Confirmatory and cross-reactivity cut points were determined to 8.0455, 23.78 and 19.03, respectively, in obese matrix and at 100 ng/mL and 500 ng/mL antibody. The ADA assay had some limitations. Drug tolerance was demonstrated up to 2 nM semaglutide for detection of 100

ng/mL ADA, respectively, for obese. However, at steady-state semaglutide concentrations of above 100 nM were reached at the 2.4 mg maintenance dose. Although the ADA assay was able to detect high levels of ADAs (>500 ng/mL) in presence of >100 nM semaglutide, sensitivity was not shown for lower levels of ADAs, so false negatives cannot be excluded.

In the previously conducted studies in the T2D clinical pharmacology programme, the same or very similar LC-MS/MS assays were used to analyse semaglutide in plasma and urine. Further, in some early studies of the T2D clinical pharmacology programme, bioanalytical LOCI assay has been used to detect semaglutide in plasma.

The plasma concentration-time data for semaglutide were analysed by non-compartmental methods and standard pharmacokinetic parameters have been calculated ($AUC_{0\ 168h}$, C_{max}, t_{max}, CL/F, $t_{½}$ and V_{ss}/F). Descriptive statistics of PK variables and power calculations have been provided. In the studies 4590 and NN9535-4588, bioequivalence was assessed for the endpoints $C_{max,ss}$ and $AUC_{0\text{-}168h}$ (log-transformed) and analysed separately using an ANCOVA model with treatment (semaglutide/single-dose pen-injector and semaglutide/PDS290 pen-injector) and stratification category (body weight 70.0−99.9 kg or 100.0−130.0 kg) as factors and the logarithm of body weight as a covariate.

Dose-proportionality between semaglutide 1.0 mg and 2.4 mg doses was assessed separately. The ratio $AUC_{0\ 168h,2.4\ mg}/AUC_{0\text{-}168h,1.0mg}$ was estimated with 95% CI. The same analysis was done for $C_{max.}$

In the T2D clinical pharmacology programme, the plasma concentration-time data for semaglutide were analysed by non-compartmental methods, and standard pharmacokinetic parameters have been calculated. Descriptive statistics of PK variables and power calculations have been provided for all PK/PD studies. In general, the pharmacokinetic endpoints were analysed and compared between treatments using normal linear models (ANCOVA) with the log-transformed endpoint as the dependent variable. Fixed and random factors were taken into account as independent variables. The software used to calculate and compare the pharmacokinetic parameters in the clinical trials was Kinetica or SAS release 9 or higher on a UNIX platform.

The applicant submitted two population pharmacokinetic models. The initial was a one-compartment model based on pharmacokinetic samples (mainly through samples, collected at about 168h since last dose) obtained in the STEP1 and STEP2 phase 3 trials. The objectives were to evaluate the dose proportionality of the pharmacokinetics of semaglutide and the impact of covariates on semaglutide exposure. An updated population model was provided upon request, as the initial model was based on sparse data only. A limited amount of rich data included in the new 2-compartment analysis.

The initial model had a one-compartment structure with first-order absorption and first-order elimination, it was used to describe the pharmacokinetics of semaglutide. The absorption rate constant was fixed to a value of 0.0296 h-1, based on earlier clinical pharmacology trials in normoglycaemic and type 2 diabetes subjects. Between-subject variability was included for CL/V and V/F and assumed to have a log-normal distribution. Residual variability was described by a proportional error model. The population pharmacokinetic model comprised 11827 pharmacokinetic observations from 2077 subjects. Model parameters are displayed in Table 13.

Table 6: Parameter estimates from the initial model of semaglutide PK

Parameter	Labels	Estimate	CI95.lower	CI95.upper	pct.RSE	IIV.pct.CV	Shrinkage.pct
KA [1/h]	Absorption rate constant	0.0296	Fixed	Fixed	Fixed	NA	NA
CL/F [L/h]	Apparent clearance	0.0475	0.0465	0.0484	1.02	17.7	16.3
V/F [L]	Apparent volume of distribution	12.4	12	12.9	1.86	39.9	45.4
CL.sex	Sex factor on CL/F	1.08	1.06	1.11	1.14	NA	NA

CL.black	Race factor on CL/F (Black or African American)	0.93	0.891	0.969	2.12	NA	NA
CL.asian	Race factor on CL/F (Asian)	1.03	0.996	1.05	1.47	NA	NA
CL.aminal	Race factor on CL/F (American Indian or Alaska Native)	1.04	0.98	1.1	2.89	NA	NA
CL.BW	Baseline body weight exponent on CL/F	0.849	0.794	0.903	3.27	NA	NA
CL.mild	Renal function factor on CL/F (Mild)	0.958	0.939	0.978	1.04	NA	NA
CL.modSev	Renal function factor on CL/F (Moderate)	0.945	0.9	0.99	2.44	NA	NA
CL.predia	Glycaemic status factor on CL/F (Prediabetes (STEP 1))	1.04	1.02	1.06	1.17	NA	NA
CL.dia	Glycaemic status factor on CL/F (Diabetes (STEP 2))	1.18	1.15	1.21	1.18	NA	NA
V.BW	Baseline body weight exponent on V/F	0.761	0.596	0.926	11.1	NA	NA
Prop. Error [%]	Proportional residual error	27.3	NA	NA	NA	NA	7.93

Based on published data (Diabetes Ther 2019 10:649–662), it appeared that a 2-compartment model including rich PK data may be more appropriate to describe the PK of semaglutide. The applicant was therefore requested to evaluate 2-compartmental behaviour in an informative dataset. In the updated population pharmacokinetic model, results of nine dense sampling studies (two single dose and seven multiple dose clinical pharmacology trials in healthy volunteers) and sparse sampling studies: one phase 2 trial, and two phase 3a trials (step 1 and 2). The Applicant performed a new modelling exercise fitting the sparse data in the obese population to a 2-compartment model with first-order elimination. The effect of each covariate was evaluated by comparing the 90% CI to the 0.80-1.25 exposure level using the full model approach. A one-compartment model was again the better model. No new parameter estimates and goodness-of-fit plots have been provided. Therefore, the predictive performance of the updated model could not be assessed. However, the parameter estimates of the updated population PK model of semaglutide was compared to the initial phase 3a population PK model of semaglutide and both models were in good agreement. As limited rich data were included in the new 2-compartment analysis for a thorough evaluation of covariates effects on other parameters than CL. The impact of changing injection sites was evaluated between injection site arm or thigh and abdomen was not significant for CL (exposure ratio 0.96). Injection site arm and thigh could not be evaluated separately.

Further, an exposure-response analysis was conducted. The relationship between the C_{avg} and weight loss and C_{avg} and gastro-intestinal adverse events was analysed. The average concentration (C_{avg}) was calculated based on the individual parameter estimates of CL/F using the reduced population pharmacokinetic model, using STEP1 and STEP2 phase 3 trials. If no concentration data was available, this concentration was derived from the population prediction of this individual. Missing body weight information at week 68 was predicted using a mixed model for repeated measures (MRMM) to the observed on-treatment body weight data. Only observations from patients that were on randomised treatment were included (thus no discontinuation data/follow-up data). An unstructured covariance matrix was used. Also, a completer dataset was constructed with only subjects who were on-treatment and had measurable plasma concentrations.

The bodyweight model is displayed below.

Bodyweight (change from baseline) = E_0 [placebo effect] + Emax * (1 + I_{sex}) * C_{avg} / (C_{avg} + EC_{50}) [Drug effect] + E_{cov} [Covariate effects of bodyweight, sex and study] + e [residual error]

Also, linear and Sigmoid drug effects were evaluated as well as additional covariates (age, BMI, race, ethnicity, glycaemic status) on E_0, Emax and EC_{50}. For weight loss categories, the same final model was used but scaled to the logit domain.

The gastro-intestinal adverse event model is displayed below:

Logit(P(GI=Y)) = E_0 [placebo effect] + E_{sema}*C_{avg} [Drug effect] + E_{cov} [Covariate effects of bodyweight, sex and study]

A total of 3171 subjects were included in the exposure-response analysis. The parameter estimates for bodyweight and gastro-intestinal adverse events is displayed in Table 14 and

Table 15.

Table 7: Parameter estimates from the final exposure-response model of body weight % change from baseline

Parameter	Full analysis set Estimate	Full analysis set SE	Completer set Estimate	Completer set SE
E0 (pct)	-2.60	0.30	-3.20	0.34
BW cov,E0 (pct)	-0.01	0.01	-0.02	0.01
Male cov,E0 (pct)	0.10	0.45	0.30	0.51
STEP 2 cov, E0 (pct)	-0.61	0.39	-0.30	0.44
Emax (pct)	-44.57	9.77	-39.43	8.49
Male cov, Emax	-0.25	0.05	-0.29	0.06
Black or African American cov, Emax	-0.18	0.06	-0.21	0.07
Asian cov, Emax	-0.26	0.04	-0.26	0.04
American Indian or Alaska Native cov, Emax	-0.30	0.14	-0.37	0.16
HbA1c cov, Emax	-0.16	0.03	-0.16	0.03
EC50 (nmol/L)	222.88	66.13	187.92	57.58

SE: Asymptotic standard error of parameter estimate

Table 8: Parameter estimates from the final exposure-response model proportion of subjects reporting gastro-intestinal effects of any kind and severity.

Parameter	Estimate	SE
Emax	1.448	0.203
EC50 (nmol/L)	15.746	9.979
E0	0.058	0.075
STEP 2 cov	-0.364	0.092
Male cov	-0.576	0.085
BW cov	0.004	0.002

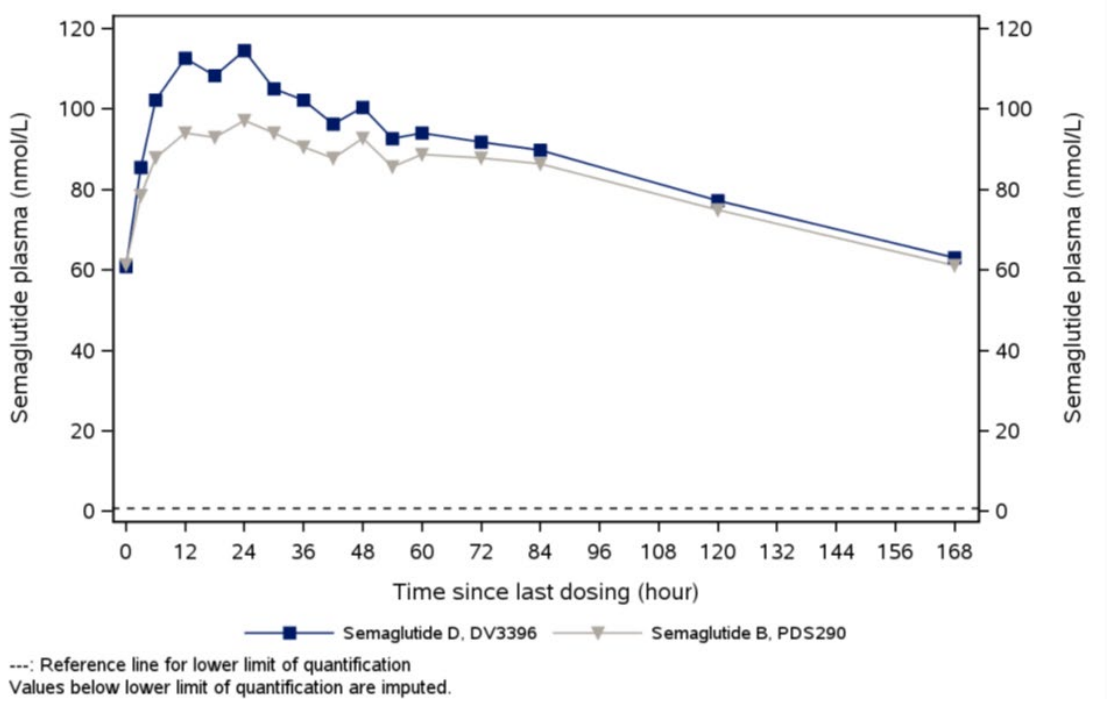
Estimated parameters are expressed on the underlying logit scale. SE: Asymptotic standard error of parameter estimate

Absorption

Absorption of semaglutide is relatively slow. Following sc injection, semaglutide 2.4 mg dosed in the to be marketed single-dose pen-injector had a median time to maximum concentration (t_{max}) of 24 hours with an observed range of 3–48 hours. Steady-state concentrations were achieved after approximately 4 weeks, with a C_{maxss} and $AUC_{0\text{-}168h}$ of 118 nmol/L and 14572 nmol*h/L, respectively. Steady-state concentration-time profiles for semaglutide 2.4 mg is presented in **Figure 3**.

The absolute bioavailability was estimated to be 89% after abdominal SC administration. Comparable steady-state concentrations have been observed between injection sites (upper arm, thigh and abdomen) for Ozempic, in the type II diabetes population (popPK study), but has not been evaluated in obese subjects. Systemic concentrations were maintained at the same level for about 7 days after administration of a single dose. Steady-state concentrations were achieved after 4-5 weeks, and fluctuation between $C_{max,ss}$ and $C_{through,ss}$ was small.

Figure 1: Semaglutide 2.4 mg dosing interval profiles at steady state – geometric mean plot – full analysis set (study 4590)



A multiple-dose pen-injector, Semaglutide PDS290, was used in the four clinical phase 3 trials of the semaglutide weight management programme (Study 4373, 4374, 4375, and 4376). To improve the ease of use, a patient-friendly single-dose pen-injector, semaglutide DV3396 has been developed. Two bioequivalence studies (4590 and NN9535-4588) were submitted to support the change from the formulation used in the phase 3a trials to the to-be-marketed formulation: the single-dose pen-injector DV3396.

In bioequivalence study 4590, bioequivalence between the DV3396 and PDS290 formulations was shown for the 2.4 mg strength, at steady-state and for the 1.0 mg strength, also at steady state (Table 16). Further, descriptive statistics of the semaglutide trough levels for other different dose levels were presented (

Table 17).

Table 9 Pharmacokinetic parameters for semaglutide 2.4 mg and 1.0 mg at steady state, to- be-marketed single-dose pen-injector vs PDS290 pen-injector (study 4590)

Treatment	FAS	N	AUC0-168h,ss nmol*h/L	Cmax,ss nmol/L	Tmax* h	CL/F (L/h)	$t_{1/2}$ h	Vss/F
semaglutide 2.4 mg, at steady state								
Test: DV3396	33	29	14572 [13937 ; 15236]	118 [112 ; 125]	24 (3;48)	0.040 (22.6)	155 (9.8)	9.8 (23.4)
Reference: PDS290	31	30	13827	102	24 (6;81)	0.043 (17.6)	151 (7.3)	11.0 (20.6)

			[13234 ; 14446]	[96.8 ; 108]		
*Ratio (90% CI)			1.0539	1.1556		
			[1.0003 ; 1.1104]	[1.0800 ; 1.2365]		
semaglutide 1.0 mg, at steady state						
Test: DV3396	33	33	5729	46.3	18 (6; 42)	0.042 (20.7)
			[5500 ; 5968]	[43.4 ; 49.3]		
Reference: PDS290	31	31	5532	42.0	24 (6; 82)	0.044 (16.9)
			[5303 ; 5770]	[39.3 ; 44.9]		
*Ratio (90% CI)			1.0357	1.1014		
			[0.9860 ; 1.0879]	[1.0202 ; 1.1891]		

FAS	Number of subjects in full analysis set
N	Number of subjects contributing to analysis, CI: Confidence interval
AUC 0-168h,ss	area under the plasma concentration-time curve from time zero to 168 hours at steady state
Cmax,ss	maximum plasma concentration at steady state
Tmax	time for maximum concentration (* median, range)
$T_{1/2}$	half-life

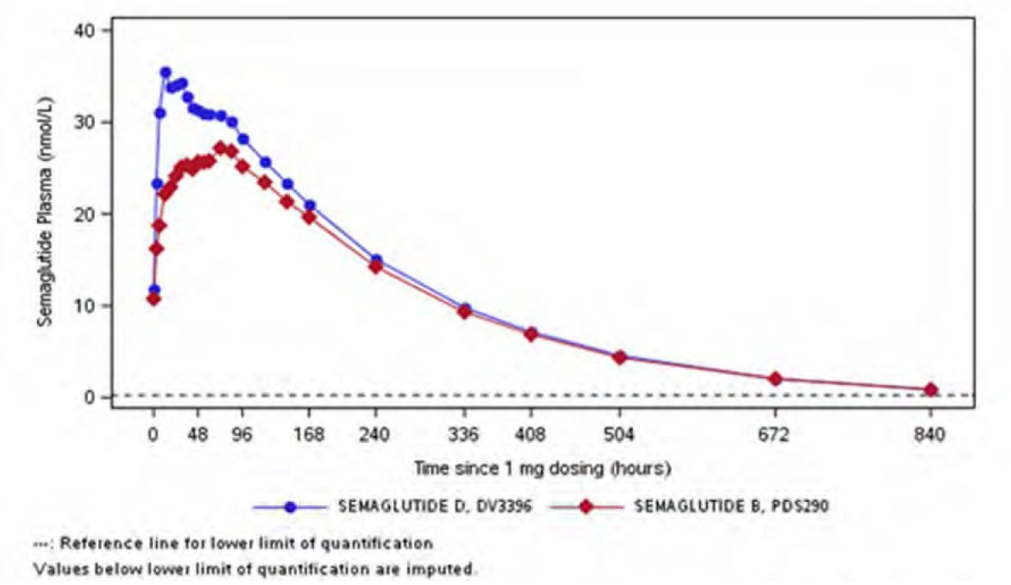
The endpoint is logarithmically transformed and analysed using an ANCOVA model with treatment and stratification as factors and logarithm of body weight as covariate

Table 10: Semaglutide trough values - descriptive statistics – full analysis set (study 4590)

	Sema 0.25 mg	Sema 0.5 mg	Sema 1 mg	Sema 1.7 mg	Sema 2.4 mg
Number of subjects	64	63	64	64	60
Test: Semaglutide DV3396					
N	33	33	33	33	30
Geometric mean (CV)	5.90 (18.4)	12.74 (18.3)	24.73 (22.6)	42.87 (33.9)	60.75 (30.3)
Reference Semaglutide PDS290					
N	31	30	31	31	30
Geometric mean (CV)	4.89 (64.0)	11.98 (20.6)	23.78 (17.9)	38.19 (41.1)	61.31 (21.7)

In the bioequivalence study NN9535-4588, bioequivalence was shown for 0.25 mg, at steady state; however, bioequivalence was not confirmed for semaglutide 1.0 mg, first dose following uptitration. Although the exposure was comparable between the formulations, the absorption profiles were different and the $C_{max,sema,1mg}$, was slightly higher, with an estimated treatment ratio and 90% CI of 1.27 [1.20 ; 1.34]. (see **Figure 4**).

Figure 2: Semaglutide profiles after 1 mg dose of semaglutide s.c.– geometric mean plot –full analysis set NN9535-4588



Distribution

The apparent volume of distribution following a s.c. administration of semaglutide was approximately 12-13 L. In vitro protein binding, mainly to albumin, was above 99% in human plasma. The high protein binding prevents semaglutide from being rapidly eliminated from the circulation.

Elimination

In the popPK model, the estimated apparent clearance was 0.05 L/h (17.7%) for a typical subject profile (white, normo-glycaemic [STEP 1], female, body weight of 110 kg, normal renal function). In study 4590 the apparent clearance of the to-be marketed single-dose pen-injector (CL/F) was 0.040 (22.6) L/h and the half-life (t1/2) 155 (9.8)h in healthy subjects.

In mass balance study 3789 with [3H]−semaglutide, the cumulative recovery of total radioactivity was 75% of the administered dose; hereof 53.0% in urine, 18.6% in faeces and 3.2% in expired air. In urine, unchanged semaglutide accounted for 3.1% of the administered dose.

Semaglutide is metabolized by proteolytic degradation of the peptide backbone and beta-oxidation of the fatty acid side-chain. Semaglutide is extensively metabolised into many different metabolites. Its most abundant metabolite in plasma was P3, in urine U6 and U7 were most abundant (study 214379). All metabolites accounted for less than 10% of the total amount of semaglutide related material and are not expected to have any activity.

Endogenous GLP-1 is metabolised by DPP-IV and NEP, but only NEP is involved in the metabolism of semaglutide. The applicant has shown that semaglutide was less sensitive to DPP-IV degradation. The pharmacokinetic data do not indicate any influence of polymorphisms of NEP on the pharmacokinetics of semaglutide.

Dose proportionality and time dependencies

Semaglutide steady-state exposure (AUC and C_{max}) increased approximately proportionally with semaglutide dose, in the dose range of 0.25-2.4 mg semaglutide. Semaglutide steady-state exposure is stable over time, with an accumulation ratio of approximately 2.

Variability

The population pharmacokinetic analyses of the STEP 1 and STEP 2 trials, based mainly on trough concentrations, estimated an approximately 18% between-subject variability in AUC and within-subject variability in the pharmacokinetics of 27%. Within- and between-subject variability in PK in healthy volunteers was low (within-subject variability: 5–10%, between-subject variability: 17-24%) For subjects with T2D, within- and between subject was evaluated in the population PK analysis and was estimated to be 13% and 27% respectively.

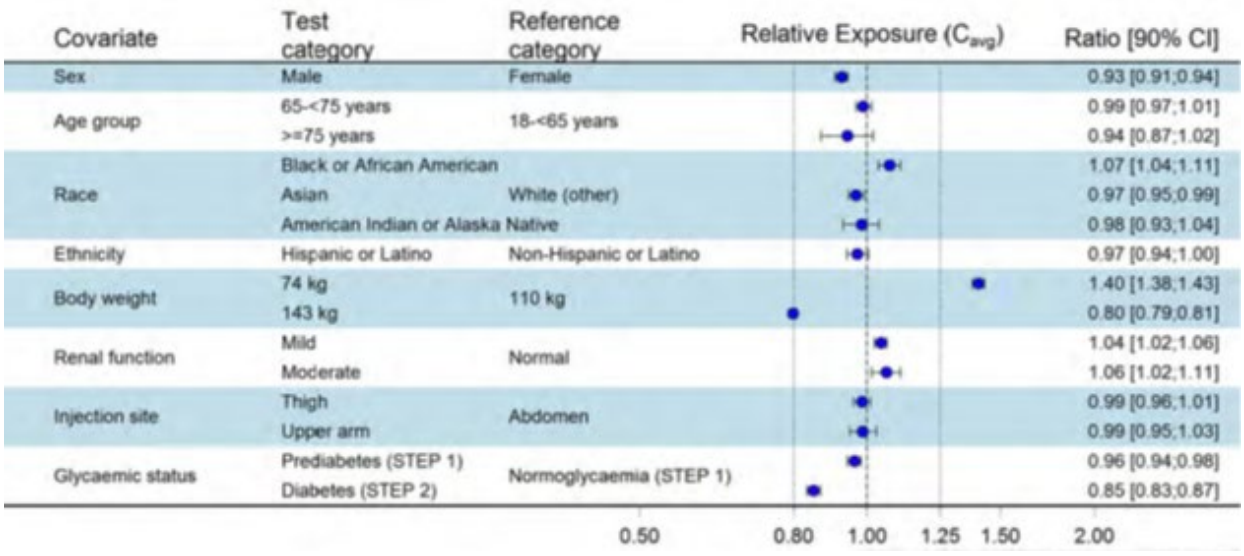
Exposure in the target population

The pharmacokinetics of semaglutide, following administration of the semaglutide 2.4 mg the single-dose pen-injector 2.4 mg, has only been characterised in study 4590 steady-state, in subjects with overweight or obesity (BMI 27.0−34.9 kg/m^2, both inclusive). All pharmacokinetic studies that were conducted to support the weight management indication were conducted in subjects with overweight or obesity and therefore reflect the pharmacokinetics in the target population.

Special populations

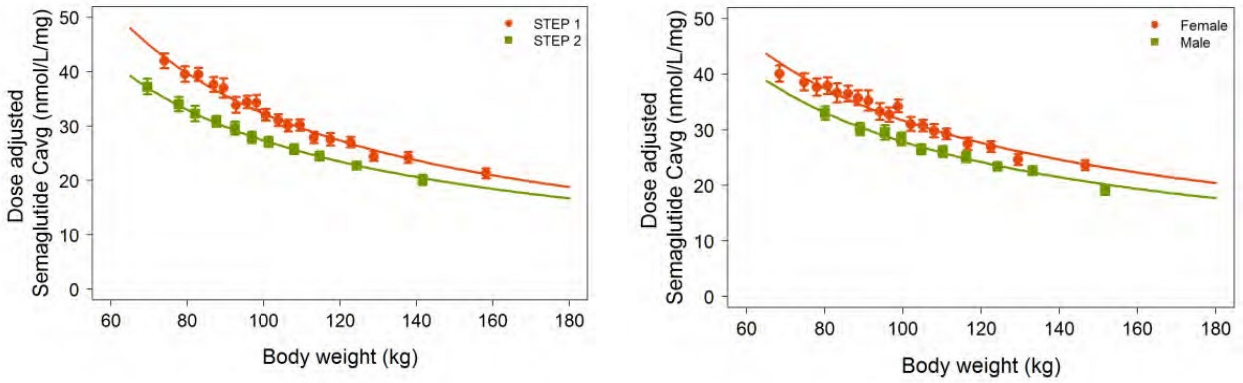
The applicant has evaluated various special populations during the weight management program and previously conducted studies to support the T2D program. In popPK, effects of intrinsic and extrinsic covariate factors on exposure were evaluated using the full model approach and results were displayed in a forest plot, **Figure 5**. The most important covariate on exposure was body weight. The effects of body weight on the expected semaglutide concentration range at a steady state following a 2.4 mg dose is shown in **Figure 6**. Semaglutide exposure tended to be lower in subjects with prediabetes and diabetes compared to normoglycaemic subjects, the difference was 4% and 15%, respectively. Other covariates such as sex, age, race, ethnicity, renal function and injection site had no or only minor effects on exposure.

Figure 3: Forest plot of covariate effects for semaglutide exposure



Data are steady-state dose-normalised average semaglutide exposures relative to a reference subject profile (non- Hispanic or Latino, normoglycaemic (STEP 1) white female aged 18-<65 years, with a body weight of 110 kg and normal renal function, who injected in the abdomen). The forest plot and the column to the right show means and 90% CI for the relative exposures. Body weight test categories (74 and 143 kg) represent the 5% and 95% percentiles, respectively in the data set. There were 1 subject with severe renal impairment included in the moderate group. Vertical dotted lines indicate the acceptance interval for bioequivalence (0.80;1.25).

Figure 4 Semaglutide exposure versus body weight by trial (A) and sex (B)



Data are dose-normalised, mean Cavg values versus body weight quantiles by trial and sex with error bars expressing 95% CI. Lines are model-derived Cavg values by body weight adjusted for other covariate effects. Data from trials STEP 1 and STEP 2.

Further dedicated studies on the effect of renal impairment (study 3616) and hepatic impairment (study 3651) on semaglutide exposure and a PopPK study in T2D patients were conducted during the T2D program. In these studies, body weight was the most important covariate on semaglutide exposure. Impaired renal function (mild to end-stage renal disease) and mild, moderate or severe hepatic impairment (Child-Pugh A, B, or C) had no or only minor effects on semaglutide exposure. The same was the case for covariates gender and race.

In **Table 18,** the age distribution of the subjects included in the clinical studies was provided.

Table 11 Age of subjects included in the weight management program.

	STEP 1 WM N (%)	STEP 2 WM in T2D N (%)	STEP 3 WM with IBT N (%)	STEP 4 Sustained WM N (%)	Total N (%)
Number of subjects	1961	807	611	803	4182
Age (years)					
<65	1805 (92.0)	633 (78.4)	565 (92.5)	755 (94.0)	3758 (89.9)
65-<75	145 (7.4)	156 (19.3)	43 (7.0)	44 (5.5)	388 (9.3)
>=75	11 (0.6)	18 (2.2)	3 (0.5)	4 (0.5)	36 (0.9)

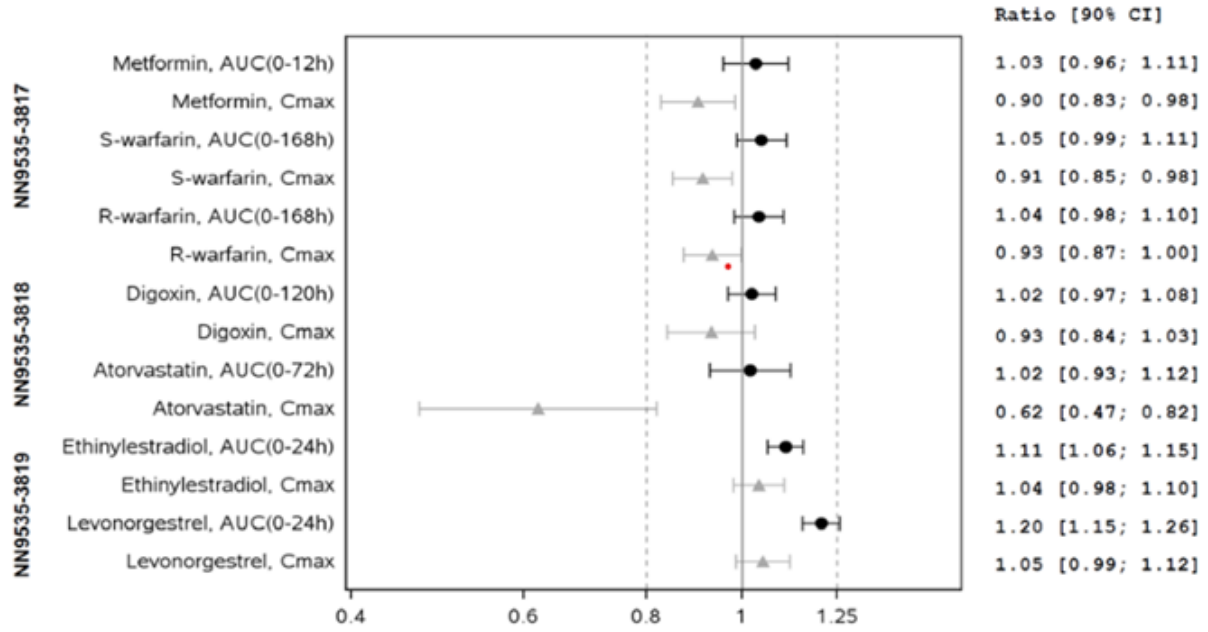
Pharmacokinetic interaction studies

In vitro studies and clinical interaction studies suggest that semaglutide has a low potential for interactions. In vitro, semaglutide did not inhibit or induce CYP enzymes, and did not inhibit drug transporters.

In study 4455, no clinically relevant effect on gastric emptying was observed with semaglutide 2.4 mg. However, in previous studies 1821 and 3685, a delay in gastric emptying has been observed, so it is assumed that semaglutide has some effect on gastric emptying.

Drug-drug interactions between semaglutide 1.0 mg and metformin, warfarin, digoxin, atorvastatin or oral contraceptive combination drug (ethinylestradiol and levonorgestrel) were evaluated. The results of these DDI studies are summarised in **Figure 7**. A lower C_{max} was observed for atorvastatin when co-administered with semaglutide, but its overall exposure (AUC) was not affected. The other investigated medication was not affected by concomitantly administered drugs. It was noted that the t_{max} was more variable and tended to be delayed for most medication. Overall, small changes were observed in AUC, C_{max}, and t_{max}.

Figure 5: Impact of semaglutide on the pharmacokinetics of co-administered oral medications – trials 3817, 3818, 3819



Note: Ratio is ETR (with/without semaglutide). Metformin, ethinylestradiol and levonorgestrel were assessed at steady state. Warfarin, digoxin and atorvastatin were assessed after a single dose. Pre-specified limit of 90% CI [0.8; 1.25].

INR was measured over a 168-hour period after a single dose of warfarin with and without semaglutide. An increase in INR indicates a prolonged blood clotting time. The average increase of clotting time after warfarin dosing during the two conditions were similar; the estimated treatment ratio (with/without semaglutide) for $iAUC_{INR,\ 0-168h}$ and INR_{max} were 1.05 [0.87; 1.28]90% CI and 1.04 [0.99; 1.10]90% CI, respectively.

2.6.2.2. Pharmacodynamics

The clinical pharmacology programme for semaglutide in weight management builds upon the clinical development programme for Ozempic. Within the Ozempic application, the PD properties of semaglutide were investigated in nine clinical pharmacology trials and one phase 2, dose-finding trial. One new PD trial (4455) was conducted and submitted to assess the effect of semaglutide 2.4 mg on the rate of gastric emptying and explored the mechanism of the weight lowering effect of semaglutide 2.4 mg.

Mechanism of action

Animal studies show that Semaglutide crosses the BBB, and its effects include central homeostatic mechanisms involving the hypothalamus and brain stem. Evidence for the direct involvement of the hedonic system is limited, yet supported by semaglutide access to the septum. More evidence suggestive of the involvement of reward-related brain regions in the hedonic regulation of food intake included activation of deeper brain regions, possibly indirectly via projections from the homeostatic system that were directly accessible for semaglutide (please see under 'Non-clinical aspects; Pharmacology').

Clinical studies show that semaglutide reduces energy intake, increases feelings of satiety, fullness and control of eating, reduces feelings of hunger, and frequency and intensity of cravings. In addition, semaglutide reduces the preference for high fat foods.

Primary and Secondary pharmacology

Primary pharmacology

Summary of pharmacodynamics of semaglutide known from Ozempic

Pharmacodynamic properties in relation to glucose metabolism

The primary mode of action responsible for the effects of the GLP-1 Ras on glycaemic control is increased insulin secretion and decreased glucagon secretion from the pancreatic islets during elevated glucose levels. Thus, several PD parameters assessing different aspect of islets function (mainly the β-cell) and responsiveness have been included as PD endpoints.

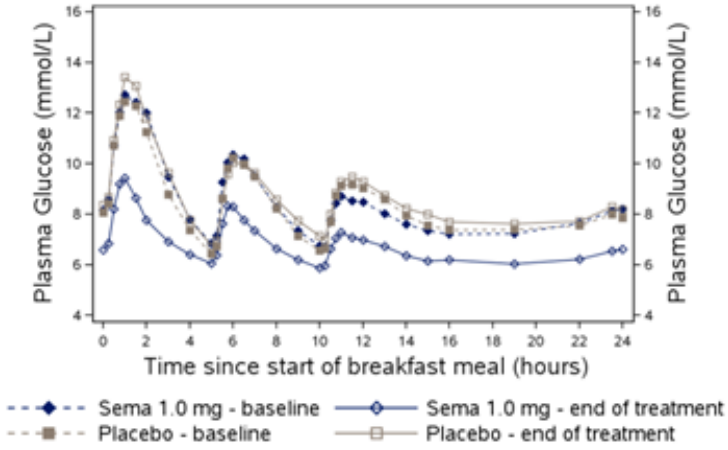
Fasting and postprandial plasma glucose responses

Semaglutide improves glycaemic control in patients with T2D by lowering fasting and postprandial glucose concentrations (**Figure 8**). The lowering of fasting plasma glucose (FPG) with semaglutide was evident already after the first dose for doses of 0.2 mg or higher (trial 1821).

Semaglutide lowered fasting glucose concentrations by 22% after 12 weeks of semaglutide treatment, the overall 24-hour glucose response (AUC0-24h) by 22% and the absolute postprandial responses (AUC_{0-5} h after each meal) by 20–29% compared with placebo assessed with three standardised meals (breakfast, lunch and protein-rich dinner) (trial 3635).

The mean postprandial increments in glucose were lowered by 0.6–1.1 mmol/L (11 20 mg/dL) with semaglutide compared with placebo. In addition, semaglutide lowered the 2-hour postprandial glucose concentration after the breakfast meal by 37% as compared to placebo; the decrease was 4.1 mmol/L (74 mg/dL) in semaglutide-treated patients. The reduced gastric emptying during the early postprandial phase contributed to a lower postprandial increase in glucose in patients treated with semaglutide as compared with placebo.

Figure 8*: 24-hour glucose profiles at baseline and steady-state in patients with T2D – trial 3635*



Note: Plasma glucose profiles after standardised meals at baseline and at steady state after 12 weeks of treatment with semaglutide 1.0 mg (N: 37) or placebo (N: 37). Abbreviations: N: number of patients; sema: semaglutide; T2D: type 2 diabetes mellitus.

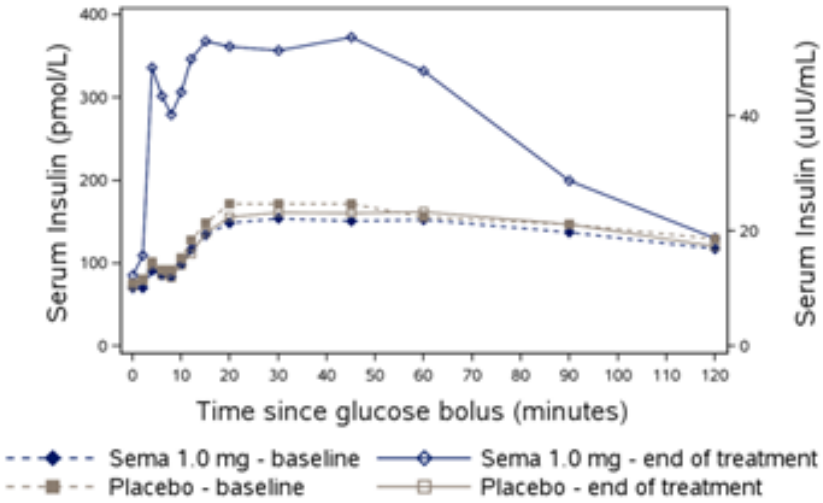
B-cell function and responsiveness

- First and second-phase insulin secretion

In patients with T2D, defects in insulin secretion occur at an early stage during the development of the disease, and a decline in first-phase insulin secretion is among the first observations. The influence of semaglutide on first and second phase insulin secretion was therefore investigated following an intravenous bolus of glucose (IVGTT) in patients with T2D (trial 3635).

First- and second-phase insulin concentration and insulin secretion rate increased approximately 3-fold and 2-fold with semaglutide as compared to placebo (**Figure 9**).

Figure 9*: First phase (0-10 min) and second phase (10-120 min) insulin response in patients with T2D – trial 3635*



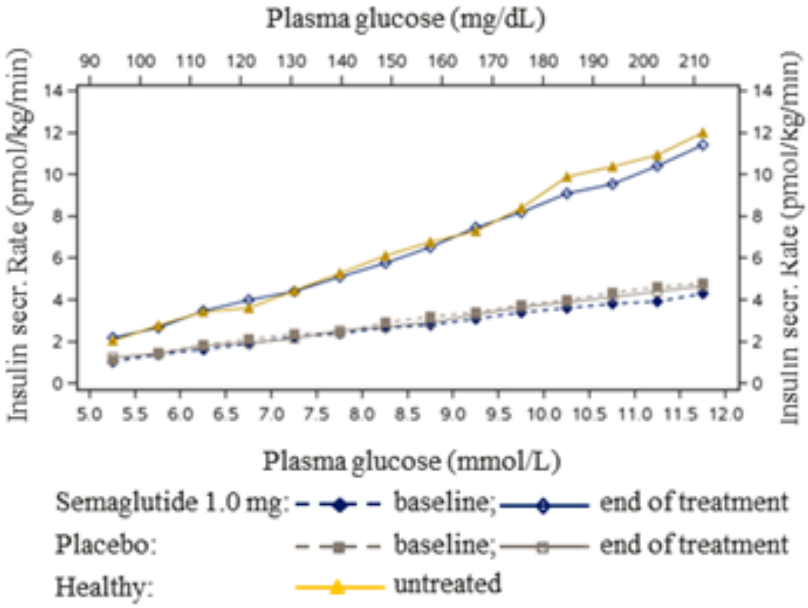
Note: IVGTT at baseline and at steady state after 12 weeks of treatment with semaglutide 1.0 mg (N: 37) or placebo (N:38). Abbreviations: IVGTT: Intravenous glucose tolerance test; N: number of patients; sema: semaglutide; T2D: type 2 diabetes mellitus.

- Glucose-dependent insulin secretory response

Native GLP-1 is known to stimulate insulin secretion in a glucose-dependent manner, and this ability was investigated for semaglutide in a graded glucose infusion test during a gradual increase of glucose from normoglycaemia to hyperglycaemia in patients with T2D (trial 3635). Healthy untreated subjects were included as a comparator group.

The insulin concentration and insulin secretion rate (ISR) corresponding to the glucose increase from 5 to 12 mmol/L (90−216 mg/dL) was ~ 2.5 fold higher with semaglutide than with placebo in patients with T2D (**Figure 10**). With semaglutide, the insulin concentration and the ISR in patients with T2D were comparable to untreated healthy subjects. The increasingly larger insulin secretion with increasing glucose concentrations demonstrates that semaglutide improved the insulin secretory response to elevated glucose levels in a glucose-dependent manner.

Figure 10: *Insulin secretion rate during graded glucose infusion test in patients with T2D and in healthy subjects – trial 3635*



- Maximum β-cell secretory capacity

An arginine stimulation test was performed to assess maximum β-cell secretory capacity on a basis of induced hyperglycaemic conditions. Semaglutide-treated patients had an approximate 4-fold larger increase in insulin secretion than placebo-treated patients (trial 3635).

- Fasting insulin and C-peptide levels

As expected of an incretin, fasting insulin and C-peptide increased 30% and 23%, respectively after 12 weeks treatment with semaglutide in patients with T2D, as compared with placebo (trial 3635).

- HOMA-IR and HOMA-B

The data in the phase 3 trials show improvements in both HOMA-B and HOMA-IR. In the PD trial (3635), there was no apparent improvement in HOMA IR that may be explained by a generally better-controlled diabetes (lower HbA1c, lower BMI) in line with the inclusion criteria of this PD trial and may thus have reduced the improvability of insulin resistance in these subjects.

Glucagon

T2D is associated with inappropriately high glucagon secretion both at fasting and at postprandial conditions, contributing to high hepatic glucose output. GLP-1 Ras induce glucose-dependent lowering of glucagon secretion, which in turn lowers the hepatic glucose output. The ability of semaglutide to decrease glucagon secretion was investigated in patients with T2D during various glucose metabolism tests. Semaglutide treatment resulted in relative reductions compared to placebo in fasting glucagon of 8-21%, postprandial glucagon response of 14-15% and mean 24-hour glucagon concentration of 12% (trials 3684 and 3635).

In the graded glucose infusion test, a glucose-dependent decrease in glucagon levels was observed with increasing glucose concentrations both with semaglutide and placebo; however, the glucagon decrease was

more pronounced with semaglutide, further supporting the glucose-dependent responses of both insulin and glucagon (trial 3635).

Counter-regulatory response to hypoglycaemia

During induced hypoglycaemia, semaglutide did not alter the counter-regulatory responses of increased glucagon, and did not impair the plasma glucose-dependent decrease in C-peptide concentrations in patients with T2D as compared to placebo (trial 3684).

There was a lower increase in concentrations of noradrenaline and cortisol for patients when treated with semaglutide compared with placebo. A decreased recognition of hypoglycaemia was also observed.

Gastric emptying

GLP-1 inhibits gastric emptying, causing a reduction in postprandial plasma glucose excursions. While decreased gastric emptying is an important physiological effect of native GLP-1, and short-acting GLP-1R agonists like exenatide and lixisenatide, decreased gastric emptying is less pronounced for long-acting GLP-1R agonist like liraglutide, dulaglutide, albiglutide and semaglutide. The effect of steady-state semaglutide on gastric emptying was assessed after 12 weeks of treatment during standardised meal settings in subjects with obesity (trial 3685) and patients with T2D (trial 1821).

Semaglutide reduced gastric emptying in subjects with obesity during the first hour after a meal (AUC of paracetamol reduced by 27%), and consistent reductions in early gastric emptying were seen in patients with T2D. The gastric emptying over the full postprandial period was not reduced, or slightly reduced for semaglutide doses of 0.2–1.6 mg (range for treatment ratios 0.87−0.96) when assessed in subjects with obesity and patients with T2D. The reduced gastric emptying during the early postprandial phase reduces the rate at which glucose appears in the circulation post-prandially, and may have contributed to the observed reductions in postprandial glucose. No effects of delayed gastric emptying on the PK properties of co-administered drugs were evident.

Pharmacodynamic properties in relation to weight loss

The GLP 1 receptor is expressed in the human brain in areas involved in satiety and appetite regulation, and changes in plasma GLP-1 concentrations increase brain activity in these areas. GLP-1 has been shown to induce decreased hunger, increased satiety and a lower energy intake and thereby weight loss in humans. In animal studies, semaglutide is taken up in specific brain regions and increases key satiety and decreases key hunger signals. Using isolated brain tissue sections, semaglutide has been shown to activate satiety related neurons and inhibit hunger-related neurons.

Body weight and composition

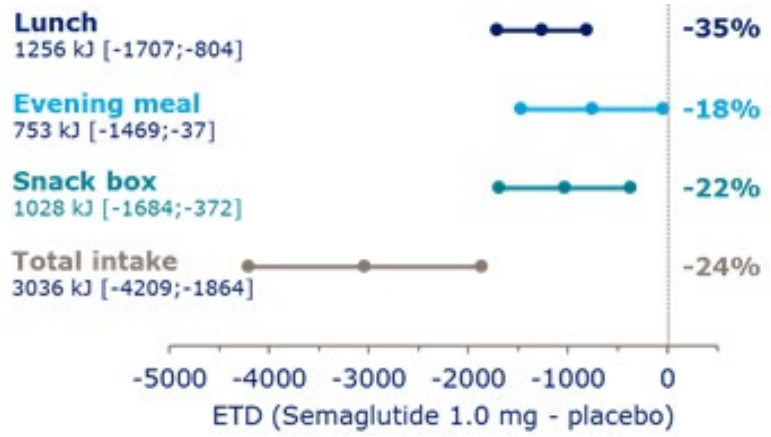
Change in body weight from baseline to end of treatment was assessed in all clinical pharmacology trials. A reduction in body weight with semaglutide was observed across trials and populations (T2D and obesity), with a mean weight loss of 4–5 kg in 12 weeks, compared with a neutral effect on body weight with placebo. The effect of semaglutide on body composition was investigated in subjects with obesity using air displacement plethysmography (trial 3685), showing that the body weight loss with semaglutide was predominantly from fat tissue with loss of fat mass being 3-fold larger than the loss of lean mass.

Appetite, energy intake and energy expenditure

Semaglutide reduced appetite, improved control of eating, reduced food cravings and reduced preference for high-fat foods compared to placebo in a dedicated trial (trial 3685) in subjects with obesity. This translated

into a substantially lower energy intake with semaglutide. The energy intake of 3 consecutive ad libitum meals was 18-35% lower with semaglutide than with placebo (**Figure 11**). Across meals on the test day, this corresponds to a reduction in energy intake of more than 3000 kJ (appr. 700 kcal) with semaglutide, corresponding to 24% lower ad libitum energy intake as compared to placebo. Based on ratings of nausea and palatability, there were no indications of food aversion or nausea during the meals being responsible for this markedly reduced food and energy intake.

Figure 11*: Effect of semaglutide on energy intake during ad libitum meals in subjects with obesity after 12 weeks of treatment – trial 3685*



Note: Figure shows ETD and corresponding 95% CI. Abbreviations: CI: confidence interval; ETD: estimated treatment difference.

Semaglutide reduced energy expenditure as assessed by resting metabolic rate (RMR) using indirect calorimetry/ventilated hood system by appr. 600 kJ per day. A minor part of the difference could be explained by the observed difference in lean body mass between treatments. No effect of semaglutide on respiratory quotient (RQ) was shown, indicating no difference in the oxidation of macronutrients following semaglutide treatment.

The semaglutide-induced weight loss due to the reduced energy intake was primarily mediated through less appetite; however, other mechanisms, including improvements in the control of eating, fewer food cravings and a lower relative preference for fatty, energy-dense foods, may also have contributed to the reduced energy intake.

Lipids

The effect of semaglutide on lipid metabolism was assessed prior to (fasting) and up to 8 hours postprandially during a standardised fat-rich breakfast meal in subjects with obesity (trial 3685). These results suggest an improvement in lipid metabolism.

PD trial 4455

For the clinical PD assessment of semaglutide up to 2.4 mg for weight management, one new clinical PD trial (trial 4455) was conducted and submitted.

This was a single-site, randomised, parallel-group, double-blind, placebo-controlled trial investigating the PD effects of semaglutide 2.4 mg in subjects with obesity (BMI 30-45 kg/m2).

The trial consisted of an up to 4-week screening period, a 20-week treatment period (including 16-week dose escalation to reach semaglutide 2.4 mg) and a 7-week post-dose follow-up period. The trial included in-house

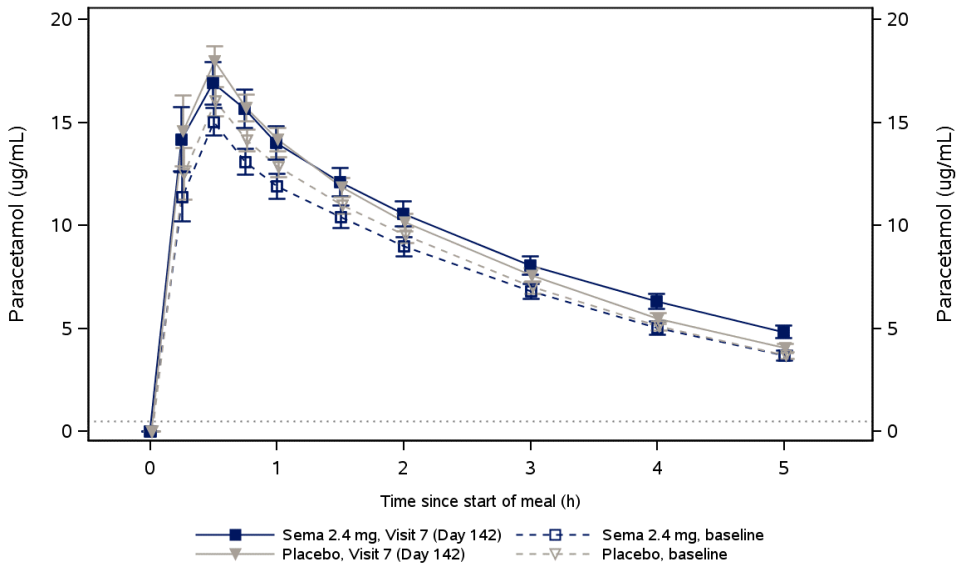
visits at baseline and at week 20. Subjects attended the study clinic for 8 visits, including two 2-days in-house visits at baseline and at week 20.

Gastric emptying was assessed by the paracetamol (acetaminophen) absorption technique. Blood samples for measurement of paracetamol were taken up to 5 hours after the meal as an indirect marker for the gastric emptying rate. Appetite (hunger, satiety, fullness, prospective food consumption), thirst, well-being and nausea was assessed using visual analogue scales (VAS) before the standardised breakfast meal and up to 5 hours postprandially, as well as immediately after completion of an ad libitum lunch. Energy intake was assessed by food consumption of a homogenous ad libitum lunch meal that was served approximately 5 hours after the standardised breakfast. Food cravings and control of eating were assessed by the Control of Eating Questionnaire (CoEQ).

A total of 125 subjects were screened, 72 subjects were randomised and exposed (36 in each treatment group), and 70 subjects completed the trial, 35 in each of the two treatment arms. Demographics and baseline characteristics were generally comparable between the treatment groups.

Mean paracetamol concentrations peaked approximately 30 minutes after the start of the meal test at baseline and at week 20 in both treatment groups. The paracetamol concentrations appeared higher in both treatment groups at week 20 compared to baseline (**Figure 12**). At week 20, there was a statistically significantly 8% higher mean $AUC_{0\text{-}5h,para}$ in the semaglutide 2.4 mg group compared to placebo. When adjusting for body weight at week 20 in the post-hoc statistical analysis no statistically significant difference in $AUC_{0–5h,para}$ between semaglutide 2.4 mg and placebo was observed, ETR 1.05 [0.99; 1.12] 95% CI; p = 0.1218.

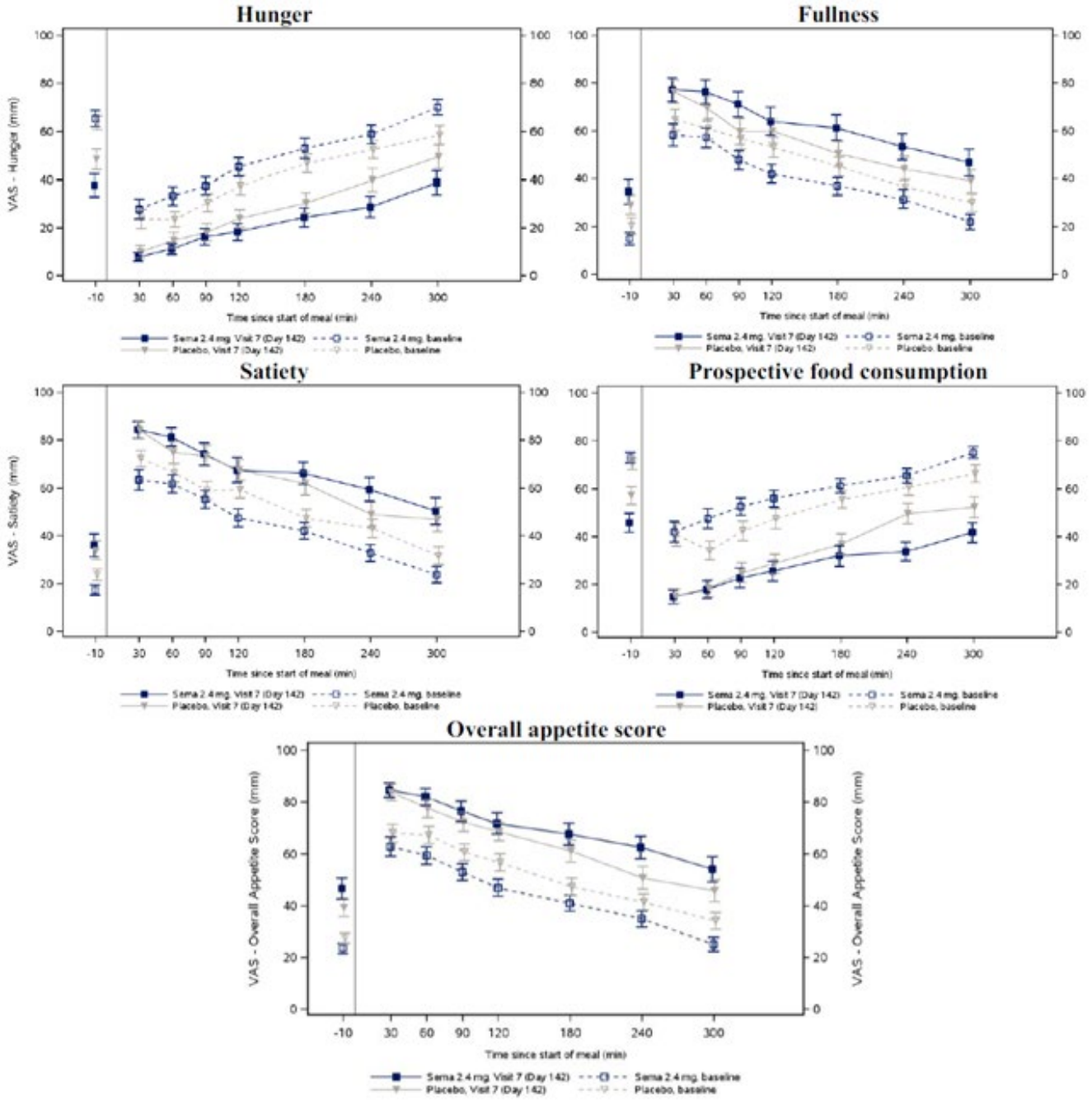
***Figure 12**: Gastric emptying – paracetamol concentration profile.*



---: Reference line for lower limit of quantification
Error bar is +/- standard error of mean.

Regarding the supportive secondary endpoints, no statistically significant difference between semaglutide 2.4 mg and placebo was observed for $AUC_{0–1h,para}$, $C_{max,para}$, $t_{max,para}$ at week 20. The effect on mean energy intake during the ad libitum lunch at week 20 was statistically significantly lower with semaglutide 2.4 mg compared to placebo with an ETD of -940 kJ, corresponding to approximately 35% lower energy intake with semaglutide 2.4 mg. The rating for OAS appeared higher with semaglutide 2.4 mg at week 20 compared to placebo, indicating less appetite in subjects treated with semaglutide 2.4 mg (see **Figure 13**).

***Figure 13**: Hunger, fullness, satiety, prospective food consumption and OAS – VAS.*



Sema: semaglutide; VAS: visual analogue scale. Error bars are +/- standard error of the mean. Vertical reference lines indicate start of the breakfast. Hunger: 0 mm = not hungry at all. 100 mm = I have never been more hungry Fullness: 0 mm = not at all full. 100 mm = totally full Satiety: 0 mm = I am completely empty. 100 mm = I cannot eat another bite Prospective food consumption: 0 mm = Nothing at all. 100 mm = a lot Overall appetite score = (satiety + fullness + [100 – hunger] + [100 – prospective food consumption])/4.

In exploratory evaluations, the appetite ratings before eating were comparable to the ratings after consumption. Further, the outcome for food intake appears linked to energy intake as there was a larger decrease at week 20 in mean amount of food consumed with semaglutide 2.4 mg (baseline: 685 g, week 20: 364 g) than with placebo, with slightly more food aversion in the patients on the trial product. Also, the results from the COEQ suggested better control of eating, less hunger and less food cravings with the use of

semaglutide 2.4 mg. Also, subjects had a mean decrease in body weight of 9.9% (10.4 kg) compared to 0.4% (0.4 kg) with placebo from baseline to week 20.

The safety and tolerability profile was consistent with the previous clinical pharmacology trials with semaglutide. Mainly gastrointestinal disorders were reported for semaglutide.

Secondary pharmacology

Cardiac repolarisation by QT interval evaluation

The potential effects of semaglutide on QTc interval and cardiac repolarisation were tested in a dedicated, thorough QTc trial, designed and conducted in accordance with recommendations in guidelines, including supra-therapeutic dose levels of semaglutide up to 1.5 mg at steady-state as agreed with the FDA.

During the 48-hour post-dose ECG recording at steady state of the supratherapeutic 1.5 mg semaglutide/placebo dose level, 11 time-matched QtcI measurements (QT interval individually corrected for heart rate) were performed (**Table 19**).

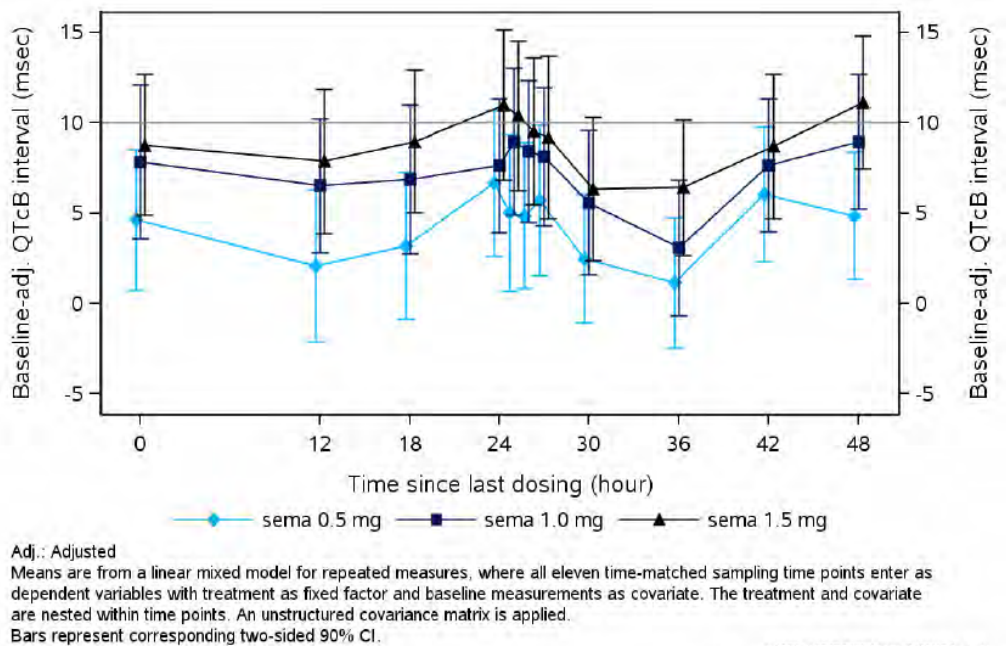
Table 19*12: QtcI interval baseline-adjusted – estimated treatment differences – semaglutide 1.5 mg vs placebo – trial 3652.*

	Estimate	90% CI	p-value
Treatment difference, sema 1.5 mg – placebo			
0 hour	-3.16	[-6.62 ; 0.29]	<.0001
12 hours	-3.38	[-7.03 ; 0.26]	<.0001
18 hours	-5.15	[-8.84 ; -1.45]	<.0001
24 hours	-4.80	[-8.33 ; -1.28]	<.0001
25 hours	-4.26	[-7.75 ; -0.77]	<.0001
26 hours	-5.81	[-9.16 ; -2.45]	<.0001
27 hours	-5.29	[-8.75 ; -1.83]	<.0001
30 hours	-3.88	[-7.14 ; -0.63]	<.0001
36 hours	-5.89	[-9.50 ; -2.28]	<.0001
42 hours	-6.56	[-10.14 ; -2.98]	<.0001
48 hours	-5.13	[-8.27 ; -1.99]	<.0001

Note: The p-value is for the one-sided test of a mean difference greater than 10 ms. Abbreviations: N: Number of subjects contributing to analysis, CI: Confidence interval

Evaluations were also made using QTcF, QTcB and QTcL corrections. No prolongation of QTcL and QTcF was observed at any of the three dose levels. For QTcB a prolongation was observed at all dose levels i.e. the upper limits of at least one of the 11 two-sided 90% Cis for the estimated mean treatment differences were above 10 ms (**Figure 14**). Bazett's correction may overcorrect the QT interval when the heart rate is elevated. Increased heart rate is a well-known class effect of GLP-1s as reproduced in this study (**Figure 14**) and hence QTcB is not appropriate for this analysis.

***Figure 14**: Baseline-adjusted QTcB interval analysis.*



Treatment with semaglutide was associated with an increase in heart rate and PR interval at all dose levels. The increase in pulse rate seemed dose dependant and varied over the day; the mean highest changes were:

• 0.5 mg : 8.48 bpm [6.87 ; 10.09]90% CI

• 1.0 mg : 9.66 bpm [8.04 ; 11.29]90% CI

• 1.5 mg: 11.10 bpm [9.58; 12.62]90% CI

The mean highest change in PR interval was apparently not dose dependant:

• 0.5 mg : 10.72 ms [6.25 ; 15.20]90% CI

• 1.0 mg : 9.22 ms [4.96 ; 13.47]90% CI

• 1.5 mg: 10.02 ms [6.15; 13.89]90% CI

The effect of semaglutide on PR appears larger than with other GLP-1Ras. When assessed by office measurements, semaglutide seems to antagonize the beta-blocker-induced pulse rate reduction. As beta-blockers were not a randomised treatment in the CVOT, the implications hereof cannot be assessed. Extrapolation of the CV outcome results to subjects without established CV disease remains difficult. In these subjects, the differences in office HR were larger than in the whole population.

Exposure response relationship

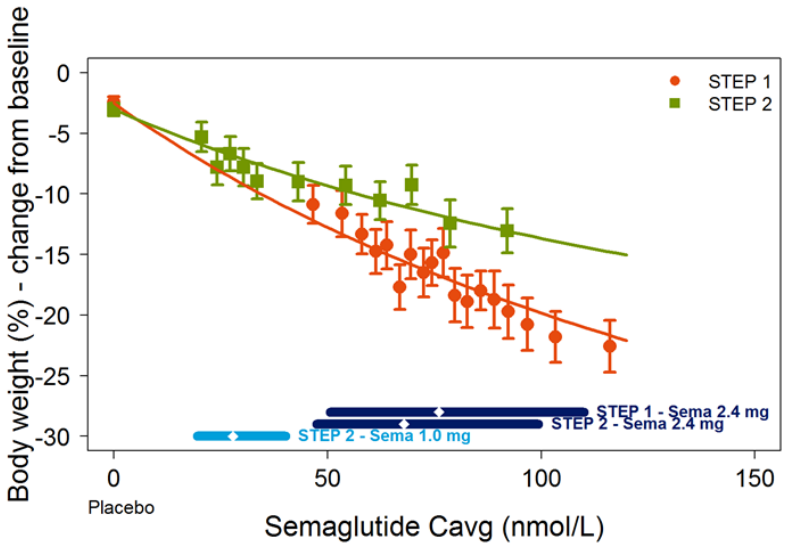
The semaglutide exposure-response analysis included data from the same two-phase 3a trials (STEP 1 and STEP 2) as used for the population PK analysis, see section 3.1.2. Methods– Qualification of models, of this assessment report for a description of the model development.

Exposure-response models were developed that aimed at establishing the characteristics of the exposure-response relationship for the following efficacy and tolerability endpoints:

- Change from baseline from week 0 to week 68 in body weight (%)
- Subjects who at any time experienced:
- Gastro-intestinal adverse events of any kind and severity
- Nausea events of any severity
- Vomiting events of any severity

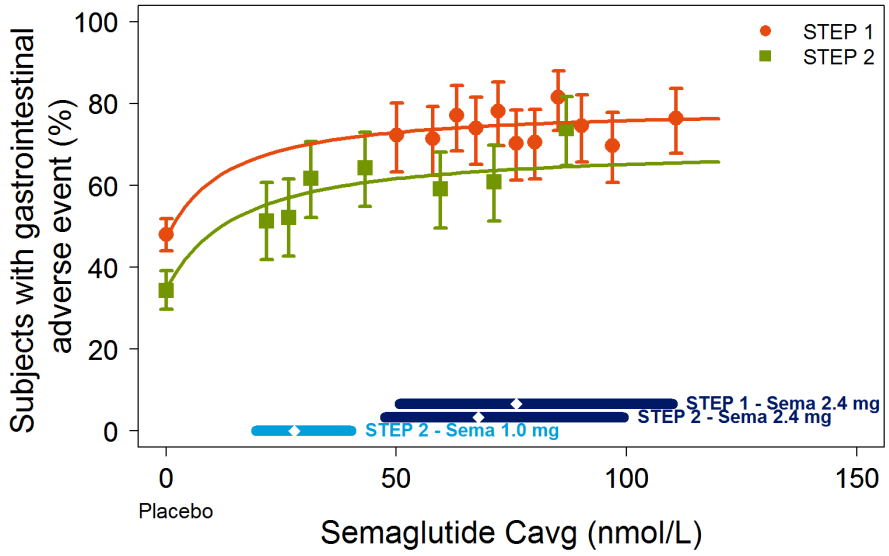
The average semaglutide steady-state concentrations in a dosing interval (C_{avg}) was used as measure of exposure. The main results are displayed below in **Figure** 15 and **Figure** 16.

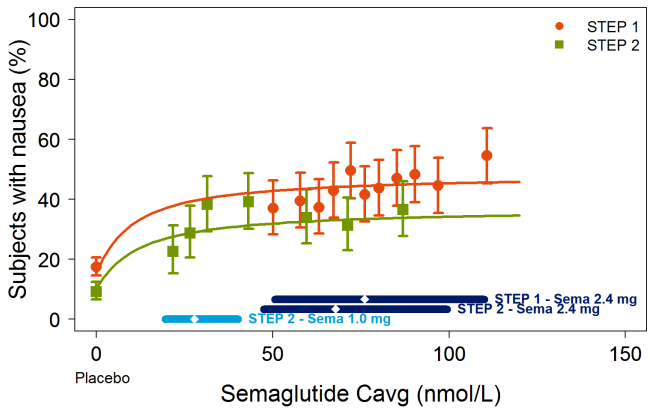
Figure 15*: Body weight % change from baseline versus semaglutide exposure STEP 1 and 2.*

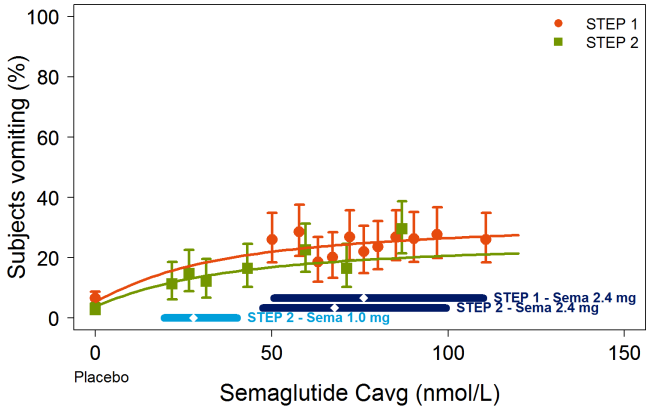


Data points with error bars are mean body weight changes with 95% CI obtained after 68 weeks of treatment versus exposure expressed as quantiles of Cavg (plus placebo at Cavg of 0 nmol/L). Lines through data are covariate-adjusted model-derived exposure-response relations. Horizontal lines with diamonds represent the median and 90% exposure range. Missing data at week 68 were predicted using a mixed model for repeated measures, using treatment as factor and baseline body weight as covariate all nested within visit. Data from trials STEP 1 and STEP 2.

***Figure 16**: Proportion of subjects reporting gastrointestinal adverse events (top panel), nausea (bottom, left panel) and vomiting (bottom, right panel) – STEP 1 and 2.*







Data are proportions with 95% CI versus exposure expressed as quantiles of model-derived C_{avg} values plus placebo (at C_{avg} of 0 nmol/L). Horizontal lines with diamonds represent the median and 90% exposure range. The lines through data represent covariate-adjusted model-derived estimates for each trial population, using the safety analysis set. Data from trials STEP 1 and STEP 2.

2.6.3. Discussion on clinical pharmacology

The pharmacokinetics of semaglutide up to a s.c. dose of 2.4 mg were extensively characterised during the weight management and T2D clinical pharmacology programme.

Methods

The bioanalytical methods, pharmacokinetic data analysis and statistical methods used in the phase I studies are consistent between studies; therefore, the study results can be easily compared. The applicant has shown that all clinical samples could be analysed in the semaglutide assay, no samples were unsuitable for analysis due to being lipemic.

Immunogenicity of semaglutide has been evaluated using ADA screening, confirmatory and cross-reactivity assays, and a Nab assay. The employed ADA-assay had limited drug tolerance and the risk of false negatives cannot be excluded.

The sensitivity of the NaB assays is adequate for detection of in vitro neutralising antibodies after 7 weeks drug wash-out but not during treatment.

The pharmacokinetic data and exposure-response data from the weight management phase III studies were analysed using population PK modelling. Although some basic information from previously developed models was used, the weight management model was developed independently from the previously developed population models with data from the T2D population.

The weight management population pharmacokinetic model was based on pharmacokinetic samples obtained in the STEP1 and STEP2 phase 3 trials. In the initial application there were concerns with the use of the 1-compartment model since it is based on sparse data only. The model structure and covariate analysis were questioned. Mainly uninformative trough concentrations were used in the model development, therefore this model cannot be used for any extrapolations, but the model can be used to characterise variability in the semaglutide trough concentrations in these trials. The submitted VPCs indicate that the variability is not adequately captured by the model, which further supports that the model should not be used for any extrapolation. Based on published data (Diabetes Ther 2019 10:649–662), it appears that a 2-compartment model including rich PK data may be more appropriate to describe the PK of semaglutide.

Upon request the applicant provided an updated Population PK model and showed that the initial one-compartment model was also the most adequate model in the presence of additional data.

The majority of available data were sparse PK samples from phase 2 and 3 trials (N=2,781, 6–8 samples per subject), and therefore robust individual estimates for all subjects was only expected for CL, with high shrinkage expected for the remaining model parameters.

The updated population PK model of semaglutide was compared to the initial phase 3a population PK model of semaglutide. The estimated individual C_{avg} values from both models were in good agreement with similar to the intra- and intersubject variabilities and the effect of various covariates on the exposure of semaglutide was similar between the two models.

The impact of changing injection sites, was evaluated between injection site arm or thigh and abdomen, was not significant for CL (exposure ratio 0.96). Injection site arm and thigh could not be evaluated separately.

Given the shortcomings of sparse data-based models, the models for Wegovy may not be fully adequate for evaluation of covariate effects e.g. injection site in future paediatric extension applications. It is questionable if the sparse PK data sampling planned in the paediatric studies will be sufficient to address this concern.

Bodyweight was the most influential covariate in both models that influenced semaglutide plasma exposure, which is in line with previous results obtained for patients with type 2 diabetes. For weight management program, the investigated bodyweight ranged between 54.4 kg and 245.6 kg, with a mean (SD) of 103.1 kg (22.2). In the T2D Ozempic program, the investigated bodyweight ranged between 39.7 kg and 198.3 kg, with a mean (SD) of 86.2 kg (22.5). So there is considerable overlap between the investigated body weight ranges.

Furthermore, the trough concentrations of semaglutide also appear to be dose-proportional on a population level as no significant covariate of dose could be identified in the population pharmacokinetic model. However, it should be noted that both models are not considered sensitive to detect any non-linearities in the pharmacokinetics of semaglutide.

The exposure-response analyses were conducted with a derived average plasma concentration of semaglutide, mainly based on trough concentrations included on the initial 1-compartment model. The variability in the upper range of the plasma concentration-time profile is usually larger. Therefore, the variability in C_{avg} is most likely underestimated. The exposure-response models are quite empirical and a lot of information is lost by neglecting the time component. No results have been presented about the adequacy of the exposure-response models to capture the variability in the exposure-response relationship in the STEP 1 and STEP 2 populations. Study effects are incorporated as fixed model parameters, which indicates that these models can only be used to describe the populations in these trials. Due to a high correlation in C_{avg} and similar intra- and intersubject variabilities between the initial 1-compartment model and the updated 2-compartment PK model exposure-response relationships are not investigated with the 2-compartment model.

Moreover, it is unclear how the imputations based on the MRMM affect the exposure-response models. Finally, there could be severe collinearity between plasma exposure and body weight (baseline and body weight change). Thus, the exposure-response analyses should be interpreted with caution.

Pharmacokinetics of Semaglutide

All pharmacokinetic studies that were conducted to support the weight management indication were conducted in subjects with overweight or obesity and therefore reflect the pharmacokinetics in the target population.

The absorption of semaglutide is relatively slow. Following s.c. injection semaglutide 2.4 mg dosed in the to-be-marketed single-dose pen-injector, had a median time to maximum concentration (t_{max}) of 24 hours with an observed range of 3–48 hours. Steady-state concentrations were achieved after approximately 4 weeks, with a C_{maxss} and $AUC_{0\text{-}168h}$ of 118 nmol/L and 14572 nmol*h/L , respectively. These results are consistent with previous results of studies with the multidose pen injector and studies with lower doses of semaglutide, that were submitted to support the T2D indication.

A multidose pen-injector, Semaglutide PDS290, was used in the four clinical phase 3 trials of the semaglutide weight management programme (Study 4373, 4374, 4375, and 4376). To support the change from the formulation used in the phase 3a trials to the to-be-marketed formulation (the single-dose pen-injector DV3396), two bioequivalence studies were submitted: trials 4590 and 4588.

In bioequivalence study 4590, bioequivalence between the DV3396 and PDS290 formulations was shown for the 2.4 mg strength, at steady-state and for the 1.0 mg strength, at steady state. However, in bioequivalence study NN9535-4588, bioequivalence between the DV3396 and PDS290 formulations was not confirmed for semaglutide 1.0 mg, first dose following uptitration. Although the exposure was comparable between the formulations, the $C_{max,sema,1mg}$, was slightly higher, with an estimated treatment ratio and 90% CI of 1.27 [1.20 ; 1.34]. Bioequivalence was shown for 0.25 mg, at steady-state.

There is some difference in absorption profile between the two formulations, which may be attributed to differences in concentration between dose levels or the presence/absence of the preservative phenol. Due to the long half-life of semaglutide, the different absorption is not resulting in significantly different concentrations at steady-state. Therefore, it is agreed that the single-dose pen-injector DV3396 can be used to deliver the maintenance dose of 2.4 mg.

The different absorption profile resulted in a 27% higher maximum concentration ($C_{max,sema,1mg}$) following the first dose after dose escalation. It cannot be excluded that the maximum semaglutide concentrations will be higher for every dose escalation step and possibly, will result in more adverse effects during uptitration. As

semaglutide is carefully uptitrated in small steps and dose can be adjusted based on tolerability in individual patient, the 30% higher concentrations can be expected to be clinically managed.

Semaglutide steady-state exposure (AUC and C_{max}) increased approximately proportionally with semaglutide dose, in the dose range of 0.25-2.4 mg semaglutide. Semaglutide steady-state exposure is stable over time. With an accumulation ratio of approximately 2. However, semaglutide exposure may increase over time, in subjects with considerable weight loss. Upon request, the applicant calculated that a reduction in BW of 20% in an individual subject would lead to an approximate 18% increase in exposure (for comparison, in STEP 1, the trial with the greatest reduction in BW, approximately 30% of subjects lost more than 20% of the baseline BW). Usually, an increase of exposure is well tolerated, however in case of tolerability issues there may be a need for delay in dose escalation or dose reduction. This is now mentioned in the SmPC section 4.2.

The within- and between-subject variability in the STEP1 and STEP2 populations appears to be comparable to patients with type 2 diabetes and a bit higher than for healthy volunteers. However, population pharmacokinetic analyses of the STEP 1 and STEP 2 trials, was based on trough concentrations only. The within- and between-subject variability of the exposure (AUC) in the STEP1 and STEP2 populations was 27% and 18%, respectively. Within- and between-subject variability in PK in healthy volunteers was low (within-subject variability: 5–10%, between-subject variability: 17-24%). For subjects with T2D, within- and between-subject was evaluated in the population PK analysis and was estimated to be 13% and 27%, respectively. It should however be noted that the estimates obtained in the population pharmacokinetic analyses are based on sparse sampling data only. This could have resulted in a significant underestimation of the variability and therefore these results should be interpreted with caution. Upon request, the applicant calculated the intra- and inter-individual variability in the obese population using the updated Pop PK-model. The inter-individual variability in exposure for subjects with overweight or obesity was estimated to be 19.2%, and the residual variability (within-subject and unexplained variability) was 25.6%. The 2-compartment analysis mainly contained sparse data with a relatively small contribution of richer PK data, so variability may still be underestimated**.**

Special Populations

The applicant has evaluated various special populations during the weight management program and previously conducted studies to support the T2D program. In popPK study III, the most important covariate on exposure was body weight. Semaglutide exposure tended to be lower in subjects with prediabetes and diabetes than normoglycaemic subjects; the difference was 4% and 15%, respectively. Other covariates such as sex, age, race, ethnicity, renal function and injection site had no or only minor effects on exposure. These observations are in line with previous observations for the T2D management indication.

Interactions

In vitro studies and clinical interaction studies suggest that semaglutide has a low potential for interaction. *In vitro,* semaglutide did not inhibit or induce CYP enzymes, and did not inhibit drug transporters.

Although semaglutide is strongly bound to plasma albumin, the therapeutic plasma concentrations following semaglutide dosing is very low compared to that of albumin, and it is considered unlikely that semaglutide will alter the protein binding of other drugs.

Drug-drug interactions between semaglutide 1.0 mg and metformin, warfarin, digoxin, atorvastatin or oral contraceptive combination drug (ethinylestradiol and levonorgestrel) were evaluated. Overall, small changes were observed in AUC, C_{max}, and t_{max}. These effects are probably reflecting a minor delay in gastric emptying with semaglutide. A lower C_{max} was observed for atorvastatin when co-administered with semaglutide, but its overall exposure (AUC) has not been affected. The other investigated medication was not affected by

concomitantly administered drugs. The observed changes in pharmacokinetics are not expected to be clinically relevant. The applicant did not evaluate the effect of semaglutide 2.4 mg on other drugs. As the observed delay in gastric emptying was less or comparable between semaglutide 2.4 mg (study 4455) and the lower dose of semaglutide 1.0 mg (study 3685) and the dose range of 0.2-1.6mg semaglutide (study 1821), the DDI studies with the 1.0 mg dose can be used to support the application of the higher 1.7 and 2.4 mg dose levels. No additional interaction studies are needed to evaluate the effect of delayed gastric emptying.

Primary pharmacology

The Ozempic clinical pharmacology programme was cross-referred for PD and PK/PD characteristics of semaglutide 2.4 mg. Within the Ozempic application, the PD properties of semaglutide were investigated in nine clinical pharmacology trials and one phase 2, dose-finding trial. A summary is provided here:

Semaglutide treatment, compared with placebo, lowered fasting and postprandial blood glucose by improving multiple aspects of beta-cell function, including insulin secretion, and reducing both fasting and postprandial glucagon concentrations, all in a glucose-dependent manner. The data in the phase 3 trials show improvements in both HOMA-B and HOMA-IR. In the PD trial (3635), there was no apparent improvement in HOMA IR that may be explained by a generally better-controlled diabetes (lower HbA1c, lower BMI) in line with the inclusion criteria of this PD trial and may thus have reduced the improvability of insulin resistance in these subjects. The mechanism of postprandial blood glucose lowering also involved a delay in gastric emptying.

Counter-regulation during hypoglycaemia was comparable with semaglutide treatment as compared with placebo. This was based on responses in concentrations of glucagon and C-peptide, and in glucose need during the clamp (AUCGIR). A decreased recognition of hypoglycaemia was also observed. It is not clear if this should be considered favourable or not: on the one hand, it may represent subject's adaptation to normalised glucose levels; on the other hand, it could represent hypoglycaemia unawareness.

The body weight loss observed with semaglutide was primarily from fat tissue. The mechanism of body weight loss involved lowered appetite, both in the fasting and postprandial state, leading to lowered daily energy intake. Semaglutide improved control of eating, reduced food cravings and reduced the preference for high-fat foods, as compared to placebo. However, semaglutide reduced energy expenditure as assessed by resting metabolic rate (RMR) using indirect calorimetry/ventilated hood system by appr. 600 kJ per day.

Newly submitted study data on PD for the current application of Wegovy

For the clinical PD assessment of semaglutide up to 2.4 mg for weight management, one new clinical PD trial (trial 4455) was conducted and submitted. Further, BE trial 4590 consisted of some PD data, and one phase 2 trial and two-phase 3a trials included data for exposure-response analysis for semaglutide 2.4 mg.

Trial 4455

Trial 4455 was a single-site, randomised, parallel-group, double-blind, placebo-controlled trial investigating the PD effects of semaglutide 2.4 mg in 72 (n=36 on semaglutide, n=36 on placebo) treatment group subjects with obesity (BMI 30-45 kg/m^2), using a generally similar overall study design and the same methodology, as the NN9535-3685 trial, for gastric emptying assessment (paracetamol absorption technique) and can be considered acceptable.

The primary endpoint, i. e. the paracetamol concentrations, appeared higher in both treatment groups at week 20 compared to baseline and no delay in gastric emptying was observed. A statistically significant increase in $AUC_{0-5h,para}$ of 8% was observed. After adjusting for body weight at week 20, the difference was

no longer statistically significant. In previous gastric emptying studies 1821 and 3685 a delay in gastric emptying has been observed with semaglutide at a dose range of 0.2-1.6 mg and at the 1.0 mg dose level, respectively. Patients in trial 4455 had more time (20 weeks) to gain tolerance to the trial product and its side-effects, compared to patients in previous studies with 12 weeks, which would have affected the gastric emptying and would explain the difference in outcome between the NN9535-3685 trial and the 4455 trial. Therefore, although there is no delay or a slight increase in gastric emptying in obese patients taking semaglutide 2.4 mg, it is still assumed that semaglutide affects gastric emptying.

The secondary endpoints of $AUC_{0-1h,para}$, $C_{max,para}$, $t_{max,para}$ showed no statistically significant differences. The effect on mean energy intake during the ad libitum lunch at week 20 was statistically significantly lower with semaglutide 2.4 mg compared to placebo with an ETD of -940 kJ, corresponding to approximately 35% lower energy intake with semaglutide 2.4 mg and was comparable to the effect with semaglutide 1.0 mg. Further, results from appetite ratings showed a statistically significant effect of appetite suppression postprandially, when semaglutide was compared with placebo at week 20. Data were comparable in the previous 3685 trial.

In exploratory evaluations, the appetite ratings before eating were comparable to the ratings after consumption. Further, the outcome for food intake appears linked to energy intake as there was a larger decrease at week 20 in the mean amount of food consumed with semaglutide 2.4 mg (baseline: 685 g, week 20: 364 g) than with placebo, with slightly more food aversion in the patients on the trial product. Also, the results from the COEQ suggested better control of eating, less hunger and less food cravings with the use of semaglutide 2.4 mg. Regarding body weight, subjects had a mean decrease in body weight of 9.9% (10.4 kg) compared to 0.4% (0.4 kg) with placebo from baseline to week 20. As expected, body weight data of the 4590 trial were comparable to those of the 4455 trial with a decrease of 8.5-8.7 kg after 21 weeks of semaglutide. Subjects treated with semaglutide eat less than subjects treated with placebo. The intake decreases, primarily based on less appetite.

Regarding safety, mainly gastrointestinal disorders were reported. The safety and tolerability profile was consistent with the previous clinical pharmacology trials with semaglutide. A mean increase in pulse of 5 beats/min was observed with semaglutide 2.4 mg, as expected since data from the QTC trial 3652 showed a comparable dose-dependent effect on heartbeat. The mean pulse appeared to be returned to baseline value at the follow-up visit.

Secondary pharmacology

Cardiac repolarisation by QT interval evaluation

The QTc trial (3652) was executed in line with regulatory requirements, and this is accepted. As evidenced by the QTc trial, semaglutide does not prolong QTc values. However, the effect of semaglutide on pulse rate was dose-dependent and appeared to be larger than with other GLP-1Ras. Consistent with the GLP-1 receptor agonist class effect, a small, persistent increase in resting pulse rate was observed with semaglutide in the clinical trial data available at the time of planning the thorough QT/QTc trial, trial 3652 (see also heart rate data from study 4455). QTcI, QTcL and QTcF changes were all below regulatory thresholds. A negative correlation between QTcB and RR interval was found; this association is demonstrated to materialize (albeit weakly) at a heart rate of 60. Consequently, overestimation may be an issue using QTcB in this study. Such association was not present for QTcI and RR intervals. Therefore QTcI (individual heart rate corrected QT interval) was pre-specified as the primary endpoint in this trial, avoiding correction methods for the primary objective that is known to be problematic for compounds with properties to elevate heart rate.

Exposure response relationship

The exposure-response analyses appear to indicate that the higher the average concentration, the more bodyweight loss can be expected. In contrast, the relationship between exposure and response for gastro-intestinal adverse events indicates that a plateau is reached for the probability of experiencing an adverse event. However, these results could be severely biased by the assumed model structures (see also section 3.1.2. Methods). The exposure-response models are quite empirical, pre-specified, and no goodness-of-fit plots or adequate numerical diagnostics have been provided. The average plasma concentration is estimated based on solely through concentrations, which could also severely bias the estimation of exposure. Therefore, the adequacy of the models to describe the relationship between plasma-exposure and bodyweight or adverse events cannot be assessed.

Bodyweight influences plasma exposure (i.e. the higher the body weight, the lower the plasma exposure). This could severely bias the relationship between plasma exposure and body weight change. Furthermore, the time component (any correlation over the observations) is completely neglected by the modelling, which could bias the exposure-response relationship. Therefore, these models should not be used for any dosing recommendations and cannot demonstrate the adequacy of the selected dosing regimen in subpopulations.

2.6.4. Conclusions on clinical pharmacology

In general, the pharmacokinetics and pharmacodynamics of semaglutide up to a s.c. dose of 2.4 mg are adequately characterised during the weight management and T2D clinical pharmacology programme.

2.6.5. Clinical efficacy

The clinical efficacy programme consists of one dose-response study and four phase 3 studies as outlined in the table below (**Table 20**). The phase 3 studies are all conducted in patients, who are obese (BMI≥30 kg/m^2) or overweight (27 kg/m2≤ BMI < 30 kg/m^2) with at least one weight-related comorbidity.

The Applicant states that all studies for the weight management programme were conducted in accordance with ICH Good Clinical Practice.

Table 20

Trial ID Country	Type of study	Trial design and type of control	Test drugs and route of administration	Number of subjects (FAS)	Subject population	Duration of treatment	Study status Type of report Location
Phase 2 trial							
NN9536-4153 AU, BE, CA, DE, IL, RU, GB, US	Dose-finding	Randomised (6:1 active:placebo), double-blind, placebo-controlled, 16-armed, parallel group, multi-centre, multinational trial with liraglutide 3.0 mg as active comparator, investigating safety and efficacy of once-daily semaglutide	Semaglutide (1.0 mg/mL) s.c., 0.05 mg, 0.1 mg, 0.2 mg, 0.3 mg, or 0.4 mg once daily. Liraglutide (6.0 mg/mL) s.c., 3.0 mg once daily. Placebo (matching each of the active treatment arms) s.c., once daily.	957 (M: 338; F:619)	Subjects with obesity without diabetes mellitus	52 weeks	Completed Full M 5.3.5.1
Phase 3a trials							
NN9536-4373 (STEP 1) AR, BE, BG, CA, DK, FI, FR, DE, IN, JP, MX, PL, RU, TW, GB, US	Efficacy and safety Weight management	Randomised (2:1), double-blind, placebo-controlled, two-armed, parallel group, multi-centre, multinational trial assessing the effect and safety of semaglutide s.c. 2.4 mg once weekly vs placebo as an adjunct to reduced-calorie diet and increased physical activity.	Semaglutide (3.0 mg/mL) s.c., 2.4 mg once weekly, or placebo	1961 (M: 508; F: 1453)	Subjects with obesity (BMI ≥30 kg/m^2), or overweight (BMI ≥27 to <30 kg/m^2) and at least one weight-related comorbidity.	68 weeks	Completed main part Full (main part) M 5.3.5.1 Extension part is ongoing as of cut-off date 01-Sep-2020
NN9536-4374 (STEP 2) AR, CA, DE, GR, IN, JP, RU, ZA, ES, AE, GB, US	Efficacy and safety Weight management in T2D	Randomised (1:1:1), double-blind, double dummy, placebo-controlled, multi-centre, multinational trial assessing the effect and safety of semaglutide s.c. 2.4 mg once weekly vs placebo as an adjunct to reduced-calorie diet and increased physical activity.	Semaglutide (1.34 mg/mL) s.c., 1.0 mg once weekly Semaglutide (3.0 mg/mL) s.c., 2.4 mg once weekly Placebo (matching each of the two active treatment arms) s.c., once weekly	1210 (M: 594; F: 616)	Subjects with overweight or obesity (BMI ≥27 kg/m^2) and T2D (HbA_{1c} 7–10%).	68 weeks	Completed Full M 5.3.5.1
NN9536-4375 (STEP 3) US	Efficacy and safety Weight management with IBT	Randomised (2:1), double-blind, placebo-controlled, two-arm, parallel-group, multi-centre trial assessing the effect and safety of semaglutide s.c. 2.4 mg once weekly vs placebo as an adjunct to intensive behavioural therapy.	Semaglutide (3.0 mg/mL; 3.2 mg/mL during last 8 weeks of treatment) s.c., 2.4 mg once weekly, or placebo	611 (M: 116; F: 495)	Subjects with obesity (BMI ≥30 kg/m^2), or overweight (BMI ≥27 to <30 kg/m^2) and at least one weight-related comorbidity.	68 weeks	Completed Full M 5.3.5.1
NN9536-4376 (STEP 4) DK, IL, NL, PT, ZA, ES, SE, CH, UA, US	Efficacy and safety Sustained weight management	Randomised (2:1), double-blind, placebo-controlled, two-armed, multi-centre, multinational withdrawal trial assessing the effect and safety of semaglutide s.c. 2.4 mg once weekly vs placebo in subjects who reached target dose during run-in period.	Semaglutide (3.0 mg/mL) s.c., 2.4 mg once weekly, or placebo	803 (M: 169; F: 634)	Subjects with obesity (BMI ≥30 kg/m^2), or overweight (BMI ≥27 to <30 kg/m^2) and at least one weight-related comorbidity, who had reached the maintenance dose of 2.4 mg at randomisation.	68 weeks	Completed Full M 5.3.5.1

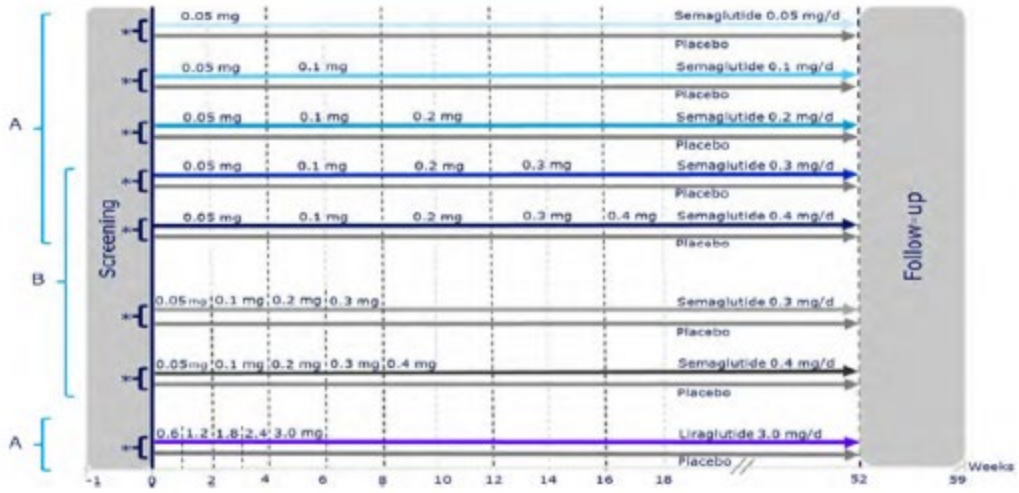
2.6.5.1. Dose response study(ies)

The phase 2 trial 4153 was a 52-week, randomised, double-blind, placebo-controlled, parallel-group, multi-centre, multinational trial with liraglutide 3.0 mg as an active comparator, and it enrolled 957 subjects with obesity, but without diabetes. The study design is shown in **Figure 17**. Dose selection was performed with daily doses of semaglutide s.c. The Applicant described that this was chosen to avoid large fluctuations in semaglutide plasma concentrations as this might have increased gastrointestinal side effects. However, as semaglutide has a half-life of a week, fluctuation in plasma concentrations are not very likely. Trial 4153 investigated 5 once-daily doses of semaglutide (0.05 mg, 0.1 mg, 0.2 mg. 0.3 mg, and 0.4 mg) with dose escalation every fourth week and a steady-state reached before increasing the dose. Two dose escalation regimens were tested. As expected, with an increase of the dosage, a larger proportion of subjects reported gastrointestinal AEs. The results from this study showed that semaglutide 0.4 mg once daily with dose escalation every fourth week was most effective in terms of weight loss (**Figure 18**), while displaying an acceptable tolerability profile.

A once-weekly dose was chosen that was not expected to exceed the plasma semaglutide concentrations achieved with once-daily 0.4 mg semaglutide. The population PK modelling estimated that a once-weekly maintenance dose of 2.4 mg semaglutide would result in similar concentrations at steady-state. The once-weekly 2.4 mg semaglutide projected lower proportions of subjects reporting gastrointestinal AEs by approximately 2% and the proportion of subjects discontinuing due to gastrointestinal AEs. Consequently, semaglutide 2.4 mg once weekly was the selected maintenance dose for the phase 3a weight management development programme, with dose escalation every four weeks

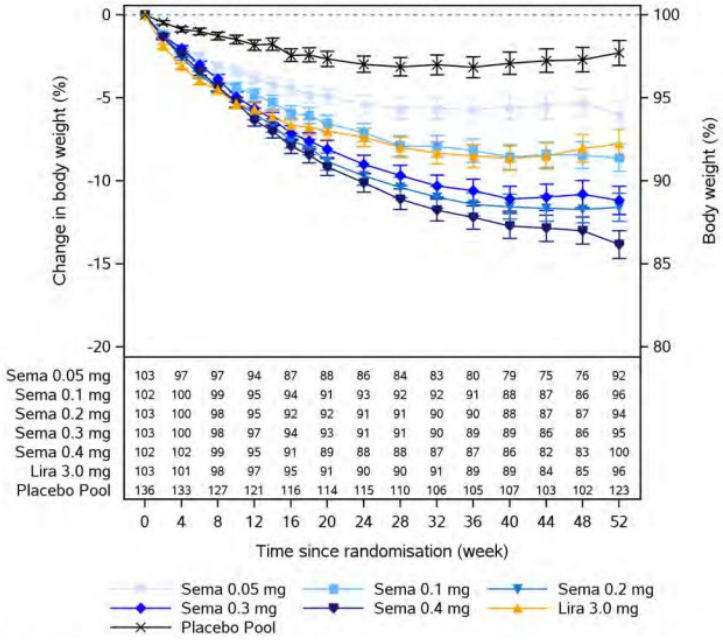
However, no subgroup evaluation was performed at this stage and therefore, no evaluation if the effect of dose may differ depending on weight or BMI at baseline. It is considered plausible that the effect on weight loss may be baseline weight dependent.

Figure 17 trial design, phase 2 trial 4153



*Each active treatment arm was blinded towards placebo with matching injection volumes, but not towards the other treatment arms. A. The dose-finding part of the trial (part A). B. The dose escalation part of the trial (part B) (see

Figure 18 Change in body weight (%) from baseline by treatment week – randomised active arms and placebo pool – ANCOVA – J2R – MI – mean plot – full analysis set



2.6.5.2. Main study(ies)

Conduct of the study

The investigators were required to have been trained in GCP. Training of the investigators in the protocol was carried out through investigator meetings and site initiation visits to ensure compliance and standardise performance across the trial. According to the protocol, the principal investigators provided written commitments to comply with GCP and conduct the trial prior to participation in the trial. Monitoring was conducted using a risk-based approach, including risk assessment, monitoring plans, centralised monitoring, and trial sites visits. The monitors reviewed the subject's medical records and other source data, e.g. the diaries and mental health assessment instruments, to ensure consistency and/or to identify omissions compared to the eCRF.

Novo Nordisk was responsible for the data management of this trial, including quality checking of the data. All subject data relating to the trial were recorded on eCRFs unless transmitted electronically to Novo Nordisk or designee (e.g. laboratory data). The investigator was responsible for verifying that data entries were accurate and correct by signing the eCRF. The original of the completed diaries should not be removed from the trial site, unless they form part of the CRF, and a copy was kept at the site.

As a consequence of the outbreak of the COVID-19 pandemic, it was decided as of 23 March 2020 to stop source data validation of remaining data, as monitors could not visit the sites and remote validation was not possible. All data were still entered into the eCRF and checked for completeness, and data cleaning and casebook sign-off were ensured.

Internal audits were performed by Novo Nordisk Quality Audits. Audit certificates that were available as of 01 July 2020. The results presented reflect the data available in the clinical database as of 11 May 2020 (all data except anti-semaglutide antibody data and pharmacokinetic data) and 01 July 2020 (anti-semaglutide

antibody data and pharmacokinetic data). The first database lock covering all data except anti-semaglutide antibody data and pharmacokinetic data took place on 11 May 2020, after which the randomisation code was unblinded.

STEP 1-4

Methods

The efficacy and safety of semaglutide s.c. 2.4 mg once weekly for weight management as an adjunct to a reduced-calorie diet and increased physical activity (STEP 1, 2 and 4) or intensive behavioural therapy (IBT) (STEP 3) were studied in four phase 3a 68-week randomised, double-blind, placebo-controlled trials which included a total of 2652 subjects randomised to semaglutide 2.4 mg and 1530 randomised to placebo.

The four-phase 3a trials (STEP 1–4) all included subjects with obesity (BMI ≥30 kg/m^2) or overweight (BMI ≥27 to <30 kg/m^2) and at least one weight-related comorbidity. STEP 2 included subjects with overweight or obesity (BMI ≥27 kg/m^2) *and* T2D (HbA_{1c} 7–10%). In STEP 1, 2 and 4, standard lifestyle intervention according to clinical guidelines was included. STEP 3 evaluated semaglutide 2.4 mg when combined with IBT. All four trials had a treatment duration of 68 weeks with an additional 7 weeks of follow-up off treatment. In STEP 1–3, the 68 weeks of treatment included 16 weeks of dose escalation to semaglutide 2.4 mg and 52 weeks on maintenance dose. The semaglutide 1.0 mg treatment arm in STEP 2 included 8 weeks of dose escalation and 60 weeks on 1.0 mg. STEP 4 evaluated the effects of stopping or continuing treatment with semaglutide after reaching the maintenance dose of 2.4 mg.

- **Study Participants**

The STEP 1 trial (4373 – weight management) was performed at 129 sites in 16 countries in Asia, Europe, North America, and South America.

The key inclusion criteria were:

- Male or female, age ≥18 years at the time of signing informed consent
- BMI ≥30.0 kg/m2 or ≥27.0 kg/m2 with the presence of at least one of the following: weight-related comorbidities (treated or untreated): hypertension, dyslipidaemia, obstructive sleep apnoea or cardiovascular disease.
- History of at least one self-reported unsuccessful dietary effort to lose body weight

The key exclusion criteria:

- HbA1c ≥48 mmol/mol (6.5%) as measured by the central laboratory at screening
- A self-reported change in body weight >5 kg (11 lbs) within 90 days before screening irrespective of medical records

The inclusion and exclusion criteria for STEP 3 trial (4375 – weight management with IBT) and STEP 4 trial (4376 – sustained weight management) were identical to the STEP 1 trial.

The STEP 2 trial (4374 – weight management in type 2 diabetes) was designed to investigate the effect of semaglutide 2.4 mg on weight management in T2D. IN this trial, the key inclusion criteria were:

- Male or female, age ≥ 18 years at the time of signing informed consent
- BMI ≥ 27.0 kg/m2
- History of at least one self-reported unsuccessful dietary effort to lose body weight
- Diagnosed with T2D ≥180 days prior to the day of screening
- Subject treated with either:
    - diet and exercise alone or
    - stable treatment with metformin, SU, SGLT2i, glitazone as single agent therapy or up to 3 OADs (metformin, SU, SGLT2i or glitazone) according to local label

  Any approved and marketed metformin, glitazone, SGLT2i or SU product or combination products are allowed. Treatment with oral agents should be stable (same drug(s), dose and dosing frequency) for at least 90 days prior to screening.
- HbA1c 7-10% (53-86 mmol/mol) (both inclusive)

The key exclusion criteria were:

- A self-reported change in body weight > 5 kg (11 lbs) within 90 days before screening irrespective of medical records
- Renal impairment measured as estimated Glomerular Filtration Rate (eGFR) value of <30 mL/min/1.73 m2 (<60 mL/min/1.73 m2 in subjects treated with SGLT2i) according to CKD-EPI creatinine equation as defined by KDIGO 201285 by the central laboratory at screening
- Uncontrolled and potentially unstable diabetic retinopathy or maculopathy. Verified by a pharmacologically pupil-dilated fundus examination performed by an ophthalmologist or an equally qualified health care provider (e.g. optometrist) within the past 90 days prior to screening or in the period between screening and randomisation

In all four STEP trials, patients with renal and hepatic impairment were excluded. The PK studies showed a similar exposure in patients with renal impairment and hepatic impairment. However, patients with renal or hepatic impairment were not included in the STEP studies. No analyses on efficacy and safety have been performed in these patients. The Applicant is requested to amend section 4.2 in the SmPC on renal and hepatic impairment in line with the SmPC of Saxenda.

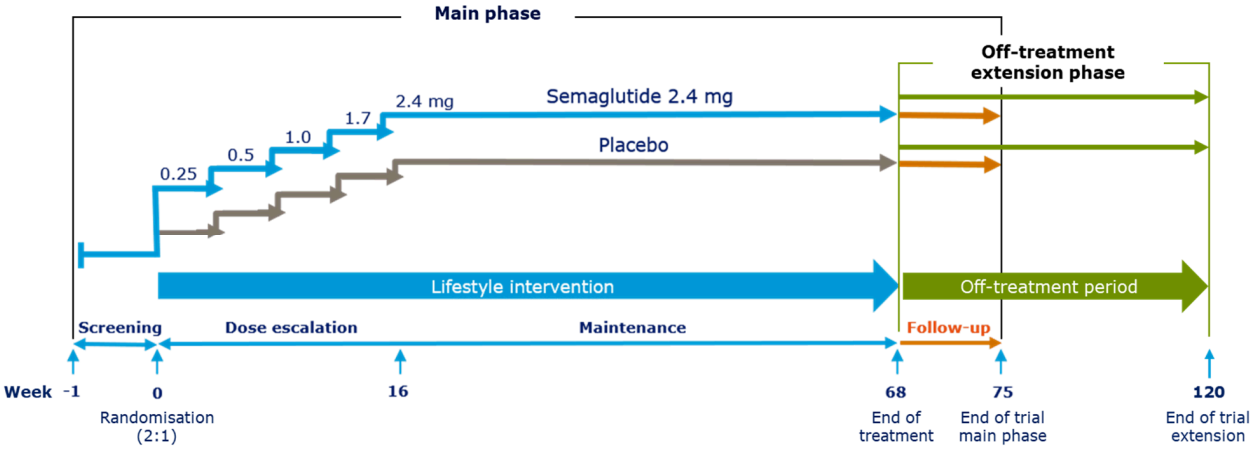
- **Treatments**

STEP 1 (4373) – weight management in overweight or obesity

STEP 1 was a 68-week, randomised, double-blind, placebo-controlled, two-armed, parallel group, multi-centre, multinational trial. The 68 weeks of treatment included 16 weeks of dose escalation and 52 weeks on maintenance dose (**Figure 19**). The treatment period was followed by a 7-week follow-up period off-treatment. This period of 7 weeks after treatment discontinuation is considered short, but as STEP 4 (see

below) is designed to investigate the maintenance of effect on weight, this is not considered a large issue in the design. A sub-population of 140 randomised subjects had their body composition assessed by DEXA at screening and end-of-treatment.

Figure 19 STEP 1 trial design

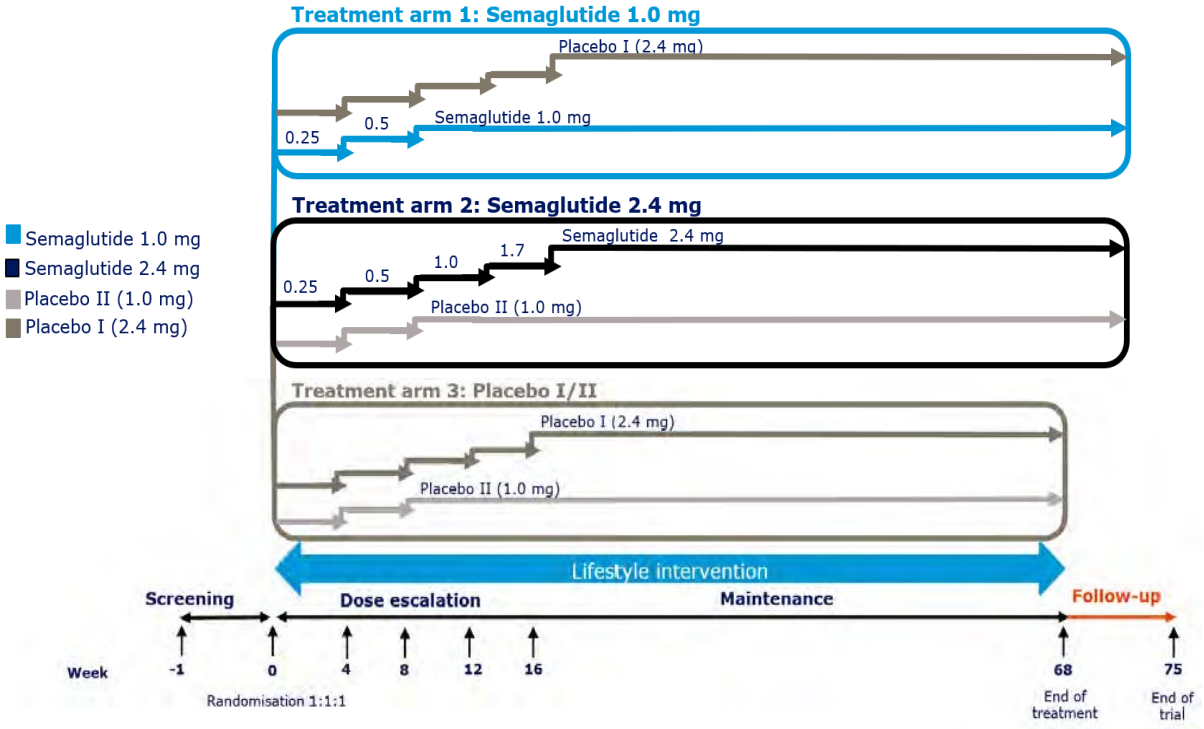


STEP 2 (4374) – weight management in type 2 diabetes

STEP 2 was a 68-week, randomised, double-blind, double dummy, placebo-controlled, multi-centre, multinational trial. In addition to comparing semaglutide s.c. 2.4 mg once weekly with placebo, a treatment arm with semaglutide s.c. 1.0 mg once weekly was included to enable comparison with the semaglutide s.c. T2D development programme and a comparison of the effect on body weight between the two semaglutide doses (1.0 and 2.4 mg). Randomisation in this study was 1:1:1. The 68 weeks of treatment with semaglutide s.c. 2.4 mg included 16 weeks of dose escalation and 52 weeks on maintenance dose (for semaglutide s.c. 1.0 mg: 8 weeks of dose escalation and 60 weeks on maintenance dose), followed by a 7-week follow-up period off treatment (.

Figure 20).

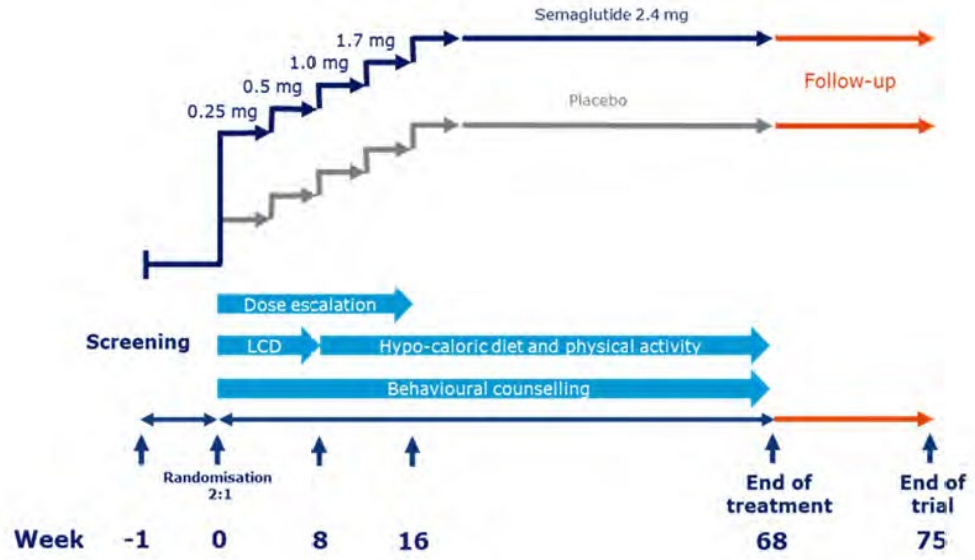
Figure 206 STEP 2 trial design



STEP 3 (4375) – weight management with IBT

STEP 3 was a 68-week, randomised, double-blind, placebo-controlled, two-armed, parallel group, multi-centre trial conducted in the US. The 68 weeks of treatment included 16 weeks of dose escalation and 52 weeks on maintenance dose. For the first 8 weeks after randomisation, dietary intervention consisted of a 1000–1200 kcal/day low-calorie diet (LCD). After 8 weeks on LCD, subjects were gradually transferred to a less strict hypo-caloric diet (1200–1800 kcal/day) combined with physical activity and frequent behavioural counselling (in combination referred to as intensive behavioural therapy or IBT). Physical activity was initiated from randomisation with a target of 100 minutes physical activity per week, gradually progressing (by 25 minutes every 4 weeks) up to 200 minutes/week. The treatment period was followed by a 7-week follow-up period off-treatment (**Figure 21**).

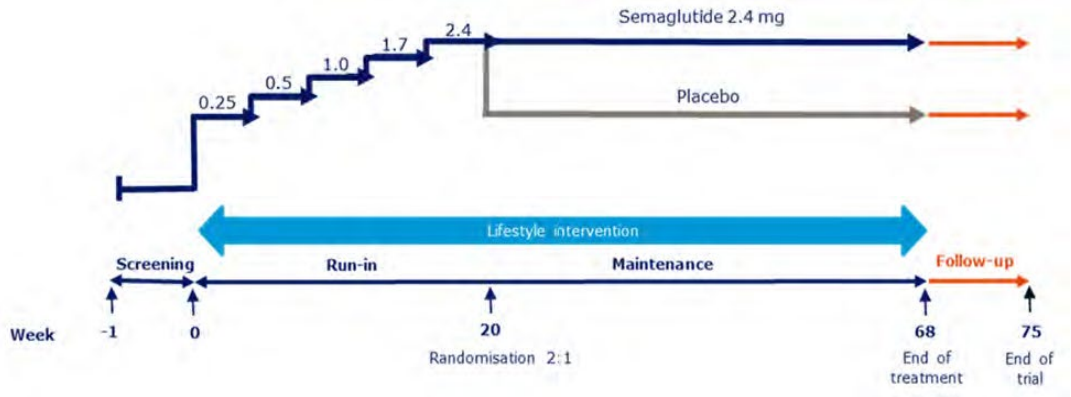
Figure 21 STEP 3 trial design



STEP 4 (4376) – sustained weight management

STEP 4 was a 68-week placebo-controlled, two-armed, double-blind, multinational, multi-centre, randomised withdrawal trial. The trial included a 20-week run-in period (including 16 weeks of dose escalation) on semaglutide followed by a randomised treatment period of 48 weeks treatment with either semaglutide 2.4 mg or placebo. Only subjects who had reached the maintenance dose of semaglutide (2.4 mg) during the run-in period were eligible for randomisation. The withdrawal design was used to assess weight development after switching to placebo and generate data to support maintained weight loss in subjects continuing semaglutide treatment compared to subjects switching to placebo (**Figure 22**).

Figure 22 STEP 4 trial design



- **Objectives**

The primary objective of the four phase 3a trials (STEP 1–4) was to compare the effect of semaglutide s.c. 2.4 mg once weekly vs placebo in subjects with overweight or obesity (and T2D in STEP 2) on body weight, either as an adjunct to a reduced-calorie diet and increased physical activity (STEP 1, 2 and 4) or to IBT (STEP 3).

The main secondary objectives of STEP 1–4 were to compare the effect of semaglutide s.c. 2.4 mg once weekly vs placebo in subjects with overweight or obesity (and T2D in STEP 2) on other factors related to body weight, cardiovascular risk factors, clinical outcome assessments including patient-reported outcomes, and glucose metabolism.

- **Outcomes/endpoints**

The primary endpoints were change from baseline to week 68 in body weight (%) (STEP 1−4) and subjects who achieve ≥5% body weight reduction from week 0 at week 68 (STEP 1−3). The confirmatory secondary endpoints differed slightly between trials and included additional body weight-related endpoints, cardiovascular and glycaemic biomarkers, and patient-reported outcomes.

An overview of the efficacy-related endpoints across the STEP trials is provided in **Table 21** and **Table 22**.

Table 13 Efficacy endpoints related to body weight, glucose metabolism and cardiovascular efficacy - STEP 1-4

	STEP 1 Weight management	STEP 2 Weight management in T2D	STEP 3 Weight management with IBT	STEP 4 Sustained weight management
Body weight-related endpoints				
Change from baseline[a] to week 68 in:				
Body weight (%)	**P**	**P**	**P**	**P**
Body weight (kg)	S	S	S	S
Waist circumference (cm)	**C**	**C**	**C**	**C**
Body-mass index (kg/m^2)	S	S	S	S
Soluble leptin receptor (ng/mL)	S			
Leptin (ng/mL)	S			
Body composition (DEXA)	S			
Change from baseline to week 8 in body weight (%)			S	
Change from week 0 to week 68 in body weight (%)				S
Subjects who achieve at week 68 (y/n):				
≥5% body weight reduction from week 0	**P**	**P**	**P**	S
≥10% body weight reduction from week 0	**C**	**C**	**C**	S
≥15% body weight reduction from week 0	**C**	**C**	**C**	S
≥20% body weight reduction from week 0	S	S	S	S
<0% body weight reduction from week 0				S
<0% body weight reduction from week 20				S
Glucose metabolism-related endpoints				
Change from baseline[a] to week 68 in:				
HbA_{1c} (% and mmol/mol)	S	**C**	S	S
FPG (mmol/L and mg/dL)	S	S	S	S
Fasting serum insulin (pmol/L and mIU/mL)	S	S	S	S
Subjects who achieve at week 68 (y/n):				
HbA_{1c} < 7.0%		S		
HbA_{1c} ≤ 6.5%		S		
Body weight reduction ≥10% and HbA_{1c} <7.0%		S		
Body weight reduction ≥15% and HbA_{1c} <7.0%		S		
Cardiovascular-related endpoints				
Change from baseline[a] to week 68 in:				
Systolic blood pressure (mmHg)	**C**	**C**	**C**	**C**
Diastolic blood pressure (mmHg)	S	S	S	S
Lipids (mmol/L and mg/dL)	S	S	S	S
C-reactive protein (CRP) (mg/L)	S	S	S	
Plasminogen activator inhibitor-1 (PAI-1) activity (AU/mL)	S	S	S	

a. In STEP 4, baseline is at week 20 (randomisation)

P: primary/co-primary endpoint; C: confirmatory secondary endpoint; S: supportive secondary endpoint

Table 22 Efficacy endpoints - patient-reported outcomes - STEP 1-4

	STEP 1 Weight management	STEP 2 Weight management in T2D	STEP 3 Weight management with IBT	STEP 4 Sustained weight management
Patient-reported outcomes				
Change from baseline[a] to week 68 in:				
SF-36 scores:				
Physical functioning	**C**	**C**	**C**	**C**
Other SF-36 scores[b]	S	S	S	S
IWQOL-Lite-CT:				
Physical function domain (5-items) score	**C**	**C**		
Other IWQOL-Lite-CT scores[c]	S	S		
Subjects who achieve at week 68 (y/n):				
Responder definition value[d] for SF-36 physical functioning score	S	S	S	S
Responder definition value[e] for IWQOL-Lite-CT physical function domain (5-items) score	S	S		

a. In STEP 4, baseline was at week 20 (randomisation); b. Other SF-36 scores: Role-physical, Bodily pain, General health, Vitality, Social functioning, Role-emotional, Mental health, Physical component summary, Mental component summary; c. Other IWQOL-Lite-CT scores: Physical score, Psychosocial score and Total score; d. Responder value = 3.7; e. Responder value = 14.6.
C: Confirmatory secondary endpoint; S: supportive secondary endpoint

The primary endpoint was the same in all four phase 3a trials: change from baseline to week 68 in body weight (%). Furthermore, STEP 1–3 included a co-primary endpoint: subjects achieving (y/n) ≥5% body weight reduction at week 68.

- **Randomisation and Blinding (masking)**

In STEP 1 and 3, eligible subjects were centrally randomised in a 2:1 manner to one of the two treatment groups at visit 2. In STEP 2, eligible subjects were randomised in a 1:1:1 manner to one of the three treatment groups at visit 2. Randomisation in STEP 2 was stratified according to background diabetes treatment and HbA1c at screening. Furthermore, the proportion of subjects treated with SUs was restricted to a maximum of 30% of all randomised subjects. In STEP 4, eligible subjects were randomised in a 2:1 manner to one of the two treatment groups at visit 12 (week 20).

Randomisation was performed using an IWRS. Subjects were assigned to the next available treatment according to the randomisation schedule.

Treatment allocation remained blinded to the subjects, the investigators and to Novo Nordisk during the entire treatment and follow-up period in the main phase of the trial and until after DBL for the main phase of the trial.

- **Sample size / Statistical methods**

The sample size and thereby the power for these trials was primarily defined to support safety.

The tests of superiority of semaglutide 2.4 mg to semaglutide placebo (or semaglutide placebo I/II or semaglutide 1.0 mg in STEP 2) for the primary and confirmatory secondary endpoints were performed using the fixed-sequence statistical strategy, at the significance level of 5%. The effective power was calculated under the assumption of independence of endpoints by multiplying the respective marginal powers successively. The assumptions on treatment effect and resulting power are given in **Table 23**, **Table 24**, **Table 25** and **Table 26**.

Table 14 Assumptions, marginal power and effective power for each endpoint in the hierarchical testing procedure given an anticipated number of 1950 randomised subjects for STEP 1

Order	Endpoint	Assumed mean (±SD) or proportion for completers		Expected mean (±SD) or proportion Semaglutide 2.4 mg	Expected difference or proportion ratio	Marginal power (%)	Effective power (%)
		Semaglutide 2.4 mg	Semaglutide placebo				
1	% weight change #	14 (±10)	3 (±10)	12.5 (±11)	9.5%-points	>99	>99
2	5% responders	82%	42%	76%	1.8	>99	>99
3	10% responders	66%	24%	60%	2.5	>99	>99
4	15% responders	46%	12%	41%	3.4	>99	>99
5	WC change (cm) #	11 (±10)	4 (±10)	10 (±10)	6 cm	>99	>99
6	sBP change (mmHg) #	6.2 (±13)	1.5 (±13)	5.5 (±13)	4 mmHg	>99	>99
7	SF-36 PF score change	6 (±10)	2 (±10)	5.4 (±11)	3.4 score-points	>99	>99
8	IWQoL-Lite PFD score change	[24] (±20)	[13] (±20)	22.5 (±21)	9.5 score-points	>99	>99

SD = standard deviation; WC = waist circumference; sBP = systolic blood pressure; SF-36 = Short Form 36 v2.0 acute; PF = physical functioning; IWQoL-Lite = Impact of Weight on Quality of Life-Lite for Clinical Trials; PFD = physical function domain; # shown as a positive number

All tests in the hierarchy are based on the primary estimand

Table 15 Assumptions, marginal power and effective power for each endpoint in the hierarchical testing procedure given an anticipated number 1200 randomised subjects (400 in each arm) for STEP 2

Order	Endpoint	Assumed mean (±SD) or proportion for completers		Expected mean (±SD) or proportion Semaglutide 2.4 mg	Expected difference or proportion ratio	Marginal power (%)	Effective power (%)
		Semaglutide 2.4 mg	Semaglutide placebo I/II				
1	% weight change #	11.6 (±10)	1.7 (±10)	10.2 (±11)	8.5%-points	> 99	> 99
2	5% responders	75%	37%	69%	1.8	> 99	> 99
3	10% responders	56%	20%	51%	2.6	> 99	> 99
4	15% responders	37%	9%	33%	3.7	> 99	> 99
5	WC change (cm) #	9.1 (±10)	2.8 (±10)	8.2 (±11)	5.4 cm	> 99	> 99
6	% weight change #, *	11.6 (±10)	8.1 (±10)	10.2 vs 7.2 (±11)	3.0%-points	97	97
7	HbA_{1c} (%) change #	1.4 (±1.0)	0.5 (±1.0)	1.3 (±1.5)	0.8%-points	> 99	96
8	sBP change (mmHg) #	5.1 (±13)	0.4 (±13)	4.4 (±14)	4 mmHg	98	94
9	SF-36 PF score change	6 (±10)	2 (±10)	5.4 (±11)	3.4 score-points	> 99	94
10	IWQoL-Lite PFD score change	24 (±20)	13 (±20)	22.5 (±21)	9.5 score-points	> 99	94

SD = standard deviation; WC = waist circumference; sBP = systolic blood pressure; SF-36 = Short Form 36 v2.0 acute; PF = physical functioning; IWQoL-Lite = Impact of Weight on Quality of Life-Lite for Clinical Trials; PFD = physical function domain; # shown as a positive number; * semaglutide 2.4 mg vs semaglutide 1.0 mg

All tests in the hierarchy are based on the primary estimand.

Table 16 Assumptions, marginal power and effective power for each endpoint in the hierarchical testing procedure given an anticipated number 600 randomised subjects for STEP 3

Order	Endpoint	Assumed mean (±SD) or proportion for completers		Expected mean (±SD) or proportion Semaglutide 2.4 mg	Expected difference or proportion ratio	Marginal power (%)	Effective power (%)
		Semaglutide 2.4 mg	Semaglutide placebo				
1	% weight loss #	17 (10)	7 (10)	15.6 (11)	8.6 %-points	> 99	> 99
2	5% responders	88%	58%	85%	1.5	> 99	> 99
3	10% responders	76%	38%	71%	1.9	> 99	> 99
4	15% responders	58%	21%	53%	2.5	> 99	> 99
5	WC change (cm) #	17 (11)	8 (11)	15.7 (12)	7.7 cm	> 99	> 99
6	sBP change (mmHg) #	9.1 (13)	4.5 (13)	8.5 (14)	4 mmHg	91	91
7	SF-36 PF score change	6 (±10)	2 (±10)	5.4 (±11)	3.4 score-points	95	86

SD = standard deviation; WC = waist circumference; sBP = systolic blood pressure; SF-36 = Short Form 36 v2.0 acute; PF = physical functioning; # shown as a positive number

All tests in the hierarchy are based on the primary estimand

Table 17 Assumptions, marginal power and effective power for each endpoint in the hierarchical testing procedure given an anticipated number of 750 randomised subjects for STEP 4

Order	Endpoint	Assumed mean (±SD) for completers		Expected mean (±SD)	Expected difference	Marginal power (%)	Effective power (%)
		Semaglutide 2.4 mg	Semaglutide placebo	Semaglutide 2.4 mg			
1	% weight change	-4 (±10)	+5 (±10)	-3.7 (±11)	8.7 %-points	> 99	> 99
2	WC change (cm)	-3 (±10)	+3 (±10)	-2.8 (±11)	5.8 cm	> 99	> 99
3	sBP change (mmHg)	-3.1 (±13)	+1 (±13)	-3 (±14)	4 mmHg	95	95
4	SF-36 PF score change	+6 (±10)	+2 (±10)	+5.9 (±11)	3.9 score-points	> 99	95

SD = standard deviation; WC = waist circumference; sBP = systolic blood pressure; SF-36 = Short Form 36 v2.0 acute; PF = physical functioning
All tests in the hierarchy are based on the primary estimand

The efficacy-related endpoints were evaluated for two pre-specified **estimands,** addressing the trial objectives in terms of two different aspects of the treatment effect of semaglutide 2.4 mg:

The treatment policy estimand was the protocol-defined primary estimand in all phase 3a trials and in the phase 2 trial 4153. It assessed the trial population-average effect of subjects being randomised to treatment with the trial product (semaglutide or placebo) after 68 weeks, as an adjunct to a reduced-calorie diet and increased physical activity (STEP 1, 2 and 4) or IBT (STEP 3), regardless of adherence to treatment or initiation of other anti-obesity therapies. The analyses of the confirmatory endpoints were controlled for multiplicity only for the treatment policy estimand, and all superiority claims were based on conclusions from the treatment policy estimand.

The hypothetical estimand assessed the trial population-average effect of actually taking the trial product (semaglutide or placebo) without any initiation of other anti-obesity therapies after 68 weeks as an adjunct to a reduced-calorie diet and increased physical activity (STEP 1, 2 and 4) or IBT (STEP 3).

Three **analysis sets** are defined:

- The full analysis set (FAS) includes all randomised subjects according to the intention-to-treat principle.
- The safety analysis set (SAS) includes all randomised subjects exposed to at least one dose of randomised treatment.
- The extension analysis set (ExAS) includes all subjects eligible for the extension trial, who gave informed consent to participate and attended at least one of the following visits in the extension period: V25ext, V26ext, V27ext or V28ext.

Two **observation periods** are defined for each subject

- In-trial: The in-trial period is defined as the uninterrupted time interval from the date of randomisation to the date of the last contact with the trial site.
- On-treatment (with trial product): A time-point is considered as 'on-treatment' if any dose of trial product has been administered within the prior 2 weeks (14 days). The on-treatment period is defined as all times which are considered on-treatment.
- In general, the on-treatment period will therefore be from the date of first trial product administration to the date of last trial product administration, excluding potential off-treatment time intervals triggered by at least two consecutive missed doses.

- For the evaluation of adverse events, the lag time for each on-treatment time interval is 7 weeks (49 days).

For the treatment policy estimand, the **primary analysis** model for continuous endpoints was a linear regression (ANCOVA) with randomised treatment as a factor and baseline assessment of the endpoint to be analysed as a covariate. In STEP 2, the stratification group for OAD treatment and HbA1c and the interaction between these were included as additional factors.

The analysis model for the binary endpoints was a logistic regression using randomised treatment as a factor and baseline assessment of the endpoint to be analysed as a covariate. In STEP 2, the stratification group for OAD treatment and HbA1c, as well as the interaction between these, were included as additional factors.

The confirmatory hypotheses were controlled for **multiplicity** using the fixed-sequence statistical strategy, testing the endpoints using a predefined hierarchical order. The test hierarchies for each of the four phase 3a trials are given in **Table 27**.

Table 18 Confirmatory endpoints and testing hierarchy

	STEP 1	STEP 2	STEP 3	STEP 4[a]
Primary endpoint(s)				
Change from baseline to week 68 in body weight (%)	1	1	1	1
Subjects who achieve (y/n) ≥5% body weight reduction	2	2	2	
Confirmatory secondary endpoints				
Subjects who achieve (y/n) ≥10% body weight reduction	3	3	3	
Subjects who achieve (y/n) ≥15% body weight reduction	4	4	4	
Change from baseline to week 68 in waist circumference	5	5	5	2
Change from baseline to week 68 in body weight (%)[b]		6		
Change from baseline in HbA_{1c}		7		
Change from baseline in systolic blood pressure	6	8	6	3
Change from baseline in SF-36 PF score	7	9	7	4
Change from baseline in IWQOL-Lite-CT PF score	8	10		

a. from week 20 (randomisation) to week 68; b. semaglutide 2.4 mg versus semaglutide 1.0 mg. All tests in the hierarchy were based on the primary (treatment policy) estimand.

For each subject, a given assessment at week 68 could be available or **missing**, depending on whether they were still on randomised treatment at week 68: Available on randomised treatment (AT), available but discontinued (AD, missing on randomised treatment (MT), and missing and discontinued (MD). Note that subjects could have a different type for different assessments.

All available data at week 68 (AT and AD) was used and missing values (MT and MD) at week 68 were imputed and the endpoints derived from the imputed values. The primary imputation approach was a multiple imputation approach using retrieved subjects (RD-MI). Missing body weight measurements at week 68 for non-retrieved subjects (MD) were imputed using assessments from retrieved subjects (AD), and missing body weight measurements at week 68 for subjects on randomised treatment (MT) were imputed by sampling from subjects on randomised treatment (AT), both in the relevant randomised treatment arm.

Sensitivity analyses investigated how assumptions on body weight development after withdrawal from the trial impacted the estimated treatment contrasts: jump to reference MI, single imputation approach as done by Sacks26, tipping-point MI, in-trial MMRM, and non-responders imputation (for binary endpoints only).

For the secondary hypothetical estimand, both continuous and binary endpoints were assessed using a mixed model for repeated measurements, or 'on-treatment MMRM'. The on-treatment MMRM was fitted using the

endpoint as response and the same factor(s) and covariate as for the primary analyses all nested within visit. An unstructured covariance matrix for measurements within the same subject was employed.

The estimated treatment difference within each subgroup (demographics and baseline disease severity) were presented.

Results

- **Participant flow**

In total, 4585 subjects were randomised in STEP 1–4: 2652 to semaglutide 2.4 mg, 1530 to placebo, and 403 to semaglutide 1.0 mg. Total patient-years of exposure (PYE) was 4770 for the on-treatment observation period (+14 days ascertainment window).

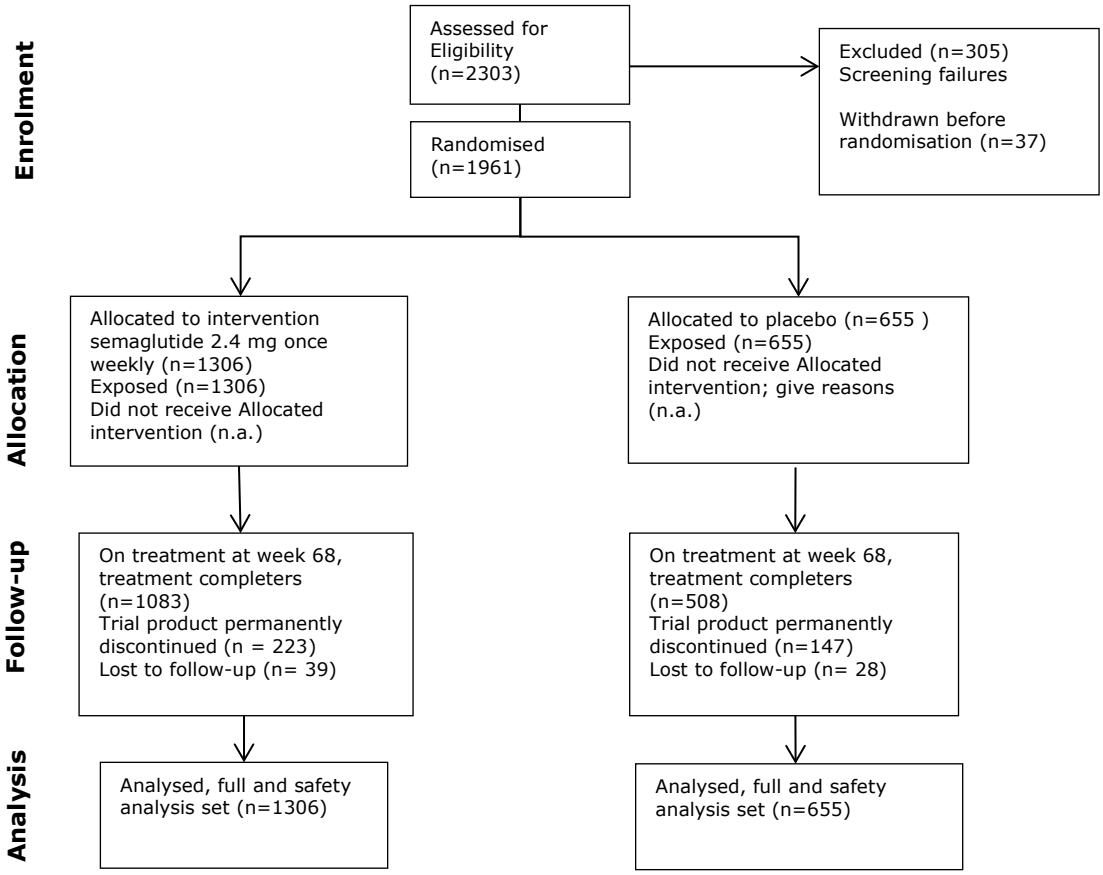
STEP 1 (4373) – weight management in overweight or obesity

In total 2303 subjects were screened, of which 305 subjects were screening failures, and 37 subjects withdrew consent before randomisation; thus, 1961 subjects were randomised 2:1 to receive either semaglutide 2.4 mg (1306 subjects) or placebo (655 subjects). 26 subjects were randomised in violation of the eligibility criteria (Section 9.3). The primary reasons were not keeping a food diary without missing more than 2 days of entries (19 subjects) and female subjects being pregnant, breast-feeding or intending to become pregnant or of child-bearing potential and not using highly effective contraception methods (6 subjects). Most of these subjects were allowed to continue on trial product, which was in accordance with the protocol.

In total, 1591 subjects (81.1%) completed treatment with the trial product, and the proportion was higher with semaglutide 2.4 mg (82.9%) than with placebo (77.6%). The proportion of subjects with at least one temporary trial product interruption was comparable for semaglutide 2.4 mg (9.1%) and placebo (8.9%). In total, 1849 subjects (94.3%) completed the trial and the proportions were comparable in the two treatment groups (semaglutide 2.4 mg vs placebo: 94.9% vs 93.0%). Slightly more subjects treated with semaglutide 2.4 mg (82.1%) attended the week 68 and week 75 visits without permanent discontinuation of the trial product, as compared with placebo (77.3%). A plot of time to withdrawal from the trial (i.e. the accumulated proportion of subjects withdrawing from the trial) displayed that increasingly more subjects withdrew from the trial with placebo at a constantly increasing rate over time. The primary reasons for withdrawal from the trial in both treatment groups were withdrawal of consent and subjects being lost for follow-up.

The participant flow is represented in **Figure** below:

Figure 23 Participant flow STEP 1 trial



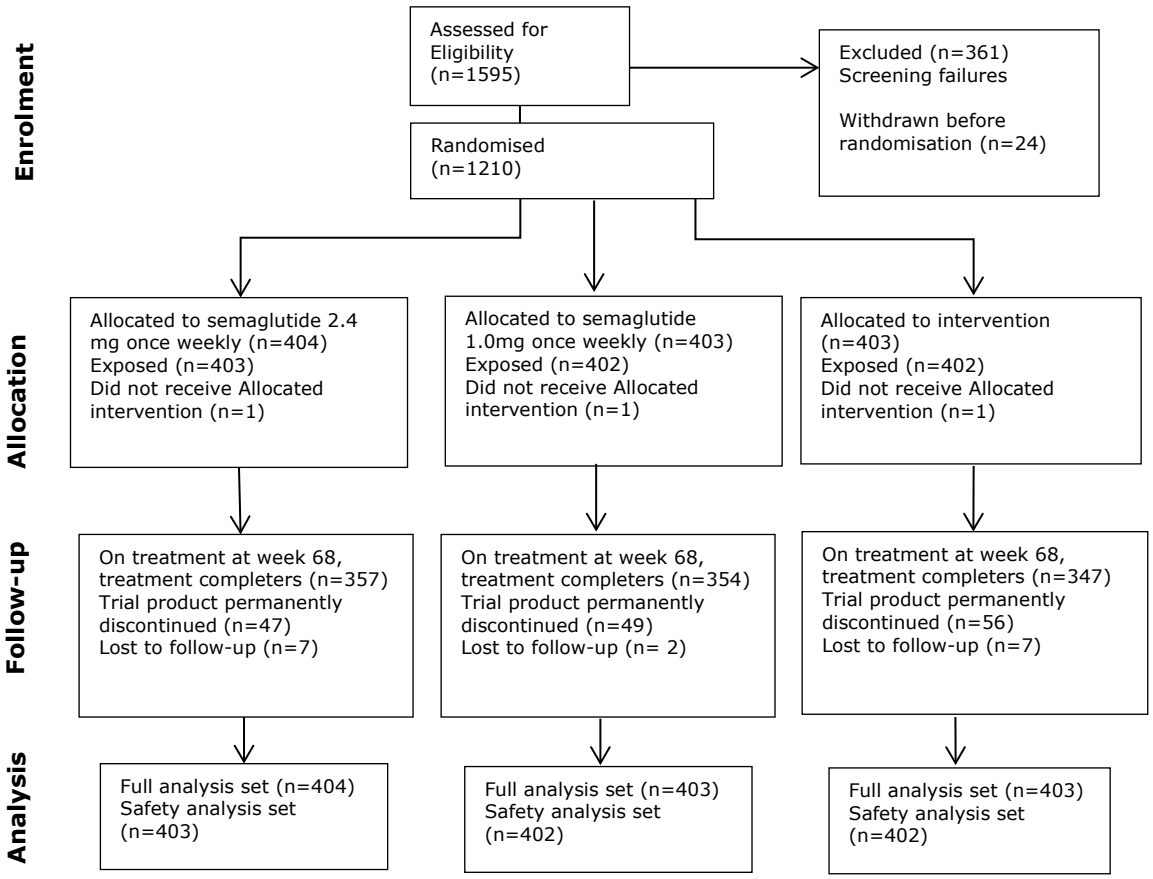
STEP 2 (4374) – weight management in type 2 diabetes

A total of 1595 subjects were screened, of which 361 were screen failures, and 24 were withdrawn before randomisation. 1210 subjects were randomised 1:1:1 to receive either semaglutide 2.4 mg (404 subjects), semaglutide 1.0 mg (403 subjects) or placebo (403 subjects). 49 subjects were randomised in violation of the eligibility criteria (Section 9.3). The primary reasons were not having kept a food diary without missing more than 2 days of entries (23 subjects), and treatment with any medication for the indication of diabetes or diabetes other than stated in the inclusion criteria within the past 90 days before screening (11 subjects). Besides the 49 subjects, 1 additional subject was discovered after DBL to be randomised in error due to violation of inclusion criterion #6. The subject was screened shortly after protocol version 2 was issued, in which the inclusion criteria were updated to specify that treatment with OADs should have been stable for at least 90 days prior to screening. The subject completed the trial. Furthermore, 1 subject with a screening eGFR of 29.27 mL/min/1.73 m2 was randomised to the semaglutide 2.4 mg group and completed the trial. The reason for this was that in the laboratory report sent to the investigator, the value was 30 mL/min/1.73 m2 due to rounding in the calculation of eGFR, which was discovered after DBL. Most of these subjects were allowed to continue on trial product, which was in accordance with the protocol. Of the 1210 randomised subjects, 1207 were exposed to the trial product; thus, FAS contained 1210 subjects, and SAS contained 1207 subjects.

In total, 1058 subjects (87.4%) completed the treatment with trial product, with comparable proportions across treatment groups. The proportions of subjects with at least one temporary trial product interruption were comparable: 8.4% with semaglutide 2.4 mg, 6.7% with semaglutide 1.0 mg and 6.9% with placebo. In total, 1164 subjects (96.2%) completed the trial with comparable proportions across treatment groups; 87.1% of the subjects attended the end-of-treatment visit (week 68) and the end-of-trial visit (week 75) without permanent discontinuation of the trial product, with comparable proportions across treatment groups. EOT Figure 14.1.9 shows a plot of withdrawal during the trial across treatment groups. The reasons for withdrawal from the trial were withdrawal of consent and subjects being lost for follow-up.

The participant flow is represented in **Figure 24** below:

Figure 24 Participant flow STEP 2 trial



STEP 3 (4375) – weight management with IBT

A total of 742 subjects were screened, of which 129 were screening failures and 2 subjects withdrew before randomisation; thus, 611 subjects were randomised 2:1 to receive either semaglutide 2.4 mg (407 subjects) or placebo (204 subjects). There was 1 subject reported to be randomised in violation of one of the eligibility criteria when entering the randomised period; history of major depressive disorder within 2 years before screening. Of the 611 randomised subjects, all were exposed to the trial product; thus, the FAS and the SAS are identical.

In total, 505 subjects (82.7%) completed treatment with trial product and with comparable proportions for the semaglutide 2.4 mg group (83.3%) and for the placebo group (81.4%). Of the total subjects, 11.3% in both treatment groups completed treatment with at least one temporary trial product interruption. Of the total subjects, 92.4% of the subjects in the semaglutide 2.4 mg group and 93.6% of the subjects in the placebo group completed the trial. Of the total subjects, 82.3% of the subjects in the semaglutide 2.4 mg group and 80.9% of the subjects in the placebo group attended the week 68 and week 75 visits without permanent discontinuation of the trial product. The time to withdrawal from the trial (i.e. the accumulated proportion of subjects withdrawing from the trial) was comparable for the two treatment groups with what appeared to be a constant rate over time. The primary reasons for withdrawing from the trial in both treatment groups were withdrawal of consent and subjects being lost to follow-up.

STEP 4 (4376) – sustained weight management

- **Recruitment / Conduct of the study**

A total of 1051 subjects were screened, of which 139 were screening failures, and 10 subjects withdrew before run-in. 902 subjects were included in the run-in period.

Run-in period

All 902 subjects in the run-in period were exposed to the trial product and were included in the SAS. Of these, 14 subjects were reported to violate one of the eligibility criteria when entering the run-in period; primarily for not having kept a food diary without missing more than 2 entries per day. 99 subjects discontinued trial product before randomisation (i.e. were classified as run-in failures). Of the 99 subjects who discontinued trial product before randomisation, 48 were due to AEs, 19 were due to being run-in failures (i.e. subjects for which the primary reason for not being randomised) was not fulfilling the randomisation criteria) and 11 were due to withdrawal of consent.

Randomised period

803 subjects were randomised 2:1 to receive either semaglutide 2.4 mg (535 subjects) or placebo (268 subjects). All 803 subjects were included in the FAS and in the SAS (only randomised subjects). Of these, 8 subjects were reported to violate one of the eligibility criteria when entering the randomised period. All subjects, except for 1 subject in the semaglutide 2.4 mg group, were exposed to the trial product after randomisation. More subjects in the semaglutide 2.4 mg group (94.2%) completed treatment defined as being on treatment at week 68 compared to the placebo group (88.4%). In the semaglutide 2.4 mg group, 98.5% completed the trial by attending the follow-up visit at week 75 compared to 97.0% in the placebo. 5.8% of subjects in the semaglutide 2.4 mg group and 5.6% in the placebo group had at least one temporary drug interruption.

- **Baseline data**

Baseline demographic and disease characteristics of the trial populations studied were designed to be representative of the expected target population for treatment with semaglutide 2.4 mg for weight management in clinical practice.

STEP 1, 3, and 4 enrolled subjects with overweight or obesity without T2D, and STEP 2 enrolled subjects with overweight or obesity and T2D. In STEP 4, only subjects who reached the maintenance dose of 2.4 mg after

20 weeks of run-in with semaglutide were randomised. These differences in trial populations are reflected in the baseline characteristics, as seen in **Table 28** and

Table 29. Subjects randomised to semaglutide 1.0 mg in STEP 2 are not included in the tables because semaglutide 2.4 mg is the intended dose for weight management. The baseline characteristics of subjects randomised to semaglutide 1.0 mg were comparable to those of the subjects in the semaglutide 2.4 mg and placebo groups of STEP 2.

Baseline body weight, BMI, waist circumference, HbA_{1c}, and FPG was lower in STEP 4 than in STEP 1–3, reflecting that subjects had completed a 20-week run-in period with semaglutide 2.4 mg prior to randomisation at week 20 (baseline). Because of this, STEP 4 is presented separately in **Table 28** and **Table 29**.

The trials enrolling subjects without T2D (STEP 1, 2 and 4) had more female than male participants, while subjects with T2D (STEP 2) were evenly distributed between men and women. Moreover, subjects with T2D were older, had a higher HbA_{1c} and FPG, and lower body weight at baseline compared to subjects without T2D. The proportion of Asian subjects was higher in STEP 2 than in the other trials. STEP 3 had more Black/African American subjects than the other trials, reflecting that this trial was conducted solely in the US.

Table 19 Baseline demographics - categorical values - STEP 1-4

	STEP 1 WM N (%)	STEP 2 WM in T2D N (%)	STEP 3 WM with IBT N (%)	STEP 4 Sustained WM N (%)	Total N (%)
Number of subjects	1961	807	611	803	4182
Age (years)					
<65	1805 (92.0)	633 (78.4)	565 (92.5)	755 (94.0)	3758 (89.9)
65-<75	145 (7.4)	156 (19.3)	43 (7.0)	44 (5.5)	388 (9.3)
>=75	11 (0.6)	18 (2.2)	3 (0.5)	4 (0.5)	36 (0.9)
Sex					
Female	1453 (74.1)	413 (51.2)	495 (81.0)	634 (79.0)	2995 (71.6)
Male	508 (25.9)	394 (48.8)	116 (19.0)	169 (21.0)	1187 (28.4)
Ethnic origin					
Not Hisp./Latino	1669 (85.1)	711 (88.1)	490 (80.2)	740 (92.2)	3610 (86.3)
Hisp./ Latino	236 (12.0)	96 (11.9)	121 (19.8)	63 (7.8)	516 (12.3)
Not Applicable	55 (2.8)	0	0	0	55 (1.3)
Unknown	1 (0.1)	0	0	0	1 (0.0)
Race					
White	1472 (75.1)	479 (59.4)	465 (76.1)	672 (83.7)	3088 (73.8)
Asian	261 (13.3)	220 (27.3)	11 (1.8)	19 (2.4)	511 (12.2)
Black/Afr. American	111 (5.7)	72 (8.9)	116 (19.0)	104 (13.0)	403 (9.6)
Other	62 (3.2)	36 (4.5)	19 (3.1)	8 (1.0)	125 (3.0)
Not Applicable	55 (2.8)	0	0	0	55 (1.3)
Body weight (kg)					
<90	501 (25.5)	289 (35.8)	155 (25.4)	365 (45.5)	1310 (31.3)
90-<100	418 (21.3)	155 (19.2)	138 (22.6)	157 (19.6)	868 (20.8)
100-<115	494 (25.2)	185 (22.9)	154 (25.2)	146 (18.2)	979 (23.4)
>=115	548 (27.9)	178 (22.1)	164 (26.8)	135 (16.8)	1025 (24.5)
BMI (kg/m^2)					
<30	117 (6.0)	145 (18.0)	38 (6.2)	238 (29.6)	538 (12.9)
30-<35	643 (32.8)	275 (34.1)	184 (30.1)	263 (32.8)	1365 (32.6)
35-<40	614 (31.3)	200 (24.8)	212 (34.7)	168 (20.9)	1194 (28.6)
>=40	587 (29.9)	187 (23.2)	177 (29.0)	134 (16.7)	1085 (25.9)
Glycaemic status					
Normo-glycaemia	1105 (56.3)	0	307 (50.2)	427 (53.2)	1839 (44.0)
Pre-diabetes	856 (43.7)	0	304 (49.8)	376 (46.8)	1536 (36.7)

Phase 3a trials: STEP 1-4 data from subjects randomised to sema 2.4 mg or placebo during the controlled periods of the trials. STEP 1-3: Baseline: Randomisation (week 0), STEP 4: Baseline: Randomisation (week 20).
Race: Other includes American Indian or Alaska Native, and Native Hawaiian or other Pacific Islander. Ethnic origin and race are recorded as 'Not applicable' for France.
%: Percentages are based on number of subjects., Hisp.: Hispanic; Afr.: African.

Table 20 Baseline demographics - continuous values - STEP 1-4

	STEP 1 Weight management	**STEP 2** Weight management in T2D	**STEP 3** Weight management with IBT	**STEP 4** Sustained weight management	**Total**
Number of subjects (FAS)	1961	807	611	803	4182
Age, years (SD)	46 (13)	55 (11)	46 (13)	46 (12)	48 (13)
Body weight, kg (SD)	105.3 (21.9)	100.2 (21.7)	105.8 (22.9)	96.1 (22.6)	102.6 (22.4)
BMI, kg/m^2 (SD)	37.9 (6.7)	35.9 (6.5)	38.0 (6.7)	34.4 (7.0)	36.8 (6.8)
Waist circumference, cm (SD)	114.7 (14.6)	115.0 (14.1)	113.0 (15.5)	105.3 (16.2)	112.7 (15.4)
HbA_{1c}, % (SD)	5.7 (0.3)	8.1 (0.8)	5.7 (0.3)	5.4 (0.3)	6.1 (1.1)
HbA_{1c}, mmol/mol (SD)	39.0 (3.5)	65.3 (8.8)	39.3 (3.7)	35.2 (3.1)	43.4 (11.9)
Fasting plasma glucose, mmol/L (SD)	5.3 (0.6)	8.6 (2.3)	5.2 (0.5)	4.9 (0.4)	5.8 (1.8)
Fasting plasma glucose, mg/dL (SD)	95.2 (10.6)	155.3 (41.3)	94.0 (9.6)	87.6 (7.7)	105.1 (31.9)
eGFR, mL/min/1.73 m^2 (CV)	96.14 (18.6)	93.28 (22.8)	96.55 (21.1)	92.23 (21.0)	94.88 (20.4)
Diabetes duration, years (SD)	N/A	8.2 (6.2)	N/A	N/A	8.2 (6.2)

Geometric mean (CV) is presented for eGFR, all other values are arithmetic means (SD).
STEP 1–4 data from subjects randomised to semaglutide 2.4 mg or placebo during the controlled periods of the trials. STEP 1–3: Baseline: Randomisation (week 0), STEP 4: Baseline: Randomisation (week 20). The last available and eligible observation at or prior to the baseline visit was selected for summary.

Information on weight-related comorbidities was systematically collected at screening. The investigator was to record in a specific form whether the subject had the following comorbidities: dyslipidaemia, hypertension, coronary artery disease, cerebrovascular disease, obstructive sleep apnoea, impaired glucose metabolism, reproductive system, liver disease, kidney disease, osteoarthritis, gout, and asthma/chronic obstructive pulmonary disease (COPD).

Comorbidities recorded at screening are summarised in **Table 30**. Subjects reported a wide range of comorbidities at screening. Notably, hypertension and dyslipidaemia were more frequent in subjects with T2D (STEP 2) compared to subjects without T2D (STEP 1, 3 and 4).

Table 30 Comorbidities at screening - STEP 1-4

	STEP 1 WM N (%)	STEP 2 WM in T2D N (%)	STEP 3 WM with IBT N (%)	STEP 4 Sustained WM N (%)	Total N (%)
Number of subjects	1961	807	611	803	4182
Number of female subjects	1453	413	495	634	2995
Hypertension	706 (36.0)	563 (69.8)	212 (34.7)	298 (37.1)	1779 (42.5)
Dyslipidaemia	725 (37.0)	549 (68.0)	212 (34.7)	288 (35.9)	1774 (42.4)
Impaired glucose metabolism	457 (23.3)		185 (30.3)	88 (11.0)	730 (17.5)
Elevated HbA1c	351 (17.9)		155 (25.4)		506 (12.1)
Impaired fasting glucose	151 (7.7)		65 (10.6)	61 (7.6)	277 (6.6)
Impaired glucose tolerance	67 (3.4)		30 (4.9)	42 (5.2)	139 (3.3)
Osteoarthritis	311 (15.9)	158 (19.6)	114 (18.7)	107 (13.3)	690 (16.5)
Symptomatic osteoarthritis of the knee	275 (14.0)	140 (17.3)	107 (17.5)	99 (12.3)	621 (14.8)
Symptomatic osteoarthritis of the hip	86 (4.4)	46 (5.7)	25 (4.1)	23 (2.9)	180 (4.3)
Reproductive system*	245 (16.9)	49 (11.9)	103 (20.8)	95 (15.0)	492 (16.4)
Menstrual disorder	163 (11.2)	36 (8.7)	73 (14.7)	76 (12.0)	348 (11.6)
Polycystic ovarian syndrome	96 (6.6)	17 (4.1)	27 (5.5)	25 (3.9)	165 (5.5)
Involuntary impaired fertility/infertility	62 (3.2)	22 (2.7)	26 (4.3)	29 (3.6)	139 (3.3)
Obstructive sleep apnoea	230 (11.7)	122 (15.1)	77 (12.6)	94 (11.7)	523 (12.5)
Asthma/chronic obstructive pulmonary disease	227 (11.6)	68 (8.4)	92 (15.1)	92 (11.5)	479 (11.5)
Liver diseases	168 (8.6)	182 (22.6)	37 (6.1)	59 (7.3)	446 (10.7)
Non-alcoholic fatty liver disease	163 (8.3)	179 (22.2)	35 (5.7)	55 (6.8)	432 (10.3)
Non-alcoholic steatohepatitis	7 (0.4)	5 (0.6)	2 (0.3)	8 (1.0)	22 (0.5)
Hyperuricaemia/gout	116 (5.9)	79 (9.8)	13 (2.1)	35 (4.4)	243 (5.8)
Kidney diseases	40 (2.0)	76 (9.4)	22 (3.6)	20 (2.5)	158 (3.8)
Kidney disease	39 (2.0)	71 (8.8)	22 (3.6)	20 (2.5)	152 (3.6)
Obesity-related kidney disease	1 (<0.1)	9 (1.1)	1 (0.2)	1 (0.1)	12 (0.3)
Coronary artery disease	49 (2.5)	59 (7.3)	10 (1.6)	7 (0.9)	125 (3.0)
Cerebrovascular disease	19 (1.0)	26 (3.2)	6 (1.0)	17 (2.1)	68 (1.6)

STEP 1-4 data from subjects randomised to semaglutide 2.4 mg or placebo during the controlled periods of the trials. Table is sorted by total frequency. In STEP 2 'Impaired glucose tolerance' or 'Impaired fasting glucose' or 'Elevated HbA1c' were not specified on comorbidities form. In STEP 4 'Elevated HbA1c' was not specified on comorbidities form. 'Elevated HbA1c' is defined as 5.7-6.4%.
*Reproductive system summarises answers from female subjects only for all three comorbidities and % is based on number of female subjects. For 'Menstrual disorder' and 'Polycystic ovarian syndrome' only answers from females are shown and % is based on female subjects. For 'Involuntary impaired fertility/infertility' answers from females and males are shown and % is based on number of subjects.

- **Numbers analysed**

In STEP 1, all the 1961 subjects were exposed to the trial product, and both FAS and SAS contained 1961 subjects. In STEP 2, of the 1210 randomised subjects, 1207 were exposed to the trial product; thus, FAS contained 1210 subjects, and SAS contained 1207 subjects. In STEP 3, of the 611 randomised subjects, all were exposed to the trial product; thus, the FAS and the SAS are identical. In STEP 4, after the run-in period,

803 subjects were randomised 2:1 to receive either semaglutide 2.4 mg (535 subjects) or placebo (268 subjects). All 803 subjects were included in the FAS and the SAS.

- **Outcomes and estimation**

Effect on body weight and related parameters

Semaglutide 2.4 mg was superior to placebo in providing a reduction in body weight (up to -15.97%), achieving a clinically relevant weight loss of ≥5%, and improving weight-related endpoints in subjects with overweight or obesity with and without T2D. As expected, the treatment effects addressing the hypothetical estimand were larger than those using the treatment policy estimand. An overview of the effect of semaglutide 2.4 mg on body weight-related parameters is given below.

Body weight – change from baseline

In all four STEP trials, substantial, clinically relevant and sustained reductions in body weight were observed, and superiority of semaglutide 2.4 mg was demonstrated for the primary endpoint: change from baseline to week 68 in body weight (%). Weight loss occurred early and continued throughout the trials.

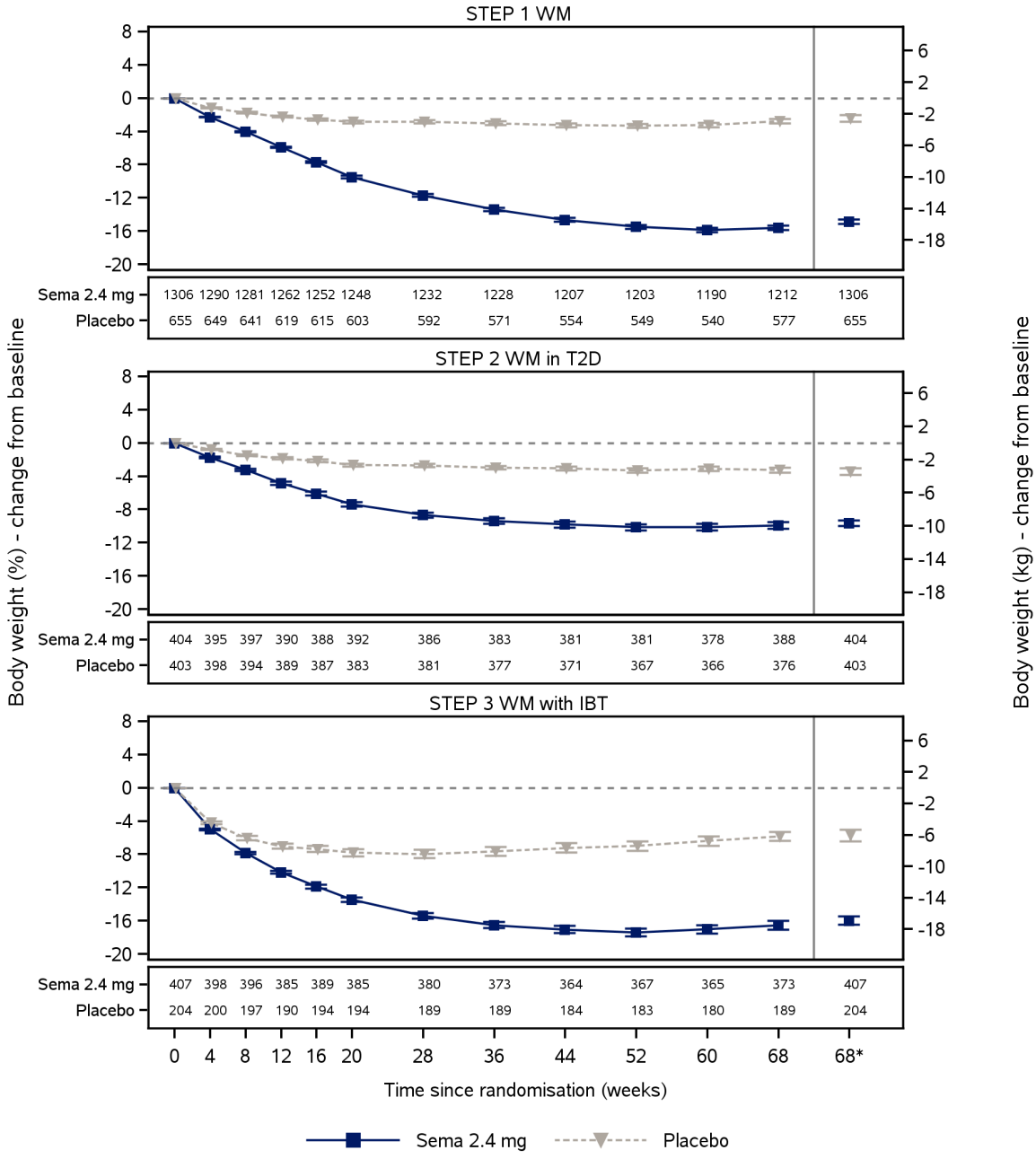
In STEP 1–3, weight loss was observed in both the semaglutide 2.4 mg group and the placebo group, but to a greater extent in subjects treated with semaglutide 2.4 mg. Subjects treated in the STEP trials with semaglutide 2.4 mg achieved reductions in mean body weight of 9.64% to 15.97% (9.67 to 16.82 kg) compared to 2.41% to 5.70% (2.61 to 6.22 kg) in subjects treated with placebo (**Figure 25** and **26**).

In subjects with T2D, where improvements in glycaemic control have been associated with weight gain, semaglutide 2.4 mg treatment resulted in a weight loss of 9.64% despite a concomitant marked decrease in HbA_{1c} of 1.6 %-point (described below, 'glycaemic results'. The magnitude of the weight loss in subjects with T2D (STEP 2) was smaller than in subjects without T2D (STEP 1 and 3), a phenomenon that has been well documented in previous weight management trials. The placebo arm of STEP 2 achieved a larger mean weight loss than what has been reported in other trials with T2D, which may be due to the more intensive lifestyle intervention applied in the weight management trials compared to T2D trials. The 3.4% weight loss observed in the placebo arm of STEP 2 suggests a compliance to lifestyle intervention in the trial.

The ETDs (semaglutide 2.4 mg relative to placebo) for mean change in body weight from baseline to week 68 were statistically significant in favour of semaglutide 2.4 mg.

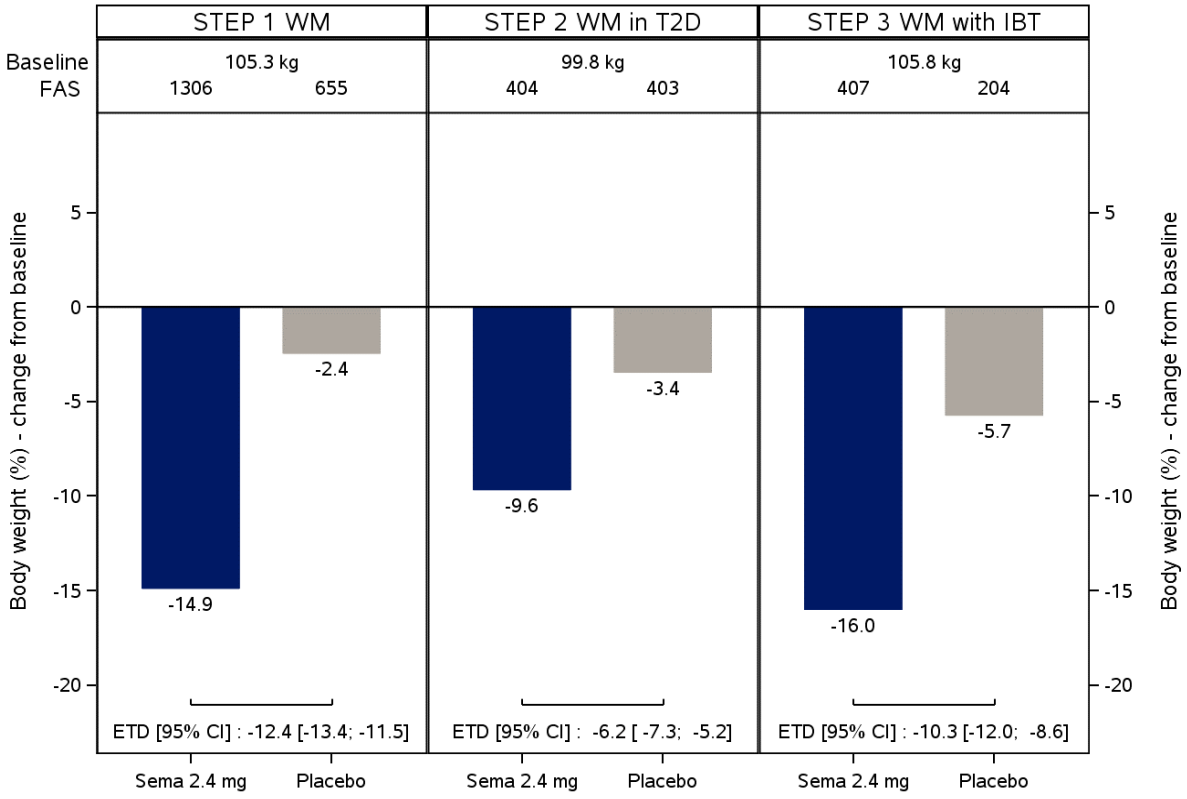
As expected, the results for the hypothetical estimand showed an even more pronounced weight loss with semaglutide 2.4 mg than those for the treatment policy estimand. Based on the hypothetical estimand; subjects treated with semaglutide 2.4 mg achieved a mean weight loss of 10.64% to 17.64% (10.61 to 18.43 kg) compared to 2.44% to 4.97% (2.70 to 5.40 kg) with placebo.

Figure 25 Body weight change from baseline by week – mean plot – treatment policy estimand – STEP 1–3



Observed data from in-trial period. Error bars are +/- standard error of the mean. *: Estimated means in % are from the primary analysis. Numbers shown in the lower panel are subjects contributing to the mean.

Figure 26 Body weight (%) change from baseline to week 68 – bar plot – treatment policy estimand – STEP 1–3



FAS: Full analysis set, ETD: Estimated treatment difference, CI: Confidence interval.
Analysis of data from in-trial period. Estimated treatment difference and corresponding confidence interval are from the primary analysis.
Numbers shown in the lower panel are subjects in the FAS.

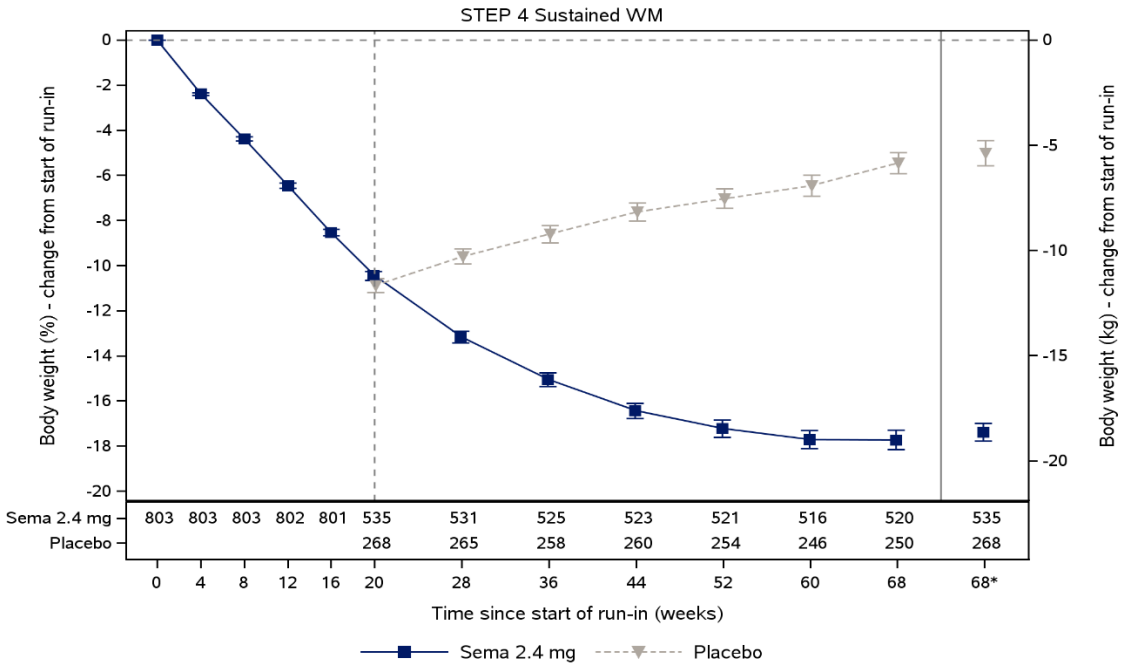
In STEP 4, all subjects received semaglutide s.c. for the first 20 weeks and had a mean weight loss of 10.6% during this period. Subjects randomised to continue semaglutide 2.4 mg treatment at week 20 continued to lose weight until the end of the treatment period while subjects randomised to placebo gradually regained weight but did not return to weight levels at the start of run-in (**Figure 27**).

Subjects randomised to continue treatment with semaglutide 2.4 mg had a further reduction in mean body weight from week 20 (baseline) to week 68 of 7.88% (7.12 kg) compared to a mean weight gain of 6.87% (6.06 kg) in subjects randomised to placebo. The ETD (semaglutide 2.4 mg relative to placebo) for mean change in body weight from baseline to week 68 was -14.75% $[-16.00; -13.50]_{95\% \text{ CI}}$ and statistically significant in favour of semaglutide 2.4 mg.

For the hypothetical estimand, treatment with semaglutide 2.4 mg resulted in a mean weight reduction from baseline to week 68 of 8.79% (7.98 kg) compared to a mean weight gain of 6.54% (5.65 kg) in the placebo group, with an ETD of -15.33% $[-16.52; -14.13]_{95\% \text{ CI}}$.

Among randomised subjects, the supportive secondary endpoint; change in body weight (%) from the start of run-in (week 0) to week 68, was -17.38% for subjects randomised to semaglutide 2.4 mg and -5.02% for subjects randomised to placebo, giving an ETD of -12.36% $[-13.71; -11.02]_{95\% \text{ CI}}$ also favouring semaglutide 2.4 mg.

Figure 27 Body weight change from start of run-in (week 0) by week – mean plot – treatment policy estimand – STEP 4



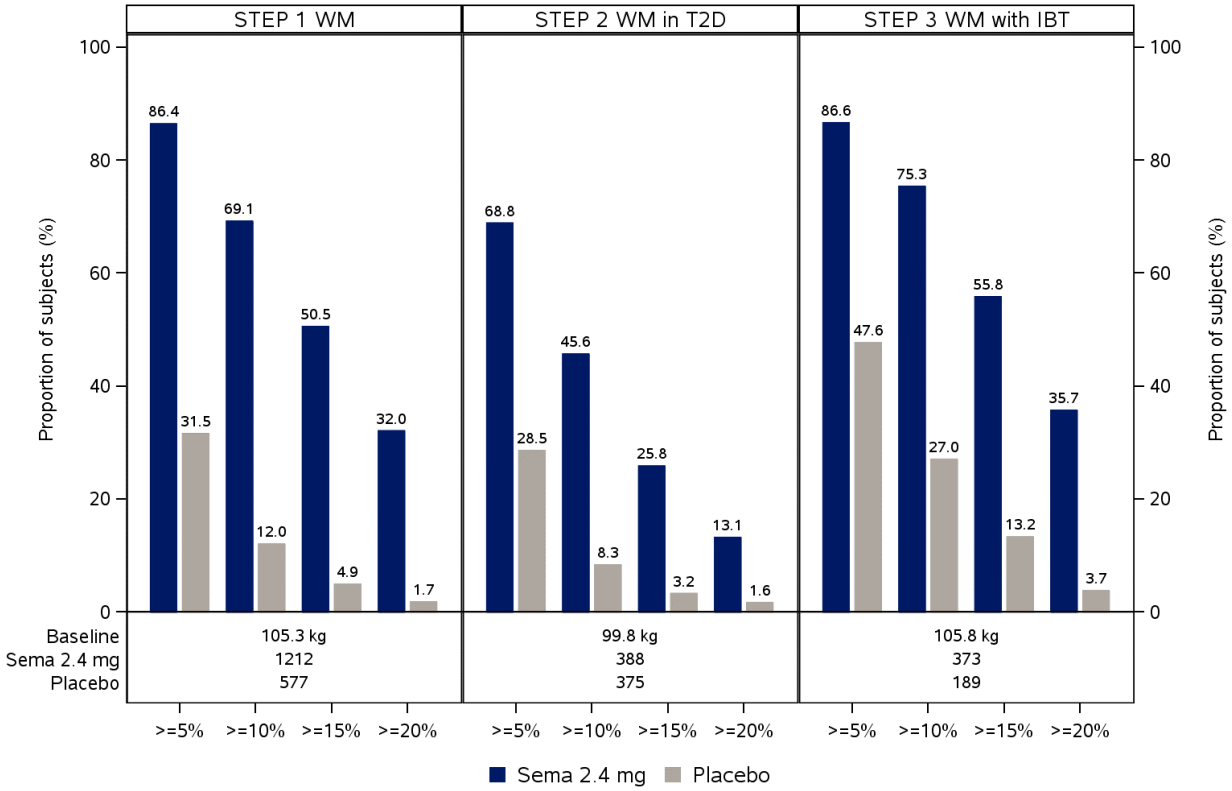
Observed data from in-trial period. Run-in period starts with week 0 visit. Error bars are +/- standard error of the mean. *: Estimated means. Numbers shown in the lower panel are subjects contributing to the mean. The full analysis set includes all randomised subjects.

Body weight - categorical response

Superiority of semaglutide 2.4 mg was demonstrated for the primary endpoint; the proportion of subjects who achieve ≥5% weight loss from baseline to week 68, in all three STEP 1–3 trials (not a primary endpoint in STEP 4).

In STEP 1–3, 68.8% to 86.6% of subjects on semaglutide 2.4 mg achieved ≥5% weight loss compared with 28.5% to 47.6% of subjects on placebo (**Figure 28**) with statistically significant ORs in favour of semaglutide 2.4 mg. Treatment with semaglutide 2.4 mg also resulted in greater proportion of subjects achieving ≥10%, ≥15%, and ≥20% body weight reduction from baseline to week 68 with ORs in favour of semaglutide 2.4 mg (and statistically significant for the confirmatory secondary endpoints proportion of subjects achieving ≥10% and ≥15% weight loss).

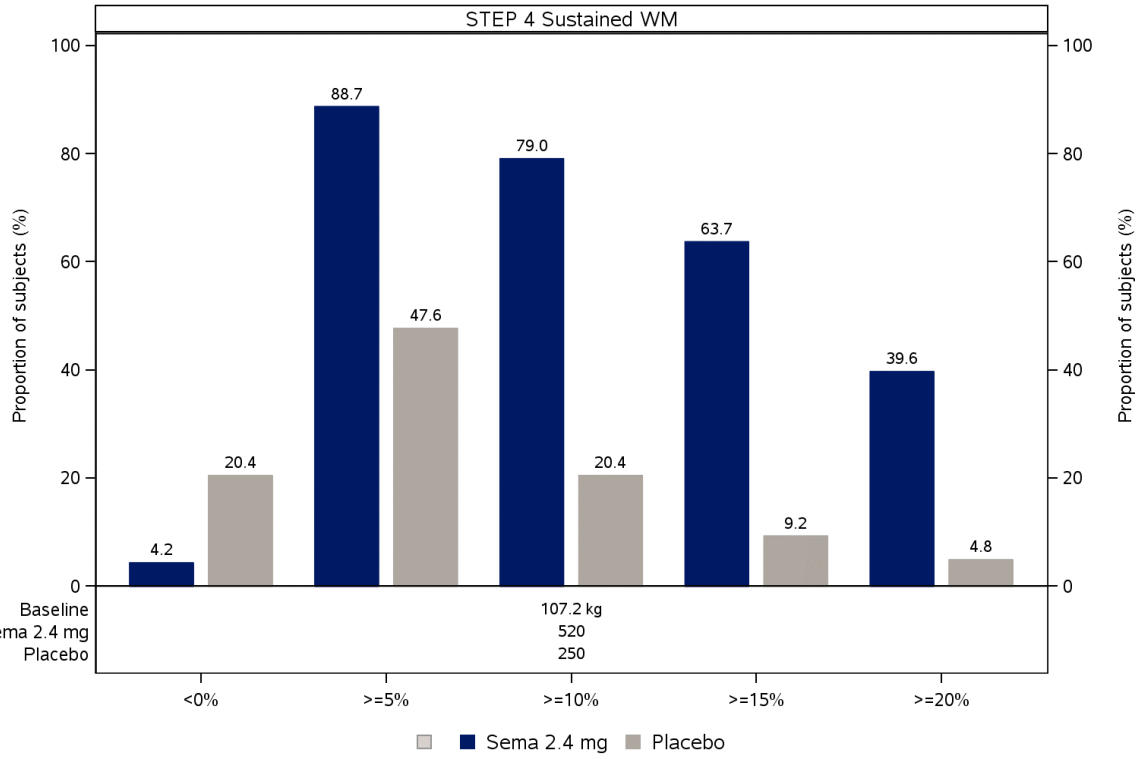
Figure 28 Proportion of subjects achieving body weight loss response criteria from baseline to week 68 – STEP 1–3



Observed data from in-trial period. Numbers shown in the lower panel are subjects with an observation at the visit.

In STEP 4, all subjects received semaglutide from week 0 to week 20, at which point they were randomised to either continue on semaglutide 2.4 mg or switch to placebo until week 68. For subjects randomised to continue on semaglutide, 2.4 mg, higher proportions of subjects had achieved ≥5%, ≥10%, ≥15%, and ≥20% body weight reduction from the start of run-in (week 0) to week 68 compared to subjects who were randomised to placebo (**Figure** 29). ORs were in favour of semaglutide 2.4 mg. The odds of gaining weight at week 68 from baseline (week 20) was 0.20 for the semaglutide 2.4 mg group and 5.01 for the placebo group, giving an OR of 0.04 $[0.03; 0.06]_{95\%\ CI}$ that favoured semaglutide 2.4 mg.

Figure 29 Proportion of subjects at week 68 achieving body weight loss response criteria or with weight gain (<0%) since start of run-in (week 0) – STEP 4



Observed data from in-trial period. Run-in period starts with week 0 visit. Numbers shown in the lower panel are subjects with an observation at the visit.

Note: All subjects received semaglutide from week 0 to week 20. At week 20 subjects were randomised to either continue on semaglutide 2.4 mg or switch to placebo until week 68.

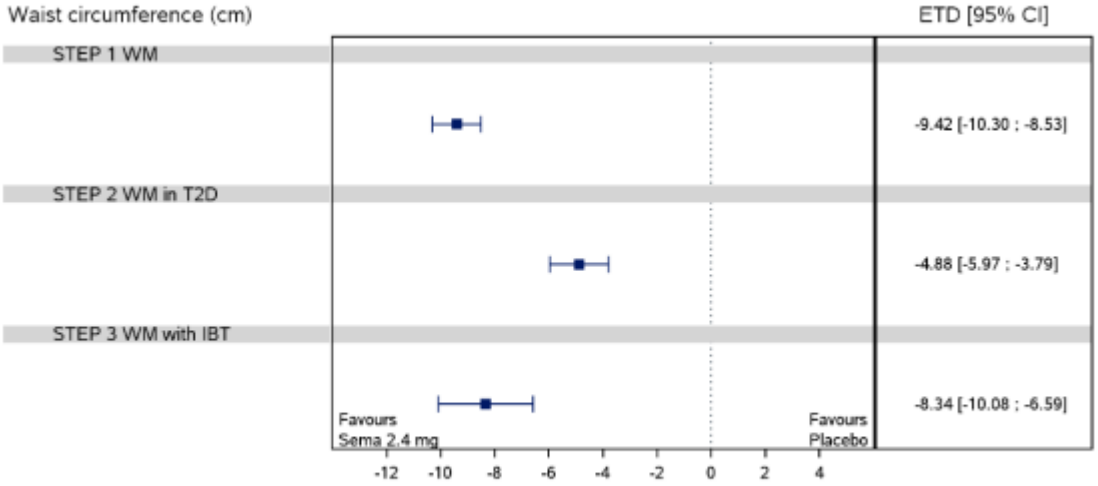
Body mass index and waist circumference

In alignment with the improvements in body weight, semaglutide 2.4 mg also reduced BMI and waist circumference in STEP 1–3.

In STEP 1–3, treatment with semaglutide 2.4 mg resulted in mean reductions in BMI from baseline to week 68 of 3.51 to 6.00 kg/m^2 for semaglutide 2.4 mg and 0.92 to 2.23 kg/m^2 for placebo, with ETDs that favoured semaglutide 2.4 mg. Comparable results were obtained when addressing the hypothetical estimand and were supported by the results from STEP 4.

In STEP 1–3, treatment with semaglutide 2.4 mg resulted in mean reductions in waist circumference from baseline to week 68 of 9.40 to 14.61 cm compared with 4.13 to 6.27 cm for placebo with ETDs that favoured semaglutide 2.4 mg (**Figure 30**). Comparable results were obtained when addressing the hypothetical estimand. These results were supported by the results from STEP 4.

Figure 307 Waist circumference change from baseline to week 68 - forest plot - treatment policy estimand - STEP 1-3



ETD: Estimated treatment difference, CI: Confidence interval.
Analysis of data from in-trial period. Estimated treatment differences and corresponding confidence intervals are from the confirmatory secondary analysis.

Reductions in waist circumference seen in STEP 1−3 were supported by the results from STEP 4 (where baseline was at week 20), where the ETD of -9.74 $[-10.94; -8.54]_{95\%\ CI}$ favoured semaglutide 2.4 mg.

Glycaemic efficacy results

Treatment with semaglutide 2.4 mg improved glucose metabolism with reductions in HbA_{1c} and FPG in all four trials. As expected, the largest HbA_{1c} reduction was observed in subjects with T2D (STEP 2) (See **Table 31** and **Figure 31**). A larger proportion of subjects achieved the HbA_{1c} targets of <7.0% (53.0 mmol/mol) and ≤6.5% (47.5 mmol/mol) with semaglutide 2.4 mg compared to placebo (**Figure 32**).

In STEP 2, superiority of semaglutide 2.4 mg versus placebo for change from baseline in HbA_{1c} at week 68 was confirmed and subjects reached a mean HbA_{1c} of 6.52% (47.80 mmol/mol) with semaglutide 2.4 mg. A larger proportion of subjects with T2D achieved the HbA_{1c} targets of <7.0% (53.0 mmol/mol) and ≤6.5% (47.5 mmol/mol) with semaglutide 2.4 mg (78.5% and 67.5% of subjects, respectively) compared to placebo (26.5% and 15.5% of subjects, respectively). Furthermore, a higher proportion of subjects achieved the composite endpoint, weight loss ≥10% and HbA_{1c} <7.0% at week 68, with semaglutide 2.4 mg vs placebo (44.6% vs 6.7%). A higher proportion of subjects also achieved both weight loss ≥15% and HbA_{1c} <7.0% at week 68 with semaglutide 2.4 mg vs placebo (25.7% vs 2.9%).

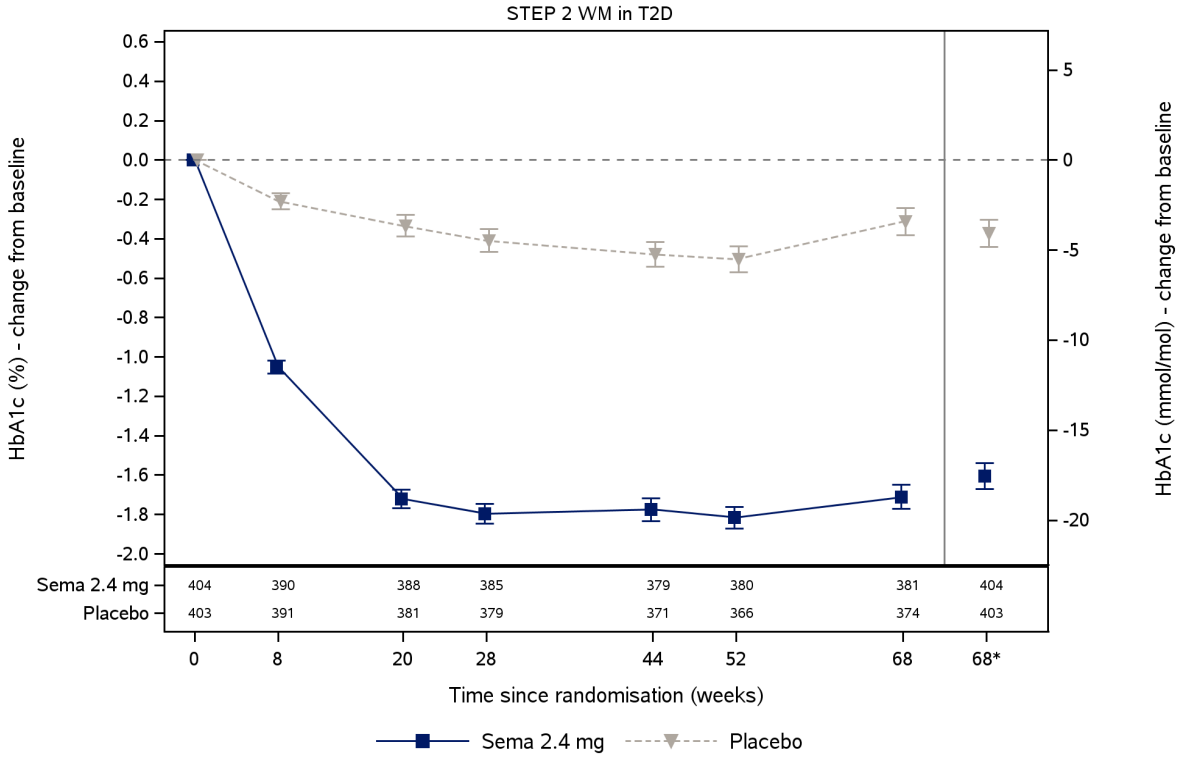
In STEP 2, the proportion of subjects who had a decrease in treatment intensity with OADs (metformin, SGLT2i, sulfonylurea and thiazolidinediones) was larger with semaglutide 2.4 mg (27.1%) compared to placebo (6.8%), which further substantiates the improvements in glycaemic parameters. In line with this, a lower proportion of subjects had an increase in treatment intensity with OADs with semaglutide 2.4 mg (4.6%) compared to placebo (23.0%).

Table 31 HbA_{1c} and fasting plasma glucose – change from baseline to week 68

Trial	HbA_{1c} Mean estimates and treatment differences (ANCOVA)						FPG Mean estimates and treatment differences (ANCOVA)					
	(%-points)			(mmol/mol)			(mmol/L)			(mg/dL)		
	Sema 2.4 mg	Placebo	Sema - placebo	Sema 2.4 mg	Placebo	Sema - placebo	Sema 2.4 mg	Placebo	Sema - placebo	Sema 2.4 mg	Placebo	Sema - placebo
STEP 1	-0.45	-0.15	-0.29	-4.89	-1.69	-3.20	-0.46	-0.03	-0.44	-8.35	-0.48	-7.87
STEP 2	**-1.60**	**-0.37**	**-1.23***	**-17.54**	**-4.07**	**-13.48***	**-2.11**	**-0.08**	**-2.03**	**-37.98**	**-1.37**	**-36.61**
STEP 3	-0.51	-0.27	-0.24	-5.59	-2.99	-2.60	-0.37	-0.04	-0.34	-6.73	-0.65	-6.09

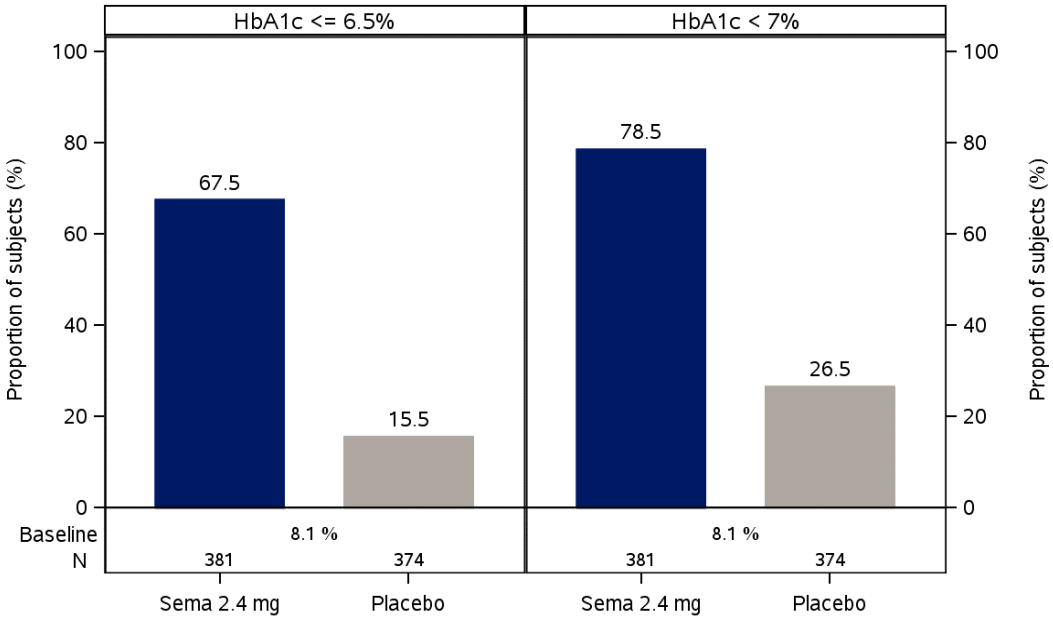
*p<0.0001. Sema: semaglutide. Subjects with T2D (dark grey, bold), subjects without T2D (light grey). Data are estimated means and estimated treatment differences from baseline to week 68 for the full analysis set.

Figure 31 HbA_{1c} change from baseline by week – mean plot - treatment policy estimand – STEP 2



HbA1c: Haemoglobin A1c.
Observed data from in-trial period. Error bars are +/- standard error of the mean. *: Estimated means are from the confirmatory secondary analysis. Numbers shown in the lower panel are subjects contributing to the mean.

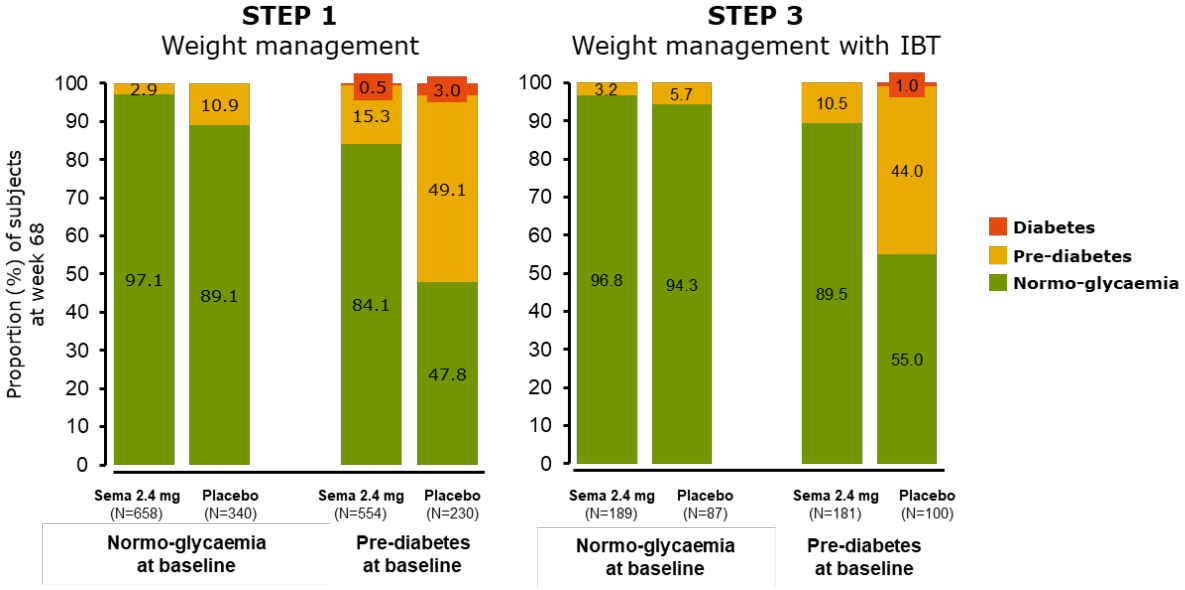
Figure 32 Proportion of subjects achieving HbA_{1c} targets at week 68 - in-trial - STEP 2



N: Number of subjects with an observation at the visit
Observed data from in-trial period.

Improvements in glucose metabolism were evident even in subjects without T2D, as a higher proportion of the subjects in STEP 1 and 3 who had pre-diabetes at baseline shifted to the category of normo-glycaemia by week 68 with semaglutide 2.4 mg (84.1% to 89.5%) compared with placebo (47.8% to 55.0%) (**Figure 33**).

Figure 33 Glycaemic category - shift from baseline - in-trial - STEP 1 and STEP 3



Observed data from the in-trial period. Proportions (%) are based on subjects with an observation at the visit.

For subjects with T2D (STEP 2), fasting serum insulin decreased by 12% with semaglutide 2.4 mg and by 6% with placebo. The estimated treatment ratio did not indicate a treatment effect. For subjects without T2D,

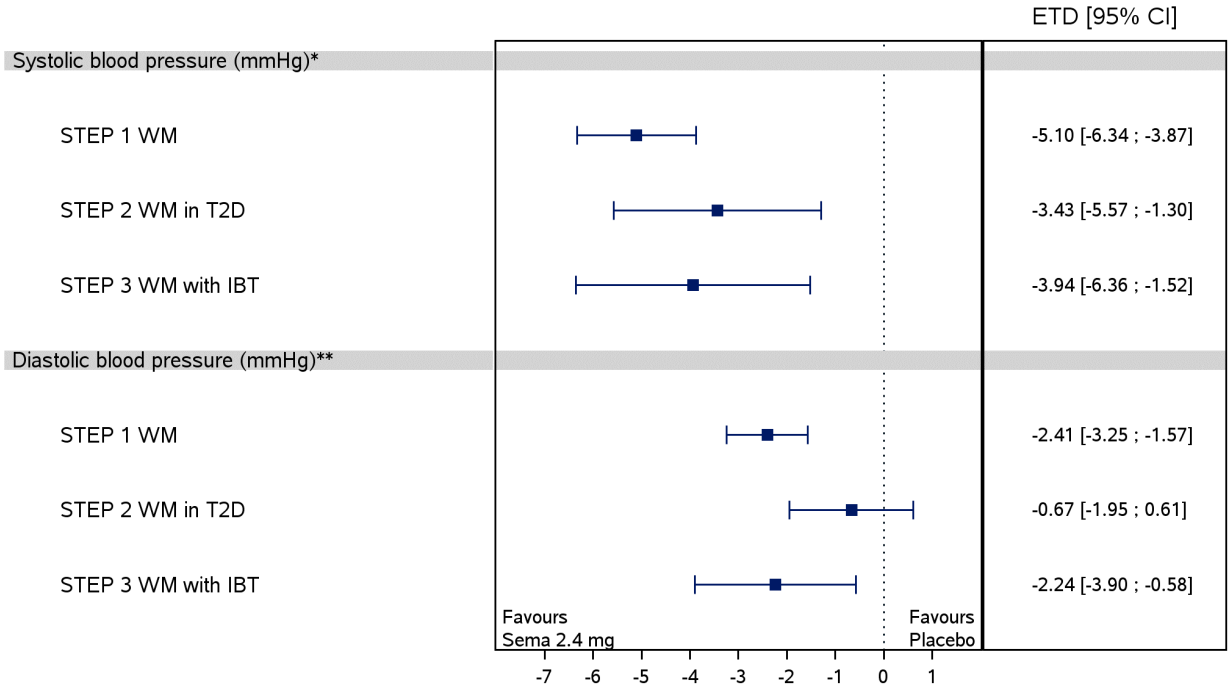
fasting serum insulin decreased by 26% in STEP 1 and 32% in STEP 3 with semaglutide 2.4 mg. A decrease was also seen with placebo: 7% in STEP 1 and 15% in STEP 3. Baseline fasting serum insulin was lower in STEP 4 than in STEP 1–3, reflecting the 20-week run-in period. In STEP 4, fasting insulin decreased further (18% from week 20) for the subjects who continued treatment with semaglutide 2.4 mg, while there was no change in fasting insulin for subjects who were switched to placebo. The estimated treatment ratio at week 68 was in favour of semaglutide 2.4 mg for STEP 1, 3 and 4.

Effect on cardiovascular parameters

Semaglutide 2.4 mg decreased systolic blood pressure (SBP) in the STEP 1–3 trials (**Figure 34** and **Table 32**). Semaglutide 2.4 mg reduced SBP (by up to 6.16 mmHg) in subjects with overweight or obesity with and without T2D at a clinically relevant level and was superior to placebo. In line with this, improvements in diastolic blood pressure (DBP) were also observed in subjects with overweight or obesity without T2D, but estimated treatment differences in favour of semaglutide 2.4 mg were found only for STEP 1 and 3. Although the mean blood pressure was within normal range across the subject populations in the STEP trials, the reductions in blood pressure were of a magnitude that would be clinically relevant for people with hypertension. The improvements in blood pressure were seen in parallel with reduced use of antihypertensive medication.

Baseline (week 20) SBP was lower in STEP 4 than in STEP 1–3, reflecting the 20-week run-in period with semaglutide s.c. No further reduction in mean SBP was observed with continued semaglutide 2.4 mg treatment after week 20, whereas SBP increased for subjects who switched to placebo at week 20. Superiority (semaglutide 2.4 mg vs placebo) was confirmed for change in SBP from baseline (week 20) to week 68 in STEP 4.

Figure 34 Systolic and diastolic blood pressure change from baseline to week 68 - forest plot - treatment policy estimand - STEP 1-3



ETD: Estimated treatment difference, CI: Confidence interval.
Analysis of data from in-trial period. Estimated treatment differences and corresponding confidence intervals are from the confirmatory secondary analysis (*) and supportive analysis (**).

Table 32 Systolic and diastolic blood pressure – change from baseline to week 68

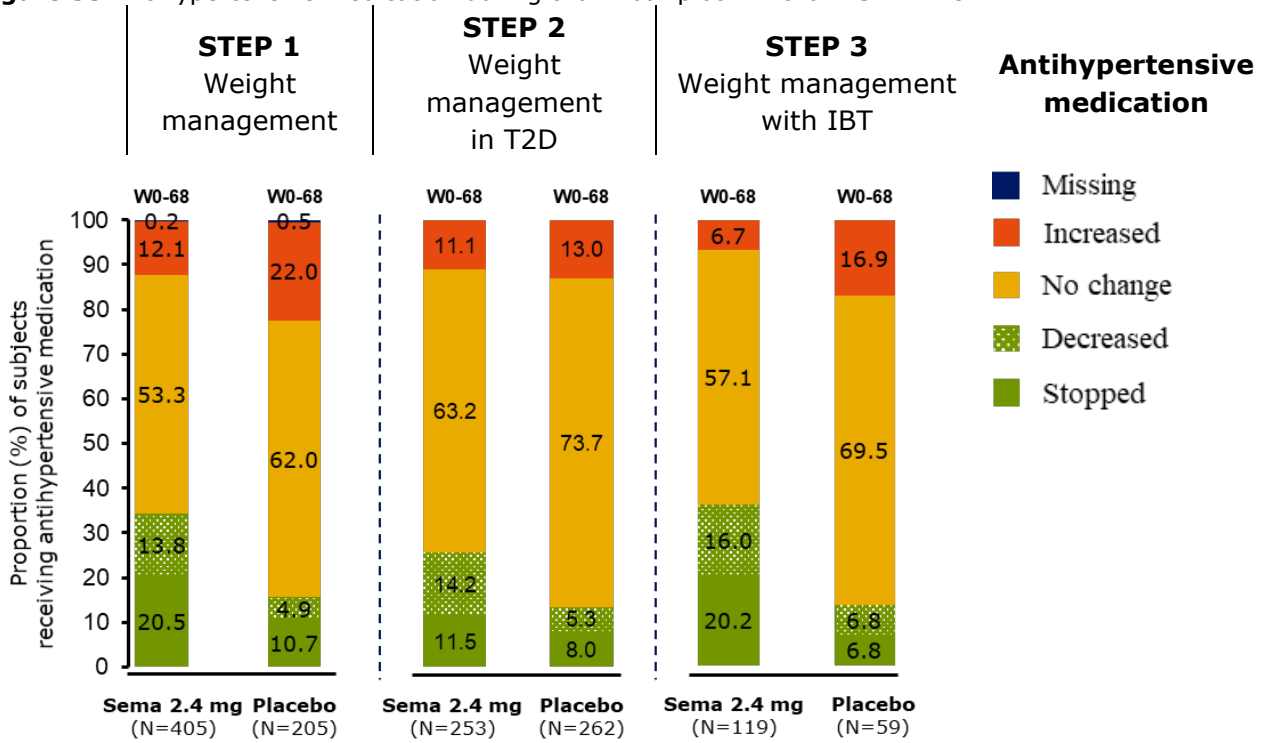
Trial	**Systolic blood pressure (mmHg)** Mean estimates and treatment differences (ANCOVA)				**Diastolic blood pressure (mmHg)** Mean estimates and treatment differences (ANCOVA)			
	Sema 2.4 mg	Placebo	Sema - placebo	P value	Sema 2.4 mg	Placebo	Sema - placebo	P value
STEP 1	-6.16	-1.06	-5.10	<.0001	-2.83	-0.42	-2.41	<.0001
STEP 2	-3.92	-0.49	-3.43	0.0016	-1.55	-0.88	-0.67	0.3070
STEP 3	-5.55	-1.62	-3.94	0.0014	-3.01	-0.77	-2.24	0.0082

Sema: semaglutide. Data are estimated means and estimated treatment differences from baseline to week 68 for the full analysis set.

Approximately one-third of subjects without T2D used antihypertensive medication between baseline and week 68 (STEP 1 and 3), while approximately two-thirds of subjects with T2D used antihypertensive medication between baseline and week 68 (STEP 2). Of these, the proportions of subjects who decreased or stopped taking antihypertensive medication during the treatment period were higher with semaglutide 2.4 mg (26% to 36%) compared to placebo (13% to 16%) in STEP 1−3 (**Figure 35**). Furthermore, lower proportions of subjects had an increase in antihypertensive medication with semaglutide 2.4 mg (7% to 13%) compared to placebo (13% to 22%). In STEP 4, a larger proportion of subjects stopped or decreased the use of antihypertensive medication between week 20 and week 68 with continued semaglutide 2.4 mg treatment (25.5%), compared to subjects who switched to placebo (12.0%), and a smaller proportion

increased antihypertensive medication with continued semaglutide 2.4 mg treatment (9.4%) than with placebo (16.4%) (see **Figure 35**).

Figure 35 Antihypertensive medication during trial – bar plot - in trial - STEP 1-3



N: Number of subjects receiving antihypertensive medication between baseline and week 68 out of the total treatment group; sema: semaglutide. %: Percentages are based on subjects with an observation at the visit. Observed data from the in-trial period.

Treatment with semaglutide 2.4 mg resulted in an overall improvement in the plasma lipid profiles in STEP 1–3 (**Table 33**). Triglycerides and FFA were reduced with semaglutide 2.4 mg in all three STEP 1–3 trials compared to placebo. Increases in HDL cholesterol were also observed with semaglutide 2.4 mg across all three trials. The change was in favour of semaglutide 2.4 mg in STEP 1 and 2, while data from STEP 3 did not indicate a treatment effect. In STEP 1 and 3, improvements with semaglutide 2.4 mg were observed for total cholesterol (including reductions in LDL and VLDL cholesterol). In subjects with T2D, a reduction in VLDL was observed with semaglutide 2.4 mg. See **Table 33** for the full evaluation of changes in lipids in STEP 1–3. Improvements from baseline (week 20) to week 68 in total cholesterol, LDL cholesterol, VLDL cholesterol, and triglycerides were observed in STEP 4, whereas no noteworthy changes were observed for HDL and FFA.

Approximately 20% of subjects without T2D (STEP 1 and 3) and 60% of subjects with T2D (STEP 2) used lipid-lowering medication between baseline and week 68. Of these subjects, comparable or slightly higher proportions of subjects decreased or stopped taking lipid-lowering medication with semaglutide 2.4 mg compared to placebo.

Table 33 Lipids – change from baseline to week 68 – STEP 1–3

Lipids	STEP 1 Weight management		STEP 2 Weight management in T2D		STEP 3 Weight management with IBT	
	Sema 2.4 mg N=1306	Placebo N=655	Sema 2.4 mg N=404	Placebo N=403	Sema 2.4 mg N=407	Placebo N=204
Total cholesterol						
Baseline mmol/L	4.91 (20.5)	4.98 (19.4)	4.42 (23.0)	4.42 (23.3)	4.80 (19.8)	4.89 (20.6)
Baseline mg/dL	189.6 (20.5)	192.1 (19.4)	170.8 (23.0)	170.8 (23.3)	185.4 (19.8)	188.7 (20.6)
Est. relative change from baseline (%)	-3.25	0.06	-1.36	-0.50	-3.85	2.12
Relative treatment difference (%) [95%CI]	-3.31 [-4.77; -1.84]		-0.86 [-3.60; 1.95]		-5.85 [-8.45; -3.17]	
LDL cholesterol						
Baseline mmol/L	2.9 (31.6)	2.9 (29.8)	2.3 (37.3)	2.3 (37.8)	2.8 (30.3)	2.9 (31.2)
Baseline mg/dL	110.29 (31.6)	112.45 (29.8)	90.10 (37.3)	90.07 (37.8)	107.74 (30.3)	111.79 (31.2)
Est. relative change from baseline (%)	-2.53	1.27	0.48	0.12	-4.73	2.59
Relative treatment difference (%) [95% CI]	-3.76 [-5.94; -1.52]		0.36 [-4.00; 4.92]		-7.14 [-10.93; -3.18]	
VLDL cholesterol[a]						
Baseline mmol/L	0.64 (45.8)	0.64 (46.5)	0.77 (49.3)	0.80 (49.7)	0.55 (49.7)	0.56 (44.5)
Baseline mg/dL	24.5 (45.8)	24.9 (46.5)	29.7 (49.3)	30.7 (49.7)	21.0 (49.7)	21.7 (44.5)
Est. relative change from baseline (%)	-21.85	-7.11	-20.68	-9.68	-22.51	-6.61
Relative treatment difference (%) [95%CI]	-15.87 [-18.77; -12.86]		-12.18 [-17.28; -6.77]		-17.03 [-22.76; -10.86]	
HDL cholesterol						
Baseline mmol/L	1.3 (25.6)	1.3 (25.0)	1.2 (23.3)	1.1 (24.2)	1.3 (24.0)	1.3 (22.6)
Baseline mg/dL	49.4 (25.6)	49.5 (25.0)	44.7 (23.3)	43.8 (24.2)	51.6 (24.0)	50.9 (22.6)
Est. relative change from baseline (%)	5.24	1.42	6.86	4.07	6.53	4.99
Relative treatment difference (%) [95%CI]	3.77 [2.20; 5.36]		2.69 [0.34; 5.09]		1.46 [-1.84; 4.88]	
Free fatty acids						
Baseline mmol/L	0.44 (57.9)	0.45 (53.8)	0.56 (54.7)	0.56 (55.4)	0.42 (59.4)	0.39 (64.8)
Baseline mg/dL	12.33 (57.9)	12.72 (53.8)	15.83 (54.7)	15.88 (55.4)	11.86 (59.4)	11.13 (64.8)
Est. relative change from baseline (%)	-17.42	-6.74	-16.31	-0.60	-11.88	4.04
Relative treatment difference (%) [95%CI]	-11.46 [-16.81; -5.76]		-15.80 [-22.05; -9.06]		-15.29 [-25.01; -4.32]	
Triglycerides						
Baseline mmol/L	1.42 (47.4)	1.44 (49.0)	1.74 (53.4)	1.79 (52.9)	1.21 (50.3)	1.25 (44.4)
Baseline mg/dL	126.21 (47.4)	127.94 (49.0)	154.90 (53.4)	159.48 (52.9)	107.91 (50.3)	110.90 (44.4)
Est. relative change from baseline (%)	-21.89	-7.26	-22.01	-9.44	-22.46	-6.54
Relative treatment difference (%) [95%CI]	-15.78 [-18.76; -12.69]		-13.88 [-19.04; -8.39]		-17.03 [-22.83; -10.79]	

Est: estimated, N: subjects in FAS. [a] VLDL was measured as a fraction of triglycerides. Results reflect the treatment policy estimand. Baseline values are observed geometric mean (CV%). Analysis of data from in-trial period. The approximate relative changes/differences were derived from estimated ratios by subtracting 1 and multiplying by 100.

C-reactive protein (CRP) is a marker of inflammation associated with increased cardiovascular risk and was measured in STEP 1–3. Mean CRP levels decreased from baseline to week 68, and the decrease was greater with semaglutide 2.4 mg vs placebo in all three trials. The estimated ratios to baseline ranged from 0.40 to 0.51 with semaglutide 2.4 mg. This corresponded to estimated reductions in CRP levels of 48.91–59.54% from baseline. In comparison, estimated ratios to baseline ranged from 0.77 to 0.85 with placebo, which corresponded to estimated reductions of 14.99–22.93%.

As part of the semaglutide s.c. for T2D development programme (Ozempic), a 104-week double-blind trial, SUSTAIN 6 (Trial NN9535-3744) was conducted. SUSTAIN 6 randomised a total of 3297 subjects with T2D and at high risk for cardiovascular events to semaglutide 0.5 mg or 1.0 mg once weekly or corresponding placebo in addition to standard-of-care. Treatment with semaglutide s.c. resulted in a 26% risk reduction in the primary composite outcome of death from cardiovascular causes, non-fatal myocardial infarction, or non-fatal stroke. This was mainly driven by a significant (39%) decrease in the rate of non-fatal stroke and a non-significant (26%) decrease in non-fatal myocardial infarction with no difference in cardiovascular death. This resulted in non-inferiority of MACE with semaglutide vs placebo. However, this represents another population than the target population of semaglutide 2.4 mg for weight reduction.

With regards to plasminogen activator inhibitor-1 (PAI-1), some unexpected findings were present, as PAI-1 increased in almost all treatment arms.

The cardiovascular effect of semaglutide 2.4 mg is further being investigated in a dedicated CVOT, SELECT (trial EX9536-4388) in subjects with established cardiovascular disease and obesity or overweight without T2D.

Patient-reported outcomes

Underlying comorbidities in people with obesity act as major confounders impacting health-related quality of life (HRQOL), however research has shown that obesity in itself can also significantly impact HRQOL by impairing physical health status and imposing limitations on daily activities and reduced physical health. Furthermore, stigmatisation and discrimination associated with obesity can contribute to impaired mental well-being. Obesity-associated decrements on HRQOL tend to be more pronounced in physical functioning compared to mental or psychosocial functioning.

Patients' perception of how they function and feel is an important consideration for physicians and patients when making treatment decisions. With the purpose of including the patients' perspectives on changes in physical functioning, confirmatory secondary efficacy endpoints were included in the phase 3a programme based on the validated Short Form Health Survey version 2 (SF-36) Physical Functioning subscale (STEP 1–4) and Impact of Weight on Quality of Life Clinical Trials (IWQOL-Lite-CT) Physical Function composite (STEP 1–2). SF-36 is one of the most commonly used generic PRO instruments measuring general health status. IWQOL-Lite-CT was developed to assess weight-related changes in physical and psychosocial functioning in subjects with overweight or obesity in clinical trials. The IWQOL-Lite-CT was developed and validated in accordance with the FDA PRO guideline. Supportive secondary endpoints were related to the remaining IWQOL-Lite-CT composites (Physical and Psychosocial) and the total score as well as the remaining SF-36

subscales and the two component summaries (Role-Physical, Bodily Pain, General Health, Vitality, Social-Functioning, Role-Emotional, Mental Health, Physical Component Summary, Mental Component Summary).

Statistically significant benefits in physical functioning were demonstrated for both SF-36 and IWQOL-Lite-CT, which occurred simultaneously with weight loss in all trials. Superiority of semaglutide 2.4 mg compared to placebo was confirmed for change from baseline to week 68 for SF-36 Physical Functioning in STEP 1, 2 and 4, and for IWQOL-Lite-CT in STEP 1 and 2 following weight loss. Superiority was not confirmed in STEP 3, but the improvement in SF-36 Physical Functioning in the semaglutide 2.4 mg group was of comparable magnitude as in STEP 1 and 2, and the lack of superiority may be explained by the relatively high response in the placebo group receiving IBT alone.

Responder definitions were used as benchmarks for what was considered a meaningful change for patients. The responder definition was the change in the individual patient-reported outcome score that had been demonstrated to have a significant treatment benefit based on patient evaluations. Thereby, the responder definition is considered to represent the patients' own perspective of a meaningful change. Greater proportions of subjects achieved a clinically meaningful improvement in SF-36 Physical Functioning according to the responder definition (≥3.7 points) at week 68 with semaglutide 2.4 mg compared to placebo across STEP 1 (40.1% vs 27.2%), STEP 2 (42.0% vs 28.9%) and STEP 3 (36.7% vs 28.0%). This was also reflected in the estimated odds ratios, which were in favour of semaglutide 2.4 mg.

With IWQOL-Lite-CT, greater proportions of subjects also achieved a clinically meaningful improvement in Physical Functioning according to the responder definition (≥14.6 points) at week 68 with semaglutide 2.4 mg compared to placebo in both STEP 1 (51.3% vs 33.0%) and in STEP 2 (42.5% vs 31.3%). This was also reflected in the estimated odds ratios, which were in favour of semaglutide 2.4 mg.

- **Ancillary analyses**

Prediction of effect on body weight based on early weight loss

The labels of anti-obesity medications such as Qsymia, Contrave /Mysimba and Saxenda include instructions to discontinue treatment if a prespecified amount of weight loss is not achieved by a certain time, to ensure that patients who are not responsive to the therapy are not unnecessarily exposed to any potential risks of the treatment.

Based on the data presented below, a specific recommendation for patients to discontinue treatment with semaglutide 2.4 mg if they do not achieve a predefined response is not considered to be relevant.

Prediction of clinically relevant body weight loss at week 68 on the basis of early body weight loss was evaluated based on STEP 4 data, supported by additional analyses based on data from STEP 1 and STEP 2. The goal was to identify subjects unlikely to achieve and sustain a clinically relevant weight loss of at least 5% after 68 weeks of treatment (non-responders). Early body weight loss was evaluated in early body weight response status at week 20 (1% to 5% body weight loss by 1%-intervals).

Due to the marked weight loss achieved during the run-in period (week 0–20) of STEP 4, very few subjects did not meet the week 20 weight loss criteria below 5%. Therefore, this presentation will focus on the week 20 (5%) weight loss criterion in STEP 4. Evaluation of early weight response at week 20 and week 28 in STEP 1 and STEP 2 is included as supportive data.

Definitions and explanation of terms:

Week 20 weight loss criterion: predefined amount of weight loss from week 0 to week 20

Week 20 (x%) responder: subject who has achieved a weight loss ≥x% at week 20

Week 20 (x%) non-responder: subject who has not achieved a weight loss ≥x% at week 20

Week 68 (5%) responder: subject who has achieved a weight loss ≥5% from week 0 to week 68

Week 68 (5%) non-responder: subject who has not achieved a weight loss ≥5% from week 0 to week 68

Positive predictive value: % week 68 responders out of the week 20 responders. A low positive predictive value means that a high number of subjects will be continued on treatment who eventually would not have achieved clinically relevant weight loss.

Negative predictive value: % week 68 non-responders out of week 20 non-responders. A low negative predictive value means that a high number of subjects will be discontinued from treatment who eventually would have achieved clinically relevant weight loss.

Sensitivity: % week 20 responders out of the week 68 responders. A high sensitivity corresponds to a high probability that a week 68 responder is correctly identified based on being classified as a week 20 responder.

Specificity: % week 20 non-responders out of the week 68 non-responders. A high specificity corresponds to a high probability that a week 68 non-responder is correctly identified based on being classified as a week 20 non-responder.

% correctly predicted subjects: the sum of correctly positive predicted subjects and correctly negative predicted subjects divided by the total number of subjects

If an early weight loss criterion (e.g. weight loss ≥5% at week 20) is to be applied as a clinically meaningful 'stopping rule' to identify those subject who do not benefit from the treatment, the criterion should ideally have both a high positive predictive value (% week 68 responders out of week 20 responders) and a high negative predictive value (% week 68 non-responders out of week 20 non-responders). If an early weight loss criterion fulfilling these requirements was applied, responsive patients would remain on the treatment, whereas unnecessary treatment of unresponsive patients would be avoided.

Prediction of clinically relevant weight loss at week 68 by week 20 weight loss

Results based on STEP 4

Most subjects (719 of 803 subjects, 89.5%) had achieved a weight loss ≥5% at week 20. Thus, the majority of the trial population were week 20 (5%) responders. The observed mean change in body weight from start of run-in (week 0) to week 20 was -10.6% across all randomised subjects with an available body weight measurement at week 20.

Change in body weight (%) from start of run-in by week 20 weight loss

A total of 88.7% of subjects in the semaglutide 2.4 mg group achieved a weight loss ≥5% from week 0 to week 68 with semaglutide 2.4 mg, compared to 47.6% with placebo.

The estimated change in body weight from start of run-in (week 0) or from baseline (week 20) to week 68 was substantially and consistently lower for week 20 non-responders compared to week 20 responders. Still, weight loss increased with increasing week 20 weight loss criteria (1% to 5%), and even subjects who were week 20 (5%) non-responders had a clinically relevant (≥5%) mean weight loss from week 0 to week 68 of -6.07% with semaglutide 2.4 mg (**Table 34**).

Table 21 Body weight (%) change from start of run-in (week 0) to week 68 by week 20 body weight loss (at least 1% to 5%) - treatment policy estimand - STEP 4

	Number of subjects		Estimated change in body weight (%) at week 68		Estimated treatment difference (%) [95% CI]
	Sema 2.4 mg	Placebo	Sema 2.4 mg	Placebo	
Week 20 responders			**Change from week 0**		
≥1%	515	249	-17.54	-5.07	-12.47 [-13.81; -11.13]
≥2%	509	249	-17.76	-5.11	-12.65 [-13.97; -11.33]
≥3%	500	245	-17.93	-5.14	-12.79 [-14.11; -11.46]
≥4%	480	240	-18.46	-5.27	-13.19 [-14.50; -11.88]
≥5%	458	233	-18.91	-5.43	-13.48 [-14.79; -12.18]
Week 20 non-responders			**Change from week 0**		
<1%	5	1	-0.28	2.19	-2.47 [-17.25; 12.31]
<2%	11	1	0.57	2.49	-1.92 [-13.73; 9.89]
<3%	20	5	-3.30	-0.68	-2.61 [-10.33; 5.10]
<4%	40	10	-4.33	0.17	-4.51 [-10.06; 1.05]
<5%	62	17	-6.07	-0.08	-5.99 [-10.26; -1.72]

All subjects were treated with semaglutide from week 0–20 (run-in). Baseline (randomisation) was at week 20. Subjects in the placebo group were treated with placebo from week 20–68.

The small number of week 20 non-responders with the lowest week 20 weight loss criteria (1% to 3%), led to wide confidence intervals and were furthermore insufficient to perform statistical analysis of clinically relevant weight loss of ≥5% at week 68.

Approximately half of the subjects who were week 20 (5%) non-responders with semaglutide still achieved a ≥5% weight reduction after a further 48 weeks of treatment with semaglutide 2.4 mg (estimated percentage of week 68 [5%] responders: 51.95%), while only a few of the week 20 (5%) non-responders who switched to placebo at week 20 became week 68 (5%) responders (estimated percentage: 11.36%). A non-responder sensitivity analysis supported these results.

Prediction of clinically relevant weight loss since start of run-in by week 20 weight loss

Positive predictive values were high with semaglutide 2.4 mg, meaning that few subjects would be continued on treatment without achieving clinically relevant weight loss (**Table 35** and **Figure 36**, top panel). In contrast, negative predictive values decreased with increasing week 20 weight loss criteria, meaning that a high number of subjects would be discontinued from treatment who eventually would have achieved clinically relevant weight loss (**Table 35** and **Figure 36**, bottom panel). Specificity was low, especially for the lower week 20 weight loss criteria. Thus, a week 20 non-response could not accurately predict a week 68 (5%) non-response. In contrast, sensitivity was high, so a week 68 (5%) responder was likely to have been correctly identified based on being a week 20 responder, regardless of the week 20 weight loss criterion applied (**Table 35**).

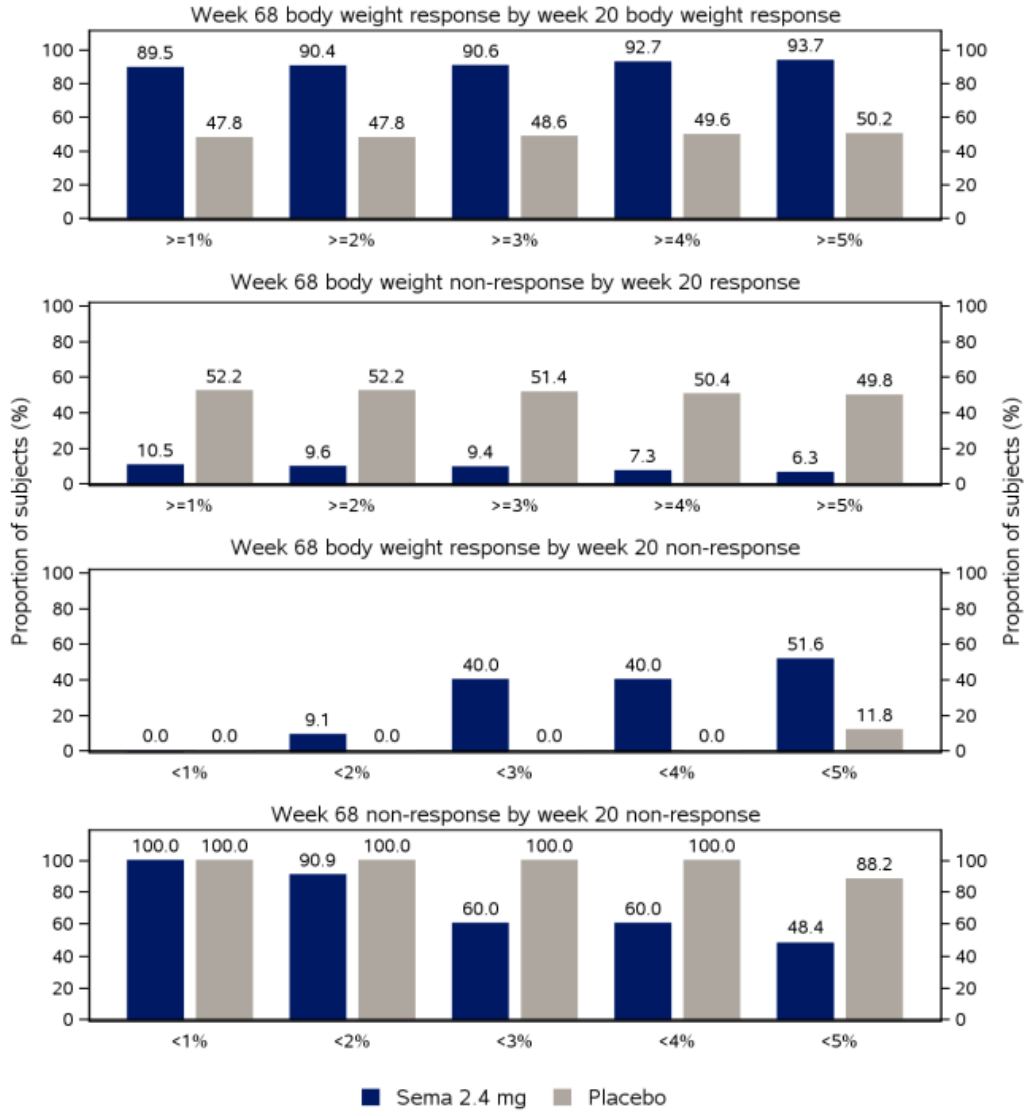
Table 22 Prediction of achieving at least 5% body weight loss since start of run-in (week 0) at week 68 by week 20 body weight loss (at least 1% to 5%) - predictive statistics - in-trial - STEP 4

	Positive predictive value (%)	Sensitivity (%)	Negative predictive value (%)	Specificity (%)	Correctly predicted (%)
Sema 2.4 mg					
Body weight loss >=1% at week 20	89.5	100.0	100.0	8.5	89.6
Body weight loss >=2% at week 20	90.4	99.8	90.9	16.9	90.4
Body weight loss >=3% at week 20	90.6	98.3	60.0	20.3	89.4
Body weight loss >=4% at week 20	92.7	96.5	60.0	40.7	90.2
Body weight loss >=5% at week 20	**93.7**	**93.1**	**48.4**	**50.8**	**88.3**
Placebo					
Body weight loss >=1% at week 20	47.8	100.0	100.0	0.8	48.0
Body weight loss >=2% at week 20	47.8	100.0	100.0	0.8	48.0
Body weight loss >=3% at week 20	48.6	100.0	100.0	3.8	49.6
Body weight loss >=4% at week 20	49.6	100.0	100.0	7.6	51.6
Body weight loss >=5% at week 20	50.2	98.3	88.2	11.5	52.8

N: Number of subjects, %: Percentages are based on total number of subjects with an observation at week 20 and week 68. Observed data from in-trial period. Run-in period starts with week 0 visit. Randomisation period starts with week 20 visit. Baseline: Randomisation (week 20). The full analysis set includes all randomised subjects.

Sensitivity analyses, where subjects with a missing body weight measurement at week 68 were assumed to be non-responders at week 68, supported the results.

Figure 36 Proportion of subjects achieving at least 5% body weight loss since start of run-in (week 0) at week 68 by week 20 body weight loss (at least 1% to 5%) – bar plot - in-trial - STEP 4



Observed data from in-trial period. Randomisation period starts with week 20 visit. Baseline: Randomisation (week 20).

Supporting data from STEP 1 and STEP 2

The (%) change in body weight from week 0 to week 68 by early body weight response status at week 20 and week 28 (1% to 5% by 1%) was analysed for STEP 1 and STEP 2. Week 28 was included in the evaluation to provide supportive data from the time point where subjects had been treated with the maintenance dose (2.4 mg) for 12 weeks.

The evaluation of data from STEP 1 (subjects without T2D) and from STEP 2 (subjects with T2D) in terms of prediction of clinically relevant weight loss at week 68 by early weight loss criteria led to comparable conclusions as for the evaluation of STEP 4. A large proportion of subjects were week 20 (5%) responders, and week 20 (5%) non-responders achieved a clinically meaningful weight loss at week 68. Comparable results were obtained when week 28 was set as the time point for assessing early weight loss.

Change in body weight (%) from start of run-in by week 20 or week 28 weight loss

Most subjects in the semaglutide 2.4 mg group were week 20 (5%) responders (STEP 1: 85.3% and STEP 2: 70.2%). Similar results were seen for week 28 (5%) responders.

The estimated change in body weight from baseline to week 68 was substantially and consistently smaller for week 20 non-responders than for week 20 responders. Still, in STEP 1, week 20 (5%) non-responders had a clinically relevant weight loss at week 68 with semaglutide 2.4 mg (estimated change from baseline: -5.30%). In STEP 2, week 20 (5%) non-responders had an estimated change from baseline in body weight of -4.10% at week 68 with semaglutide 2.4 mg. Comparable results were seen for week 28 criteria.

Prediction of clinically relevant weight loss at week 68 by week 20 or week 28 weight loss

In STEP 1 and STEP 2, positive predictive values were high in the semaglutide 2.4 mg group, whereas negative predictive values decreased with increasing weight loss criteria. In STEP 1, the negative predictive value of week 20 (5%) non-responders was 42.3%, meaning that 57.7% of week 20 (5%) non-responders with semaglutide 2.4 mg still achieved a clinically relevant weight loss ≥5% at week 68. Similarly, in STEP 2, the negative predictive value of week 20 (5%) non-responders was 62.7%, meaning that 37.3% of week 20 (5%) non-responders still achieved a clinically relevant weight loss ≥5% at week 68.

Within each of the two trials, predictive values were similar for week 28 (5%) criteria and week 20 (5%) criteria, except for the negative predictive value in STEP 1, which was lower for the week 20 (5%) criterion compared to the week 28 (5%) criterion. Sensitivity analyses supported the results for STEP 1 and STEP 2.

Summary of results

Analyses were performed based on data from STEP 4 to investigate how well the amount of weight loss achieved after 20 weeks of treatment predicts which subjects will not achieve and sustain a weight loss of at least 5% after 68 weeks of treatment (non-responders).

In STEP 4, a substantial weight loss was achieved during the 20-week run-in, and very few subjects did not meet the week 20 (5%) weight loss criterion. This criterion gave a high positive predictive value, but a low negative predictive value, meaning that few subjects would continue treatment without achieving a clinically relevant weight loss, but also that a large fraction of subjects would stop treatment although they were likely to achieve a clinically relevant weight loss, had they continued. The results of the supportive analyses of STEP 1 and 2 data were consistent with the results obtained for STEP 4.

Based on the results of these analyses, a specific recommendation for patients to discontinue treatment with semaglutide 2.4 mg if they do not achieve a predefined weight loss is not considered to be relevant, since none of the predefined early weight loss criteria identified the majority of non-responders.

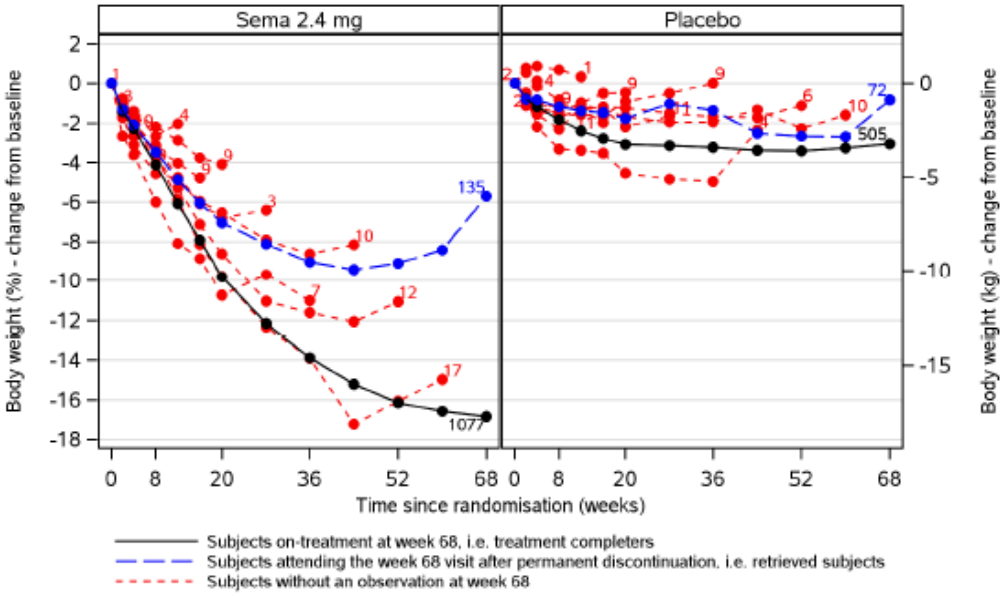
Missing data patterns:

The number of subjects who discontinued trial product prematurely for each trial and who attended the 68-week visit are shown in the four figures below (blue dashed lines, **Figures 37-40**). The mean body weight of those who discontinued are also shown.

Those who discontinue treatment have a higher bodyweight at week 68 compared to those who stay on treatment both in the placebo group and in the semaglutide treatment group, and the difference between completers and non-completers are higher in the semaglutide group compared with the placebo group. But

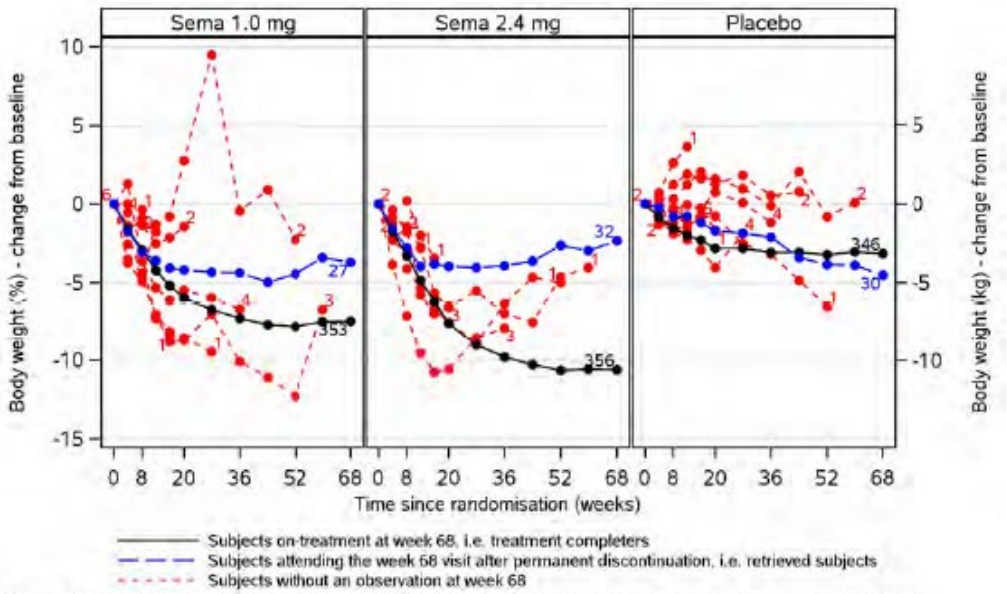
for the STEP 2 study, the bodyweight among those who discontinue treatment is higher in the semaglutide group than in the placebo group at week 68.

Figure 37 STEP 1: Body weight (%) change from baseline by week – missing data pattern plot



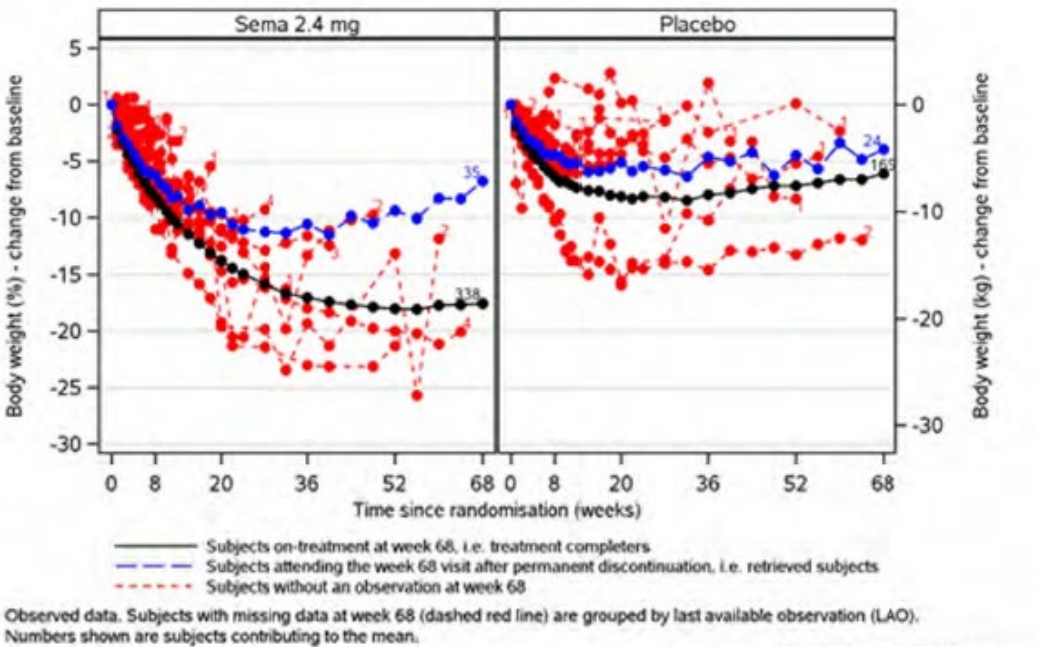
Observed data. Subjects with missing data at week 68 (dashed red line) are grouped by last available observation (LAO).
Numbers shown are subjects contributing to the mean.

Figure 8 STEP 2: Body weight (%) change from baseline by week – missing data pattern plot



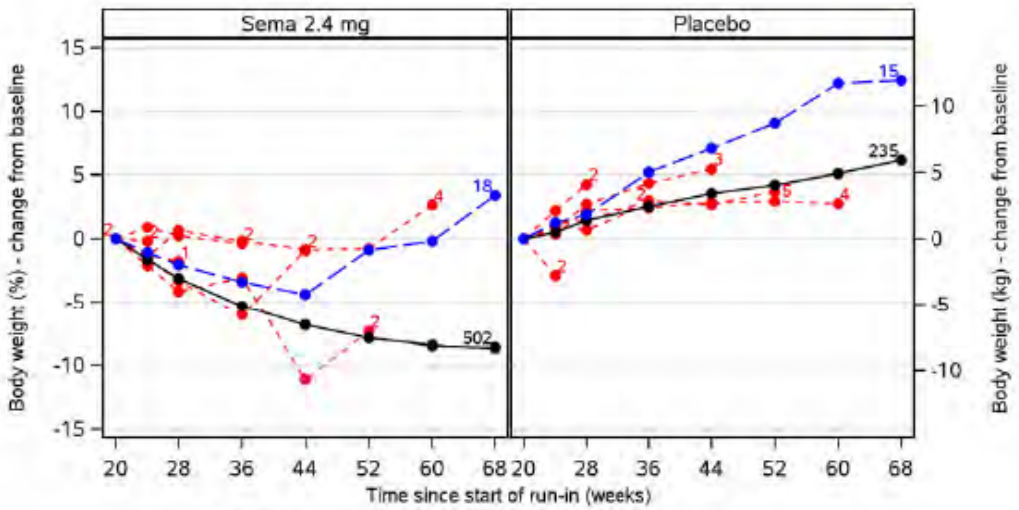
Observed data. Subjects with missing data at week 68 (dashed red line) are grouped by last available observation (LAO).
Numbers shown are subjects contributing to the mean.

Figure 39 STEP 3: Body weight (%) change from baseline by week – missing data pattern plot



Observed data. Subjects with missing data at week 68 (dashed red line) are grouped by last available observation (LAO). Numbers shown are subjects contributing to the mean.

Figure 40 STEP 4: Body weight (%) change from baseline by week – missing data pattern plot

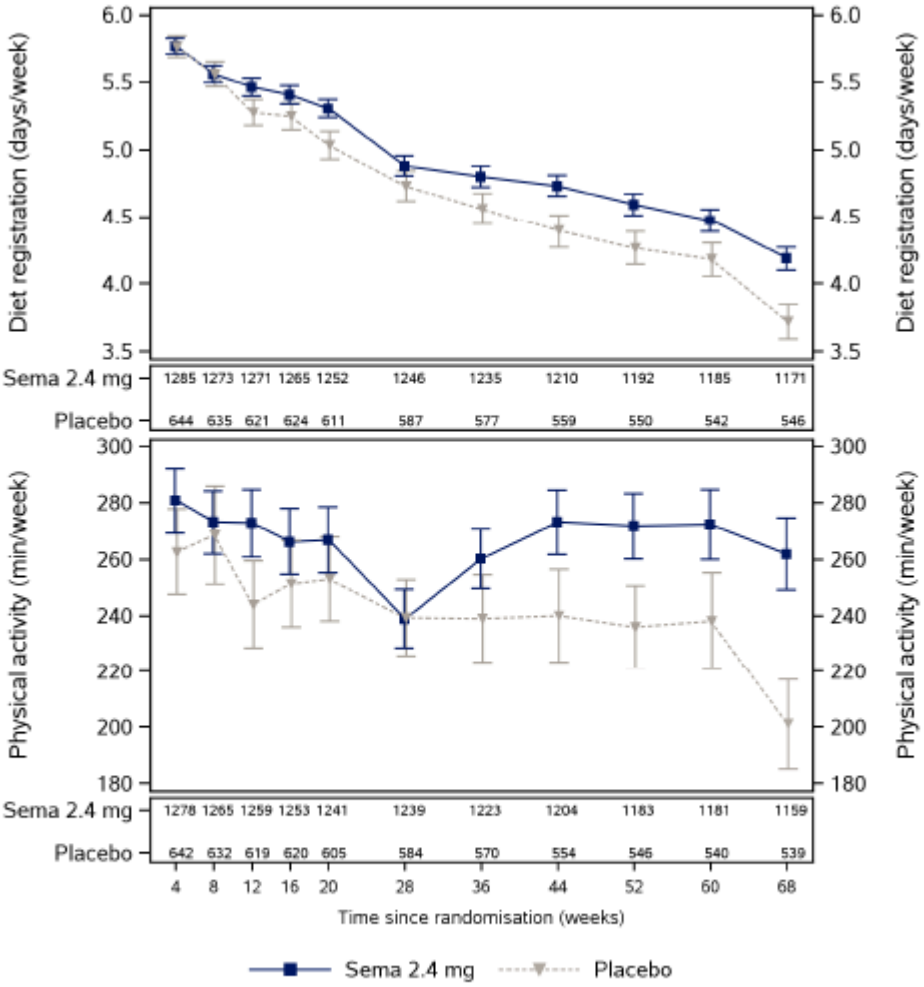


Observed data. Randomised period starts with week 20 visit. Baseline: Randomisation (week 20). Subjects with missing data at week 68 (dashed red line) are grouped by last available observation (LAO). Numbers shown are subjects contributing to the mean.

Adherence to diet and increased physical activity

In STEP 1, adherence to diet registration and increased physical activity during the trial was higher in the semaglutide group compared with placebo (**Figure 41**).

Figure 41 STEP 1: Diet and physical by week – mean plot – observed in – trial data



Observed data from in-trial period. Error bars are +/- standard error of the mean. Diet registration: Number of days per week with at least one entry in the food diary. Physical activity: Number of minutes per week of physical activity. Note that for both diet and physical activity registration the presented data relates to weeks prior to the actual visit. Numbers shown in the lower panel are subjects contributing to the mean.

- **Summary of main efficacy results**

The following tables (**Tables 36-39**) summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 23. Summary of efficacy for trial 4373, STEP 1 – weight management in overweight or obesity

Title: STEP 1, Effect and safety of semaglutide 2.4 mg once-weekly in subjects with overweight or obesity

Study identifier	Trial 4373 Protocol number: NN9536-4373 EudraCT number: 2017-003436-36		
Design	randomised, double-blind, double dummy, placebo-controlled, multi centre, multinational trial		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		68 weeks, including 16 weeks dose-escalation not applicable 7 weeks
Hypothesis	Superiority		
Treatments groups	Semaglutide 2.4 mg once weekly		Semaglutide 2.4 mg, 68 weeks including 16 weeks dose-escalation, n=1306
	placebo		Placebo. 68 weeks, n=655
Endpoints and definitions	Primary endpoint	Body weight (%)	Change from baseline in body weight %
	Co-Primary endpoint	⩾5% body weight reduction	⩾5% body weight reduction from week 0
	Confirmatory Secondary endpoint	waist circumference (cm)	Change from baseline in waist circumference (cm)
	Confirmatory Secondary endpoint	⩾ 10% body weight reduction	⩾10% body weight reduction from week 0
	Confirmatory Secondary endpoint	⩾15% body weight reduction	⩾15% body weight reduction from week 0
	Confirmatory Secondary endpoint	SBP (mmHg)	Change from baseline in systolic blood pressure (SBP)
	Confirmatory Secondary endpoint	SF-36 PF (score)	Change from baseline SF-36 PF score
	Confirmatory Secondary endpoint	IWQOL-Lite-CT PF (score)	Change from baseline IWQOL-Lite-CT PF score
Database lock	11 May 2020 (all data except anti-semaglutide antibody data and pharmacokinetic data) 01 July 2020 (anti-semaglutide antibody data and pharmacokinetic data)		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent to treat (ITT)		
Descriptive statistics and estimate variability	Treatment group	Semaglutide 2.4 mg	placebo
	Number of subjects	1306	655
	Change body weight (%) (Mean)	-14.9	-2.4
	⩾5% body weight reduction (% of patients)	83.5	31.1

	Change waist circumference (cm) (mean)	-13.5	-4.1
	⩾ 10% body weight reduction (% of patients)	66.1	12.0
	⩾ 15% body weight reduction (% of patients)	47.9	4.8
	Change SBP (mmHg) (mean)	-6.2	-1.1
	Change SF-36 (score) (mean)	2.2	0.4
	Change IWQOL-Lite-CT PF (score)	14.7	5.3
Effect estimate per comparison	Primary endpoint Body weight (%) mean	Comparison groups	Semaglutide 2.4 mg vs placebo
		ETD	-12.4
		95% CI	-13.4 to -11.5
		P-value	< 0.0001
	Co-Primary endpoint ⩾5% body weight reduction	Comparison groups	Semaglutide 2.4 mg vs placebo
		ETD	52.4
		95% CI	48.1 to 56.8
		Odds of achieving baseline body weight loss ⩾5%	11.2
		95% CI	8.9 to 14.2
		P-value	<0.0001
	Confirmatory Secondary endpoint waist circumference (cm)	Comparison groups	Semaglutide 2.4 mg vs placebo
		ETD	-9.4
		95% CI	-10.3 to -8.5
		P-value	<0.0001
	Confirmatory Secondary endpoint ⩾10% body weight reduction	Comparison groups	Semaglutide 2.4 mg vs placebo
		ETD	54.1
		95% CI	50.4 to 57.9
		Odds of achieving baseline body weight loss ⩾10%	14.7
		95% CI	11.1 to 19.4
		P-value	< 0.0001
	Confirmatory Secondary endpoint ⩾15% body weight reduction	Comparison groups	Semaglutide 2.4 mg vs placebo
		ETD	43.1
		95% CI	39.8 to 46.3
		Odds of achieving baseline body weight loss ⩾15%	19.3
		95% CI	12.9 to 28.8
		P-value	<0.0001

	Confirmatory Secondary endpoint SBP (mmHg)	Comparison groups	Semaglutide 2.4 mg vs placebo
		ETD	-5.1
		95% CI	-6.3 to -3.9
		P-value	<0.0001
	Confirmatory Secondary endpoint SF-36 (score)	Comparison groups	Semaglutide 2.4 mg vs placebo
		ETD	1.8
		95% CI	1.2 to 2.4
		P-value	<0.0001
	Confirmatory Secondary endpoint IWQOL-Lite-CT PF (score)	Comparison groups	Semaglutide 2.4 mg vs placebo
		ETD	9.4
		95% CI	7.5 to 11.4
		P-value	<0.0001

CI: Confidence interval; ETD: Estimated treatment difference; SBP: systolic blood pressure

Table 24. Summary of efficacy for trial 4374, STEP 2 – weight management in type 2 diabetes

Title: STEP 2, Effect and safety of semaglutide 2.4 mg once-weekly in subjects with overweight or obesity and type 2 diabetes			
Study identifier	Trial 4374 Protocol number: NN9536-4374 EudraCT number: 2017-003414-10		
Design	randomised, double-blind, double-dummy, placebo-controlled, multi centre, multinational trial		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		68 weeks, including 16 weeks dose-escalation not applicable 7 weeks
Hypothesis	Superiority		
Treatments groups	Semaglutide 2.4 mg once weekly		Semaglutode 2.4 mg, 68 weeks including 16 weeks dose-escalation, n=404
	Semaglutide 1.0 mg once weekly		Semaglutide 1.0 mg, 68 weeks including 8 weeks, dosescalation, n=403
	placebo		Placebo. 68 weeks, n=403
Endpoints and definitions	Primary endpoint	Body weight (%)	Change from baseline in body weight %
	Co-Primary endpoint	⩾5% body weight reduction	⩾5% body weight reduction from week 0
	Confirmatory Secondary endpoint	waist circumference (cm)	Change from baseline in waist circumference (cm)
	Confirmatory Secondary endpoint	⩾ 10% body weight reduction	⩾10% body weight reduction from week 0

	Confirmatory Secondary endpoint	⩾15% body weight reduction	⩾15% body weight reduction from week 0
	Confirmatory Secondary endpoint	HbA1c (%)	Change from baseline in HbA1c (%)
	Confirmatory Secondary endpoint	SBP (mmHg)	Change from baseline in systolic blood pressure (SBP)
	Confirmatory Secondary endpoint	SF-36 PF (score)	Change from baseline SF-36 PF score
	Confirmatory Secondary endpoint	IWQOL-Lite-CT PF (score)	Change from baseline IWQOL-Lite-CT PF score
Database lock	20 May 2020 (all data except anti semaglutide antibody data and pharmacokinetic data) 26 June 2020 (anti-semaglutide antibody data and pharmacokinetic data)		

Results and Analysis

Analysis description	**Primary Analysis**			
Analysis population and time point description	Intent to treat (ITT)			
Descriptive statistics and estimate variability	Treatment group	Semaglutide 2.4 mg	Semaglutide 1.0 mg	placebo
	Number of subjects	404	403	403
	Change body weight (%) (Mean)	-9.6	-7.0	-3.4
	⩾5% body weight reduction (% of patients)	67.4	57.1	30.2
	Change waist circumference (cm) (mean)	-9.4	-6.9	-4.5
	⩾ 10% body weight reduction (% of patients)	44.5	29.7	10.2
	⩾ 15% body weight reduction (% of patients)	25.0	11.5	4.3
	Change HbA1c (mmol (%))	-17.5 (-1.6)	-15.9 (-1.5)	-4.1 (-0.4)
	Change SBP (mmHg) (mean)	-3.9	-2.9	-0.5
	Change SF-36 (score) (mean)	2.5	2.4	1.0
	Change IWQOL-Lite-CT PF (score)	10.1	8.7	5.3
Effect estimate per comparison	Primary endpoint Body weight (%) mean	Comparison groups		Semaglutide 2.4 mg vs placebo
		ETD		-6.2
		95% CI		-7.3 to-5.2

		P-value	< 0.0001
	Co-Primary endpoint ⩾5% body weight reduction	Comparison groups	Semaglutide 2.4 mg vs placebo
		Odds of achieving baseline body weight loss ⩾5%	4.9
		95% CI	3.6 to 6.6
		P-value	<0.0001
	Confirmatory Secondary endpoint waist circumference (cm)	Comparison groups	Semaglutide 2.4 mg vs placebo
		ETD	-4.9
		95% CI	-6.0 to -3.8
		P-value	<0.0001
	Confirmatory Secondary endpoint ⩾10% body weight reduction	Comparison groups	Semaglutide 2.4 mg vs placebo
		Odds of achieving baseline body weight loss ⩾10%	7.41
		95% CI	4.89 to 11.24
		P-value	<0.0001
	Confirmatory Secondary endpoint ⩾15% body weight reduction	Comparison groups	Semaglutide 2.4 mg vs placebo
		Odds of achieving baseline body weight loss ⩾15%	7.65
		95% CI	4.11 to 14.22
		P-value	<0.0001
	Confirmatory Secondary endpoint HbA1c (mmol (%))	Comparison groups	Semaglutide 2.4 mg vs placebo
		ETD	-13.5 (-1.2)
		95% CI	-15.5 to -11.4 (-1.4 to -1.1)
		P-value	<0.0001
	Confirmatory Secondary endpoint SBP (mmHg)	Comparison groups	Semaglutide 2.4 mg vs placebo
		ETD	-3.4
		95% CI	-5.6 to -1.3
		P-value	<0.05
	Confirmatory Secondary endpoint SF-36 (score)	Comparison groups	Semaglutide 2.4 mg vs placebo
		ETD	1.5
		95% CI	0.4 to 2.6
		P-value	<0.01
	Confirmatory Secondary endpoint IWQOL-Lite-CT PF (score)	Comparison groups	Semaglutide 2.4 mg vs placebo
		ETD	4.8
		95% CI	1.8 to 7.9
		P-value	<0.0001

CI: Confidence interval; ETD: Estimated treatment difference; SBP: systolic blood pressure

Table 25. Summary of efficacy for trial 4375, STEP 3 – weight management with IBT

Title: STEP 3, Effect and safety of semaglutide 2.4 mg once-weekly as adjunct to intensive behavioural therapy in subjects with overweight or obesity			
Study identifier	Trial 4375 Protocol number: NN9536-4375 EudraCT number: not applicable (trial was conducted in US only)		
Design	randomised, double-blind, double dummy, placebo-controlled, multi centre, multinational trial		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		68 weeks, including 16 weeks dose-escalation not applicable 7 weeks
Hypothesis	Superiority		
Treatments groups	Semaglutide 2.4 mg once weekly with IBT		Semaglutode 2.4 mg, 68 weeks including 16 weeks dose-escalation, with IBT n= 407
	Placebo with IBT		Placebo 68 weeks with IBT, n= 204
Endpoints and definitions	Primary endpoint	Body weight (%)	Change from baseline in body weight %
	Co-Primary endpoint	⩾5% body weight reduction	⩾5% body weight reduction from week 0
	Confirmatory Secondary endpoint	waist circumference (cm)	Change from baseline in waist circumference (cm)
	Confirmatory Secondary endpoint	⩾ 10% body weight reduction	⩾10% body weight reduction from week 0
	Confirmatory Secondary endpoint	⩾15% body weight reduction	⩾15% body weight reduction from week 0
	Confirmatory Secondary endpoint	SBP (mmHg)	Change from baseline in systolic blood pressure (SBP)
	Confirmatory Secondary endpoint	SF-36 PF (score)	Change from baseline SF-36 PF score
Database lock	19 May 2020		
Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent to treat (ITT)		
Descriptive statistics and estimate variability	Treatment group	Semaglutide 2.4 mg	placebo
	Number of subjects	407	204
	Change body weight (%) (Mean)	-16.5	-5.8
	⩾5% body weight reduction (% of patients)	86.6	47.6

	Change waist circumference (cm) (mean)	-15.2	-6.1
	⩾ 10% body weight reduction (% of patients)	75.3	27.0
	⩾ 15% body weight reduction (% of patients)	55.8	13.2
	Change SBP (mmHg) (mean)	-5.6	-1.6
	Change SF-36 (score) (mean)	2.5	1.7
Effect estimate per comparison	Primary endpoint Body weight (%) mean	Comparison groups	Semaglutide 2.4 mg vs placebo
		ETD	-10.3
		95% CI	-12 to -8.6
		P-value	< 0.0001
	Co-Primary endpoint ⩾5% body weight reduction	Comparison groups	Semaglutide 2.4 mg vs placebo
		Odds of achieving baseline body weight loss ⩾5%	6.1
		95% CI	4.0 to 9.3
		P-value	<0.0001
	Confirmatory Secondary endpoint waist circumference (cm)	Comparison groups	Semaglutide 2.4 mg vs placebo
		ETD	-8.3
		95% CI	-10.0 to -6.6
		P-value	<0.0001
	Confirmatory Secondary endpoint ⩾10% body weight reduction	Comparison groups	Semaglutide 2.4 mg vs placebo
		Odds of achieving baseline body weight loss ⩾10%	7.4
		95% CI	4.9 to 11.0
		P-value	< 0.0001
	Confirmatory Secondary endpoint ⩾15% body weight reduction	Comparison groups	Semaglutide 2.4 mg vs placebo
		Odds of achieving baseline body weight loss ⩾15%	7.9
		95% CI	4.9 to 12.6
		P-value	<0.0001
	Confirmatory Secondary endpoint SBP (mmHg)	Comparison groups	Semaglutide 2.4 mg vs placebo
		ETD	-3.9
		95% CI	-6.4 to -1.5
		P-value	0.001
	Confirmatory Secondary endpoint SF-36 (score)	Comparison groups	Semaglutide 2.4 mg vs placebo
		ETD	0.84

		95% CI	-0.23 to 1.92
		P-value	0.12

CI: Confidence interval; ETD: Estimated treatment difference; IBT: Intensive Behavioural Therapy; SBP: systolic blood pressure

Table 26. Summary of efficacy for trial 4376, STEP 4 - sustained weight management

Title: STEP 4, Effect and safety of semaglutide 2.4 mg once-weekly in subjects with overweight or obesity who have reached target dose during the run-in period			
Study identifier	Trial 4376 Protocol number: NN9536-4376 EudraCT number: 2017-003473-34		
Design	randomised, double-blind, double dummy, placebo-controlled, multi centre, multinational trial		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		48 weeks 20 weeks 7 weeks
Hypothesis	Superiority		
Treatments groups	Semaglutide 2.4 mg once weekly		Semaglutide 2.4 mg, 48 weeks n=535
	Placebo		Placebo 48 weeks, n=268
Endpoints and definitions	Primary endpoint	Body weight (%)	Change from baseline in body weight %
	Confirmatory Secondary endpoint	waist circumference (cm)	Change from baseline in waist circumference (cm)
	Confirmatory Secondary endpoint	SBP (mmHg)	Change from baseline in systolic blood pressure (SBP)
	Confirmatory Secondary endpoint	SF-36 PF (score)	Change from baseline SF-36 PF score
Database lock	16 April 2020		
Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent to treat (ITT)		
Descriptive statistics and estimate variability	Treatment group	Semaglutide 2.4 mg	placebo
	Number of subjects	535	268
	Change body weight (%) (Mean)	-7.88	+6.87
	Change waist circumference (cm) (mean)	-6.9	+3.2
	Change SBP (mmHg) (mean)	0	+5
	Change SF-36 (score) (mean)	+1	-1.2

Effect estimate per comparison	Primary endpoint Body weight (%) mean	Comparison groups	Semaglutide 2.4 mg vs placebo
		ETD	14.75
		95% CI	-16.00 to -13.50
		P-value	< 0.0001
	Confirmatory Secondary endpoint waist circumference (cm)	Comparison groups	Semaglutide 2.4 mg vs placebo
		ETD	-9.74
		95% CI	-10.94 to -8.54
		P-value	<0.0001
	Confirmatory Secondary endpoint SBP (mmHg)	Comparison groups	Semaglutide 2.4 mg vs placebo
		ETD	-3.92
		95% CI	-5.82 to -2.03
		P-value	<0.0001
	Confirmatory Secondary endpoint SF-36 (score)	Comparison groups	Semaglutide 2.4 mg vs placebo
		ETD	2.45
		95% CI	1.59 to 3.32
		P-value	<0.0001

CI: Confidence interval; ETD: Estimated treatment difference; SBP: systolic blood pressure

2.6.5.3. Clinical studies in special populations

Subgroup analyses based on baseline demographic and disease factors

To investigate whether there were differences in efficacy response to semaglutide 2.4 mg in sub-populations, the evaluation of change from baseline in body weight (%) was conducted for predefined subgroups. In general, lower baseline values were observed in STEP 4 due to baseline being defined as the start of the on-treatment period after randomisation (week 20).

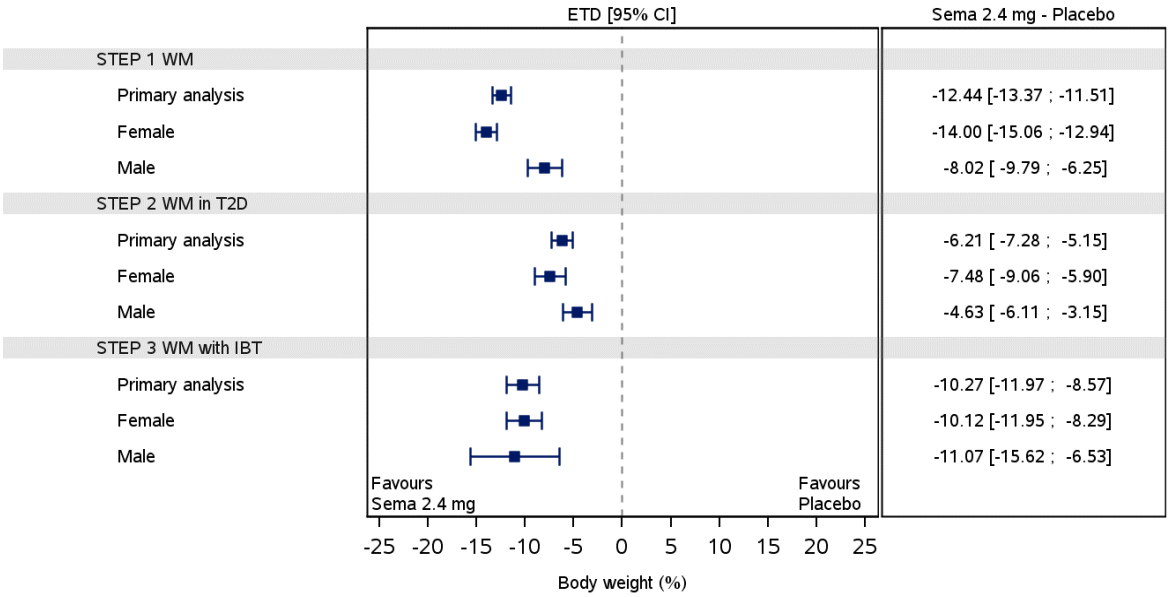
Apart from sex (STEP 1, 2, 4) and baseline body weight (STEP 1 and STEP 4), the efficacy response to semaglutide 2.4 mg was consistent across sub-populations, and the beneficial effect of semaglutide 2.4 mg compared to placebo was generally seen across all sub-populations.

Sex

The majority of subjects in STEP 1, 3, and 4 were female. Male and female subjects were more evenly distributed in STEP 2.

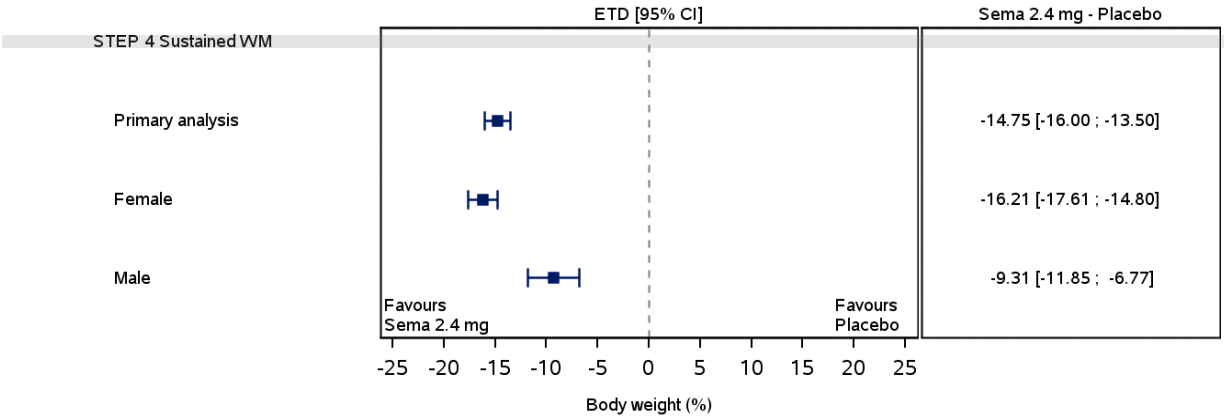
In STEP 1, 2, and 4, female subjects lost on average more weight compared with male subjects, as shown by the larger ETDs of semaglutide 2.4 mg versus placebo (**Figure 42** and **43)**. However, this effect was not seen in STEP 3. Body weight was previously identified as the most important covariate for semaglutide exposure, with higher exposures at lower body weights. Higher exposure may contribute to the larger weight loss seen in female subjects, as baseline mean body weight was lower in female subjects across all four trials.

Figure 42 Body weight (%) change from baseline by sex – estimated treatment difference – forest plot – treatment policy estimand – STEP 1-3



FAS: Full analysis set.
Analysis of data from in-trial period.

Figure 43 Body weight (%) change from baseline by sex – estimated treatment difference – forest plot – treatment policy estimand – STEP 4



FAS: Full analysis set.
Analysis of data from in-trial period. Randomisation period starts with week 20 visit. Baseline: Randomisation (week 20).

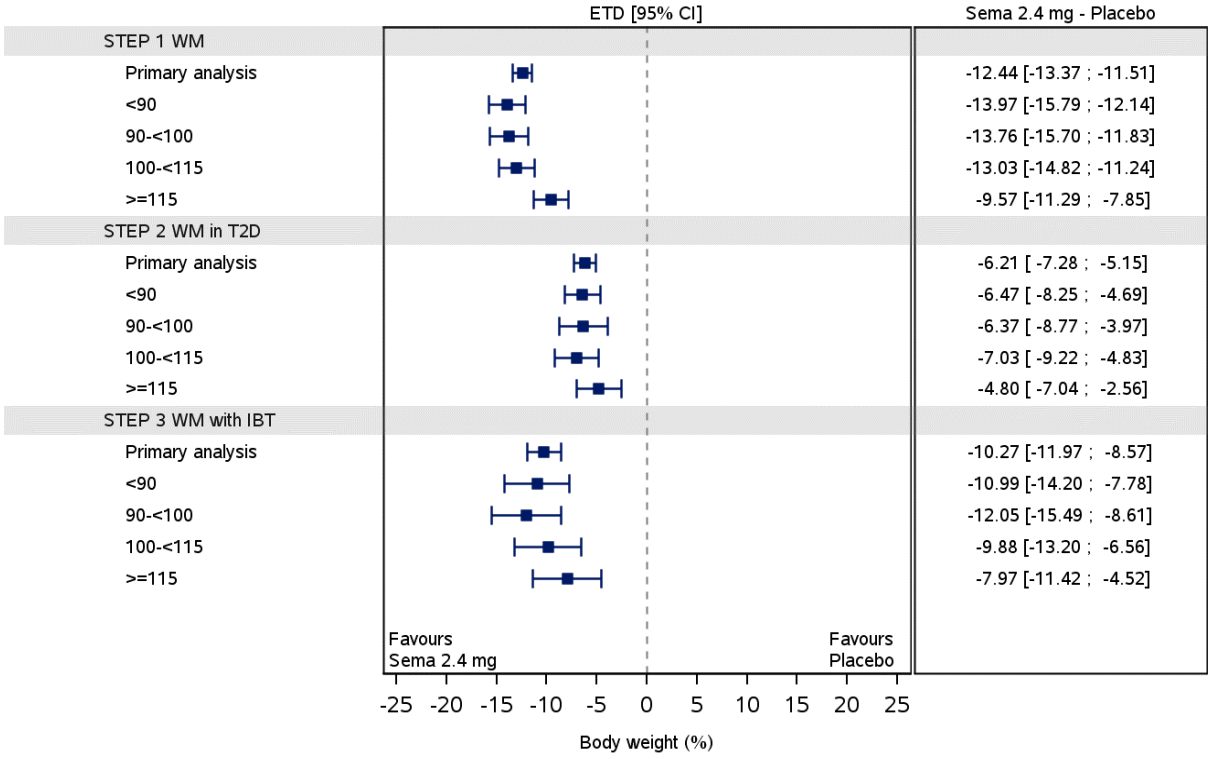
Exposure-response relationships were explored as part of the dose setting for phase 3 based on data from 4153. Here it appeared that the weight loss increased in an exposure-dependent manner within both sexes although weight loss at a given exposure level was slightly larger in females than males. A larger weight loss in STEP 1 as compared to STEP 2 was observed. Factors contributing to this difference may include sex distribution between the two trials. Sex were compared across trials showing that the weight loss increased in an exposure-dependent manner in both male and female subjects. Within both trials, it appeared that the weight loss at a given exposure level was larger in females than males. Overall, these analyses suggested that exposure differences cannot explain all differences between genders in terms of weight loss.

Baseline body weight

Subjects were evenly distributed across the baseline body weight categories (**Figure 44**) within the trials, with the exception of STEP 2 and STEP 4, which had higher proportions of subjects with baseline body weight <90 kg. Mean baseline body weight within the categories was comparable across treatment groups in each trial.

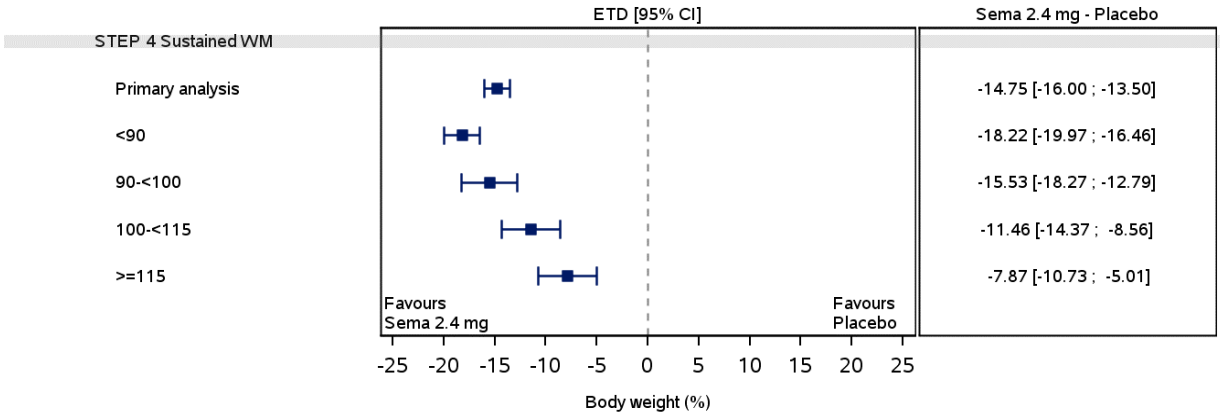
Subjects in STEP 1 and STEP 4 with higher baseline body weight lost on average less weight (%) than subjects with lower baseline body weight. This effect was less pronounced in STEP 2 and STEP 3 (**Figure 44, Figure 45**). There was a small treatment effect of baseline BMI in STEP 3 and STEP 4. No treatment-subgroup interaction was seen for baseline BMI in STEP 1 and STEP 2.

Figure 44 Body weight (%) change from baseline by baseline body weight (kg) – estimated treatment difference – forest plot – treatment policy estimand – STEP 1-3



FAS: Full analysis set.
Analysis of data from in-trial period.

Figure 45 Body weight (%) change from baseline by baseline body weight (kg) – estimated treatment difference – forest plot – treatment policy estimand – STEP 4



FAS: Full analysis set.
Analysis of data from in-trial period. Randomisation period starts with week 20 visit. Baseline: Randomisation (week 20).

Weight loss in subjects with gastrointestinal AEs

A descriptive analysis of the effect of gastrointestinal AEs on weight loss (change in body weight [%] from baseline to week 68) was evaluated in two sub-populations – subjects with and without:

- Any gastrointestinal AEs
- Nausea, vomiting, and/or diarrhoea (the most frequently occurring gastrointestinal AEs)

Weight loss occurred irrespective of gastrointestinal AEs, as there were minimal differences in weight loss in these two sub-populations. In STEP 1 trial, 969/1306 subjects treated with semaglutide 2.4 mg had gastrointestinal AE, and patients with gastrointestinal AEs had a weight change at 68 weeks of treatment of (mean (SD)) -15.8% (10.1) vs -15.1% (10.0) in patients without gastrointestinal AEs. In STEP 2 trial 256/404 patients treated with semaglutide 2.4 mg had gastrointestinal AE and body weight change of -10.4% (8.3) vs -9.0% (7.5) in patients without gastrointestinal AEs. Including only patients with AEs of nausea, diarrhoea and/or vomiting in STEP 1 779/1306 patients had these AEs and had a body weight change of -16.1% (10.4) vs –14.8% (9.6) in patients without at 68 weeks of treatment with semaglutide 2.4 mg. In STEP 2 this was 191/404 patients with a weight change of -10.5% (8.2) vs -9.4% (7.8).

Analyses across age groups

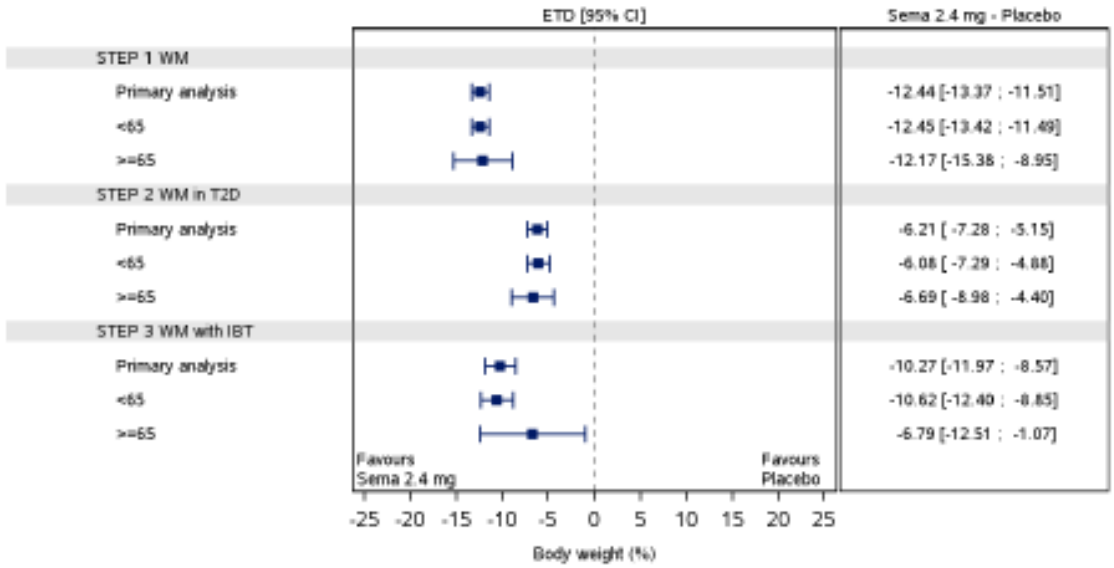
In the 4 pivotal trials 388 out of 4182 subjects were between 65 and 74 years of age, and 36 patients were 75 years of age or older (**Table 40**). No information on the number of subjects aged 85+ years are provided.

Table 40, number of patients included with age 65-74 and 75+.

	Age 65-74 (Older subjects number /total number)	**Age 75+ (Older subjects number /total number)**
Controlled Trials	388/4182	36/4182

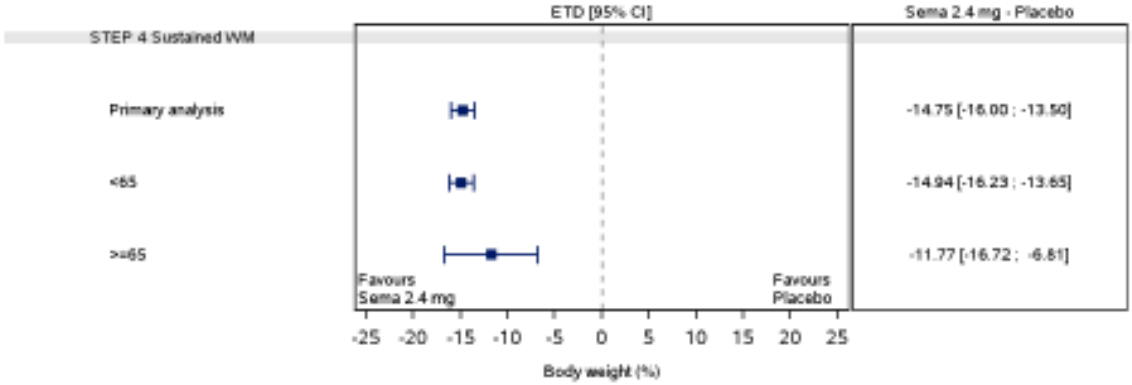
Analyses across age groups (<65 years and ≥65 years) are shown in **Figures 46** and **47**, and the effect on bodyweight was similar across age subgroups.

Figure 46 Body weight (%) change from baseline by age – estimated treatment difference – forest plot – treatment policy etimand – FAS – STEP1, 2 and 3



FAS: Full analysis set.
Analysis of data from in-trial period.

Figure 47 Body weight (%) change from baseline by age – estimated treatment difference – forest plot – treatment policy etimand – FAS – STEP 4



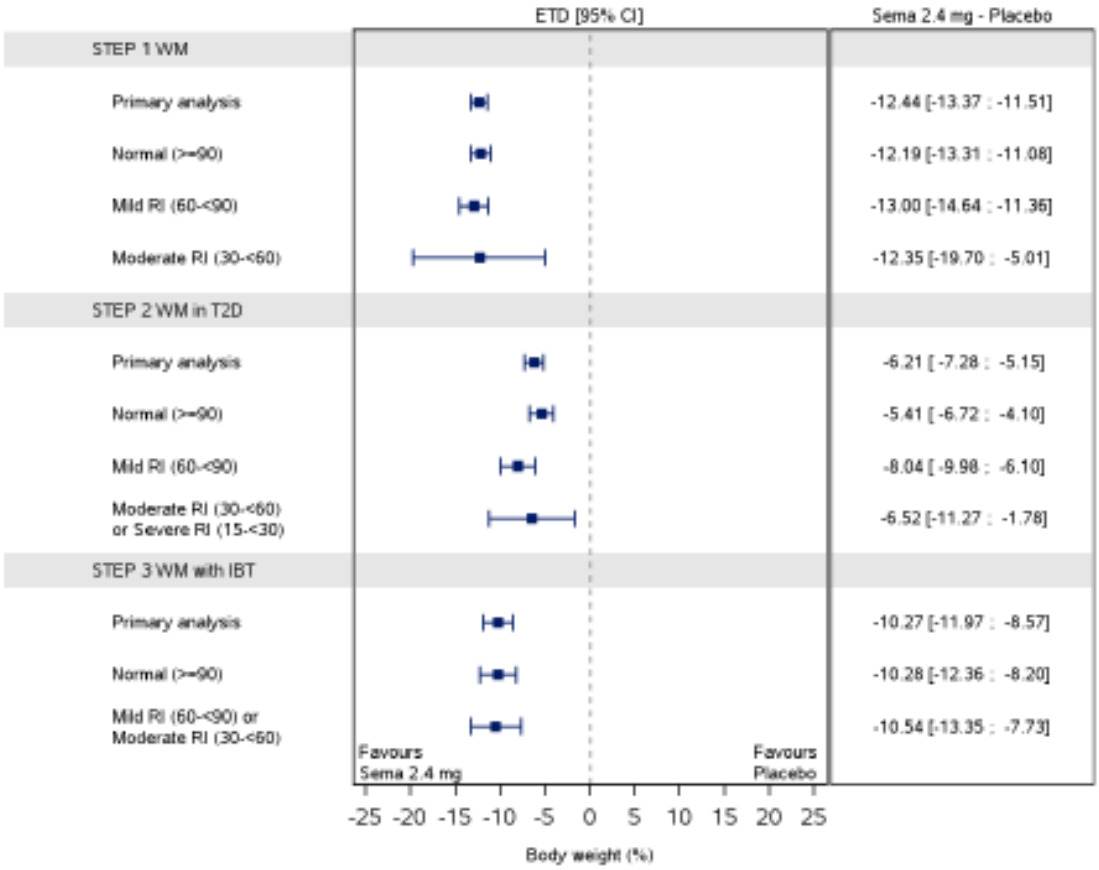
FAS: Full analysis set.
Analysis of data from in-trial period. Randomisation period starts with week 20 visit. Baseline: Randomisation (week 20).

Analyses based on renal function

Analysis based on eGFR subgroups are shown in **Figure 48** and **49**.

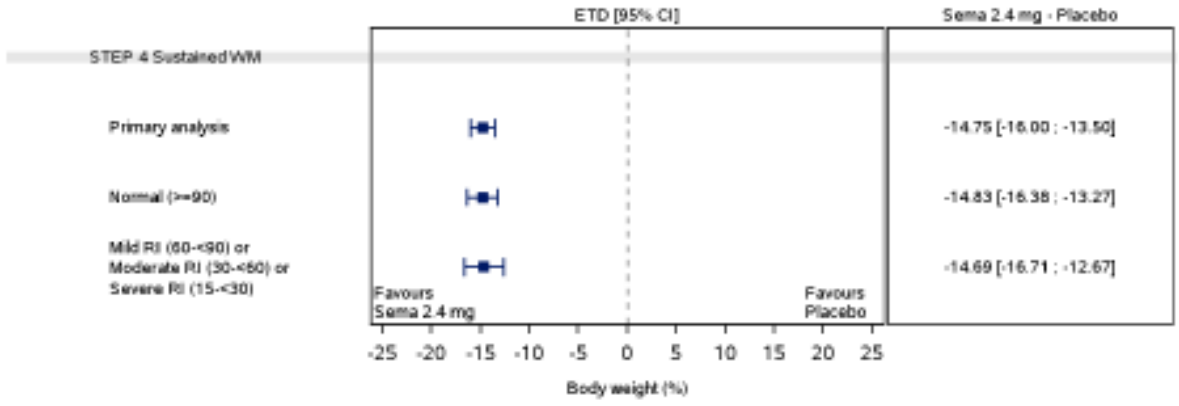
The effect on bodyweight was similar in subjects with normal renal function, mild renal impairment and moderate renal impairment. In STEP 4, one subject with severe renal impairment was pooled with subjects with mild or moderate renal impairment.

Figure 48 Body weight (%) change from baseline by baseline eGFR – estimated treatment difference – forest plot – treatment policy estimand – FAS – STEP 1, 2 and 3



FAS: Full analysis set.
Analysis of data from in-trial period.

Figure 49 Body weight (%) change from baseline by baseline eGFR – estimated treatment difference – forest plot – treatment policy estimand – FAS – STEP 4



FAS: Full analysis set.
Analysis of data from in-trial period. Randomisation period starts with week 20 visit. Baseline: Randomisation (week 20).

2.6.5.4. Supportive study(ies)

Body composition

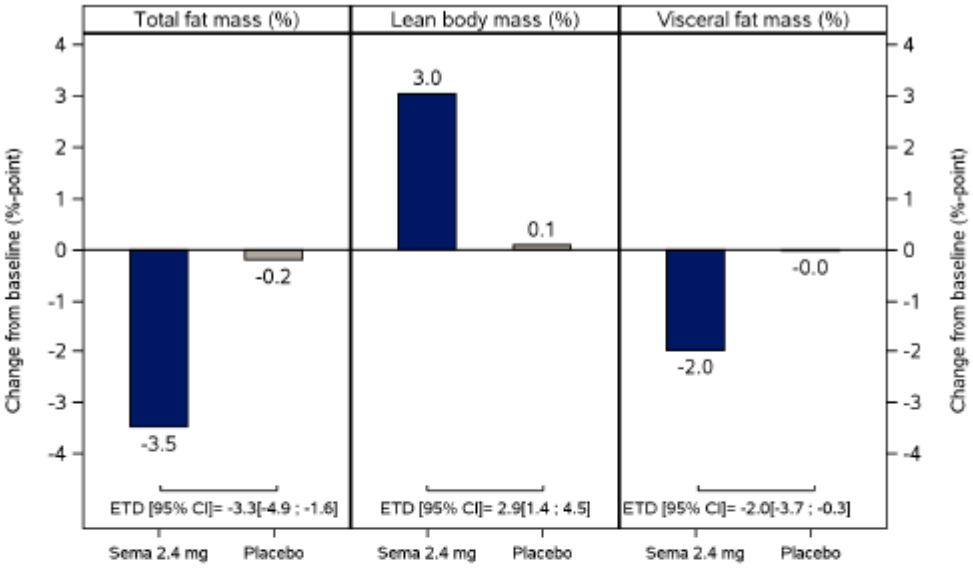
Changes in body composition (total fat mass, total lean body mass, and regional visceral fat mass) from baseline to week 68 were included as a supportive secondary endpoint for a subpopulation of 140 US subjects in STEP 1.

Body composition was measured using dual energy X-ray absorptiometry (DEXA). Treatment with semaglutide 2.4 mg was accompanied by greater reduction in fat mass than in lean body mass leading to an improvement in body composition compared to placebo after 68 weeks. Furthermore, this reduction in total fat mass was accompanied by a reduction in regional visceral fat.

Compared to placebo, treatment with semaglutide 2.4 mg resulted in improvements in proportions of total body fat (ETD: -3.29 %-points, 95% CI -4.94 to -1.65), lean body mass (ETD: 2.94 %-points, 95% CI 1.40 to 4.49), and regional visceral fat mass (ETD: -1.98 %-points, 95% CI -3.69; -0.27) (**Figure 50**).

These results suggest that most of the total weight loss was attributable to a reduction in fat tissue, including regional visceral fat.

Figure 50 Body composition (kg and %) change from baseline to week 68 – bar plot – treatment policy estimand – DEXA sub-population



ETD: Estimated treatment difference, CI: Confidence interval, DEXA: Dual energy x-ray absorpmetry.
Analysis of data from in-trial period.

nn9536/nn9536-4373/ctr_20200811_er
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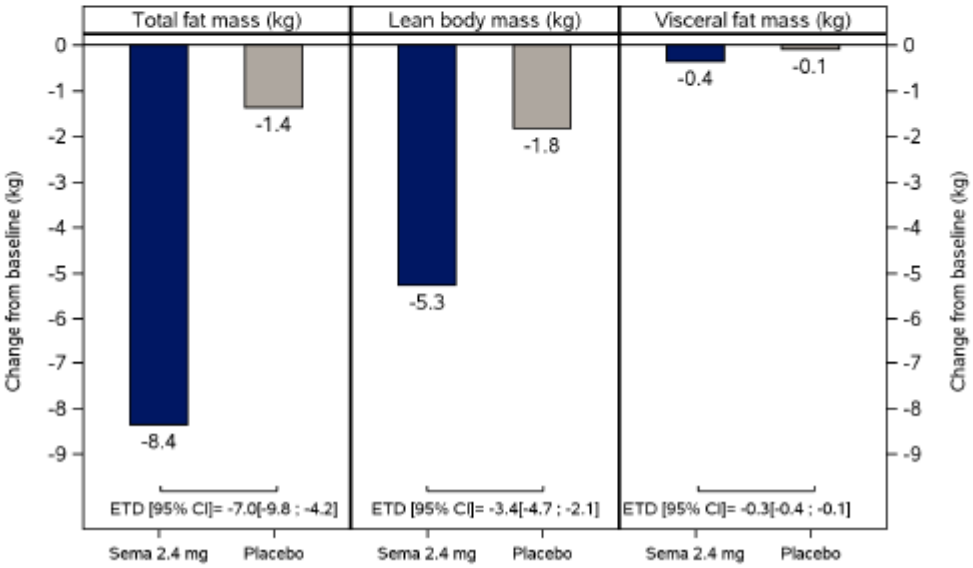


ETD: Estimated treatment difference, CI: Confidence interval, DEXA: Dual energy x-ray absorpmetry.
Analysis of data from in-trial period.

Anti-semaglutide antibodies

Overall, the low immunogenicity observed with semaglutide s.c. 2.4 mg is consistent with that reported for semaglutide s.c. 1 mg for T2D (Ozempic) and other GLP-1 analogues with high homology to the human GLP-1 amino acid backbone.

In STEP 1 and STEP 2, the proportion of subjects that tested positive for anti-semaglutide antibodies at any time point post-baseline was low (50 subjects, 2.9% of subjects randomised to semaglutide 2.4 mg). The antibodies levels were low for all weeks; with mean levels ranging from 2.01−4.93 %B/T and median titres of either 15 or 30. Antibodies cross-reacting with endogenous GLP-1 were detected in 28 subjects

(corresponding to 1.6% of all subjects randomised to semaglutide 2.4 mg). No subjects had anti-semaglutide antibodies with *in vitro* neutralising effect against semaglutide or endogenous GLP-1.

Of the 50 subjects with a treatment-induced antibody response, 21 subjects had a transient antibody response, and of these, 20 subjects had anti-semaglutide antibodies at a single visit during treatment only. For the remaining 29 subjects with a treatment-induced antibody response, a persistent response was observed with anti-semaglutide antibodies at several visits during the trial (with at least 16 weeks in between) and/or antibodies at the follow-up visit. Of these 29 subjects with a persistent response, 19 subjects were positive for anti-semaglutide antibodies at the follow-up visit, and of these, 5 subjects were positive at the follow-up visit only.

Pre-existing antibodies at baseline occurred in 1 subject; this subject was antibody negative at all visits post-baseline, hence the antibodies were not boosted following treatment with semaglutide 2.4 mg.

The formation of anti-semaglutide antibodies did not appear to influence the semaglutide plasma concentrations, based on PK data in subjects that tested positive for anti-semaglutide antibodies.

The formation of anti-semaglutide antibodies did not appear to influence the efficacy as measured by body weight (%) change from baseline. In STEP 2, the formation of anti-semaglutide antibodies did not appear to influence the efficacy in subjects with T2D, as measured by HbA_{1c}.

Based on the reported AEs in subjects positive for anti-semaglutide antibodies, there was no indication that the formation of anti-semaglutide antibodies impacted the safety profile of semaglutide 2.4 mg.

However, some differences have been observed on weight loss and allergic reactions between patients with and without antibodies. This will be discussed below in Section 3.3.8. 'Clinical safety, immunological events'.

2.6.6. Discussion on clinical efficacy

Dose response studies

The phase 2 trial 4153 investigated 5 once-daily doses of semaglutide (0.05 mg, 0.1 mg, 0.2 mg. 0.3 mg, and 0.4 mg) with dose escalation every fourth week and a steady-state reached before increasing the dose. As expected, with an increase of the dosage, a larger proportion of subjects reported gastrointestinal AEs. A once-weekly dose was chosen for phase 3 that was not expected to exceed the plasma semaglutide concentrations achieved with once-daily 0.4 mg semaglutide.

Design and conduct of clinical studies

Four phase 3a trials (STEP 1–4) have been performed to investigate the efficacy of semaglutide 2.4 mg for weight management. STEP 1, 3 and 4 are performed in obese individuals without T2D or in overweight patients with the presence of at least one weight related comorbidity, but without T2D. STEP 2 was performed in overweight or obese patients with T2D. The key in- and exclusion criteria are acceptable, as they are in line with the proposed indication in Section 4.1 of the SmPC.

In the 4 pivotal trials 388 out of 4182 subjects were between 65 and 74 years of age, and 36 patients were 75 years of age or older. The limited evidence in patients older than 75 years of age is reflected in the SmPC. In STEP 2 (subjects with type 2 diabetes), HbA_{1c} should be within 7-10%. Concomitant treatment with insulin was not allowed in the STEP 2 study.

The four STEP trials all include a 68 weeks treatment period with a fixed titration period in the first 16 weeks and a follow-up period for 7 weeks. The randomisation for the treatment arm vs. placebo was 2:1, except for STEP 2. In STEP 2 (in T2D patients), an additional treatment arm was included with the dosage of 1.0 mg once weekly, which is currently an indicated dosage for the treatment of diabetes. Randomisation in this study was 1:1:1.

These are well-designed studies, and the treatment duration period is considered sufficient to assess the effect on the primary outcome. The follow-up period of 7 weeks after treatment discontinuation is considered short, but as STEP 4 is designed to investigate the maintenance of effect on weight, this is not considered a large issue in the design.

The primary endpoints were in accordance with regulatory guidance (Guideline on clinical evaluation of medicinal products used in weight management (2016 EMA/CHMP/311805/2014)). Also, the confirmatory secondary endpoint on weight related outcomes (HbA1c and SBP) are in line with the guideline and in addition, reported patient-related outcomes were defined as confirmatory secondary endpoints. The treatment effect of semaglutide is much larger than of products currently on the market and exceeds the presumptions of the Guideline.

The randomisation procedure and blinding procedure for all studies are acceptable. The sample size of the studies is based on reaching sufficient power to support safety and, given the assumptions, provides 86 to 99% power for the primary and secondary efficacy endpoints, which can be considered overpowered for efficacy.

The primary analysis was based on a treatment-policy estimand with appropriate choices for handling intercurrent events, using data after non-adherence or initiation of other anti-obesity treatments. This is a conservative approach and acceptable. As secondary, a hypothetical estimand was used, ignoring data after non-adherence or initiation of anti-obesity treatment, which will provide supportive evidence of the treatment effect as if all patients adhered and did not need initiation of other therapy. The Applicant has proposed the inclusion of these data in the label (in footnotes in section 5.1), although these data were not included in the testing hierarchy (SmPC).

The analysis sets chosen and the observation periods correspond with the chosen estimands and are considered acceptable.

The analysis of the primary and key secondary endpoints used ANCOVA with stratification factor as fixed effects (in STEP 2) and baseline value as covariate. Binary endpoints were analysed using logistic regression with the same factors. Both are considered standard and acceptable. The sequential testing strategy is acceptable. It allows concluding the hypotheses tested in the hierarchy at a controlled level of alpha.

Missing data was handled using a retrieved drop-out multiple imputation using data from the same treatment arm. This follows the primary estimand and is acceptable. Sensitivity analyses (jump-to-reference, LOCF, tipping point, MMRM and non-responder imputation) were defined to test the robustness of the primary analysis.

For the hypothetical estimand, analysis was performed using a mixed model for repeated measures using on-treatment data, which is acceptable for this secondary estimand and supportive for the primary analysis.

Efficacy data and additional analyses

The described conduct of the study is in line with GCP. Due to the COVID-19 pandemic, no source data verification was performed after 23th of March 2020, but a large proportion of the data was verified across

the STEP trials. As only a small percentage of the verified data was changed due to SDV or other monitoring, the non-verified data are considered reliable.

The baseline variables were overall balanced across treatment groups in each trial. However, the most important baseline variable, bodyweight, was not well balanced in STEP 2 and STEP 3. In the STEP 2 study, the difference was 0.6 kg. This is, however, considered too small to have affected the results. In STEP 3, the difference between treatment groups was 3.2 kg, with the highest mean bodyweight in the semaglutide treatment group (106.9 kg). As higher body weight is associated with lower exposure to semaglutide, the results from this study could be considered a conservative estimate and is therefore not pursued any further. Baseline mean bodyweight between studies also differed. As such, the mean body weight in subjects with type 2 diabetes (STEP 2) was 100 kg, whereas body weight in subjects without type 2 diabetes was 105-106 kg (STEP 2 and STEP 3). In the STEP 1-4 trials, treatment with semaglutide 2.4 mg consistently and significantly decreased weight during the trial period of 68 weeks compared to placebo. In STEP 1, the ETD was -12.4% body weight (95% CI -13.4% to -11.5%). In STEP 3, i.e. with IBT, a comparable observation was found (body weight ETD -10.3%, 95% CI -12.0% to -8.6%). Somewhat surprisingly, the mean weight change appears comparable between patients treated with semaglutide 2.4 mg in STEP 1 (mean -15.6% (SD +/- 10.1)) vs. STEP 3 with IBT (mean -16.5% (SD +/- 10.1)). An additional effect of IBT during treatment with semaglutide 2.4 mg based on these results could be considered modest.

The clinical relevance of the weight loss with semaglutide 2.4 mg is further supported by the evaluation of categorical response on body weight loss (i.e. > 5%, >10%, >15% (confirmatory) and >20% (exploratory) body weight loss). The results show a large percentages of responders with a clinically relevant body weight loss (> 5% body weight loss, semaglutide 2.4 mg vs placebo: STEP 1 86.4% vs 31.5%, STEP 2 68.8% vs. 28.5%, STEP 3 86.6% vs 47.6%). The effects on body weight loss with semaglutide 2.4 mg were accompanied by a loss in waist circumference. A sub-study with DEXA assessments suggests an improved body composition.

In the STEP 2 trials, i.e. in patients with T2D, the effect on body weight was less pronounced compared to the findings in STEP 1 and 3, but still statistically significant compared to placebo (ETD -6.2%, 95% CI -7.3% to -5.2%). This could be expected based on previous results in patients with T2D and treatment with GLP-1 analogues (liraglutide 3.0 mg, SCALE trial). The effect on the weight with treatment with semaglutide 2.4 mg is stronger than the currently authorised semaglutide 1.0 mg (ETD -2.65, 95% CI -3.66 to -1.64).

As described above, in the STEP 2 trial, T2D patients using insulin were excluded. Currently, Ozempic (semaglutide 1.0 mg) is registered for the treatment of diabetes, also combined with insulin treatment. To evaluate if patients with T2D and using insulin should be in- or excluded for treatment with semaglutide 2.4 mg for the indication of weight loss, the data from the SUSTAIN trials with Ozempic 1.0 mg were evaluated. In the SUSTAIN trials, semaglutide 1.0 mg has been evaluated in T2D patients without insulin (SUSTAIN 1, trial 3623) and as add-on in patients already using insulin (SUSTAIN 5, trial 3627). Weight at baseline is comparable in both trials (baseline weight total group SUSTAIN 1: 91.9 kg, SUSTAIN 5: 91.7 kg). The effect on weight of semaglutide 1.0 mg vs. placebo in these trials appears similar (weight change (kg); SUSTAIN 1, semaglutide 1.0 mg -4.53 kg, placebo -0.98, ETD -3.56, 95% CI -4.74 to -2.38; SUSTAIN 5 (add-on baseline insulin use) semaglutide 1.0 mg -6.42 kg, placebo -1.36, ETD -5.06, 95% CI -6.08 to -4.04). Also HbA1c effects were similar in both trials (change HbA1c (%) SUSTAIN 1: -1.53, 95%CI -1.81 to -1.25, SUSTAIN 5: ETD -1.75, 95%CI -2.01 to -1.50). Although there is no data in T2D patients using insulin and using add-on semaglutide 2.4 mg, it is considered plausible, based on the data with semaglutide 1.0 mg, that these patients also benefit from treatment with semaglutide 2.4 mg.

Subjects who discontinued treatment had a higher bodyweight at week 68 than those who stayed on treatment, which was seen in the semaglutide group as well in the placebo group, which is not surprising. In STEP 1 and 3 there was steep increase in body weight among those who discontinued, but the body weight was still lower than the placebo group. In STEP 4, patients that switched after 20 weeks of semaglutide 2.4 mg to placebo regained weight as expected. However, 48 weeks later, a mean body weight reduction of 5.02% was still present compared to baseline. These findings do not suggest that there is a rebound effect with a risk of gaining weight compared to baseline, after stopping semaglutide 2.4 mg.

The STEP 2 trial shows an improvement in glycaemic control in T2D patients using semaglutide 2.4 mg vs placebo, with an ETD of HbA1c (%) -1.23% (95% CI -1.42 to -1.05). This difference is comparable to the HbA1c effect of the currently registered semaglutide 1.0% (HbA1c semaglutide 2.4 mg vs 1.0 mg ETD -0.2, 95% CI -0.3 to 0.0). Therefore, it could be suggested that for T2D patients, there is mainly an additional benefit using semaglutide 2.4 mg for improvement in weight management, but not on glycaemic control. Evaluating the proportion of clinically relevant HbA1c changes, the proportion of patients that reached the target of HbA1c <7% was larger in the semaglutide group (78.5%) vs placebo (26.5%). As treatment with oral glucose lowering agents or insulin could be changed during the trial period, this could affect the interpretation of these results. The patients that started insulin differed between the treatment groups (2 subjects (0.5%) in the semaglutide 2.4 mg group, 5 subjects (1.2%) in the semaglutide 1.0 mg group and 18 subjects (4.5%) in the placebo group). Also the proportion of patients that decreased OAD (semaglutide 2.4 mg 27.1% and semaglutide 1.0 mg 24.0% compared to placebo 6.8%) or increased OAD (semaglutide 2.4 mg 4.6% and semaglutide 1.0 mg 4.9% compared to placebo 23.0%). However, the difference between semaglutide 2.4 mg and 1.0 mg is modest.

In the patients without diabetes (i.e. STEP 1 and 3), improvement of glycaemic control was noted during semaglutide 2.4 mg. The clinical relevance of the small effects on HbA1c and FPG is doubtful. However, some patients with pre-diabetes improved to normoglycaemia (semaglutide 2.4 mg vs placebo: STEP 1 84.1% vs 47.8%, STEP 3 89.5% vs 55%), which is considered relevant.

Treatment with semaglutide 2.4 mg also decreased SBP (confirmatory) and DBP (exploratory) in STEP 1-3 studies. Again, this effect was less pronounced for T2D patients in the STEP 2 trial and there was no effect on diastolic blood pressure in subjects with type 2 diabetes. Also, the effect on lipids (exploratory) was found across the trials, but there were some discrepancies. In subjects with type 2 diabetes, the effect was smaller compared to subjects without type 2 diabetes and there was no effect on LDL cholesterol in subjects with type 2 diabetes. This could partly be explained by a large number of subjects using lipid lowering medication in the STEP 2 trial, i.e. 60%, as could be expected from a population with T2D. This may hamper an additional measurable effect on LDL by semaglutide. The baseline level of LDL was also lower in the STEP 2 trial (baseline mean LDL 2.3) compared to STEP 1 (baseline mean LDL 2.9). It is questionable if the difference in lipid lowering medication explains all the differences between the effect in subjects with and without T2D. However, for the other lipid levels (i.e. triglyceride, FFA, VLDL and HDL) a beneficial effect was observed in the STEP 2 trial with semaglutide 2.4 mg. In the STEP 3 study and STEP 4 study there was no effect on HDL cholesterol. The finding in the STEP 3 trial could be explained by the smaller treatment effect of semaglutide in the STEP 3 trial on HDL by the additional effect of IBT observed in both treatment groups. This may influence the interpretation of the treatment results compared to STEP 1. However, the effect of IBT (comparing the data on lipid profile of STEP 1 and 3) is less for the other lipid levels. Although heterogeneity was observed in the results on serum lipids, in general a positive effect on serum lipids was observed.

With regards to plasminogen activator inhibitor-1 (PAI-1), some unexpected findings were present. The Applicant has explained that the PAI-1 activity was analysed on a central laboratory, and that the routine

biochemistry analyses were analysed at other central accredited laboratories. The analysis of PAI-1 was for research only, whereas the other laboratories for the routine measures had standardised and strict quality control measures. Therefore, the unexpected findings on PAI-1 do not question the reliability of the other laboratory measures.

The clinical relevance of the PRO's was discussed in the Scientific advice. The PRO's of the SF-36 PF and IWQOL-Lite-CT PF score were analysed as confirmatory secondary endpoints (change from baseline). The additional SF-36 and IWQOL-Lite-CT scores were supportive endpoints. The effect of semaglutide 2.4 mg vs. placebo on both PRO's was more and statistically significant in STEP 1 (SF-36 PF ETD 1.80, 95% CI 1.18 to 2.42; IWQOL-Lite-CT PF ETD 9.43, 95% CI 7.50 to 11.35) and STEP 2 (SF-36 PF ETD 1.52, 95% CI 0.44 to 2.61; IWQOL-Lite-CT PF ETD 4.83, 95% CI 1.79 to 7.86). The treatment differences are consistent and statistically significant, but appear small and the clinical relevance of these ETDs are not demonstrated. A greater proportion of subjects achieving clinically meaningful improvements in physical functioning were seen for both PRO's in STEP 1 and 2. However, these results were supportive secondary endpoints and do not demonstrate a clinically relevant finding.

The Applicant performed additional sub-group analyses. The Applicant describes that apart from sex (STEP 1, 2, 4) and baseline body weight (STEP 1 and STEP 4), the efficacy response to semaglutide 2.4 mg was consistent across sub-populations. In STEP 1 and 2, female subjects lost on average more weight compared with male subjects (semaglutide 2.4 mg vs placebo, STEP 1 male ETD -8.02, 95% CI -9.79 to -6.35, female ETD -14.00, 95% CI -15.06 to -12.94; STEP 2 male ETD -4.63, 95% CI -6.11 to -3.15, female ETD -7.48, 95% CI -9.06 to -5.09). As described above and especially in STEP 1, the number of female patients was considerably larger than males, which could drive the mean overall results. Additional analyses showed that the weight loss increased in an exposure-dependent manner within both males and females. Within both STEP 1 and 2 trials, the weight loss at a given exposure level appears larger in females than males. These analyses suggested that exposure differences cannot explain all differences between genders and that a difference in baseline weight between male and female subjects does not explain the treatment difference.

The effects of gender were, however, not observed in the STEP 3 trial, were treatment with semaglutide 2.4 mg vs placebo was evaluated combined with IBT. The Applicant explains this lack of observed gender difference in weight partly by the small sample size and by consequence a large confidence interval. Nevertheless, the point estimate in female subjects on weight changes was lower compared to male subjects (weight change (%) semaglutide 2.4 mg vs placebo STEP 3; primary analysis -10.27, 95%CI -11.97 to -8.57; female -10.12, 95%CI -11.95 to -8.29; male -11.07, 95%CI -15.62 to -6.53). Differences in adherence to the intensive lifestyle intervention may partly explain these results. Although uncertainties remain regarding the mechanism and consistency on gender differences on the effect of semaglutide 2.4 mg treatment for weight loss, in both genders a clinically relevant weight loss is observed.

A reduced treatment effect based on baseline body weight was mainly present in the group of patients with a body weight > 115kg (body weight change in % STEP 1 overall ETD -14.74, 95% CI -16.00 to -13.50, baseline body weight > 115kg overall ETD -7.87, 95% CI -10.73 tot -5.0). It could therefore be anticipated that there will be an overall lower % body weight change in patients with an initial high body weight vs low body weight, who initiates treatment with semaglutide 2.4 mg. However, as the effect remains significant and clinically relevant, this is not considered a large issue.

The treatment effect in subjects with type 2 diabetes (STEP 2) was markedly lower than in subjects without type 2 diabetes (STEP 1 and STEP 3). Based on data from the Saxenda clinical development programme and published literature on weight loss in patients with T2D, it was expected to see a lower treatment effect in subjects with T2D (STEP 2) than in subjects without T2D (STEP 1, 3 and 4). The physiological explanation

with regards to the counteracting insulinotropic effect can to some extend supports the difference in weight loss. The glucosuria theory supports that weight loss attenuates when the patient goes from being hyperglycaemic to normoglycaemic. Even though the weight loss is lower in subjects with T2D, the placebo-controlled weight loss is considered clinically relevant.

It could be speculated that the known gastro-intestinal side effects are largely contributing to the effect on weight loss. Especially considering the large proportion of patients with gastrointestinal AEs. However, the additional analysis dividing patients with and without gastrointestinal AEs, only a modest difference of approximately 1% between the groups in weight change is observed. This does not appear to be an explanation for the observed weight loss during semaglutide treatment.

In all 4 studies, the maintenance dose of 2.4 was tested and compared with placebo. The dose was escalated every 4th week, and at week 16, the maintenance dose was reached. If the subjects did not tolerate the target dose of 2.4 mg, the dose was decreased to 1.7 mg. There is insufficient evidence to support a lower maintenance dose. Treatment should therefore be discontinued if the maintenance dose 2.4 mg is not tolerated. The Applicant has provided weight loss data on those subjects which were persistently treated with a lower dose of semaglutide than 2.4 mg from week 52 to 68. In those 70 subjects, the weight loss was 19%. The Applicant also provided body weight data on subjects who lowered the dose or who did never reach the final dose of 2.4 mg. Despite a temporarily or permanently lower dose in these subjects, a clinically relevant weight loss was seen in these subjects in STEP 1, STEP 2, and STEP 3.

To evaluate the application of a 'stopping rule', as described in the Guideline (Guideline on clinical evaluation of medicinal products used in weight management (2016 EMA/CHMP/311805/2014)), the Applicant provided analyses for the predictive value of non-responders (responders defined as at least 5% body weight loss at 20 weeks of treatment) with semaglutide 2.4% on clinically relevant weight loss (>5%) after 68 weeks in the STEP 4 trial and in additional analyses in STEP 1 and 2 trial. In the STEP 4 trial, the majority of subjects (719 of 803 subjects, 89.5%) had achieved a weight loss ≥5% at week 20. Approximately half of the subjects who were week 20 (5%) non-responders with semaglutide still achieved a ≥5% weight reduction after a further 48 weeks of treatment with semaglutide 2.4 mg (estimated percentage of week 68 [5%] responders: 51.95%), while only few of the week 20 (5%) non-responders who switched to placebo at week 20 became week 68 (5%) responders (estimated percentage: 11.36%). The Applicant proposes not to include a stopping rule in the SmPC. Using a stopping rule at week 28 will exclude patients from relevant treatment, as among early non-responders the proportion of patients achieving a weight loss at week 68 was substantial (40.5% and 31.9%). However, even without a stopping rule, regular evaluation concerning treatment discontinuation is needed and this is considered to fall within the regular clinical practice.

In STEP 1 adherence to diet registration and increased physical activity were assessed. Adherence to diet registration and increased physical activity during the trial was higher in the semaglutide group compared with placebo. The Applicant discussed that the dietary registration might be explained by the lower appetite and weight loos, as subjects with the lower appetite are more motivated to record their diet than subjects who cannot control their diet. The weight loss could also lead to higher motivation of physical activity. The difference in physical activity at the end of the trial was 60 minutes per week, and even though this is a substantial difference, it is not likely that the weight loss is caused by this difference.

In STEP 1 a sub-study that included DEXA scans were conducted. The study showed a statistically significant reduction in total fat mass of -7.0 kg (95% CI: -9.8; -4.2) and in visceral fat mass of -0.3 kg (95% CI: -0.4; -0.1). Lean body weight also decreased more with semaglutide than with placebo, but relative to total body weight, lean body weight increased. These results underline that the weight loss with semaglutide 2.4 mg is

mainly due to loss of fat mass, which is acknowledged. The loss of lean body weight is a usual phenomenon during a weight loss programme.

2.6.7. Conclusions on the clinical efficacy

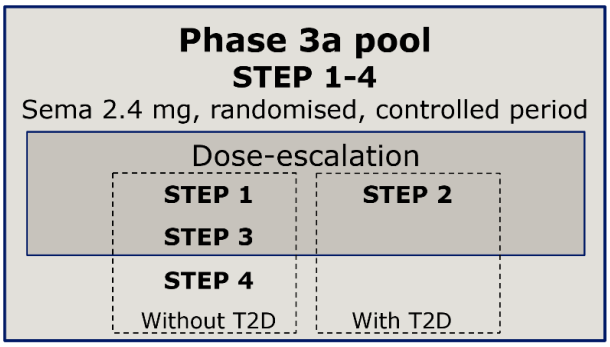
The STEP 1 and 3 trials showed convincingly that semaglutide 2.4 mg induces clinically relevant body weight loss in obese patients with or without IBT. In STEP 2 the effect in subjects with type 2 diabetes was lower than the effect seen in subjects without type 2 diabetes. Also in male vs. female subjects the effect on body weight was lower and in patients with a higher body weight (> 115kg) at baseline. However, in all groups the achieved weight loss is considered clinically relevant.

2.6.8. Clinical safety

The four phase 3a trials (referred to as STEP 1−4) serve as the primary foundation for evaluating the safety of semaglutide 2.4 mg, as these trials investigated the intended target population, had a similar treatment duration, investigated once-weekly dosing of semaglutide 2.4 mg and contribute with the majority of the total exposure to semaglutide 2.4 mg. Safety data from the phase 2 dose-finding trial contribute to the dose-response evaluation.

Figure 51 provides an overview of the pool, groups and trials used to evaluate the different safety topics and populations. The pooling strategy was agreed.

Figure 51 Overview of the pool, groups and trials evaluating different safety topics or different populations



T2D: type 2 diabetes. STEP 2: Safety evaluations include assessments of both the 2.4 mg dose and the 1.0 mg dose (only evaluated for safety areas specific to a T2D population, i.e. retinal disorders and hypoglycaemic episodes).

2.6.8.1. Patient exposure

The phase 3a pool comprises STEP 1–4 and includes the semaglutide 2.4 mg groups (the intended maintenance dose) and the placebo groups and uses the randomised, placebo-controlled period of the trials. The 20-week run-in period of STEP 4 is omitted since this period is not placebo-controlled. The phase 3a pool represents the majority of the total exposure, with 2650 subjects exposed to semaglutide 2.4 mg and 1529 to placebo.

The phase 3a dose-escalation group comprises STEP 1–3, but excludes STEP 4, as the randomised, placebo-controlled period of this trial did not include dose-escalation, which had taken place during the uncontrolled, 20-week run-in period. The phase 3a dose-escalation group was used for the evaluation of gastrointestinal AEs, which are most frequent during the dose-escalation phase. The phase 3a *with* T2D trial (STEP 2) was used for the safety evaluation, specifically in subjects with T2D (including evaluation of hypoglycaemic episodes and retinal disorders). The phase 3a *without* T2D group comprised STEP 1, 3 and 4 and was used to evaluate hypoglycaemia in subjects without T2D and the impact of glycaemic status (normo-glycaemic or pre-diabetes). The evaluation of dose-response on safety was based on STEP 2 (semaglutide 1.0 and 2.4 mg once weekly) and the phase 2 dose-finding trial 4153 (semaglutide 0.05, 0.1, 0.2, 0.3 and 0.4 mg once daily).

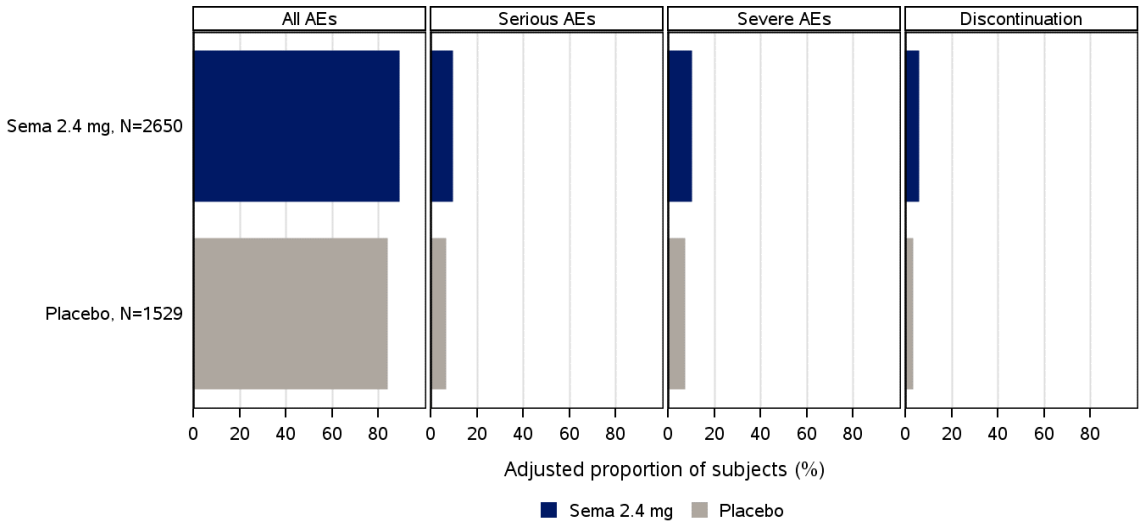
The treatment groups were generally well-balanced with regards to demographics, baseline characteristics, medical history, concomitant illnesses and concomitant medication at baseline and where differences were present, these could be explained by a lower proportion of subjects with T2D in the semaglutide 2.4 mg group compared to the placebo group, due to differences in randomisation ratio between STEP 2 (1:1) and the other STEP trials (2:1).

The subject disposition was similar in the two treatment groups, with the exception of less subjects that permanently discontinued trial product with semaglutide 2.4 mg than with placebo and more subjects that permanently discontinued trial product due to AEs with semaglutide 2.4 mg than with placebo (driven by gastrointestinal AEs).

2.6.8.2. Adverse events

The proportions of subjects with AEs, SAEs and severe AEs were slightly larger with semaglutide 2.4 mg compared to placebo in the phase 3a pool (**Figure 52**).

Figure 52 Adverse events overview – on treatment – phase 3a pool



Phase 3a pool: STEP 1-4 data from subjects randomised to Sema 2.4 mg or Placebo during the controlled periods of the trials.
Adverse events with onset prior to randomisation are not included.
AE: Adverse event
Discontinuation: Adverse events leading to permanent treatment discontinuation.
The % is adjusted using the Cochran-Mantel-Haenszel method to account for differences between trials.

Most of the AEs were non-serious and mild or moderate, and most subjects had recovered by the end of the trials. The proportion of subjects with AEs leading to permanent treatment discontinuation was low in both treatment groups but larger with semaglutide 2.4 mg than with placebo (5.7% vs 3.0%), driven by gastrointestinal AEs.

Regardless of treatment group, the reporting of the first event mainly occurred during the first 20 weeks of treatment, i.e. during the dose-escalation period. However, the time to first event was shorter with semaglutide 2.4 mg than with placebo with approximately 50% of subjects reporting their first event during the first 5 weeks, a pattern that was again driven by gastrointestinal disorders.

AEs were reported by a comparable proportion of subjects with semaglutide 2.4 mg and placebo within all SOCs, except for gastrointestinal disorders and nervous system disorders (**Figure 53**). A difference between semaglutide 2.4 mg and placebo was also seen for the 2 SOCs: general disorders and administration site conditions and skin and subcutaneous tissue disorders.

As expected for a drug within the GLP-1 RA drug class, Gastrointestinal disorders were the most frequent types of reported AEs, and these events were reported more often with semaglutide 2.4 mg compared to placebo. The following PTs were reported by ≥5% of subjects and more often with semaglutide 2.4 mg compared to placebo: Nausea (38.3% vs 14.0%), Diarrhoea (26.8% vs 14.3%), Constipation (21.8% vs 10.2%), Vomiting (21.8% vs 5.7%), Abdominal pain (8.4% vs 4.0%), Dyspepsia (7.6% vs 2.7%), Abdominal pain upper (7.1% vs 3.6%), Eructation (6.5% vs 0.4%), Abdominal distension (6.3% vs 4.3%) and Flatulence (5.3% vs 3.7%). (see **Figure 54**).

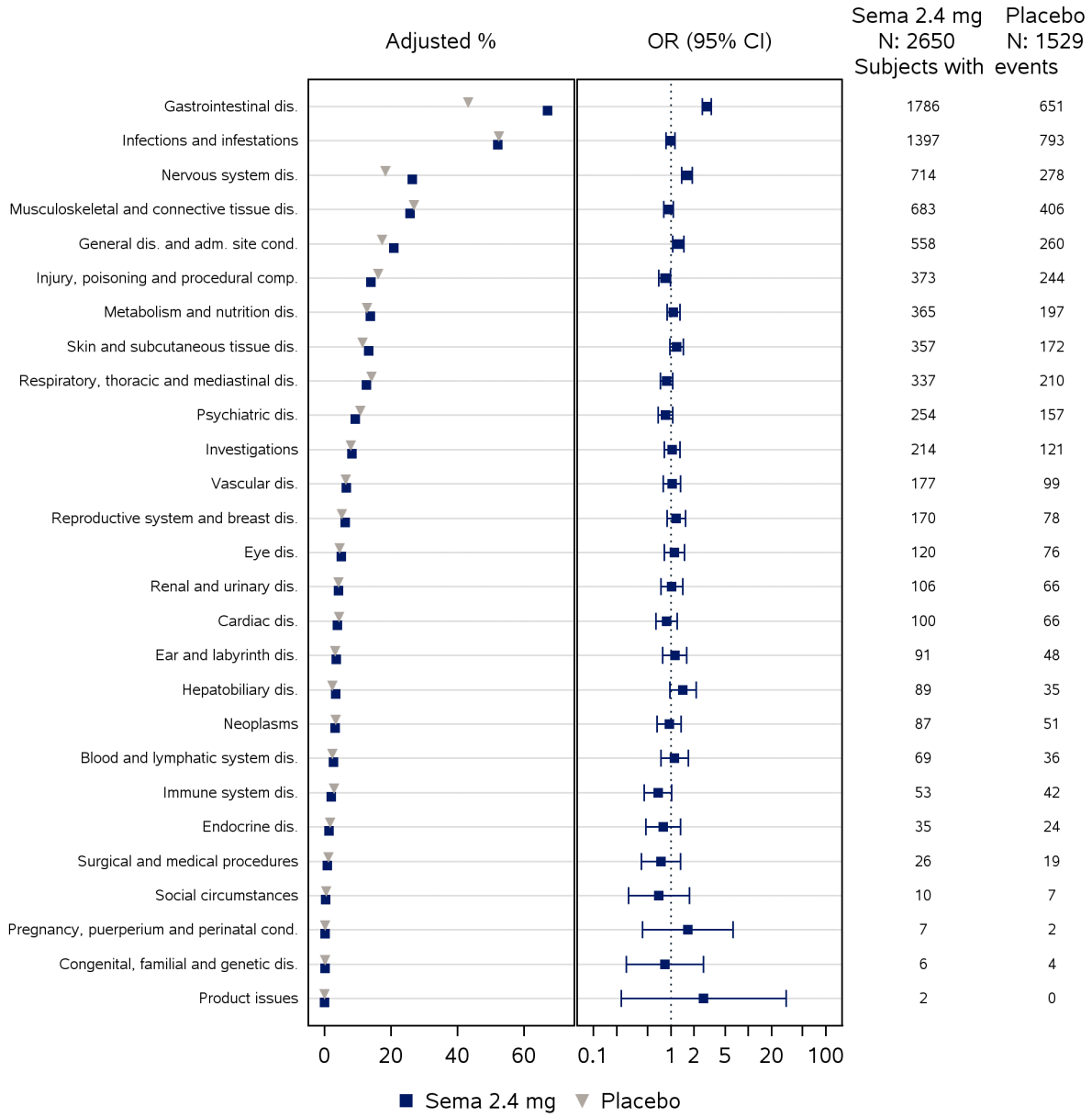
A larger proportion of subjects with semaglutide 2.4 mg compared to placebo reported events within the SOC Nervous system disorders. This difference was driven by the PTs Headache (12.8% vs 8.7%) and Dizziness (6.8% vs 3.3%) that were reported for more than 5% of subjects. There was 1 SAE of Headache, and there were 3 subjects who permanently discontinued treatment with trial product due to Headache. There was 1 SAE of Dizziness with semaglutide 2.4 mg assessed as severe, the subject recovered from the event. 2 subjects permanently discontinued treatment with the trial product due to Dizziness.

General disorders and administration site conditions showed a small difference with more AEs in subjects treated with semaglutide 2.4 mg compared to placebo; this difference was mainly driven by the PT Fatigue (7.9% vs 3.6%). Using the grouped term for Fatigue, the proportion of subjects with semaglutide 2.4 mg vs placebo was 10.6% vs 5.1% in the phase 3a dose-escalation group.

The PT Decreased appetite belonging to the SOC Metabolism and nutrition disorders was reported by ≥5% of subjects, and these events occurred more often with semaglutide 2.4 mg compared to placebo (7.8% vs 2.8%).

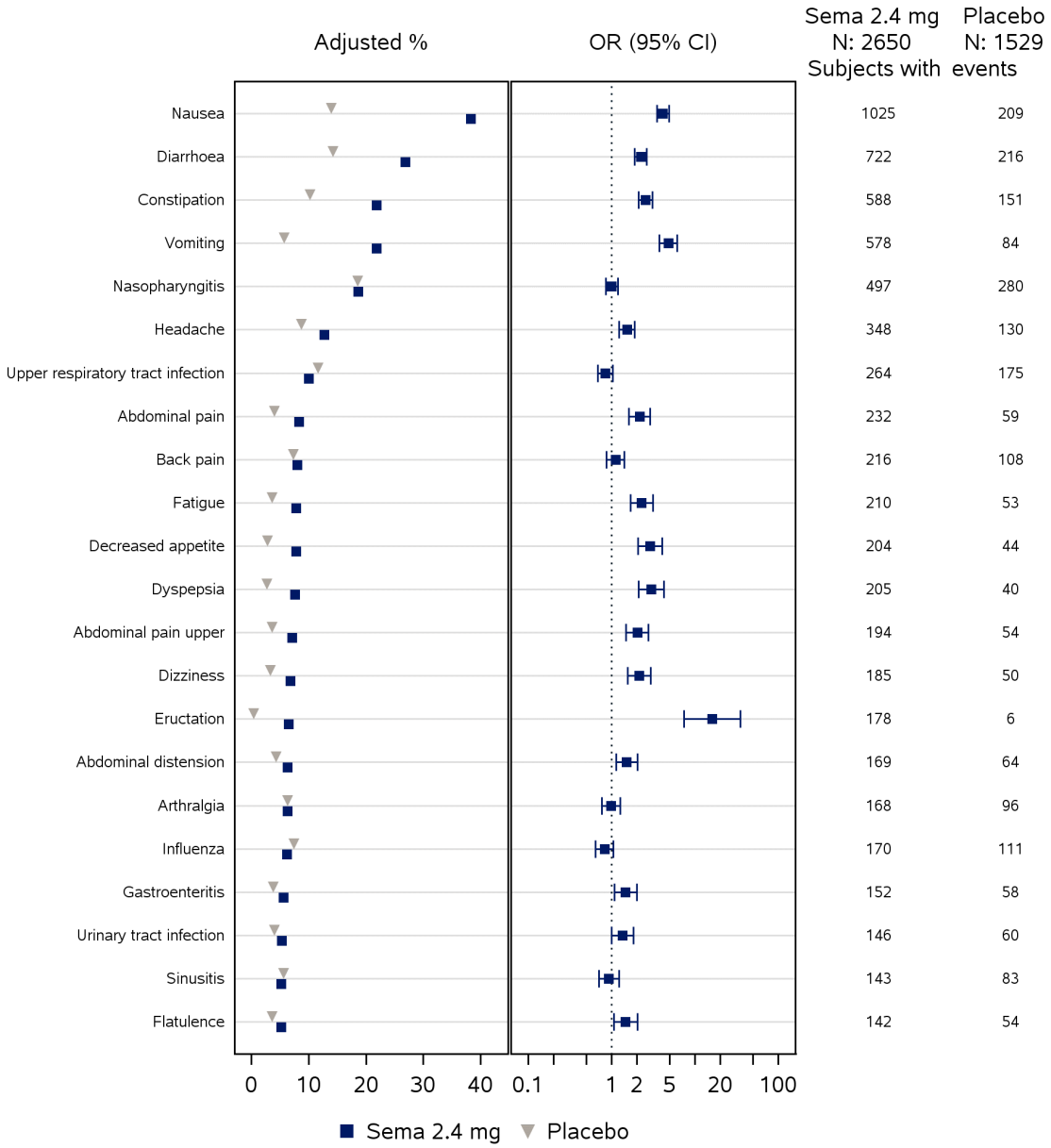
Less common PTs reported more frequently with semaglutide 2.4 mg than with placebo (by ≥2 to <5% of subjects) were overall well-known side effects of the GLP-1 RA class, with the only addition being alopecia. A higher proportion of subjects with semaglutide 2.4 mg than placebo in the phase 3a pool (3.3% vs 1.4%) reported AEs for the PT Alopecia that belongs to the SOC Skin subcutaneous tissue disorders. There were 3 events with semaglutide 2.4 mg and 1 event with placebo leading to permanent treatment discontinuation.

Figure 53 Adverse events by system organ class – on-treatment – phase 3a pool



Phase 3a pool: STEP 1-4 data from subjects randomised to Sema 2.4 mg or Placebo during the controlled periods of the trials.
Adverse events with onset prior to randomisation are not included.
Sorted in descending order by system organ class based on the proportion of subjects in the Sema 2.4 mg arm experiencing at least one event.
%: Percentage of subjects experiencing at least one event, OR: Odds ratio, CI: Confidence interval, N: Number of subjects, dis.: disorders, cond.: conditions, adm.: administration, comp.: complications. Neoplasms include benign, malignant and unspecified (incl cysts and polyps)
The % is adjusted using the Cochran-Mantel-Haenszel method to account for differences between trials.
Each of the groupings of adverse events were analysed using a binary logistic regression model with randomised treatment and trial as factors.
Subjects are considered on-treatment if any dose of trial product has been administered within the prior 49 days.
MedDRA version 22.1

Figure 54 Adverse events by PT – most frequent (>=5%) – forest plot – on-treatment – phase 3a pool



Phase 3a pool: STEP 1-4 data from subjects randomised to Sema 2.4 mg or Placebo during the controlled periods of the trials.
Adverse events with onset prior to randomisation are not included.
Preferred terms are included if the frequency of events is greater than or equal to 5% in any of the treatment arms.
Sorted in descending order by preferred term based on the proportion of subjects in the Sema 2.4 mg arm experiencing at least one event.
%: Percentage of subjects experiencing at least one event, OR: Odds ratio, CI: Confidence interval, N: Number of subjects
The % is adjusted using the Cochran-Mantel-Haenszel method to account for differences between trials.
Each of the groupings of adverse events were analysed using a binary logistic regression model with randomised treatment and trial as factors.
Subjects are considered on-treatment if any dose of trial product has been administered within the prior 49 days.
MedDRA version 22.1

2.6.8.3. Serious adverse event/deaths/other significant events

Deaths

A total of 8 deaths were reported in the completed clinical trials: 7 deaths in the STEP trials and 1 death in the phase 2 dose-finding trial (trial 4153). There were no deaths in the clinical pharmacology trials. All reported deaths were among subjects who had been exposed to trial product and occurred between randomisation and until DBL in the individual trials.

Based on the phase 3a pool (which covered 6 of the 8 reported deaths), there was no difference between semaglutide 2.4 mg and placebo in the proportion of subjects who died (3 subjects [0.1%] in the semaglutide 2.4 mg group and 3 subjects [0.2%] in the placebo group). The 3 deaths in the semaglutide 2.4 mg group were classified as cardiovascular deaths, which included one death where the cause of death was undetermined. The 3 deaths in the placebo group were all classified as death due to malignancy. The last 2 reported deaths included: 1 death in the semaglutide 1.0 mg group in STEP 2, which was classified as an undetermined cause of death, and 1 death in the semaglutide 0.4 mg once-daily fast escalation group in trial 4153, which was classified as due to malignancy.

Other serious events

The proportion of subjects with SAEs was larger with semaglutide 2.4 mg (9.3%) than with placebo (6.4%), driven by gallbladder disorders and gastrointestinal AEs.

The majority of subjects were reported to have recovered from their SAEs. The proportions of subjects with SAEs reported as not recovered, recovered with sequelae, and deaths were comparable between semaglutide 2.4 mg and placebo. About half of the events were severe with both semaglutide 2.4 mg and placebo. For the majority of the events, the investigator-assessed the relationship to the trial product as unlikely.

The proportion of subjects with SAEs (**Table 41**) leading to permanent treatment discontinuation was comparable with semaglutide 2.4 mg (1.0%) and placebo (0.8%).

Table 41 SAEs – overview – on-treatment – phase 3a pool

	Sema 2.4 mg				Placebo			
	N	(Adj.%)	E	Adj.R	N	(Adj.%)	E	Adj.R
Number of subjects	2650				1529			
Patient years of exposure (PYE)	3309.5				1885.4			
SAEs	246	(9.3)	341	10.5	100	(6.4)	132	6.8
Fatal	2	(<0.1)	2	<0.1	3	(0.2)	3	0.2
Leading to Permanent treatment discontinuation	26	(1.0)	31	0.9	13	(0.8)	14	0.8

N: Number of subjects experiencing at least one event, %: Percentage of subjects experiencing at least one event, E: Number of events, R: Event rate per 100 patient-years of exposure, Adj.: Adjusted
Phase 3a pool: STEP 1-4 data from subjects randomised to Sema 2.4 mg or Placebo during the controlled periods of the trials. Adverse events with onset prior to randomisation are not included. The % and R are adjusted using the Cochran-Mantel-Haenszel method to account for differences between trials. Subjects are considered on-treatment if any dose of trial product has been administered within the prior 49 days.

Adverse events leading to permanent or temporary treatment discontinuation

Overall, the proportion of subjects with AEs leading to permanent treatment discontinuation was higher with semaglutide 2.4 mg than with placebo (5.7% vs 3.0%), driven by gastrointestinal disorders, mainly the PTs: nausea, vomiting, diarrhoea, abdominal pain upper, and constipation.

Evaluations relevant to dosing

Dose-dependency was evaluated for STEP 2 (semaglutide 1.0 mg and 2.4 mg) and focused on areas for which treatment differences disfavouring semaglutide 2.4 mg vs placebo had been observed in the phase 3a pool, including single PTs (gastroenteritis, headache, dizziness, fatigue, decreased appetite and alopecia), gastrointestinal disorders, gallbladder-related disorders, hypoglycaemic episodes, retinal disorders, lipase and amylase, and pulse. The evaluation was supplemented with exposure-response analyses for gastrointestinal AEs based on STEP 1 and 2.

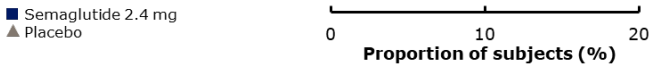
Dose-response was observed for gastrointestinal AEs (mainly nausea, diarrhoea, vomiting constipation and eructation). A dose-response was also seen for AEs of fatigue and decreased appetite. The results for STEP 2 were overall consistent with the observations from the phase 2 dose-finding trial.

Safety focus areas

An overview of the results for the safety focus areas is provided in **Figure 55.**

Figure 55 Safety focus areas excluding gastrointestinal disorders

Safety focus areas	Semaglutide 2.4 mg				Placebo			
	N	%	E	R	N	%	E	R
Phase 3a pool	**Total N: 2650 PYE: 3309 ; PYO: 3557**				**Total N: 1529 PYE: 1885 ; PYO: 2049**			
Psychiatric disorders	254	9.3	341	10.0	157	10.7	210	12.1
Cardiovascular disorders*	223	8.7	288	8.3	166	10.9	218	10.9
Cardiovascular events (EAC)*	15	0.6	17	0.5	11	0.7	15	0.7
Neoplasms*	187	6.9	227	6.3	108	7.1	126	6.2
Breast neoplasms*	23	1.1	24	0.9	13	1.2	13	0.9
Skin neoplasms*	21	0.8	25	0.7	16	1.1	17	0.8
Colorectal neoplasms*	22	0.8	25	0.7	12	0.8	12	0.6
Malignant neoplasms*	28	1.1	29	0.8	17	1.1	19	0.9
Pancreatic cancer*	0	0	0	0	0	0	0	0
Allergic reactions	183	6.9	207	6.2	102	6.8	115	6.2
Injection site reactions	113	4.2	163	4.7	72	4.9	122	6.5
Gallbladder-related disorders	70	2.5	85	2.4	24	1.6	26	1.5
Hepatic disorders	60	2.3	70	2.1	42	2.7	54	2.7
Rare events	21	0.8	22	0.7	9	0.6	11	0.6
Acute renal failure	8	0.4	10	0.3	5	0.3	5	0.3
Pancreatitis	3	0.1	3	<0.1	1	<0.1	1	<0.1
Acute pancreatitis (EAC)	4	0.2	5	0.2	1	<0.1	1	<0.1
Phase 3a with T2D trial (STEP 2)	**Total N: 403; PYO: 573**				**Total N: 402; PYO: 567**			
Retinal disorders*	28	6.9	36	6.3	17	4.2	19	3.4
Hypoglycaemic episodes level 2+3	26	6.5	58	10.9	10	2.5	17	3.2
Phase 3a without T2D group	**Total N: 2247; PYE: 2776**				**Total N: 1127; PYE: 1357**			
Hypoglycaemia	13	0.6	20	0.7	8	0.7	10	0.8



%: proportion of subjects with event(s); E: number of events; EAC: event adjudication committee; N: number of subjects with event(s); PYE: patient years of exposure; PYO: patient years of observation; R: events per 100 PYE/PYO; Total N: total number of subjects in the pool, group or trial.
Safety topics assessed using the in-trial period are marked with an asterisk (*), otherwise the on-treatment period is used. Areas are presented by MedDRA search supplemented by EAC-confirmed events of Acute pancreatitis and Cardiovascular events and by Hypoglycaemic episodes level 2 or 3 (ADA 2018 classification). Breast neoplasms are evaluated based on female subject only.

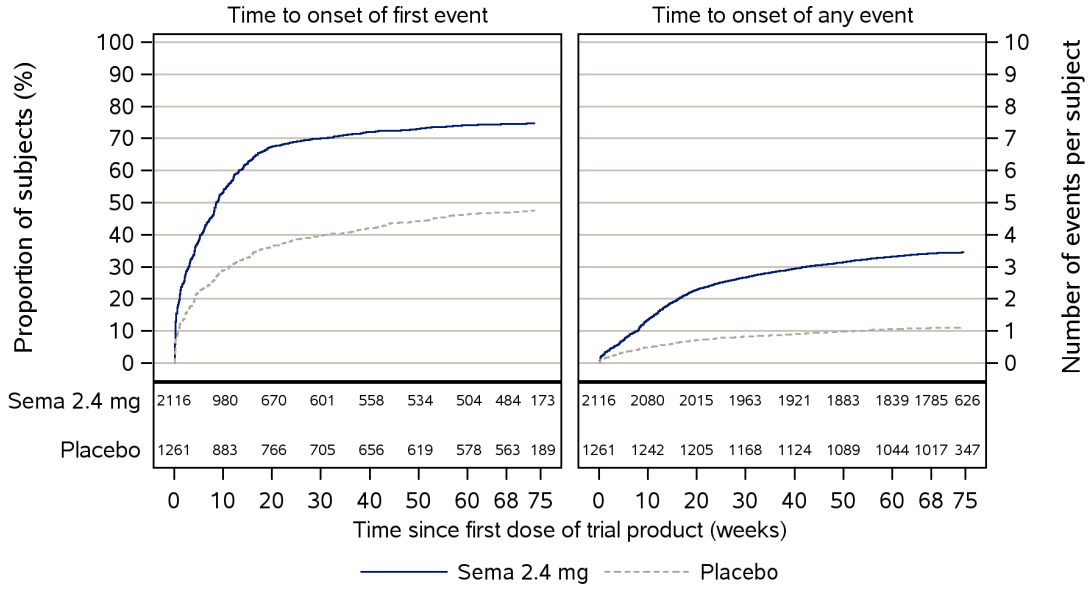
Gastrointestinal disorders

A dose-escalation regimen, with 4-week increments to reach the 2.4 mg maintenance dose, was used to mitigate the risk of gastrointestinal side effects and improve the tolerability profile.

Since the incidence of gastrointestinal AEs is highest during the dose-escalation period and decreases over time as subjects get used to treatment (or those who do not tolerate treatment have discontinued treatment), the evaluation of gastrointestinal disorders was based on the phase 3a dose-escalation group comprising STEP 1–3.

Based on the dose-escalation group, gastrointestinal AEs were reported for 72.9% of subjects on semaglutide 2.4 mg compared to 47.1% of subjects on placebo. As expected, the incidence of gastrointestinal AEs was highest during the initial 20 weeks of treatment (covering the dose-escalation period), after which it started to level off and become more on par with the level in the placebo group (**Figure 56**).

Figure 56 Gastrointestinal disorders over time – pre-defined MedDRA search – on-treatment – phase 3a dose escalation group



Phase 3a dose escalation group: STEP 1-3 data from subjects randomised to Sema 2.4 mg or Placebo during the controlled periods of the trials.
Numbers shown in the lower panel are subjects at risk.
Subjects are considered on-treatment if any dose of trial product has been administered within the prior 49 days.
MedDRA version 22.1

Gastrointestinal AEs led to permanent discontinuation of trial product in 4.3% of subjects in the semaglutide 2.4 mg group vs 0.7% in the placebo group.

The majority of events were mild or moderate in severity and had onset during the dose-escalation period. Nausea, Diarrhoea, Vomiting and Constipation were the most frequently reported gastrointestinal AEs and reported more frequently with semaglutide 2.4 mg than with placebo. The proportion of subjects reporting any Abdominal pain was higher with semaglutide 2.4 mg (19.7%) than with placebo (10.0%).

The proportion of subjects reporting any Gastritis during the randomised periods of the trials was higher with semaglutide 2.4 mg (3.6%) than with placebo (1.3%). The prevalence of any Gastritis increased until week

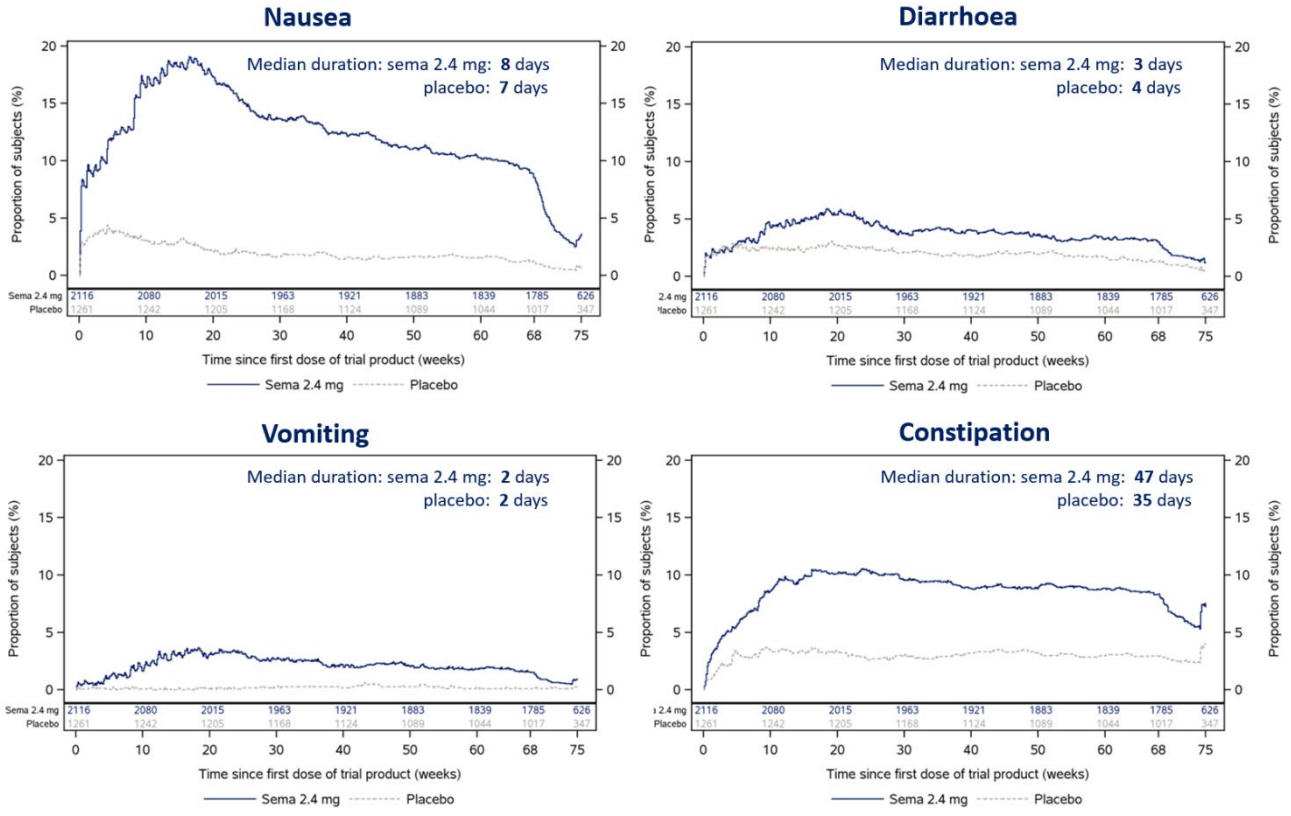
50 where it reached a plateau with approximately 1.1% of subjects in the semaglutide 2.4 mg having Gastritis at any given day.

A higher proportion of subjects reported Haemorrhoids with semaglutide 2.4 mg than with placebo (2.1% vs 0.4%).

Timing and duration of gastrointestinal AEs

With semaglutide, the prevalence of gastrointestinal AEs increased during the initial 20 weeks of treatment, where it peaked with approximately 38% of subjects having at least one gastrointestinal AE on a given day. In the placebo group, the prevalence of gastrointestinal AEs was stable during the study at approximately 11%. The prevalences of Nausea, Diarrhoea, Vomiting and Constipation increased during dose escalation and thereafter, the prevalence of Nausea, Diarrhoea and Vomiting gradually decreased over time (**Figure 57**). However, the prevalence of nausea was still much higher with semaglutide compared to placebo after 68 weeks (approximately 10 vs 1%). Importantly, the prevalence of Constipation remained increased throughout the trials.

Figure 57 Timing and duration of events of Nausea, Diarrhoea, Vomiting and Constipation – on-treatment – phase 3a dose escalation group



Phase 3a dose escalation group: STEP 1-3 data from subjects randomised to Sema 2.4 mg or Placebo during the controlled periods of the trials. Numbers shown in the lower panels are subjects at risk. The event duration distribution was estimated using the Kaplan-Meier estimator. Subjects are considered on-treatment if any dose of trial product has been administered within the prior 49 days. MedDRA version 22.1.

This increase in gastrointestinal AEs and gastrointestinal AEs leading to premature trial product discontinuation was dose-dependent (STEP 2 and trial 4153).

Gallbladder related disorders

During the on-treatment period in the phase 3a pool, AEs of gallbladder-related disorders were reported by a higher proportion of subjects and with a higher event rate with semaglutide 2.4 mg (2.5%, 2.4 events per 100 PYE) than with placebo (1.6%, 1.5 events per 100 PYE). There were more events of gallbladder-related disorders with semaglutide 2.4 mg compared to placebo in the phase 3a pool driven by events of Cholelithiasis (1.6% vs 1.1%). The increased risk of events of gallbladder-related disorders with semaglutide 2.4 mg compared to placebo may be at least partly explained by the larger weight loss.

Pancreatitis and pancreatic enzymes

Based on the EAC-confirmed events of acute pancreatitis in the phase 3a pool during the on-treatment period, there was a slightly increased risk of acute pancreatitis with semaglutide 2.4 mg compared to placebo. There were 4 EAC-confirmed events of acute pancreatitis with semaglutide 2.4 mg (0.2%) and 1 with placebo (<0.1).

All 4 events were confirmed as acute pancreatitis by adjudication. The adjudication process identified two additional events in the semaglutide 2.4 mg arm: 1 investigator reported AE with the PT lipase increased and 1 recurrent event in a subject with an already reported AE of acute pancreatitis. Thus, 6 EAC-confirmed events of acute pancreatitis were identified in total: 5 events in 4 subjects (0.2%) with semaglutide 2.4 mg and 1 event in 1 subject (<0.1%) with placebo. In all cases, the subjects had symptoms of upper abdominal pain and elevated pancreatic enzymes.

For 3 of the 4 events in the semaglutide 2.4 mg group, imaging data were available and were for 2 of the events consistent with gallstones but actually not with acute pancreatitis, and for 1 event, there were no abnormal findings. For the event in the placebo group, imaging data were consistent with acute pancreatitis and gallstones and thus seemed to be a gallstone-related pancreatitis, and the event resolved after acute cholecystectomy.

Mean lipase and amylase levels increased with semaglutide 2.4 mg. At week 68, lipase levels seemed to have reached a plateau with a 39% increase while amylase levels had increased by 16% and seemingly had not levelled off.

Cardiovascular outcomes

The effect of semaglutide 2.4 mg once weekly on cardiovascular outcomes is currently being investigated in a dedicated CVOT, SELECT (trial EX9536-4388) in subjects with established cardiovascular disease and obesity or overweight (without T2D).

Overall, there was no increased risk of cardiovascular disorders for semaglutide 2.4 mg vs placebo, based on the phase 3a pool (and the in-trial period). AEs of cardiovascular disorders were reported by a lower proportion of subjects with semaglutide 2.4 mg than with placebo (8.7% vs 10.9%).

A total of 20 EAC-confirmed first MACEs were reported by the same proportion of subjects with semaglutide 2.4 mg and placebo (0.5% for both treatments). The estimated HR for time to first EAC-confirmed MACE was 0.991 [0.400; 2.456]95% CI for semaglutide 2.4 mg relative to placebo, indicating no increased cardiovascular risk.

Pulse

Across STEP 1–3 and the run-in period of STEP 4, pulse increases were observed in the semaglutide 2.4 mg group. The ETD (semaglutide 2.4 mg vs placebo) for mean increases in pulse from baseline to week 68

ranged from 1−4 bpm. The pulse increases were comparable to what has been reported with semaglutide s.c. for T2D (2−5 bpm for semaglutide 1.0 mg vs placebo) and oral semaglutide for T2D (3−4 bpm for semaglutide 14 mg vs placebo).

A total of 26.0% of subjects in the semaglutide 2.4 mg group had an increase (from baseline) in pulse of ≥20 beats/min at one or more timepoints during the on-treatment period compared to 15.6% in the placebo group.

There was no treatment difference in the reporting of AEs within the HLGT Cardiac arrhythmias (sema 2.4 mg: 2.3%, 2.1 events per 100 PYE, placebo: 2.0%, 1.9 events per 100 PYE) in the phase 3a pool.

Neoplasms

In the phase 3a pool, AEs of neoplasms (benign and malignant) were reported by a comparable proportion of subjects and at a comparable event rate with semaglutide 2.4 mg vs placebo (6.9% vs 7.1% and 6.3 vs 6.2 events per 100 PYO) for the in-trial period, and with no apparent treatment differences on SOC and HLGT level. Comparable proportions of subjects with semaglutide 2.4 mg and placebo reported AEs within specific focus areas for neoplasms (benign and malignant): breast (1.1% vs 1.2%), skin (0.8% vs 1.1%) and colorectal (0.8% vs 0.8%).

Few AEs of malignant neoplasms were reported in the phase 3a pool and by a similar proportion of subjects for semaglutide 2.4 mg (1.1%) and placebo (1.1%). There were no apparent imbalances between semaglutide 2.4 mg and placebo in the types of malignant neoplasms reported. Approximately half of the events were serious. Three events in the placebo group had a fatal outcome.

No events of pancreatic cancer were reported. No events of medullary thyroid carcinoma (MTC) were reported. Calcitonin level ≥50 ng/L was detected in one subject at the baseline visit only.

Hepatic disorders

Based on the phase 3a pool, hepatic disorder AEs were reported by a comparable proportion of subjects and at comparable event rates with semaglutide 2.4 mg and placebo (2.3% vs 2.7% and 2.1 vs 2.7 events per 100 PYE). The majority of the events were mild and related to increases in hepatic enzymes. Hepatic steatosis was reported for slightly fewer subjects with semaglutide 2.4 mg (0.5%) compared to placebo (1.0%).

There were no cases of Hy's law (concurrent elevations of AST/ALT and TBL and no alternative aetiology) in the semaglutide 2.4 mg for weight management programme. Mean levels of ALT decreased with both semaglutide 2.4 mg and placebo, both to a larger extent with semaglutide 2.4 mg (26% vs 13%). AST and ALP decreased by 12% and 10%, respectively, with semaglutide 2.4 mg but remained fairly stable with placebo (decreases of 4% and 3%). Mean total bilirubin increased by 15% with semaglutide 2.4 mg and by 6% with placebo.

Renal failure

In the phase 3a pool, there were few AEs of acute renal failure and these were reported for a comparable proportion of subjects with semaglutide 2.4 mg and placebo (0.4% vs 0.3%) and with identical event rates (0.3 events per 100 PYE in both groups). Most events were mild or moderate, and the majority of subjects recovered. The majority of the events were assessed as unlikely related to trial product and none of the events in either treatment group led to permanent treatment discontinuation.

There was no apparent association between AEs of vomiting or diarrhoea and AEs of acute renal failure.

Ratio to baseline levels for the renal function parameters eGFR and creatinine (phase 3a dose escalation group) were comparable with semaglutide 2.4 mg and placebo at end of treatment (week 68). Improvements were seen for UACR (assessed in the phase 3a with T2D trial [STEP 2]) that decreased by 24% with semaglutide 2.4 mg and increased by 17% with placebo.

Hypoglycaemia

In the phase 3a without T2D group (STEP 1, 3 and 4), the proportion of subjects and rates of events of hypoglycaemia were low and comparable between semaglutide 2.4 and placebo (0.6% vs 0.7% of subjects and 0.7 vs 0.8 events per 100 PYE). There were no SAEs in either of the two treatment groups, none of the events were severe and none of the AEs led to permanent trial product discontinuation.

In the phase 3a with T2D trial (STEP 2), the proportion of subjects with hypoglycaemic episodes and the rate of episodes (ADA 2018/IHSG 2017 level 2: glucose <3 mmol/L)) was higher with semaglutide 2.4 mg compared to placebo (6.2% vs 2.5% of subjects and 10.7 vs 3.2 episodes per 100 PYE). Only 1 hypoglycaemic episode was reported as severe. The episode occurred in a subject in the semaglutide 2.4 mg group during dose escalation. More than half of the hypoglycaemic episodes (level 2 and 3) occurred when trial product was used in combination with SUs, which themselves are associated with an increased risk of hypoglycaemia.

Retinal adverse events

In STEP 2, a total of 85 AEs of retinal disorders were identified by the pre-defined MedDRA search. These events were reported by a larger proportion of subjects with semaglutide 1.0 mg and 2.4 mg compared to placebo (6.2%, 6.9% and 4.2%, respectively). Risk of new onset or worsening of diabetic retinopathy was also higher with high-dose semaglutide in STEP 2, with such events observed in 12, 19 and 11 subjects with semaglutide 1.0 mg, semaglutide 2.4 mg and placebo, respectively. No SAEs were reported for any of the treatment groups and the majority of the events were mild. The events were identified during routine assessments and were not based on emergence of eye-related symptoms. For the majority of events, no treatment was deemed necessary, only observation.

Eye examinations (fundus photography or a dilated fundoscopy) were performed at baseline, at week 52 and at end of treatment (week 68).

Psychiatric disorders

During the on-treatment period, AEs of psychiatric disorders were reported at a comparable frequency and rate with semaglutide 2.4 mg (9.3% of subjects, 10.0 events per 100 PYE) and placebo (10.7% of subjects, 12.1 events per 100 PYE) in the phase 3a pool.

2.6.8.4. Laboratory findings

Mean values of haematological parameters and biochemistry parameters (not covered under a safety focus area) were within the normal range, stable over time and comparable for semaglutide 2.4 mg and placebo. For creatine kinase, the ratio to baseline at week 20 decreased 22% in the semaglutide 2.4 mg group compared to 3% decrease in the placebo group. These levels did not decrease further at the week 52 visit or at the end of-treatment visit (week 68).

2.6.8.5. Safety in special populations

Subgroup analyses

The potential impact of various intrinsic and extrinsic factors on the safety profile of semaglutide 2.4 mg versus placebo was evaluated based on data from the on-treatment period for the phase 3a pool.

Sex

More pronounced treatment differences in the reporting of AEs for females vs males were seen for the Gastrointestinal disorders SOC incl. the PTs Nausea, Diarrhoea, Constipation and Vomiting; the Metabolism and nutrition disorders SOC incl. the PT Decreased appetite; the Nervous system disorders SOC incl. the PTs Headache and Dizziness.

These more pronounced treatment differences are likely related to the lower body weight and thus a higher exposure in females. There was no marked difference in exposure between males and females when adjusting for other covariates than baseline body weight

Age

More pronounced treatment differences in the reporting of AEs with increasing age (largest for subjects ≥75 years and lowest for subjects <65 years) were seen for the Gastrointestinal disorders SOC incl. PTs Nausea, Vomiting, Constipation and GERD, the Nervous system disorders SOC incl. the PT Dizziness; the PT Fatigue.

Race

Asian subjects compared to the other subgroups by race had a more pronounced treatment difference in the reporting of AEs with PT Decreased appetite; no treatment difference in the reporting of AEs with PT Headache.

Black/African American subjects compared to the other subgroups by race had less pronounced treatment differences in the reporting of AEs within the Gastrointestinal disorders SOC mostly due to lower reporting of AEs with PTs Diarrhoea and Vomiting. Treatment differences for AEs, SAEs, severe AEs and AEs leading to permanent trial product discontinuation appeared comparable across subgroups by ethnic origin except for AEs leading to permanent discontinuation of trial product where no treatment difference was observed in subjects of Hispanic or Latino origin.

Body weight/BMI

More pronounced treatment differences in the reporting of AEs among subjects with a baseline body weight of <90 kg were seen for the PT Decreased appetite and the PT Fatigue.

The more pronounced treatment difference in reporting of AEs of Decreased appetite among subjects with a baseline body weight of <90 kg could be related to the higher exposure in these subjects. Furthermore, in subjects with a baseline body weight of <90 kg a larger proportion of subjects treated with semaglutide 2.4 mg compared to placebo reported AEs within the Infections and infestations SOC distributed across many different PTs; no such treatment difference was seen in the total population. Among subjects with a baseline BMI < 30 kg/m2, the treatment difference in reporting of AEs was slightly more pronounced than in the other BMI subgroups, but less pronounced for reporting of SAEs, and there was no treatment difference in the reporting of severe AEs and AEs leading to permanent discontinuation of trial product in this subgroup.

Among subjects with a BMI ≥40 kg/m2, the treatment differences in reporting of SAEs and severe AEs were more pronounced than in the subjects with BMI ≥30 to <35 kg/m2 or ≥35 to <40 kg/m2. The higher

reporting of SAEs appeared to be driven by AEs within the Hepatobiliary disorders and Gastrointestinal disorders SOCs, while the higher reporting of severe AEs appeared to be driven by AEs within the Gastrointestinal disorders SOC.

Renal function

For subjects with mild renal impairment versus subjects with normal renal function at baseline, there were no noteworthy treatment differences in reporting of AEs, SAEs, severe AEs and AEs leading to permanent discontinuation of trial product.

Among subjects with moderate renal impairment at baseline, the treatment differences in reporting of SAEs, severe AEs and AEs leading to permanent discontinuation of trial product were more pronounced than in the subjects with normal renal function or mild renal impairment at baseline.

More pronounced treatment differences in the reporting of AEs with decreasing renal function (mostly for moderate renal impairment vs normal renal function) were seen for the Gastrointestinal SOC incl. the PTs Nausea, Abdominal pain, Dyspepsia, Flatulence and GERD; the PT Decreased appetite; the Nervous system disorders SOC incl. the PTs Dizziness and Headache.

Region

The treatment differences in the proportion of subjects reporting of AEs within the Gastrointestinal disorders SOC varied across regions:

- Africa (~ -2%-points)
- East Asia (~ 11%-points)
- Europe and North America (~24%-points)
- South America (~29%-points)
- Asia (excluding East Asia) (~44%-points).

For subjects from South America and Asia, there were more pronounced treatment differences in reporting several gastrointestinal AEs.

Weight loss

The safety profile of subjects within the semaglutide 2.4 mg group who lost 20% or more of their body weight compared to those who did not, did not give rise to any safety concerns. The AE types more frequently reported among subjects with a large weight loss were gastrointestinal, decreased appetite, Alopecia, Dizziness, Headache and Cholelithiasis.

2.6.8.6. Immunological events

Based on the phase 3a pool, immunogenicity-related AEs were reported by comparable proportion of subjects with semaglutide 2.4 mg and placebo (allergic reactions: 6.9% vs 6.8%; injection site reactions: 4.2% vs 4.9%).

The proportion of subjects that tested positive for anti-semaglutide antibodies at any time point post-baseline was low (2.9% of subjects with antibody assessment in STEP 1 and 2). For almost half of these subjects, the responses were transiently induced, and they only tested positive at a single timepoint. The antibodies levels were low for all weeks, with mean levels ranging from 2.01% to 4.93% B/T and median titres of either 15 or

30. Antibodies cross-reacting with endogenous GLP 1 were detected in 1.6% of subjects randomised to semaglutide 2.4 mg. No subjects had anti-semaglutide antibodies with in vitro neutralising effect against semaglutide or endogenous GLP-1.

The formation of anti-semaglutide antibodies influenced the efficacy of semaglutide. Weight loss was 2 kg less in individuals with antibodies compared to individuals without. Compared to individuals without antibodies, individuals with anti-semaglutide antibodies had an increased risk of allergic reactions (15.7 vs 6.9%) and injection site reactions (5.9 vs 4.5%).

There were no anaphylactic reactions reported in the STEP trials, with 3052 subjects exposed to semaglutide (2650 subjects to semaglutide 2.4 mg and 402 to semaglutide 1.0 mg.

2.6.8.7. Safety related to drug-drug interactions and other interactions

Please see considerations under 'Clinical Pharmacology'.

2.6.8.8. Discontinuation due to adverse events

Overall, the proportion of subjects with AEs leading to permanent treatment discontinuation was higher with semaglutide 2.4 mg than with placebo (5.7% vs 3.0%), driven by gastrointestinal disorders, mainly the PTs: nausea, vomiting, diarrhoea, abdominal pain upper, and constipation.

2.6.8.9. Post marketing experience

2.6.9. Discussion on clinical safety

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

The four phase 3a trials (referred to as STEP 1−4) serve as the primary foundation for evaluating the safety of semaglutide 2.4 mg, as these trials investigated the intended target population, had a similar treatment duration, investigated once-weekly dosing of semaglutide 2.4 mg and contribute with the majority of the total exposure to semaglutide 2.4 mg.

A total of 3052 subjects were exposed to semaglutide (2650 to semaglutide 2.4 mg and 402 to semaglutide 1.0 mg) and 1529 to placebo during the randomised periods of STEP 1–4. This is considered sufficient to evaluate the safety profile of semaglutide 2.4 mg in the target population.

Disposition and characteristics

The subject disposition was similar in the semaglutide and placebo groups, with the exception of fewer subjects that permanently discontinued trial product with semaglutide 2.4 mg than with placebo and more subjects that permanently discontinued trial product due to AEs with semaglutide 2.4 mg than with placebo (driven by gastrointestinal AEs).

In the phase 3a pool, there were more female subjects than male subjects (71.6% vs 29.4%); most subjects were White (73.8%) and of non-Hispanic/non-Latino ethnicity (86.3%), and they had a mean age of 48 years, a mean body weight of 102.6 kg and had a mean BMI of 36.8 kg/m2. The number of black and Asian individuals may be too small to establish a robust benefit-risk ratio.

The treatment groups were generally well-balanced regarding demographics, baseline characteristics, medical history, concomitant illnesses and concomitant medication at baseline.

Adverse events

The proportions of subjects with AEs (88.5 vs 83.6%), SAEs (9.3 vs 6.4%) and severe AEs (9.9 vs 6.9%) were larger with semaglutide 2.4 mg compared to placebo in the phase 3a pool. A larger proportion of subjects with AEs led to permanent treatment discontinuation with semaglutide 2.4 mg (5.7 vs 3.0%): this was driven by gastrointestinal AEs.

In the phase 3a pool, AEs were reported by a higher proportion of subjects with semaglutide 2.4 mg and placebo within the SOCs Gastrointestinal disorders, Nervous system disorders, General disorders and administration site conditions, and Skin and subcutaneous tissue disorders.

Gastrointestinal disorders were the most frequent types of reported AEs, and these events were reported more often with semaglutide 2.4 mg compared to placebo. The following PTs were reported by ≥5% of subjects and more often with semaglutide 2.4 mg compared to placebo: Nausea (38.3% vs 14.0%), Diarrhoea (26.8% vs 14.3%), Constipation (21.8% vs 10.2%), Vomiting (21.8% vs 5.7%), Abdominal pain (8.4% vs 4.0%), Dyspepsia (7.6% vs 2.7%), Abdominal pain upper (7.1% vs 3.6%), Eructation (6.5% vs 0.4%), Abdominal distension (6.3% vs 4.3%) and Flatulence (5.3% vs 3.7%). These types of events are well-known for semaglutide and for the GLP-1 RA class in general, but the incidence of these adverse events appears larger than those with low dose GLP-RA in patients with diabetes. However, the same pattern was seen when comparing the placebo groups. The rate of gastrointestinal disorders with semaglutide 2.4 mg was around 8% higher (246.3 vs. 227.9 events per 100 patient-years of exposure) compared to Saxenda This increase may be relevant for patients, but the effect of semaglutide on weight loss has approximately twice the magnitude as seen with Saxenda.

A larger proportion of subjects with semaglutide 2.4 mg compared to placebo reported events within the SOC Nervous system disorders. This difference was driven by Headache (12.8% vs 8.7%) and Dizziness (6.8% vs 3.3%) that were reported for more than 5% of subjects. The frequency of reporting of Headache and Dizziness with semaglutide 2.4 mg was similar to that of liraglutide 3.0 mg in Saxenda for weight loss, but higher than with the highest doses within the T2D programmes. A possible explanation for this difference between the weight management programmes and the T2D programmes appear to be the differences in indication and population characteristics and in the weight loss obtained. However, other explanations may also be possible. Nevertheless, headache and dizziness have already been reported as a very common adverse event in the SPC.

General disorders and administration site conditions showed a small difference with more AEs in subjects treated with semaglutide 2.4 mg compared to placebo, this difference was mainly driven by fatigue: the proportion of subjects with semaglutide 2.4 mg vs placebo was 10.6% vs 5.1% in the phase 3a dose-escalation group. This difference also appears larger than that with high dose liraglutide for weight loss. The company hypothesizes that the increased proportion of patients with fatigue may be a secondary effect to the gastrointestinal events that was experienced more often in subjects with semaglutide 2.4 mg compared to placebo. Indeed, subjects in the semaglutide 2.4 mg group who reported Fatigue also reported more gastrointestinal AEs than subjects in the semaglutide 2.4 mg group who did not report Fatigue

The PT Decreased appetite belonging to the SOC Metabolism and nutrition disorders was reported by ≥5% of subjects, and these events occurred more often with semaglutide 2.4 mg compared to placebo (7.8% vs

2.8%). This is not unexpected. Decreased appetite may be related to the gastrointestinal side effects and/or it may also play a role in the weight losing effects of semaglutide.

A higher proportion of subjects with semaglutide 2.4 mg compared to placebo in the phase 3a pool (3.3% vs 1.4%) reported AEs for the PT Alopecia that belongs to the SOC Skin and subcutaneous tissue disorders. There were 3 events with semaglutide 2.4 mg and 1 event with placebo leading to permanent treatment discontinuation. Hair loss in relation to weight loss has been reported in other studies and is described in labels for other weight management drugs. A direct effect of semaglutide is not likely Subjects obtaining a weight loss of ≥20% with semaglutide 2.4 mg reported events of Alopecia more often than subjects with a weight loss <20% Furthermore, when comparing the time of onset of individual events of Alopecia and weight loss (%) at the time of onset, most subjects reporting events of Alopecia had a larger than average weight loss regardless of treatment with semaglutide 2.4 mg or placebo. Hair less is reported in the SPC as common.

A larger proportion of subjects with semaglutide 2.4 mg compared to placebo in the phase 3a pool (2.1% vs 1.3%) reported AEs for the PT Migraine that belongs to the SOC Nervous system disorders, which is comparable to the finding for the PT Headache.

Deaths, serious adverse events and adverse events leading to treatment discontinuation

A total of 8 deaths were reported in the semaglutide 2.4 mg for weight management programme: 6 deaths were exposed to semaglutide and 2 to placebo. The proportion of subjects with AEs with fatal outcome was low and comparable with semaglutide 2.4 mg and placebo (0.1% vs 0.2% of subjects) in the phase 3a pool.

The proportion of subjects with SAEs was larger with semaglutide 2.4 mg (9.3%) compared to placebo (6.4%) in the phase 3a pool; this was driven mainly by gallbladder-related disorders and gastrointestinal AEs. The proportion of subjects with SAEs leading to permanent treatment discontinuation was comparable with semaglutide 2.4 mg (1.0%) and placebo (0.8%). In the phase 3a pool, the proportion of subjects with AEs leading to permanent treatment discontinuation were higher with semaglutide 2.4 mg than with placebo (5.7% vs 3.0%), driven by gastrointestinal disorders.

Adverse events of special interest

Gastrointestinal AE's

Gastrointestinal AEs were the most commonly reported events and were reported more frequently with semaglutide 2.4 mg than with placebo (72.9 vs 47.1%). The majority of events were mild or moderate in severity and had onset during the dose-escalation period. Nausea, Diarrhoea, Vomiting and Constipation were the most frequently reported gastrointestinal AEs and reported more frequently with semaglutide 2.4 mg than with placebo. Abdominal pain and gastritis were also more reported with semaglutide 2.4 mg than with placebo. A higher proportion of subjects reported Haemorrhoids with semaglutide 2.4 mg than with placebo (2.1% vs 0.4%). Obesity and constipation are well-known risk factors for the development of haemorrhoids. Among subjects reporting Haemorrhoids in the semaglutide 2.4 mg group, 42% did not report Constipation, thus missing a plausible explanation for a causal relationship to semaglutide. No increased risk of haemorrhoids with GLP-1 RA has been observed previously. The majority of events of haemorrhoids was co-reported with constipation or appeared to be related to constipation, which is a very common adverse reaction that is already addressed in the SmPC.

With semaglutide, the prevalence of gastrointestinal AEs increased during the initial 20 weeks of treatment, where it peaked with approximately 38% of subjects having at least one gastrointestinal AE on a given day. In the placebo group, the prevalence of gastrointestinal AEs was stable during the study at approximately 11%. The prevalences of Nausea, Diarrhoea, Vomiting and Constipation increased during dose escalation and thereafter, the prevalence of Nausea, Diarrhoea and Vomiting gradually decreased over time. However, the prevalence of nausea was still much higher with semaglutide compared to placebo after 68 weeks (approximately 10 vs 1%). This is in contrast to nausea in previous studies with GLP-1 RA. The higher prevalence of nausea in the current studies compared to previous studies may be explained by differences in design. In contrast to the previous studies, subjects were allowed to proceed with trial product after temporary treatment discontinuations or dose reductions in the current studies. Nausea only led to permanent discontinuation of trial product in only 1.8% of subjects in the semaglutide 2.4 mg group**.**

Gall bladder related disorders

During the on-treatment period in the phase 3a pool, AEs of gallbladder-related disorders were reported by a higher proportion of subjects and with a higher event rate with semaglutide 2.4 mg (2.5%, 2.4 events per 100 PYE) than with placebo (1.6%, 1.5 events per 100 PYE). There were more events of gallbladder-related disorders with semaglutide 2.4 mg compared to placebo in the phase 3a pool driven by events of Cholelithiasis (1.6% vs 1.1%). This effect may be more pronounced than that with other GLP-1 RAs, but this may be at least partly explained by the larger weight loss with semaglutide.

Pancreatitis

Based on the EAC-confirmed events of acute pancreatitis in the phase 3a pool during the on-treatment period, there was an increased risk of acute pancreatitis with semaglutide 2.4 mg compared to placebo. There were 4 EAC-confirmed events of acute pancreatitis with semaglutide 2.4 mg (0.2%) and 1 with placebo (<0.1).

Mean lipase and amylase levels increased with semaglutide 2.4 mg, and at week 68, lipase levels seemed to have reached a plateau with a 39% increase while amylase levels had increased by 16% and seemingly had not levelled off. In line with other studies, in the absence of other signs and symptoms of acute pancreatitis, elevations in pancreatic enzymes alone are not predictive of acute pancreatitis. Nevertheless, in the long term, chronic deleterious effects on the pancreas may become apparent.

Cardiovascular disorders

In the phase 3a pool, AEs of cardiovascular disorders (MedDRA search) were reported at slightly lower frequency and rate with semaglutide 2.4 mg (8.7% of subjects, 8.3 events per 100 PYO) vs placebo (10.9% of subjects, 10.9 events per 100 PYO). For SAEs within cardiovascular disorders, a comparable proportion of subjects had events with semaglutide 2.4 mg and placebo (1.6% vs 1.8%).

There was a total of 20 EAC-confirmed first MACEs, and these were reported by the same proportion of subjects with semaglutide 2.4 mg and placebo (0.5% for both treatments).

Across STEP 1–3 and the run-in period of STEP 4, increases in pulse were observed in the semaglutide 2.4 mg group. The ETD (semaglutide 2.4 mg vs placebo) for mean increases in pulse from baseline to week 68 ranged from 1−4 bpm. The pulse increases were comparable to what has been reported with semaglutide s.c. for T2D (2−5 bpm for semaglutide 1.0 mg vs placebo) and with oral semaglutide for T2D (3−4 bpm for semaglutide 14 mg vs placebo). A total of 26.0% of subjects in the semaglutide 2.4 mg group had an increase (from baseline) in pulse of ≥20 beats/min at one or more timepoints during the on-treatment period compared to 15.6% in the placebo group.

There was no treatment difference in the reporting of AEs within the HLGT Cardiac arrhythmias (sema 2.4 mg: 2.3%, 2.1 events per 100 PYE, placebo: 2.0%, 1.9 events per 100 PYE) in the phase 3a pool.

A cardiovascular outcome trial with semaglutide 2.4 mg is ongoing. In patients with diabetes, positive effects of lower dose semaglutide on cardiovascular events have been demonstrated (SUSTAIN 6).

Neoplasms

The proportion of subjects reporting AEs of overall neoplasms (benign and malignant) were comparable between semaglutide 2.4 mg (6.9%) and placebo (7.1%). AEs of breast, skin and colorectal neoplasms (benign and malignant) were all reported by a comparable proportion of subjects for semaglutide 2.4 mg and placebo.

Few AEs of malignant neoplasms were reported in the phase 3a pool and by a similar proportion of subjects for semaglutide 2.4 mg (1.1%) and placebo (1.1%). There were no apparent imbalances between semaglutide 2.4 mg and placebo in the types of malignant neoplasms reported.

No events of pancreatic cancer or medullary thyroid carcinoma were reported.

Liver function

There was a balanced reporting of AEs between semaglutide 2.4 mg and placebo and the evaluation of biochemical markers of liver function overall and in individuals with outlier values. There were no cases of Hy's law in the semaglutide 2.4 mg for the weight management programme. At the end of treatment, mean ALT levels (decreases of 26% vs 13%) and AST (decreases of 12% vs 4%) decreased to a greater extent with semaglutide 2.4 mg compared to placebo. The improvement in ASAT and ALAT saw in this population is likely related to the semaglutide-induced weight loss.

Renal failure

AEs of acute renal failure in the phase 3a pool were reported by comparable proportions of subjects and rate of events with semaglutide 2.4 mg and placebo.

Comparable to what has been observed with semaglutide s.c. for T2D and oral semaglutide for T2D, ratio to baseline levels for the renal function parameters eGFR and creatinine (phase 3a dose-escalation group) were comparable with semaglutide 2.4 mg and placebo at the end of treatment (week 68). Improvements were seen for UACR (assessed in the phase 3a with T2D trial [STEP 2]) that decreased by 24% with semaglutide 2.4 mg and increased by 17% with placebo.

Hypoglycaemia

In the phase 3a without T2D group, the proportion of subjects with AEs of hypoglycaemia was low and comparable with semaglutide 2.4 mg (0.6%) and placebo (0.7%).

In subjects with T2D, the proportion of subjects with level 2 episodes of hypoglycaemia (6.2% vs 2.5%) and the rate of episodes (10.7 vs 3.2 episodes per 100 PYE) was higher with semaglutide 2.4 mg compared to placebo. The majority of the episodes occurred when semaglutide 2.4 mg was used in combination with SU, which is in line with what is seen with semaglutide s.c. for T2D and oral semaglutide for T2D. However, many patients with hypoglycaemia were not using SU. In addition, there was one severe hypoglycaemic episode with semaglutide. This occurred in a patient without SU treatment. The fact that semaglutide may cause (severe) hypoglycaemia in patients without SU is now clearly stated in the SmPC.

Retinopathy

Retinal disorders were included as a safety focus area for the STEP 2 trial (diabetes patients) in the semaglutide 2.4 mg for the weight management programme. In STEP 2, subjects with uncontrolled and potentially unstable diabetic retinopathy or maculopathy were not eligible for enrolment in the trial. A total of 85 AEs of retinal disorders were identified by the pre-defined MedDRA search. These events were reported by a larger proportion of subjects with semaglutide 1.0 mg and 2.4 mg compared to placebo (6.2%, 6.9% and 4.2%, respectively). One subject discontinued treatment with trial product permanently and one subject had a dose reduction of the trial product; both subjects were treated with semaglutide 1.0 mg. There appears to be a dose-response for events of new onset or worsening of diabetic retinopathy at higher doses (observed in 19 subjects with semaglutide 2.4 mg compared to 12 subjects with semaglutide 1.0 mg), despite similar initial glucose-lowering effects.

The semaglutide s.c. for T2D CVOT (SUSTAIN 6) also showed a higher risk of retinopathy with semaglutide s.c. compared to placebo (50 subjects (3.0%) vs 29 subjects (1.8%); and a HR of 1.76 [1.11; 2.78]95% CI for time to first event). The increased risk was primarily seen in pre-disposed patients with pre-existing diabetic retinopathy and poor glycaemic control at baseline and who were being treated with insulins at baseline. In SUSTAIN 6, it has been suggested that the events that occurred with semaglutide and placebo represent an early worsening in connection to intensified treatment. However, in SUSTAIN 6, compared to placebo, the incidence of retinopathy events continued to increase up to 2 years after initiation of treatment (longer than that observed in insulin studies with large decreases in HbA1c). In addition, in the CVOT in patients with pre-existent retinopathy, an increased risk with semaglutide compared to placebo was not only seen in patients with large decreases in HbA1c, but also in patients with HbA1c reductions <0.5%. Importantly, in STEP 2, the increased risk of retinopathy with semaglutide was not associated with larger decreases in HbA1c and cannot be interpreted as early worsening**.** To evaluate this issue, a dedicated randomised clinical trial with semaglutide s.c. (NN9535 4352, FOCUS) is currently being conducted to assess the long-term effects of treatment with semaglutide 1.0 mg on diabetic retinopathy development and progression when added to standard of care in subjects with T2D. Incorporation of a new dose arm into the FOCUS trial is not feasible.

Novo Nordisk has found limited protein and mRNA expression of GLP-1 receptors in normal human eyes with expression being confined to single neurons in the ganglion cell layer. No GLP-1 receptor expression was detected in eyes of individuals with advanced stages of diabetic retinopathy including in areas characterised by neovascularisation. Although a, direct effect cannot be excluded, these data offer some level of reassurance.

Additional reassurance comes from SUSTAIN FORTE. In this study identical proportions of subjects with AEs within 'Diabetic retinopathy' were seen in each semaglutide dose group (sema 1.0 mg: 7/480 subjects, 1.5%; sema 2.0 mg: 7/479 subjects, 1.5%).

In further considering that data from Sustain 6 indicated increased risk of EAC-confirmed diabetic retinopathy complications only in patients with pre-existent DRP, the Applicant's position not to add retinopathy in patients without diabetes as a potential risk in the RMP is accepted (from the Ozempic EPAR: "Among patients without pre-existing diabetic retinopathy, events of EAC-confirmed diabetic retinopathy complications were few and there was no imbalance in events of diabetic retinopathy complications between patients treated with semaglutide as compared with placebo (5 vs 4 events). Supporting a lack of effect in those patients without baseline retinopathy, no difference was observed in patients with a baseline fundoscopy evaluated to be normal.").

Considering that an exclusion criterion was added in STEP 2 regarding uncontrolled and potentially unstable diabetic retinopathy or maculopathy and that subjects with pre-existent diabetic retinopathy were identified

in the SUSTAIN 6 CVOT as being at highest risk, this population may be very vulnerable. The company provided data on the effects of semaglutide on DRP and MACE in patients with "uncontrolled or potentially unstable diabetic retinopathy" in SUSTAIN 6 (semaglutide 0.5 and 1.0 mg in patients with diabetes). The estimated HRs in the 'uncontrolled or potentially unstable diabetic retinopathy' subpopulation in SUSTAIN 6 are consistent with those in the overall population. However, the absolute effects are of a different magnitude. In the 'uncontrolled or potentially unstable diabetic retinopathy' subpopulation for every 100 patients that were treated, semaglutide prevented 3 MACE events, but caused 6 events of serious DRP.

The Applicant has updated SmPC section 4.4, stating that there is no experience with semaglutide 2.4 mg in patients with type 2 diabetes with uncontrolled or potentially unstable diabetic retinopathy, and that semaglutide 2.4 mg is not recommended in these patients. Further, the imbalance in diabetic retinopathy complications between semaglutide arms of the STEP 2 trial should is reflected in SmPC section 4.8.

Infections

It would appear that the use of semaglutide 2.4 mg in combination with low-calorie diet and exercise (STEP 3) is associated with an increased risk of severe and serious infections. However, there was only a small number of subjects for whom severe infections were reported with no clustering of events over time in the trial. Overall, these data do not permit firm conclusions

Psychiatric disorders

During the on-treatment period, AEs of psychiatric disorders were reported at a comparable frequency and rate with semaglutide 2.4 mg (9.3% of subjects, 10.0 events per 100 PYE) and placebo (10.7% of subjects, 12.1 events per 100 PYE) in the phase 3a pool

Laboratory values

Overall, no noteworthy changes to haematology or biochemistry parameters (not part of a safety focus area) were observed; this is in line with previous experience from semaglutide s.c. for T2D and oral semaglutide for T2D.

Blood pressure

In the phase 3a dose-escalation group, SBP and DBP decreased from baseline to end of treatment with both semaglutide 2.4 mg and placebo but more with semaglutide 2.4 mg (-6 mmHg and 3 mmHg) than with placebo (1 mmHg for both).

Allergic reactions and injection site reaction

In the phase 3a pool, the proportion of subjects reporting AEs of allergic reaction were comparable with semaglutide 2.4 mg (6.9%) and placebo (6.8%).

In the phase 3a pool, the proportion of subjects reporting AEs of injection site reaction were comparable with semaglutide 2.4 mg (4.2%) and placebo (4.9%).

Subgroup analyses

Gender, age and renal function

There were no consistent differences between males and females in gastrointestinal AEs Gastrointestinal AEs, the most commonly observed AEs with GLP-1 RAs, were reported more often by subjects with age 65 to <75

years and subjects with moderate renal impairment at baseline (based on a very low number of subjects in this subgroup). Results for the age group ≥75 years should be interpreted with caution. In this age group only 23 subjects treated with semaglutide 2.4 mg and 13 subjects treated with placebo. Based on the apparent lack of impact of baseline age on exposure in STEP 1 and 2, it appears unlikely that the more pronounced treatment difference in proportion of subjects with gastrointestinal AEs with increasing age (partly driven by differences within the placebo group) should be due to a difference in exposure across subgroups by age. However, greater sensitivity of some older individuals cannot be excluded. The revised text in the SmPC (SmPC, Section 4.2 'Posology') allows for delayed dose escalation or lowering to the previous dose until symptoms have improved, which is considered sufficient to mitigate the risk for females and elderly people. Nevertheless, the revised SmPC now also states that greater sensitivity of some older individuals cannot be excluded.

Considering the low number of patients with moderate renal impairment, semaglutide should be used with care in these individuals. This was added to the text of the SmPC.

Weight loss

The safety profile of subjects within the semaglutide 2.4 mg group who lost 20% or more of their body weight compared to those who did not differed for several AE types. The AE types more frequently reported among subjects with a large weight loss were gastrointestinal, decreased appetite, Alopecia, Dizziness, Headache and Cholelithiasis. Changes in the dose are not necessary with subsequent weight loss. First, within the range of exposures observed for the 2.4 mg dose level (e.g. 90% range of model-derived Cavg in STEP 1 was 51−110 nmol/L), a 18% difference in exposures (as a consequence of weight loss) was considered to be of negligible clinical relevance. Second, the revised text in the posology section of the SmPC allows for delayed dose escalation or lowering to the previous dose until symptoms have improved, which should be sufficient for any patient irrespective of their speed and size of weight loss. Third, SAEs and severe AEs were reported by similar proportions and AEs leading to permanent discontinuation of trial product by a lower proportion of subjects with a weight loss ≥20% vs <20%.

Race and region

The treatment differences in the proportion of subjects reporting of AEs within the Gastrointestinal disorders SOC varied across regions. For example, treatment differences in the proportion of subjects reporting of AEs within the Gastrointestinal disorders were only 2% points in Africa, 24% points in Europe and 44% points in Asia (excl east Asia). These differences are very remarkable. A clear explanation for the regional differences in reporting of gastrointestinal AEs is lacking. There may be cultural differences in how gastrointestinal AEs are perceived and reported across regions.

Antibodies

In STEP 1 and STEP 2, the proportion of subjects that tested positive for anti-semaglutide antibodies at any time point post-baseline was low (50 subjects, 2.9% of subjects randomised to semaglutide 2.4 mg). The company concluded that the formation of antibodies did not influence the efficacy and the occurrence of adverse events. For efficacy, the mean body weight %-changes from baseline for STEP 1 and STEP 2 were approximately 2%-points lower for subjects with antibodies, compared to subjects without antibodies. However, we agree with the company that the low number of subjects with antibodies compared to the subjects without antibodies precludes statistical interpretation (STEP 1: 39 vs 1267 subjects, STEP 2: 12 vs 391 subjects). The 2%-points difference in efficacy may be a chance finding. This may also be true for the

safety parameters Allergic reactions and Injection site reaction. The difference between subjects with antibodies compared to subjects without antibodies is driven by few subjects with antibodies (8 subjects with Allergic reactions and 3 subjects with Injection site reactions), hence a causal relationship cannot be concluded.

2.6.10. Conclusions on the clinical safety

In general, the safety profile of semaglutide subcutaneous (s.c.) 2.4 mg once weekly for weight management appears similar to that of other GLP-1 receptor agonists. However, the incidence of gastrointestinal adverse events appears larger than in previous studies with GLP-1 RA's. In addition, several new adverse events were identified (hair loss, dizziness, headache, hypotension, orthostatic hypotension) and reported in the SmPC. In contrast to previous studies, gastrointestinal adverse events only slightly decreased over time. Also, in contrast to previous studies, semaglutide caused hypoglycaemia in patients with diabetes without SU. Moreover, "uncontrolled or potentially unstable diabetic retinopathy" was added as a warning to the SmPC.

2.7. Risk Management Plan

2.7.1. Safety concerns

Summary of safety concerns	
Important identified risks	• Diabetic retinopathy complications (only for patients with T2D)
Important potential risks	• Pancreatic cancer • Medullary thyroid cancer
Missing information	• Pregnancy and lactation • Patients with severe hepatic impairment

2.7.2. Pharmacovigilance plan

Study Status	**Summary of objectives**	**Safety concerns addressed**	**Milestones**	**Due dates**
Category 1 – Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation (key to benefit–risk) **– semaglutide s.c. for T2D, oral semaglutide for T2D, and semaglutide s.c. 2.4 mg for WM**				
None				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are specific obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances (key to benefit–risk) **– semaglutide s.c. for T2D, oral semaglutide for T2D, and semaglutide s.c. 2.4 mg for WM**				
None				
Category 3 – Required additional pharmacovigilance activities (by the CHMP/PRAC or NCA) **– semaglutide s.c. for T2D, oral semaglutide for T2D, and semaglutide s.c. 2.4 mg for WM**				
MTC-22341		Medullary thyroid cancer	**Semaglutide s.c. for T2D**	

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Medullary Thyroid Carcinoma Surveillance Study: a Case-Series Registry Ongoing	A medullary thyroid cancer case series registry of at least 15 years duration to systematically monitor the annual incidence of medullary thyroid carcinoma in the US and to identify any increase related to the introduction of semaglutide into the marketplace.		Submitted protocol	January 2019
			Final report	May 2035
			Oral semaglutide for T2D	
			Submitted protocol	November 2020
			Final report	February 2037
			Semaglutide s.c. 2.4 mg for WM	
			Submitted protocol	TBD
			Final report	TBD
NN9535-4447 Epidemiological assessment of the risk for pancreatic cancer associated with the use of Ozempic (semaglutide s.c.) and Rybelsus (oral semaglutide) in patients with type 2 diabetes Ongoing[a]	The study will evaluate whether exposure to Ozempic increases the risk of pancreatic cancer in patients with T2D.	Pancreatic cancer	**Semaglutide s.c. for T2D**	
			Adopted protocol	20 Sep 2018
			Final report	September 2025
			Oral semaglutide for T2D	
			Adopted protocol	Pending
			Final report	September 2025
NN9535-4352 FOCUS – Long-term effects of semaglutide on diabetic retinopathy in subjects with type 2 diabetes Ongoing	The study will assess the long-term effects of semaglutide treatment on development and progression of diabetic retinopathy	Diabetic retinopathy complications	Adopted protocol	19 Nov 2018
			Final report	November 2025

2.7.3. Risk minimisation measures

Safety concern	Risk minimisation measures
Important identified risk Diabetic retinopathy complications	*Routine risk minimisation measures:* SmPC Sections 4.4 and 4.8 and PL Sections 2 and 4. *Additional risk minimisation measures:* None
Important potential risk Pancreatic cancer	*Routine risk minimisation measures:* None *Additional risk minimisation measures:* None
Important potential risk Medullary thyroid cancer	*Routine risk minimisation measures:* Non-clinical findings are presented in the SmPC Section 5.3 *Additional risk minimisation measures:* None
Missing information Pregnancy and lactation	*Routine risk minimisation measures:* SmPC Section 4.6 and PL Section 2. *Additional risk minimisation measures:* None
Missing information Patients with severe hepatic impairment	*Routine risk minimisation measures:* SmPC Sections 4.2 and 5.2. *Additional risk minimisation measures:* None

2.7.4. Conclusion

The CHMP considers that the risk management plan version 5.1 is acceptable.

2.8. Pharmacovigilance

2.8.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.8.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.9. Product information

2.9.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.9.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Wegovy (semaglutide) is included in the additional monitoring list as it is a biological product authorised after 1 January 2011.

Therefore the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

In this application, data collected by Novo Nordisk (sponsor, applicant) are presented to support the use of semaglutide s.c. 2.4 mg once weekly (hereafter referred to as semaglutide 2.4 mg) as an adjunct to a reduced-calorie diet and increased physical activity for weight management, including weight loss and weight maintenance, in adults with an initial body mass index (BMI) of

- ≥30 kg/m^2 (obesity), *or*
- ≥27 kg/m^2 to <30 kg/m^2 (overweight) in the presence of at least one weight-related comorbidity.

The prevalence of obesity has reached epidemic proportions and continues to increase. Obesity is associated with several health-related complications. Most concerning, obesity increases the risk of developing cardiovascular disease and certain types of cancers, which are some of the leading causes of early death in these patients. In addition, obesity is a well-established risk factor for other serious conditions including, but not limited to, T2D, hypertension, dyslipidaemia, obstructive sleep apnoea, osteoarthritis, urinary incontinence, asthma and non-alcoholic steatohepatitis. Obesity also significantly impacts health-related quality of life by impairing physical health status and imposing limitations on daily activities. Furthermore, stigmatization and discrimination associated with obesity can contribute to impaired mental well-being. The risk of obesity-related complications and comorbidities increases with increasing BMI, and a weight loss of 5−10% has significant health benefits by improving obesity-related comorbidities, including slowing progression to T2D, and improving physical symptoms and quality of life. Studies suggest a beneficial impact of weight loss on cardiovascular risk and mortality in people with obesity, with or without T2D.

3.1.2. Available therapies and unmet medical need

Lifestyle intervention in diet and exercise is first-line treatment for obesity, but most people with obesity struggle to achieve and maintain their weight loss, most likely due largely to a homeostatic mechanism involving counteractive biological responses. Bariatric surgery offers an effective alternative for some people with severe obesity, but surgery carries a risk connected with the procedure and for complications afterwards and requires close follow-up, which can be cumbersome and costly. For people with obesity, there is a lack of safe and efficacious treatment options that can provide a reduction in body weight approaching what can be obtained by surgical procedures, and at the same time enables the patient to maintain the weight loss. Pharmacotherapy may serve as a valuable alternative to bariatric surgery as a supplement to lifestyle intervention to achieve and sustain a clinically relevant weight loss. Currently, only a very limited number of pharmacological options are approved for weight management.

Collectively, the Applicant describes an unmet medical need for a convenient, efficacious and safe weight lowering drug with beneficial effects on obesity-related comorbidities. The GLP-1 RA drug class is associated with multiple benefits; they have a well-documented safety profile, reduce body weight, improve blood pressure, lipid profile and other cardiovascular risk factors, and glucose metabolism.

3.1.3. Main clinical studies

The efficacy and safety of semaglutide s.c. 2.4 mg once weekly for weight management as an adjunct to a reduced-calorie diet and increased physical activity (STEP 1, 2 and 4) or intensive behavioural therapy (IBT) (STEP 3) were studied in four phase 3a 68-week randomised, double-blind, placebo-controlled trials which included a total of 2652 subjects randomised to semaglutide 2.4 mg and 1530 randomised to placebo.

The four phase 3a trials (STEP 1–4) all included subjects with obesity (BMI ≥30 kg/m^2) or overweight (BMI ≥27 to <30 kg/m^2) and at least one weight-related comorbidity. STEP 2 included subjects with overweight or obesity (BMI ≥27 kg/m^2) *and* T2D (HbA_{1c} 7–10%). In STEP 1, 2 and 4, standard lifestyle intervention according to clinical guidelines was included. STEP 3 evaluated semaglutide 2.4 mg when combined with IBT. All four trials had a treatment duration of 68 weeks with an additional 7 weeks of follow-up off treatment. In STEP 1–3, the 68 weeks of treatment included 16 weeks of dose escalation to semaglutide 2.4 mg and 52 weeks on maintenance dose. The semaglutide 1.0 mg treatment arm in STEP 2 included 8 weeks of dose escalation and 60 weeks on 1.0 mg. STEP 4 evaluated the effects of stopping or continuing treatment with semaglutide after reaching the maintenance dose of 2.4 mg (at 20 weeks).

The primary endpoint in all four STEP trials was the change from baseline to 68 weeks in body weight (%), and in STEP 1-3 the proportion of subjects who achieve at week 68 ≥ 5% body weight loss.

3.2. Favourable effects

Body weight related outcomes

In the four STEP trials, treatment with semaglutide 2.4 mg vs placebo resulted in consistent and statistically significant weight loss. In STEP 1, treatment with semaglutide 2.4 mg resulted in a body weight change of -15 % with an ETD vs placebo of -12.4% (95% CI -13.4 to -11.5). A comparable effect was observed in STEP 3 (ETD -10.3%, 95% CI -12 to -8.6). The effect was less pronounced in T2D patients in STEP 2 (ETD -6.2%,

95% CI -7.3 to -5.2). This was accompanied by a larger decrease in waist circumference (confirmatory secondary endpoint) with semaglutide vs placebo in all four STEP trials.

Also the proportion of subjects achieving ≥5% body weight change (co-primary endpoint in STEP 1-3) was significantly larger with semaglutide 2.4 mg treatment (semaglutide vs. placebo STEP 1 83.5% vs 31.1%; STEP 2 67.4% vs 30.2%; STEP 3 86.6% vs 47.6%). In addition, the proportion of patients achieving a weight loss of ≥10% (confirmatory secondary endpoint in STEP 1-3) was larger with semaglutide 2.4 mg (semaglutide vs placebo: STEP 1, 66.1% vs 12.0%; STEP 2 44.5% vs 10.2%; STEP 3 75.3% vs 27.0%,

In STEP 4, weight maintenance was investigated. After the run-in period of 20 weeks with semaglutide treatment, weight loss continued in the patients continuing semaglutide (point estimate -7.9%), while in patients switching to placebo, this resulted in mean weight gain (point estimate +6.9%, semaglutide vs placebo ETD -14.8%, 95% CI -16.00 to -13.50)

The subgroup analyses showed a larger effect on weight loss of semaglutide 2.4 mg in female subjects compared with male subjects (STEP 1 body weight change (%) female subjects ETD -14.0, 95% CI -15.1 to -12.9, male subjects ETD -8.0, 95% CI -9.8 to -6.3).

The effect of semaglutide 2.4 mg on weight loss was also larger in subjects with a baseline weight < 90 kg compared with subjects with a baseline weight > 115kg (STEP 1 body weight change (%) baseline weight < 90 kg group ETD -14.0, 95% CI -15.8 to -12.1, baseline weight > 115 kg group ETD -9.6, 95% CI -11.3 to -7.9).

Glycaemic parameters

STEP 2 shows an improvement in HbA1c (confirmatory secondary endpoint) in T2D patients using semaglutide 2.4 mg vs placebo at 68 weeks, with an ETD of HbA1c (%) -1.23% (95% CI -1.42 to -1.05). In the exploratory analyses, the proportion of patients that reached the target of HbA1c <7% was larger in the semaglutide group (78.5%) vs placebo (26.5%). The patients that started insulin differed between the treatment groups (2 subjects (0.5%) in the semaglutide 2.4 mg group compared to 18 subjects (4.5%) in the placebo group). Also the proportion of patients that decreased OAD (semaglutide 2.4 mg 27.1% compared to placebo 6.8%) or increased OAD (semaglutide 2.4 mg 4.6% compared to placebo 23.0%).

The analyses in the patients without diabetes (i.e. STEP 1 and 3) on glycaemic control were exploratory and resulted in a larger HbA1c reduction with semaglutide vs placebo at 68 weeks (STEP 1 ETD -0.29%, 95% CI -0.32 to -0.26; STEP 3 ETD -0.24%, 95% CI -0.29 to -0.19).

Effect on cardiovascular parameters

Treatment with semaglutide 2.4 mg also resulted in decreased SBP (confirmatory secondary endpoint) in STEP 1-3 (STEP 1 ETD -5.1 mmHg, 95% CI -6.3 to -3.9, STEP 2 ETD -3.4 mmHg, 95% CI -5.6 to -1.3, STEP 3 ETD -3.9, 95% CI -6.4 to -1.5). Also, the effect on lipids was found across the trials, except on an effect on LDL in the STEP 2 trial.

Patient-reported outcomes

The PRO's of the SF-36 PF and IWQOL-Lite-CT PF score were analysed as confirmatory secondary endpoints. The effect of semaglutide 2.4 mg vs placebo on both PRO's was more and statistically significant in STEP 1

(SF-36 PF ETD 1.80, 95% CI 1.18 to 2.42; IWQOL-Lite-CT PF ETD 9.43, 95% CI 7.50 to 11.35) and STEP 2 (SF-36 PF ETD 1.52, 95% CI 0.44 to 2.61; IWQOL-Lite-CT PF ETD 4.83, 95% CI 1.79 to 7.86). A larger proportions of subjects achieving clinically relevant improvements in physical functioning were seen for both PRO's in STEP 1 and 2 (supportive secondary endpoint).

Body composition

In STEP 1 a sub-study that included DEXA scans were conducted. The study showed a statistically significant reduction in total fat mass of -7.0 kg (95% CI: -9.8; -4.2) and in visceral fat mass of -0.3 kg (95% CI: -0.4; -0.1). Lean body weight also decreased more with semaglutide than with placebo, but relative to total body weight, lean body weight increased.

3.3. Uncertainties and limitations about favourable effects

Stopping rule

To evaluate the application of a 'stopping rule', as described in the Guideline (Guideline on clinical evaluation of medicinal products used in weight management (2016 EMA/CHMP/311805/2014)), the Applicant provided analyses for the predictive value of non-responders (responders defined as at least 5% body weight loss at 20 weeks of treatment) with semaglutide 2.4% on clinically relevant weight loss (>5%). In STEP 4, the majority of subjects (719 of 803 subjects, 89.5%) had achieved a weight loss ≥5% at week 20. Approximately half of the subjects who were at week 20 (5%) non-responders with semaglutide still achieved a ≥5% weight reduction after a further 48 weeks of treatment with semaglutide 2.4 mg (estimated percentage of week 68 [5%] responders: 51.95%), while only few of the week 20 (5%) non-responders who switched to placebo at week 20 became week 68 (5%) responders (estimated percentage: 11.36%). It is considered acceptable not to include a stopping rule in the SmPC. Using a stopping rule at week 28 will exclude patients from relevant treatment, as among early non-responders the proportion of patients achieving a weight loss at week 68 was substantial (40.5% and 31.9%). However, even without a stopping rule, regular evaluation concerning treatment discontinuation is needed and this is considered to fall within the regular clinical practice.

Sex

The percentage of female subjects vs male subjects was larger in all four STEP trials. The effect on weight was larger in female subjects in the subgroup analyses, and therefore the inclusion of relatively more females could lead to an overestimation of the effect of semaglutide on weight loss in general. Additional analyses showed that the weight loss increased in an exposure-dependent manner for both males and females. Within both STEP 1 and 2 trials, the weight loss at a given exposure level appears larger in females than males. These analyses suggested that exposure differences cannot explain all differences between genders and that a difference in baseline weight between male and female subjects does not explain the treatment difference.

Effect of baseline weight

It is considered plausible that the effect on weight loss may be baseline weight dependent. Additional analyses on the change in body weight (% and kg) based on baseline body weight were performed and the

subgroup analyses showed a lower ETD for weight loss in % in patients with a baseline weight > 115 kg vs. patients with a baseline weight < 90 kg (body weight change (%) STEP 1 baseline weight > 115 kg group ETD -9.6, 95% CI -11.3 to -7.9, baseline weight < 90 kg group ETD -14.0, 95% CI -15.8 to -12.1). Although the dosage of semaglutide 2.4 mg appears suitable in general, it could be anticipated that there will be an overall lower % body weight change in patients with an initial high body weight vs low body weight, who initiates treatment with semaglutide 2.4 mg. efficacy. But the achieved weight loss in patients with a weight > 115kg is considered clinically relevant.

Effect of diabetes

The effects of semaglutide 2.4 mg vs placebo in patients with T2D (STEP 2) were less pronounced compared to the effect in patients without T2D (STEP 1 and 3), but remained statistically significant (STEP 2, body weight change (%) semaglutide vs placebo ETD -6.2%, 95% CI -7.3% to -5.2%). This could be expected based on previous results in patients with T2D and treatment with GLP-1 analogues (liraglutide 3.0 mg, SCALE trial), but it has not been explicitly addressed in the SmPC. Also, the effects on waist circumference and SBP were less pronounced in T2D patients. In the STEP 2 trial, T2D patients using insulin at baseline were excluded. However, Ozempic (semaglutide 1.0 mg) for the treatment of diabetes is registered also combined with insulin treatment. In the SUSTAIN trials, semaglutide 1.0 mg has been evaluated in T2D patients without insulin (SUSTAIN 1, trial 3623) and as add-on in patients already using insulin (SUSTAIN 5, trial 3627) and the effect on weight of semaglutide 1.0 mg vs. placebo in these trials appears similar (weight change (kg); SUSTAIN 1, semaglutide 1.0 mg -4.53 kg, placebo -0.98, ETD -3.56, 95% CI -4.74 to -2.38; SUSTAIN 5 (add-on baseline insulin use) semaglutide 1.0 mg -6.42 kg, placebo -1.36, ETD -5.06, 95% CI -6.08 to -4.04). Although there is no data in T2D patients using insulin and using add-on semaglutide 2.4 mg, it is considered plausible, based on the data with semaglutide 1.0 mg, that these patients also benefit from treatment with semaglutide 2.4 mg.

Longer term effects

The results of the STEP 4 trial suggest that continuous treatment with semaglutide 2.4 mg is needed to maintain the achieved weight loss after 68 weeks. However, no additional weight loss is expected after this period, and it remains uncertain if, after a longer period of treatment, weight gain may occur. An ongoing study (STEP 5, trial 4378) will evaluate the effect after 2 years of treatment with semaglutide 2.4 mg.

Cardiovascular effects

A beneficial effect accompanied the effect on weight loss on waist circumference and SBP. There were, however, some discrepancies with regards to the lipid profile. In subjects with type 2 diabetes, the effect was smaller compared to subjects without T2D and there was no effect on LDL cholesterol in subjects with T2D. This could partly be explained by a large number of subjects using lipid lowering medication in the STEP 2 trial, i.e. 60%, as could be expected from a population with T2D. This may hamper an additional measurable effect on LDL by semaglutide. In the STEP 3 study and STEP 4 study, there was no effect on HDL cholesterol. Although heterogeneity was observed in the results on serum lipids, there appears to be positive effect on serum lipids in general. But the interpretation of the data should be done with caution as these were supportive endpoints. A cardiovascular benefit has not yet been shown for the treatment with semaglutide 2.4 mg, but will be evaluated in an ongoing study (SELECT, trial 4388) (see below).

Patient reported outcomes

The effect of semaglutide 2.4 mg vs. placebo on both PRO's (i.e. SF-36 PF and IWQOL-Lite-CT PF) was more and statistically significant in STEP 1 and STEP 2. The ETD difference (STEP 1 ETD 1.80, STEP 2 ETD 1.52) did, however, not reach the primary responder threshold (SF-36 PF 3.7 points, IWQOL-Lite-CT PF 14.6 points) for clinically meaningful change on individual level. These results support a consistent and statistically significant effect, but the clinical relevance is not demonstrated based on these results.

3.4. Unfavourable effects

A total of 3052 subjects were exposed to semaglutide (2650 to semaglutide 2.4 mg and 402 to semaglutide 1.0 mg) and 1529 to placebo during the randomised periods of STEP 1–4. This is considered sufficient to evaluate the safety profile of semaglutide 2.4 mg in the target population.

Adverse events

The proportions of subjects with AEs (88.5 vs 83.6%), SAEs (9.3 vs 6.4%) and severe AEs (9.9 vs 6.9%) were larger with semaglutide 2.4 mg compared to placebo in the phase 3a pool. A larger proportion of subjects with AEs led to permanent treatment discontinuation with semaglutide 2.4 mg (5.7 vs 3.0%): this was driven by gastrointestinal AEs. The time to first event was shorter with semaglutide 2.4 mg than with placebo, with approximately 50% of subjects reporting their first event during the first 5 weeks.

Deaths, serious adverse events and adverse events leading to treatment discontinuation

A total of 8 deaths were reported in the semaglutide 2.4 mg for weight management programme: 6 deaths were exposed to semaglutide and 2 to placebo. The proportion of subjects with AEs with fatal outcome was low and comparable with semaglutide 2.4 mg and placebo (0.1% vs 0.2% of subjects) in the phase 3a pool.

The proportion of subjects with SAEs was larger with semaglutide 2.4 mg (9.3%) compared to placebo (6.4%) in the phase 3a pool; this was driven mainly by gallbladder-related disorders and gastrointestinal AEs. The proportion of subjects with SAEs leading to permanent treatment discontinuation was comparable with semaglutide 2.4 mg (1.0%) and placebo (0.8%). In the phase 3a pool, the proportion of subjects with AEs leading to permanent treatment discontinuation were higher with semaglutide 2.4 mg than with placebo (5.7% vs 3.0%), driven by gastrointestinal disorders.

Adverse events of special interest

Gastrointestinal AE's

Gastrointestinal AEs were the most commonly reported events and were reported more frequently with semaglutide 2.4 mg than with placebo (72.9 vs 47.1%). The majority of events were mild or moderate in severity and had onset during the dose-escalation period.

The following PTs were reported by ≥5% of subjects and more often with semaglutide 2.4 mg compared to placebo: Nausea (38.3% vs 14.0%), Diarrhoea (26.8% vs 14.3%), Constipation (21.8% vs 10.2%), Vomiting (21.8% vs 5.7%), Abdominal pain (8.4% vs 4.0%), Dyspepsia (7.6% vs 2.7%), Abdominal pain upper (7.1% vs 3.6%), Eructation (6.5% vs 0.4%), Abdominal distension (6.3% vs 4.3%) and Flatulence (5.3% vs 3.7%).

The PT Decreased appetite belonging to the SOC Metabolism and nutrition disorders was reported by ≥5% of subjects, and these events occurred more often with semaglutide 2.4 mg compared to placebo (7.8% vs

2.8%). This is not unexpected. Decreased appetite may be related to the gastrointestinal side effects and/or it may also play a role in the weight losing effects of semaglutide.

Gall bladder related disorders

During the on-treatment period in the phase 3a pool, AEs of gallbladder-related disorders were reported by a higher proportion of subjects and with a higher event rate with semaglutide 2.4 mg (2.5%, 2.4 events per 100 PYE) than with placebo (1.6%, 1.5 events per 100 PYE). There were more events of gallbladder-related disorders with semaglutide 2.4 mg compared to placebo in the phase 3a pool driven by events of Cholelithiasis (1.6% vs 1.1%).

Neoplasms

The proportion of subjects reporting AEs of overall neoplasms (benign and malignant) were comparable between semaglutide 2.4 mg (6.9%) and placebo (7.1%). AEs of breast, skin and colorectal neoplasms (benign and malignant) were all reported by a comparable proportion of subjects for semaglutide 2.4 mg and placebo.

Few AEs of malignant neoplasms were reported in the phase 3a pool, and by a similar proportion of subjects for semaglutide 2.4 mg (1.1%) and placebo (1.1%). There were no apparent imbalances between semaglutide 2.4 mg and placebo in the types of malignant neoplasms reported.

No events of pancreatic cancer or medullary thyroid carcinoma were reported.

Liver function

There was a balanced reporting of AEs between semaglutide 2.4 mg and placebo and the evaluation of biochemical markers of liver function overall and in individuals with outlier values. There were no cases of Hy's law in the semaglutide 2.4 mg for the weight management programme. At the end of treatment, mean levels of ALT (decreases of 26% vs 13%) and AST (decreases of 12% vs 4%) decreased to a greater extent with semaglutide 2.4 mg compared to placebo. The improvement in ASAT and ALAT saw in this population is likely related to the semaglutide-induced weight loss.

Renal failure

AEs of acute renal failure in the phase 3a pool were reported by comparable proportions of subjects and rate of events with semaglutide 2.4 mg and placebo.

Comparable to what has been observed with semaglutide s.c. for T2D and oral semaglutide for T2D, ratio to baseline levels for the renal function parameters eGFR and creatinine (phase 3a dose-escalation group) were comparable with semaglutide 2.4 mg and placebo at the end of treatment (week 68). Improvements were seen for UACR (assessed in the phase 3a with T2D trial [STEP 2]) that decreased by 24% with semaglutide 2.4 mg and increased by 17% with placebo.

Psychiatric disorders

During the on-treatment period, AEs of psychiatric disorders were reported at a comparable frequency and rate with semaglutide 2.4 mg (9.3% of subjects, 10.0 events per 100 PYE) and placebo (10.7% of subjects, 12.1 events per 100 PYE) in the phase 3a pool.

Laboratory values

Overall, no noteworthy changes to haematology or biochemistry parameters (not part of a safety focus area) were observed; this is in line with previous experience from semaglutide s.c. for T2D and oral semaglutide for T2D.

Blood pressure

In the phase 3a dose-escalation group, SBP and DBP decreased from baseline to end of treatment with both semaglutide 2.4 mg and placebo but more with semaglutide 2.4 mg (-6 mmHg and 3 mmHg) than with placebo (1 mmHg for both).

Allergic reactions and injection site reaction

In the phase 3a pool, the proportion of subjects reporting AEs of allergic reaction were comparable with semaglutide 2.4 mg (6.9%) and placebo (6.8%).

In the phase 3a pool, the proportion of subjects reporting AEs of injection site reaction were comparable with semaglutide 2.4 mg (4.2%) and placebo (4.9%).

3.5. Uncertainties and limitations about unfavourable effects

In the phase 3a pool, there were more female subjects than male subjects (71.6% vs 29.4%); most subjects were White (73.8%) and of non-Hispanic/non-Latino ethnicity (86.3%), and they had a mean age of 48 years, a mean body weight of 102.6 kg and had a mean BMI of 36.8 kg/m2. The number of black and Asian individuals may be too small to establish a robust benefit-risk ratio.

Gastrointestinal events compared to other GLP-1 RA studies

The types of gastrointestinal adverse events are well-known for semaglutide and for the GLP-1 RA class in general, but the incidence of these adverse events appears larger than those with low dose GLP-RA in patients with diabetes. However, the same pattern was seen when comparing the placebo groups. In addition, the rate of gastrointestinal disorders with semaglutide 2.4 mg was around 8% higher (246.3 vs. 227.9 events per 100 patient-years of exposure) compared to Saxenda. This increase may be relevant for patients, but the text of the SPC now allows for delayed dose escalation or lowering to the previous dose until symptoms have improved.

Timing of gastrointestinal adverse events

With semaglutide, the prevalence of gastrointestinal AEs increased during the initial 20 weeks of treatment, where it peaked with approximately 38% of subjects having at least one gastrointestinal AE on a given day. The prevalence of gastrointestinal AEs was stable during the study at approximately 11% in the placebo group. The prevalences of Nausea, Diarrhoea, Vomiting and Constipation increased during dose escalation and after that, the prevalence of Nausea, Diarrhoea and Vomiting gradually decreased over time.

The prevalences of Nausea, Diarrhoea, Vomiting and Constipation increased during dose escalation and after that the prevalence of Nausea, Diarrhoea and Vomiting gradually decreased over time. However, the prevalence of nausea was still much higher with semaglutide compared to placebo after 68 weeks (approximately 10 vs 1%). This is in contrast to nausea in previous studies with GLP-1 RA. The higher prevalence of nausea in the current studies compared to previous studies may be explained by differences in design. In contrast to the previous studies, subjects were allowed to proceed with trial product after temporary treatment discontinuations or dose reductions in the current studies. Nausea only led to permanent discontinuation of trial product in only 1.8% of subjects in the semaglutide 2.4 mg group**.**

Haemorrhoids

Haemorrhoids were also more reported with semaglutide 2.4 mg than with placebo (2.1% vs 0.4%). Obesity and constipation are well-known risk factors for the development of haemorrhoids. The majority of events of haemorrhoids was co-reported with constipation or appeared to be related to constipation, which is a very common adverse reaction that is already addressed in the SmPC.

Nervous system disorders

A larger proportion of subjects with semaglutide 2.4 mg compared to placebo reported events within the SOC Nervous system disorders. This difference was driven by the PTs Headache (12.8% vs 8.7%) and Dizziness (6.8% vs 3.3%) that were reported for more than 5% of subjects. The frequency of reporting of Headache and Dizziness with semaglutide 2.4 mg was similar to that of liraglutide 3.0 mg in Saxenda for weight loss, but higher than with the highest doses within the T2D programmes. A possible explanation for this difference between the weight management programmes and the T2D programmes appear to be the differences in indication and population characteristics and in the weight loss obtained. However, other explanations may also be possible. Nevertheless, headache is already reported as a very common adverse event in the SPC. Narratives for the 5 SAEs of Vertigo reported by subjects randomised to semaglutide 2.4 mg in the STEP trials have been provided. Overall, the SAEs of Vertigo were reported as resolved without any changes to trial product.

Fatigue

General disorders and administration site conditions showed a small difference with more AEs in subjects treated with semaglutide 2.4 mg than placebo; this difference was mainly driven by fatigue: the proportion of subjects with semaglutide 2.4 mg vs placebo was 10.6% vs 5.1% in the phase 3a dose-escalation group. The effect of semaglutide on fatigue also appears larger than that with high dose liraglutide for weight loss. The company hypothesizes that the increased proportion of patients with fatigue may be a secondary effect on the gastrointestinal events experienced more often in subjects with semaglutide 2.4 mg compared to placebo. Indeed, subjects in the semaglutide 2.4 mg group who reported Fatigue also reported more gastrointestinal AEs than subjects in the semaglutide 2.4 mg group who did not report Fatigue.

Alopecia

A higher proportion of subjects with semaglutide 2.4 mg than placebo in the phase 3a pool (3.3% vs 1.4%) reported AEs for the PT Alopecia that belong to the SOC Skin subcutaneous tissue disorders. There were 3 events with semaglutide 2.4 mg and 1 event with placebo leading to permanent treatment discontinuation. Although alopecia is not reported for other GLP-1 RAs, hair loss in relation to weight loss has been reported in other studies and is described in labels for other weight management drugs. The events of Alopecia reported with semaglutide 2.4 mg are most likely a result of weight loss. Subjects obtaining a weight loss of ≥20% with semaglutide 2.4 mg reported events of Alopecia more often than subjects with a weight loss <20% Furthermore, when comparing the time of onset of individual events of Alopecia and weight loss (%) at the time of onset, most subjects reporting events of Alopecia had a larger than average weight loss regardless of treatment with semaglutide 2.4 mg or placebo.

Alopecia is already reported in the SPC as a common adverse event.

Pancreatitis

Based on the EAC-confirmed events of acute pancreatitis in the phase 3a pool during the on-treatment period, there was an increased risk of acute pancreatitis with semaglutide 2.4 mg compared to placebo.

There were 4 EAC-confirmed events of acute pancreatitis with semaglutide 2.4 mg (0.2%) and 1 with placebo (<0.1).

Mean lipase and amylase levels increased with semaglutide 2.4 mg, and at week 68, lipase levels seemed to have reached a plateau with a 39% increase while amylase levels had increased by 16% and seemingly had not levelled off. In line with other studies, in the absence of other signs and symptoms of acute pancreatitis, elevations in pancreatic enzymes alone are not predictive of acute pancreatitis.

Cardiovascular disorders

In the phase 3a pool, AEs of cardiovascular disorders (MedDRA search) were reported at slightly lower frequency and rate with semaglutide 2.4 mg (8.7% of subjects, 8.3 events per 100 PYO) vs placebo (10.9% of subjects, 10.9 events per 100 PYO). A comparable proportion of subjects had events with semaglutide 2.4 mg and placebo (1.6% vs 1.8%).

A total of 20 EAC-confirmed first MACEs were reported by the same proportion of subjects with semaglutide 2.4 mg and placebo (0.5% for both treatments).

Across STEP 1–3 and the run-in period of STEP 4, increases in pulse were observed in the semaglutide 2.4 mg group. The ETD (semaglutide 2.4 mg vs placebo) for mean increases in pulse from baseline to week 68 ranged from 1−4 bpm. The pulse increases were comparable to what has been reported with semaglutide s.c. for T2D (2−5 bpm for semaglutide 1.0 mg vs placebo) and oral semaglutide for T2D (3−4 bpm for semaglutide 14 mg vs placebo).

There was no treatment difference in the reporting of AEs within the HLGT Cardiac arrhythmias (sema 2.4 mg: 2.3%, 2.1 events per 100 PYE, placebo: 2.0%, 1.9 events per 100 PYE) in the phase 3a pool.

A cardiovascular outcome trial with semaglutide 2.4 mg is ongoing. In patients with diabetes, positive effects of lower dose semaglutide on cardiovascular events have been demonstrated (SUSTAIN 6).

Hypoglycaemia

In the phase 3a without T2D group, the proportion of subjects with AEs of hypoglycaemia was low and comparable with semaglutide 2.4 mg (0.6%) and placebo (0.7%).

In subjects with T2D, the proportion of subjects with level 2 episodes of hypoglycaemia (6.2% vs 2.5%) and the rate of episodes (10.7 vs 3.2 episodes per 100 PYE) was higher with semaglutide 2.4 mg compared to placebo. The majority of the episodes occurred when semaglutide 2.4 mg was used in combination with SU, which is in line with what is seen with semaglutide s.c. for T2D and oral semaglutide for T2D. However, many patients with hypoglycaemia were not using SU. In addition, there was one severe hypoglycaemic episode with semaglutide. This occurred in a patient without SU treatment. The fact that semaglutide may cause (severe) hypoglycaemia in patients without SU is now clearly stated in the SmPC.

Retinopathy

Retinal disorders were included as a safety focus area for the STEP 2 trial (diabetes patients) in the semaglutide 2.4 mg for the weight management programme. In STEP 2, subjects with uncontrolled and potentially unstable diabetic retinopathy or maculopathy were not eligible for enrolment in the trial. A total of 85 AEs of retinal disorders were identified by the pre-defined MedDRA search. These events were reported by a larger proportion of subjects with semaglutide 1.0 mg and 2.4 mg compared to placebo (6.2%, 6.9% and 4.2%, respectively). One subject discontinued treatment with trial product permanently, and one subject had a dose reduction of the trial product; both subjects were treated with semaglutide 1.0 mg. There appears to

be a dose-response for events of new onset or worsening of diabetic retinopathy at higher doses (observed in 19 subjects with semaglutide 2.4 mg compared to 12 subjects with semaglutide 1.0 mg), despite similar initial glucose-lowering effects.

The semaglutide s.c. for T2D CVOT (SUSTAIN 6) also showed a higher risk of retinopathy with semaglutide s.c. compared to placebo (50 subjects (3.0%) vs 29 subjects (1.8%); and a HR of 1.76 [1.11; 2.78]95% CI for time to first event). The increased risk was primarily seen in pre-disposed patients with pre-existing diabetic retinopathy and poor glycaemic control at baseline and who were being treated with insulins at baseline. In SUSTAIN 6, it has been suggested that the events that occurred with semaglutide and placebo represent an early worsening in connection to intensified treatment. However, in SUSTAIN 6, compared to placebo, the incidence of retinopathy events continued to increase up to 2 years after initiation of treatment (longer than that observed in insulin studies with large decreases in HbA1c). In addition, in the CVOT in patients with pre-existent retinopathy, an increased risk with semaglutide compared to placebo was not only seen in patients with large decreases in HbA1c, but also in patients with HbA1c reductions < 0.5%. Importantly, in STEP 2, the increased risk of retinopathy with semaglutide in STEP 2 was not associated with larger decreases in HbA1c and cannot be interpreted as early worsening.

To further evaluate this issue, a dedicated randomised clinical trial with semaglutide s.c. (NN9535 4352, FOCUS) is currently being conducted to assess the long-term effects of treatment with semaglutide at a target dose of 1.0 mg on diabetic retinopathy development and progression when added to standard of care in subjects with T2D. Incorporation of a new dose arm into the FOCUS trial is not feasible

For support of the position that a direct effect of semaglutide on the retina seems unlikely, the Applicant further refers to non-clinical data. Across nonclinical toxicology studies in mice, rats and cynomolgus monkeys with semaglutide, no treatment-related findings on the retina or the optic nerve has been observed by ophthalmoscopy or histopathology at exposures up to 22-fold the clinical exposure of semaglutide 2.4 mg.

Using specific methods Novo Nordisk has found limited protein and mRNA expression of GLP-1 receptors in normal human eyes with expression being confined to single neurons in the ganglion cell layer. No GLP-1 receptor expression was detected in eyes of individuals with advanced stages of diabetic retinopathy including in areas characterised by neovascularisation. The Applicant also states that review of the post-marketing safety data for Saxenda (liraglutide, structurally similar to semaglutide) showed no association between liraglutide and retinopathy. Although a direct effect cannot be excluded, these data offer some level of reassurance. Additional reassurance comes from SUSTAIN FORTE. In this study identical proportions of subjects with AEs within 'Diabetic retinopathy' were seen in each semaglutide dose group (sema 1.0 mg: 7/480 subjects, 1.5%; sema 2.0 mg: 7/479 subjects, 1.5%).

In further considering that data from Sustain 6 indicated increased risk of EAC-confirmed diabetic retinopathy complications only in patients with pre-existent DRP, the Applicant's position not to add retinopathy in patients without diabetes as a potential risk in the RMP is accepted (from the Ozempic EPAR: "Among patients without pre-existing diabetic retinopathy, events of EAC-confirmed diabetic retinopathy complications were few and there was no imbalance in events of diabetic retinopathy complications between patients treated with semaglutide as compared with placebo (5 vs 4 events). Supporting a lack of effect in those patients without baseline retinopathy, no difference was observed in patients with a baseline fundoscopy evaluated to be normal.").

Considering that an exclusion criterion was added in STEP 2 "regarding active uncontrolled and potentially unstable diabetic retinopathy or maculopathy and that subjects with pre-existent diabetic retinopathy were identified in the SUSTAIN 6 CVOT as being at highest risk, the unstable population may be very vulnerable.,

The Company provided data on the effects of semaglutide on DRP and MACE in patients with "uncontrolled or potentially unstable diabetic retinopathy" in SUSTAIN 6 (semaglutide 0.5 and 1.0 mg in patients with diabetes). The estimated HRs in the 'uncontrolled or potentially unstable diabetic retinopathy' subpopulation in SUSTAIN 6 are consistent with those in the overall population. However, the absolute effects are of a different magnitude. In the 'uncontrolled or potentially unstable diabetic retinopathy' subpopulation for every 100 patients that were treated, semaglutide prevented 3 MACE events, but caused 6 events of serious DRP. A strict warning was added to the SmPC.

Infections

It would appear that the use of semaglutide 2.4 mg in combination with low-calorie diet and exercise (STEP 3) is associated with an increased risk of severe and serious infections (perhaps through increased loss of lean body mass and/or some other mechanism resulting in decreased immunity). However, there was only a small number of subjects for whom severe infections were reported with no clustering of events over time in the trial. Overall, these data do not permit firm conclusions.

Subgroup analyses

Gender, age and renal function

There were no consistent differences between males and females in gastrointestinal AEs, the most commonly observed AEs with GLP-1 RAs. Gastrointestinal AEs were reported more often by subjects with age 65 to <75 years and subjects with moderate renal impairment at baseline (based on a very low number of subjects in this subgroup). Results for the age group ≥75 years should be interpreted with caution. In this age group only 23 subjects treated with semaglutide 2.4 mg and 13 subjects treated with placebo. Based on the apparent lack of impact of baseline age on exposure in STEP 1 and 2, it appears unlikely that the more pronounced treatment difference in proportion of subjects with gastrointestinal AEs with increasing age (partly driven by differences within the placebo group) should be due to a difference in exposure across subgroups by age. However, greater sensitivity of some older individuals cannot be excluded. The revised text in the SmPC (SmPC, Section 4.2 'Posology') allows for delayed dose escalation or lowering to the previous dose until symptoms have improved, which is considered sufficient to mitigate the risk for females and elderly people. Nevertheless, the revised SPC now also states that greater sensitivity of some older individuals cannot be excluded.

Considering the low number of patients with moderate renal impairment, semaglutide should be used with care in these individuals. This is now added to the SmPC**.**

Weight loss

The safety profile of subjects within the semaglutide 2.4 mg group who lost 20% or more of their body weight compared to those who did not differed for several AE types. The AE types more frequently reported among subjects with a large weight loss were gastrointestinal, decreased appetite, Alopecia, Dizziness, Headache and Cholelithiasis. changes in the dose are not necessary with subsequent weight loss. First, within the range of exposures observed for the 2.4 mg dose level (e.g. 90% range of model-derived Cavg in STEP 1 was 51−110 nmol/L), a 18% difference in exposures (as a consequence of weight loss) was considered to be of negligible clinical relevance. Second, the revised text in the posology section of the SmPC allows for delayed dose escalation or lowering to the previous dose until symptoms have improved, which should be sufficient for any patient irrespective of their speed and size of weight loss. Third, SAEs and severe AEs were

reported by similar proportions and AEs leading to permanent discontinuation of trial product by a lower proportion of subjects with a weight loss ≥20% vs <20%.

Race and region

Asian subjects compared to the other subgroups by race had a more pronounced treatment difference in the reporting of AEs with PT Decreased appetite; no treatment difference in the reporting of AEs with PT Headache. The more pronounced treatment difference in reporting of AEs of Decreased appetite among Asian subjects could be related to the higher exposure in these subjects due to a lower body weight.

The treatment differences in the proportion of subjects reporting of AEs within the Gastrointestinal disorders SOC varied across regions. For example, treatment differences in the proportion of subjects reporting of AEs within the Gastrointestinal disorders were only 2% points in Africa, 24% points in Europe and 44% points in Asia (excl east Asia). These differences are very remarkable. For subjects from South America and (East)Asia, there were more pronounced treatment differences in reporting several gastrointestinal AEs. A clear explanation for the regional differences in reporting of gastrointestinal AEs. There may be cultural differences in how gastrointestinal AEs are perceived and reported across regions.

Immunogenicity

In STEP 1 and STEP 2, the proportion of subjects that tested positive for anti-semaglutide antibodies at any time point post-baseline was low (50 subjects, 2.9% of subjects randomised to semaglutide 2.4 mg). The company concluded that the formation of antibodies did not influence the efficacy and the occurrence of adverse events. For efficacy, the mean body weight %-changes from baseline for STEP 1 and STEP 2 were approximately 2%-points lower for subjects with antibodies, compared to subjects without antibodies. However, we agree with the company that the low number of subjects with antibodies compared to the subjects without antibodies precludes statistical interpretation (STEP 1: 39 vs 1267 subjects, STEP 2: 12 vs 391 subjects). The 2%-points difference in efficacy may be a chance finding. This may also be true for the safety parameters Allergic reactions and Injection site reaction. The difference between subjects with antibodies compared to subjects without antibodies is driven by few subjects with antibodies (8 subjects with Allergic reactions and 3 subjects with Injection site reactions), hence a causal relationship cannot be concluded.

3.6. Effects Table

Table 42. Effects Table for semaglutide 2.4 mg in weight management

Effect	Short Description	Unit	Treatment (semaglu-tide 2.4 mg)	Control (placebo)	Uncertainties/ Strength of evidence	References
Favourable Effects						
Body weight change	Change in body weight from baseline at 68 weeks	%	-16.0 to -9.6	-2.4 to -5.7	**SoE**: STEP 1 ETD -12.4, 95% CI -13.4 to -11.5. p <0.0001, STEP 2 ETD -6.2, 95% CI -7.3 to -5.2, p < 0.0001, STEP 3 ETD – 10.3, 95% CU -12 to -8.6, p <0.0001	Trial 4373 Trial 4374 Trial 4375
Waist circumference	Change in waist circumference from baseline at 68 weeks	cm	-15.2 to -9.4	-6.1 to -4.1	**SoE**: STEP 1 ETD -9.4, 95% CI -10.3 to -8.5, p < 0.0001; STEP 2 ETD -4.9, 95% CI -6.0 to -3.8, p < 0.0001; STEP 3 ETD -8.3, 95% CI -10.0 to -6.6, p < 0.0001	Trial 4373 Trial 4374 Trial 4375

Effect	Short Description	Unit	Treatment (semaglu-tide 2.4 mg)	Control (placebo)	Uncertainties/ Strength of evidence	References
HbA1c	Change in HbA1c from baseline at 68 weeks	mmol/ mol (%)	-17.5 (-1.6)	-4.1 (-0.4)	**SoE**: STEP 2 ETD -13.5 (-1.2), 95% CI -15.5 to -11.4 (-1.4 to -1.1), p < 0.0001	Trial 4374
SBP	Change in SBP from baseline at 68 weeks	mmHg	-6.2 to -3.9	-1.6 to -0.5	**SoE**: STEP 1 ETD -5.1, 95% CI -6.3 to -3.9, p < 0.0001; STEP 2 ETD -3.4, 95% CI -5.6 to -1.3, p < 0.05; STEP 3 ETD -3.9, 95% CI -6.4 to -1.5, p = 0.001	Trial 4373 Trial 4374 Trial 4375
SF-36	Change in SF-36 score from baseline at 68 weeks	Score	2.2 to 2.5	0.4 to 1.7	**Unc**: STEP 1 ETD 1.80, 95% CI 1.18 to 2.42, p < 0.0001; STEP 2 ETD 1.52, 95% CI 0.44 to 2.61, p < 0.01; STEP 3 ETD 0.84, 95% CI -0.23 to 1.92, p = 0.12	Trial 4373 Trial 4374 Trial 4375
Unfavourable Effects						
AEs	proportion	%	88.5	83.6		Phase 3a pool
SAE	proportion	%	9.3	6.4		Phase 3a pool
Gastrointestinal AEs	proportion	%	72.9	47.1		Phase 3a pool
acute pancreatitis	proportion	%	0.2	<0.1		Phase 3a pool
EAC-confirmed cardiovascular events	proportion	%	0.6	0.7		Phase 3a pool
level 2 episodes of hypoglycaemia	proportion	%	6.2	2.5		STEP 2 / Trial 4374
retinal disorders	proportion	%	6.9 (sema 2.4 mg) 6.2 (sema 1 mg)	4.2		Phase 3a pool

Abbreviations: CI, confidence interval; ETD, estimated treatment difference; SBP, systolic blood pressure.

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The effect of semaglutide 2.4 mg treatment on weight loss is considerably larger compared to currently available treatments. The effect of semaglutide on weight loss was found in all four STEP trials and supports a consistent effect of semaglutide 2.4 mg. In addition, the weight loss achieved is considered clinically relevant and persists after 68 weeks of treatment. However, the effects on weight loss are clearly less pronounced in patients with T2D, in male patients and patients with a higher baseline weight. But also in these subgroups the achieved weight loss is considered clinically relevant.

The obtained weight loss is considered an important benefit and it is also accompanied by improvements in SBP and glycaemic parameters, the latter mostly in T2D patients. These improvements may lead to a decrease in health-related complications, but a benefit on cardiovascular outcome has not yet been shown. A cardiovascular outcome trial with semaglutide 2.4 mg is ongoing.

Based on the results of STEP 4, it is expected that treatment needs to be continued long-term to maintain the achieved weight loss, as after cessation of treatment, weight gain occurs. In addition, no further weight loss is expected after 68 weeks, and it remains uncertain if, after longer ongoing treatment, weight gain may occur again. A stopping rule at week 28 was not introduced in the SmPC, as among early non-responders the proportion of patients achieving a weight loss at week 68 was substantial. However, even without a stopping rule, regular evaluation concerning treatment discontinuation is needed and this is considered to fall within the regular clinical practice.

In general, the safety profile of semaglutide subcutaneous (s.c.) 2.4 mg once weekly for weight management appears similar to that of other GLP-1 receptor agonists. However, the incidence of gastrointestinal adverse events appears larger than in previous studies with GLP-1 RA's for the treatment of diabetes. These events can be an important burden for patients. On the other hand, gastrointestinal adverse events are transient, and will diminish over time.

Several new adverse events were identified (hair loss, dizziness, headache). These events may be burdensome for patients, but it is likely that all will disappear after treatment is stopped.

Semaglutide caused also hypoglycaemia in patients with diabetes without SU. This is an important issue that is now clearly stated in the SmPC.

Subjects with uncontrolled and potentially unstable diabetic retinopathy or maculopathy were not eligible for enrolment in the trial. The increased risk of retinopathy in these patients is a possible very serious issue. To evaluate this issue in more detail, a dedicated randomised clinical trial with low dose semaglutide s.c. (NN9535 4352, FOCUS) is currently being conducted to assess the long-term effects of treatment with semaglutide on diabetic retinopathy development and progression when added to standard of care in subjects with T2D. Nevertheless, questions about possible direct effects on the retina remain. A warning in patients with uncontrolled and potentially unstable diabetic retinopathy or maculopathy has been added to the SmPC.

3.7.2. Balance of benefits and risks

Obesity is associated with several health-related complications and most patients experience large difficulties with achieving weight loss. Treatment options (non-surgical) leading to clinically relevant weight loss are considered important. The effect of semaglutide on body weight is considered clinically relevant and larger than that observed in previous studies with GLP-1 RAs.

The effects of semaglutide 2.4 mg on cardiovascular events are uncertain, but a specific outcome trial with high dose semaglutide is ongoing. This trial will also provide data on adverse events during long term treatment. Considering the expected need for long-term treatment, no large safety issues are considered acceptable. The safety profile of semaglutide 2.4 mg appears similar to that of other GLP-1 receptor agonists, and no important new safety signals were identified.

3.7.3. Additional considerations on the benefit-risk balance

Several adverse events are more pronounced with the high dose semaglutide compared to the lower dose in diabetes and several new adverse events were identified. These events may be burdensome for patients, but they will likely disappear after the dose is decreased or alternatively after treatment is stopped. The concern of diabetic retinopathy will be monitored together with the high dose semaglutide used for the treatment of diabetes mellitus indication.

3.8. Conclusions

The overall benefit/risk balance of Wegovy is positive, subject to the conditions stated in section 'Recommendations'.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Wegovy is favourable in the following indication(s):

Wegovy is indicated as an adjunct to a reduced-calorie diet and increased physical activity for weight management, including weight loss and weight maintenance, in adults with an initial Body Mass Index (BMI) of

- *≥30 kg/m^2 (obesity), or*
- *≥27 kg/m^2 to <30 kg/m^2 (overweight) in the presence of at least one weight-related comorbidity e.g. dysglycaemia (prediabetes or type 2 diabetes mellitus), hypertension, dyslipidaemia, obstructive sleep apnoea or cardiovascular disease.*

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

Other conditions and requirements of the marketing authorisation

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.