CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

215256Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Office of Clinical Pharmacology Review

BLA Number	215256
Link to EDR	\\CDSESUB1\evsprod\NDA215256\215256.enx
Submission Date	December 4, 2020
Submission Type	505(b)(1), Priority
Brand Name	(b) (4) WEGOVY
Generic Name	Semaglutide injection
Dosage Form and Strength	0.25 mg/0.5 mL, 0.5 mg/0.5 mL, 1 mg/0.5 mL, 1.7 mg/0.75 mL or 2.4 mg/0.75 mL in a pre-filled, disposable, single-dose pen-injector
Route of Administration	Subcutaneous
Proposed Indication	As an adjunct to a reduced calorie meal plan and increased physical activity for chronic weight management (b) (4) (b) (4) in adult patients with an initial body mass index (BMI) of • 30 kg/m^2 or greater (obesity), or • 27 kg/m^2 or greater (excess weight) in the presence of at least one weight-related comorbid condition
Applicant	Novo Nordisk Inc.
Associated IND	126360
OCP Review Team	Sang Chung, PhD, Justin Earp, PhD, Jayabharathi Vaidyanathan, PhD
OCP Final Signatory	Jayabharathi Vaidyanathan, PhD

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1. EXECUTIVE SUMMARY

Novo Nordisk In. (applicant) submitted an original New Drug Application (NDA) for semaglutide subcutaneous (SC) injection as an adjunct to a reduced calorie meal plan and increased physical activity for chronic weight management [redacted] (b) (4) in adults.

Semaglutide is a long-acting analog of human glucagon-like peptide-1 (GLP-1) and the proposed therapeutic dosing is 2.4 mg once weekly.

The drug product is supplied as a solution in a pre-filled, disposable, [redacted] (b) (4) single-dose pen-injector. The primary evidence of effectiveness using the proposed dosing regimen was obtained from the pivotal Trial 4373 (STEP 1) for weight management and Trial 4374 (STEP 2) for weight management in Type 2 Diabetes Mellitus (T2DM).

1.1 Recommendations

The Office of Clinical Pharmacology/Division of Cardiometabolic and Endocrine Pharmacology (OCP/DCEP) has reviewed the clinical pharmacology data submitted under NDA 215256 and recommends approval. Key review issues with specific recommendations and comments are summarized below:

Review Issues	Recommendations and Comments
Supportive evidence of effectiveness	Body weight (%) change from baseline to that of placebo at Week 68 [estimand (95% confidence interval)] was -12.4 [-13.4, -11.5] ($p<0.0001$) or -6.21 [-7.3,-5.2] ($p<0.0001$) for STEP 1 or STEP 2, respectively. The most common adverse event (AE) was gastrointestinal AEs. There were no new or unexpected safety observations.
General dosing instructions	The therapeutic and maintenance dose is 2.4 mg once weekly. Dose-escalation is used to mitigate gastrointestinal (GI) adverse event (AE). The starting dose is 0.25 mg and then following a dose escalation regimen with dose increases every 4 weeks (to doses of 0.5, 1.0, and 1.7 mg once weekly) until 2.4 mg once weekly is reached. This should be administered subcutaneously into the abdomen, thigh or upper arm with change of the injection sites.
Dosing in patient subgroups	There is no specific dosing for any patient subgroups. The dose can be temporarily decreased to 1.7 mg weekly, for a maximum of 4 weeks if patients do not tolerate the maintenance 2.4 mg dose.

Bridge between the "to-be-marketed" and clinical trial formulations	The to-be-marketed (TBM) drug product [i.e., single-dose pen-injector (DV3396) with formulation D] was bridged to the clinical product [i.e., multi-dose cartridge-based PDS290 pen-injector with formulation B] using the pivotal pharmacokinetic (PK) bioequivalence (BE) trial (Trial 4590). Semaglutide BE was demonstrated following TBM drug product compared to clinical product.

1.2 Post-Marketing Requirements and Commitments

None.

2. SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT

2.1 Pharmacology and Clinical Pharmacokinetics

Semaglutide is a long-acting GLP-1 receptor agonist (GLP-1 RA), which consists of human GLP-1 analog, C18 fatty di-acid and a hydrophilic spacer. Semaglutide has a long half-life (i.e., 155 hours) supporting once weekly injection. Semaglutide has prolonged plasma half-life compared to endogenous GLP-1 due to the increased stability of GLP-1 against DPP-4 enzyme with amino acid substitution from endogenous GLP-1 and increased protein binding from both the fatty acid side chain and spacer.

The following is a summary of the clinical pharmacokinetics of semaglutide at steady-state in subjects with overweight (BMI: $\geq$ 27.0 to <30 kg/m^2) or obesity (BMI: $\geq$ 30 kg/m^2):

Absorption:	• The maximum plasma concentration (C_{max}) was reached at a median time of 24 hours with range of 3 to 48 hours. • The area under concentration-time profile ($AUC_{0\text{-}7days}$) and Cmax were 5729 nmol*h/L and 46.3 nmol/L, respectively. • A steady-state was known to reach approximately in 4-5 weeks following once weekly administration. • PK of semaglutide was proportional between 1 mg and 2.4 mg once weekly.
Distribution:	• The volume of distribution (Vss/F) was 9.8 L (CV, 23.4%).
Elimination:	• The elimination half-life was 155 hours. • The clearance (CL/F) was 0.04 L/h (CV, 22.6%) • The primary elimination involves known protein catabolism

2.2 Dosing and Therapeutic Individualization

2.2.1 General dosing

The therapeutic and maintenance dose is 2.4 mg once weekly starting with 0.25 mg once weekly and then following a dose escalation regimen with dose increases every 4 weeks (to doses of 0.5, 1.0, and 1.7 mg once weekly) till 2.4 mg once weekly is reached.

2.2.2 Therapeutic individualization

No separate dose/dosing regimen is recommended in patient subgroups due to intrinsic (age, sex, race, body weight, renal impairment or hepatic impairment) and extrinsic factors.

Dose-escalation was used to mitigate GI AEs (e.g., nausea and/or vomiting), based on the Phase 2 dose-finding information, and prior experience from semaglutide for T2DM and GLP-1 RA drug class.

The dose can be temporarily decreased to 1.7 mg weekly, for a maximum of 4 weeks if patients do not tolerate the maintenance 2.4 mg dose.

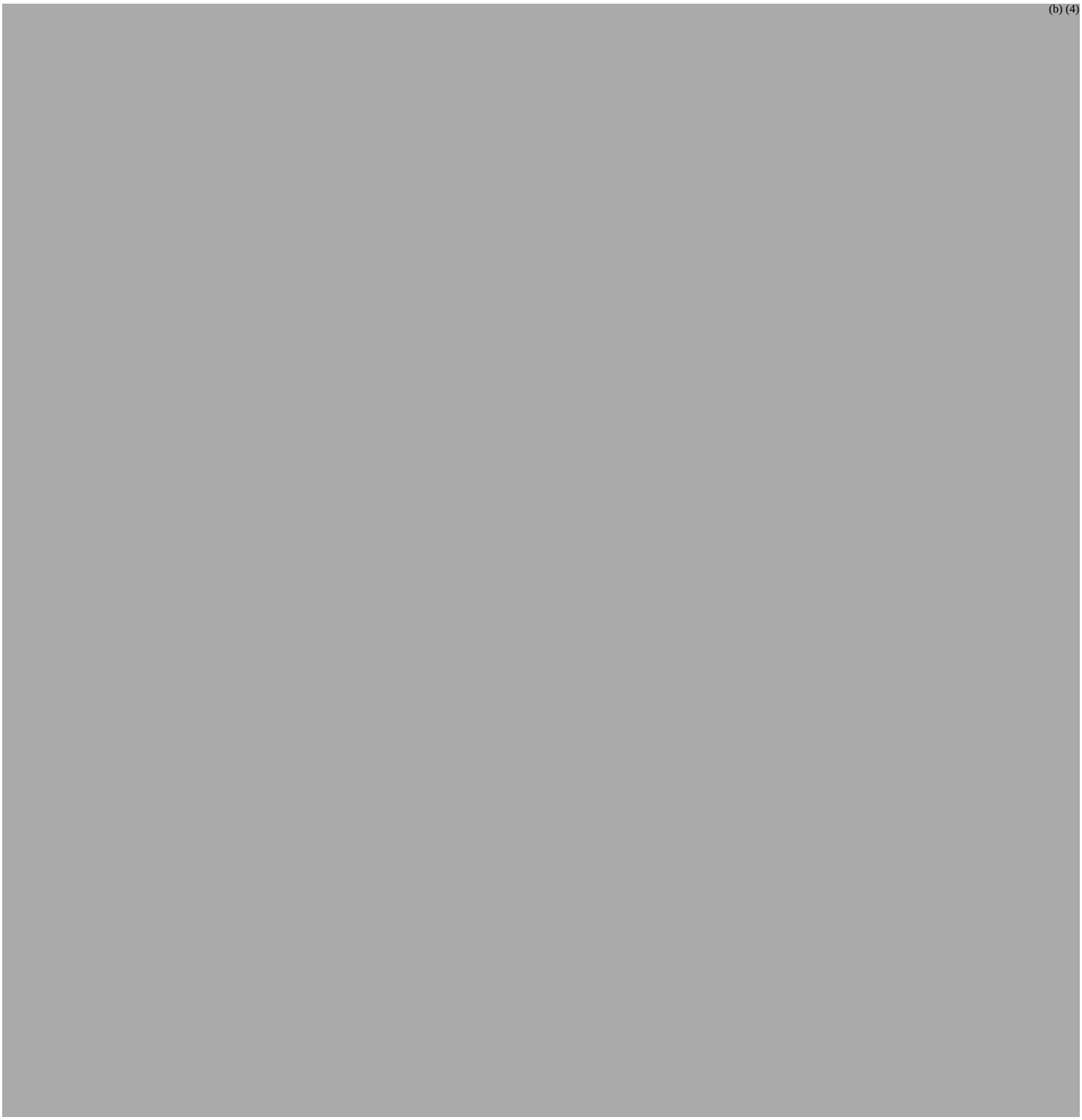
2.3 Outstanding Issues

None.

2.4 Summary of Labeling Recommendations

The Office of Clinical Pharmacology recommends the following labeling recommendations be included in the final package insert:

(b) (4)



3. COMPREHENSIVE CLINICAL PHARMACOLOGY REVIEW

3.1 Overview of the Product and Regulatory Background

Semaglutide has been approved for T2DM as follows:

- Once weekly SC administration (NDA 209637 for Ozempic®) on December 5, 2015 with the starting dose of 0.25 mg and then increasing to 0.5 mg once weekly after 4 weeks of 0.25 mg dosing and further to 1 mg once weekly if additional glycemic control is needed after 4 weeks on 0.5 mg dose.
- Once daily oral administration (NDA 213051 for Rybelsus®) on September 20, 2019 with the starting dose of 3 mg once daily and then increase to 7 mg once daily after 30 days of 3 mg dosing and further to 14 mg once daily if additional glycemic control is needed after at least 30 days on the 7 mg dose.

Semaglutide was administered using formulation with two strengths (Formulation B – 1 mg/mL and 3 mg/mL) in Phase 3 programs. Injection volumes were significantly different among doses due to limited strengths of formulation (Table 1). Injection volume has been shown previously to affect semaglutide PK. The applicant presented a plan at the EOP2 meeting for developing a formulation with more strengths (Formulation D, Table 1) to minimize variability in injection volume among doses after completion of Phase 3 trials. In addition to the proposed changes in the formulation, the applicant proposed to use a new single-dose pen-injector (DV3396) for each of the five doses of semaglutide in TBM product compared to a multi-dose cartridge pen-injector (PDS290) in Phase 3 trials (Table 1). The Agency recommended a pivotal PK bridging for the proposed changes in formulation and device of TBM product compared to those of clinical product. The Agency and applicant agreed on the trial design for the pivotal PK bridging trial including the primary PK endpoints at steady-state following the proposed dosing regimen and inclusion of PD (body weight change) as a secondary endpoint.

The clinical pharmacology information was evaluated in two Phase 1 trials (Trial 4590 for the pivotal PK bridge and Trial 4455 for gastric emptying assessment), one Phase 2 trial (Trial 4135 for dose-finding), two Phase 3 trials (Trial 4373 to support weight management and Trial 4374 to support weight management in T2DM), and population analysis on PK and exposure-response relationship. Further, clinical pharmacology information related to intrinsic and extrinsic factors is referred to those of Ozempic.

Table 1 Semaglutide drug products used in Phase 3 and TBM
(Source; Table 1-1, 2.7.1, eCTD)

Product	Phase 3a					TBM				
Delivery device	PDS290 (multi-dose cartridge pen-injector)					DV3396 (single-dose pen-injector)				
Type of dose	Escalation				Mainte-nance	Escalation				Mainte-nance
Dose	0.25 mg	0.5 mg	1 mg	1.7 mg	2.4 mg	0.25 mg	0.5 mg	1 mg	1.7 mg	2.4 mg
Injection volume	0.25 mL	0.5 mL	0.34 mL	0.57 mL	0.80 mL	0.5 mL	0.5 mL	0.5 mL	0.75 mL	0.75 mL
Formulation	B					D				
Semaglutide concentration (strength)	1.0 mg/mL		3.0 mg/mL			0.5 mg/mL	1.0 mg/mL	2.0 mg/mL	2.27 mg/mL	3.2 mg/mL

3.2 General Pharmacological and Pharmacokinetic Characteristics

Semaglutide is a long-acting GLP-1 RA with structural modification of human GLP-1 (7-37) to reduce degradation by the DPP-4 enzyme and attachment of a long-chain fatty acid (octadecanedioic acid) through a hydrophilic linker (ado and glutamate) to enhance protein binding (Figure 1). The molecular mass of semaglutide is 4113.6 Da.

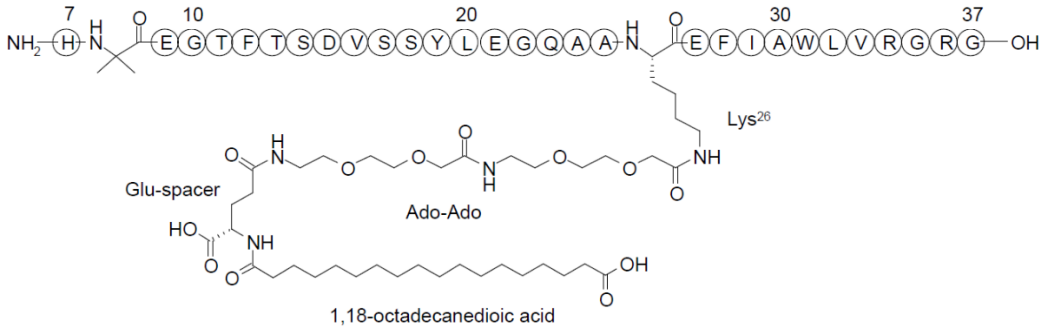


Figure 1 Structure of semaglutide
(Source: Figure 1, Module 2.4. eCTD)

3.2.1 Mechanism of Action:

Semaglutide acts as a GLP-1 RA that binds to and activates the GLP-1 receptor.

GLP-1 is a physiological regulator of appetite and caloric intake, and the GLP-1 receptor is present in several areas of the brain involved in appetite regulation. In addition, GLP-1 can reduce blood glucose through a mechanism where it stimulates insulin secretion and lowers glucagon secretion, both in a glucose-dependent manner. The mechanism of blood glucose lowering also involves a delay in gastric emptying in the early postprandial phase.

3.2.2 Pharmacokinetics:

3.2.2.1 Absorption

The steady-state PK of semaglutide was evaluated following the proposed dosing regimen with TBM product in overweight subjects or with obesity (Trial 4590).

The median (minimum, maximum) time to peak serum concentration (T_{max}) was 24 (3,48) hours (Figure 2).

The PK was apparently dose-proportional at steady state as ratios of semaglutide PK between 1 mg and 2.4 mg was close to ratio of dose (2.4); ratios of AUC and C_{max} were 2.57 (2.49,2.65) and 2.57 (2.42,2.73), respectively. Semaglutide concentration at trough (Ctrough) were measured before increasing the dose to the next level and results indicate that values of Ctrough were

proportional to doses (Figure 2, right). The observed Ctrough in Phase 3 trial (STEP 2) was proportional to dose (Figure 3).

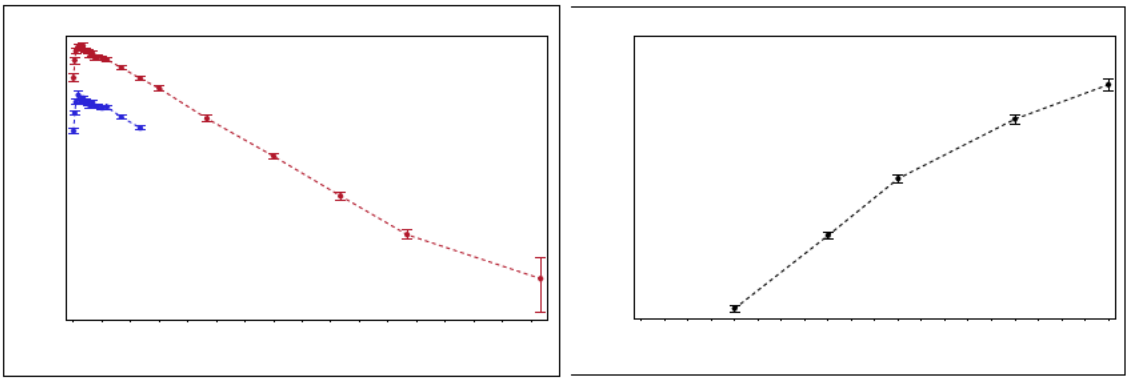


Figure 2 Mean (SE) semaglutide concentration-time profile (left, blue symbol for 1 mg and red symbol for 2.4 mg) and Ctrough (right) at steady-state (on log scale) in overweight subjects or with obesity (Trial 4590)

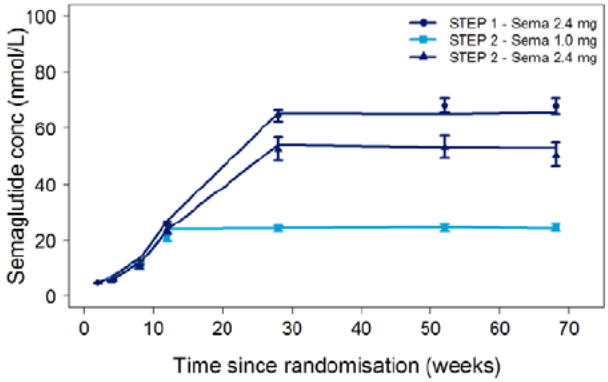


Figure 3 Observed semaglutide Ctrough since first dose
(Source; Figure 5-1, Modeling report)

3.2.2.2 Distribution and elimination

There was no apparent change in CL/F (0.042 L/h vs. 0.040 L/h) or half-life (Figure 2) between doses (1 mg vs. 2.4 mg) at steady-state. Results indicate that there was no significant dose- and/or time-dependent change in semaglutide disposition.

The estimated CL/F and Vd/F were 0.05 L/h (CV, 17.7%) and 12.4 L (CV, 39.9%), respectively, for a typical subject in population PK analysis.

3.3 Clinical Pharmacology Questions

3.3.1 Does the clinical pharmacology information provide supportive evidence of effectiveness?

Yes, the data presented in this NDA provides supportive evidence of effectiveness for SC semaglutide dosing regimen. Refer to Section 3.3.2 for additional details.

3.3.2 *Is the proposed general dosing regimen appropriate for the general patient population for which the indication is being sought?*

Yes, the proposed dosing regimen is appropriate for the weight management from a clinical pharmacology perspective.

Results of exposure-response analysis for Trial STEP 1 and 2 indicate that the efficacy (i.e., weight loss) increased in proportion to exposure in the proposed dosing regimen (Figure 4, left). In STEP 1-3, semaglutide 2.4 mg showed reductions in mean body weight of 9.6 to 16.0% (9.7 to 16.8 kg) compared to 2.4 to 5.7% (2.6 to 6.2 kg) in placebo arm. The gastrointestinal adverse events also increased with increasing dose/exposure from 1 mg to 2.4 mg (Figure 4, right). It was concluded that the safety and tolerability profiles including GI AEs were consistent to prior experience with semaglutide and GLP-1 RA without no new or unexpected observations.

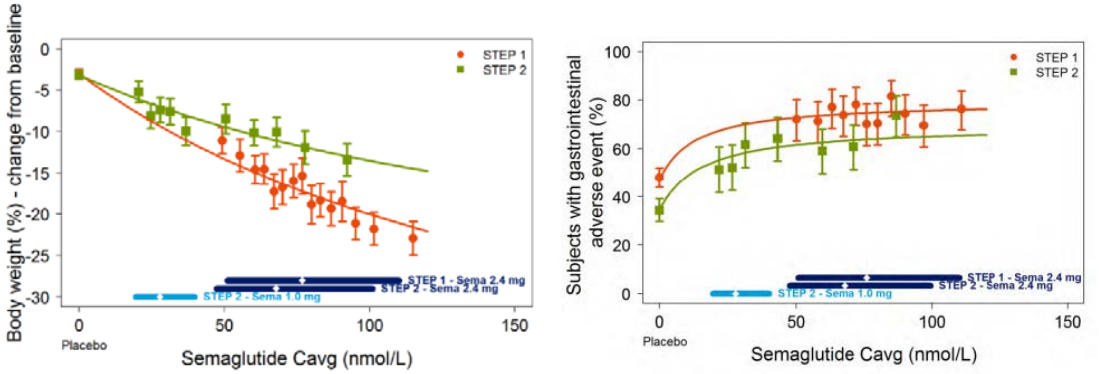


Figure 4 Relationship between body weight change (right) or proportion of subjects reporting GI AEs of any kind and severity (left) and exposure (Cavg)

Cavg; derived from individual parameter estimated of CL/F, target dose and dosing interval

(Source; Figure 5-10 and 5-17, 5.3.3.5, Modeling Report, eCTD)

The applicant conducted a dose-finding trial following daily subcutaneous doses of semaglutide and observed apparent maximum body weight reduction (Figure 5, left) and acceptable tolerability profiles (Figure 14, Appendix) at 0.4 mg/day. For the dose selection of Phase 3 trial, the applicant chose 2.4 mg once weekly as it was close to the total weekly dose following 0.4 mg/daily and with a lower Cmax according to the exposure simulation (Figure 5, right).

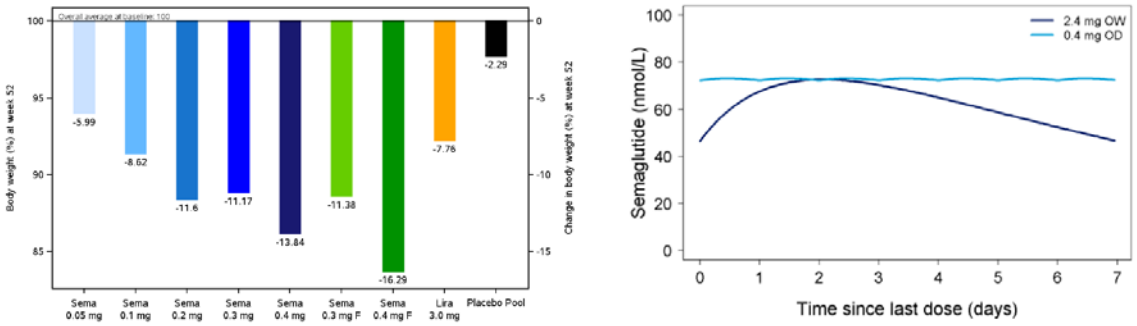


Figure 5 Dose-body weight at Week 52 (Trial 4153, left) and simulated mean PK profiles for once-daily 0.4 mg (Trial 4153) and once weekly 2.4 mg semaglutide (right)

(Source; Figure 11-3, CSR, Trial 4153, Figure 18, Modeling report)

Missed dosing: Exposure profiles were simulated using the population PK model to support labeling for a worst-case scenario of missed dose (i.e., 5 days delay and scheduled 2 days after the delay in dosing) as described in Ozempic labeling. The scenario was predicted to reduce Ctrough by approximately 46% and increase Cmax by 12%. Those changes returned to typical fluctuation within 3 once weekly dosing intervals (Figure 6). Further the scenario was implemented in Phase 3 trial protocols. Therefore, the following proposed labeling is acceptable.

Proposed labeling in Section 2.2 Important Administration Instructions:

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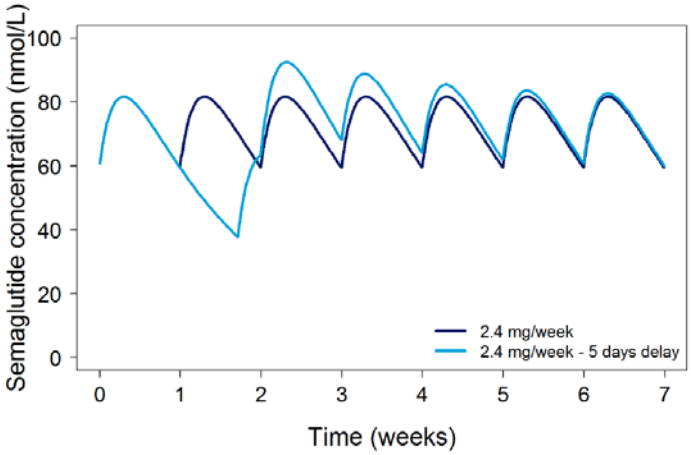


Figure 6 **Simulated semaglutide concentration profiles following delayed doses**
(Source; Figure 5-7, Modeling report, Population PK and Exposure-response Analysis)

Effect on QT/QTc interval:
The applicant did not conduct a dedicated QT/QTc trial following the proposed therapeutic dose of 2.4 mg once weekly. The applicant referred results of previously conducted thorough QTc (TQT) trial in Ozempic, which was conducted following 1.5 mg once weekly in healthy subjects (Trial 3652). The trial result indicates that there is no prolongation of the QTc interval [ΔΔQTcF (90%CI) = 0.2 ms (-2.8, 3.2) for 1.5 mg] and no concentration-QTc (C-QT) relationship. Further, there was no apparent increase in ΔΔQTcF above zero during the treatment period (up to 48 hours). The applicant concluded that results of Trial 3652 were adequate to support the weight management indication with the proposed therapeutic dose of 2.4 mg once weekly based on the estimated population average exposure (e.g., Cavg and Cmax) comparability between the TQT trial (Trial 3652) and Phase 3 trials for the target populations (e.g., STEP 1-2) (Figure 7). However, the exposure range following the proposed dosing in the target populations seems to be not fully covered by that of the TQT trial. Although the applicant concluded that there was no apparent difference in the proportion of subjects with ECG abnormalities between the treatment groups in

Phase 3 trials, ECGs data had limitation as they were interpreted by investigators without QT prolongation data. To qualitatively evaluate the C-QT at semaglutide concentrations beyond coverage by Trial 3652, subjects with potential Cavg outlier (i.e., arbitrarily defined as greater than 150 nmol/L) were identified (a total of 3 from STEP1-2) and QTcF data from those subjects indicate that there was no apparent C-QT relationship.

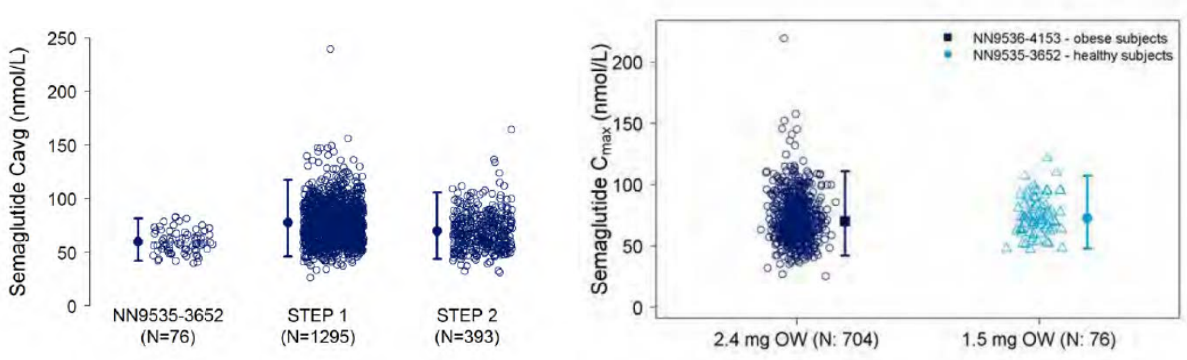


Figure 7 Relationship between estimated semaglutide exposure between Trial 3652 and STEP 1-2
(Source; Figure 4-1, 2.7.2, eCTD)

Immunogenicity:
The proportion for subjects with positive anti-drug antibody (ADA) at any time post-baseline was 2.9% (N=50) in STEP 1-2, and approximately half of positive ADA measures was transient. Neutralizing antibody cross-reacting with endogenous GLP-1 (NAb) was 1.6% for semaglutide treatment arm. According to Ozempic labeling, ADA was developed in 1.0% subjects and NAb was detected in 0.6% subjects. In general, ADA and NAb detection rates are low and its impact on PK was not significant (Figure 8).

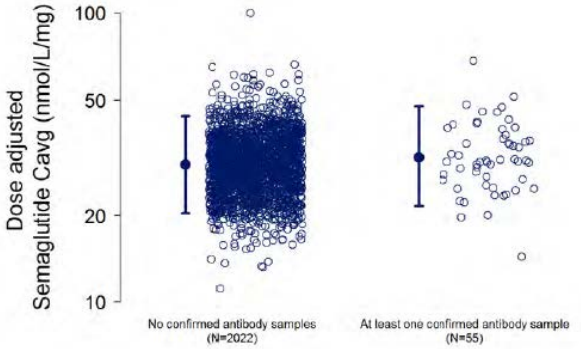


Figure 8 Semaglutide exposures for subjects with and without anti-semaglutide antibodies
(Source; Figure 4-2, 2.7.2, eCTD)

3.3.3 Is an alternative dosing regimen and management strategy required for subpopulations based on intrinsic factors?

3.3.3.1 Race, Sex, Body weight, Age, and Renal Function

Results from the clinical pharmacology trials and population PK analysis of data from Phase 3 trials indicate that dose adjustment is not required for patients based on intrinsic factors such as sex, body weight, race, ethnicity or renal function (Figure 9). Although semaglutide exposure decreased with increase in body weight, the therapeutic dose 2.4 mg once weekly provide adequate exposure over the body weight range of 54 to 246 kg in the clinical trials. Analysis results are consistent with prior experience at Ozempic.

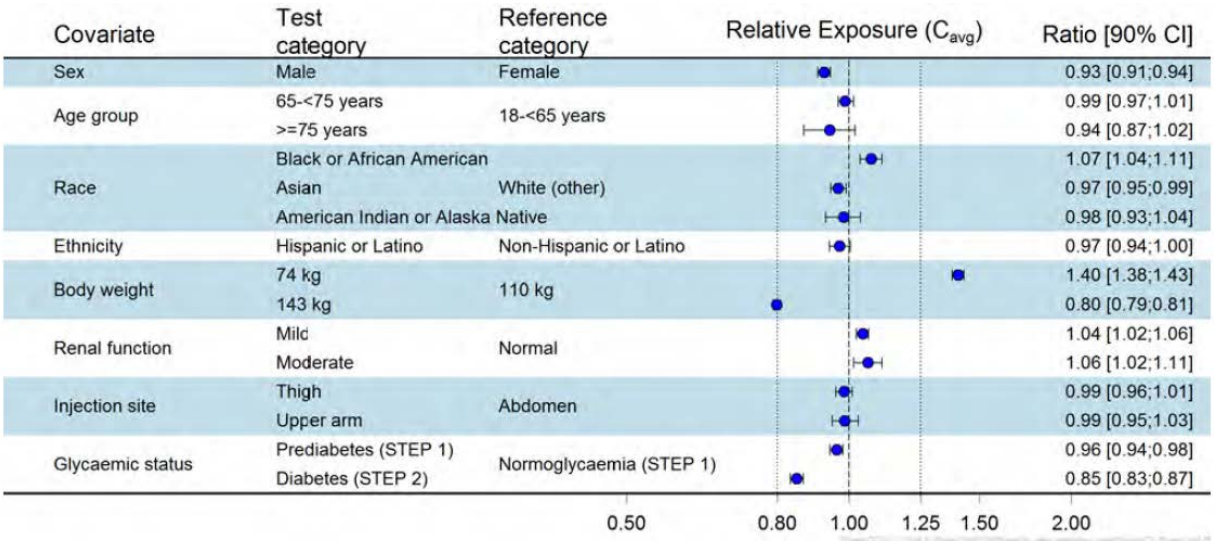


Figure 9 Forest plot for covariate effects for semaglutide exposure
(source, Figure 3-4, 2.7.2, eCTD)

3.3.4 Are there clinically relevant drug-drug interactions and what is the appropriate management strategy?

The applicant referred to the information in Ozempic labeling for drug-drug interactions. In addition, the sponsor conducted a drug interaction study with paracetamol (also known as acetaminophen).

Although it was concluded that semaglutide 1.0 mg did not significantly affect gastric emptying time (GET) in Ozempic labeling, the applicant evaluated the drug interaction potential for semaglutide 2.4 mg with paracetamol as the relationship between semaglutide dose and GET was not clear. Single dose of paracetamol 1500 mg was administered with a standard breakfast at baseline without semaglutide (Visit 2) and when semaglutide was at steady-state at Visit 7 (Week 20, at steady-state with 2.4 mg) in subjects with obesity (N=35). Paracetamol was administered on the second day of semaglutide 2.4 mg dosing (Visit 7) (see trial design in Appendix).

It was concluded that there was no significant impact of 2.4 mg on paracetamol PK according to the post-hoc analysis (Table 2). There was statistically significant effect of semaglutide on paracetamol PK (8% difference in paracetamol AUC_{0-5h}, Table 2). However, there was

approximately 10% body weight reduction in the semaglutide treatment arm compared to no significant changes in the placebo arm. The observed differential body weight change between treatment arms may directly affect paracetamol PK in addition to its impact through the GET delay. To address the impact of weight reduction on paracetamol PK, the applicant conducted post-hoc analysis using body weight adjusted paracetamol PK. The post-hoc analysis indicate that the body weight adjustment resulted in no statistical significance (Table 2). Conclusions based on the post-hoc analysis is acceptable to support labeling related to the impact of semaglutide 2.4 mg on paracetamol PK from a clinical pharmacology perspective.

Table 2 Effect of semaglutide on gastric emptying – paracetamol AUC and C_{max} (Trial 4455)
(Source; Table 3-4, 2.7.2, eCTD)

	Estimate	95% CI	p-value
PRIMARY ANALYSIS			
AUC paracetamol, 0-5h (ug*h/mL)			
Treatment ratio			
Sema 2.4 mg / Placebo	1.08	[1.02 ; 1.14]	0.0054
AUC paracetamol, 0-1h (ug*h/mL)			
Treatment ratio			
Sema 2.4 mg / Placebo	0.99	[0.87 ; 1.12]	0.8474
Cmax paracetamol, 0-5h (ug/mL)			
Treatment ratio			
Sema 2.4 mg / Placebo	0.94	[0.82 ; 1.07]	0.3299
POST-HOC ANALYSIS – adjusting for body weight at week 20			
AUC paracetamol, 0-5h (ug*h/mL)			
Treatment ratio			
Sema 2.4 mg / Placebo	1.05	[0.99 ; 1.12]	0.1218
AUC paracetamol, 0-1h (ug*h/mL)			
Treatment ratio			
Sema 2.4 mg / Placebo	0.94	[0.82 ; 1.06]	0.3069
Cmax paracetamol, 0-5h (ug/mL)			
Treatment ratio			
Sema 2.4 mg / Placebo	0.90	[0.79 ; 1.04]	0.1464

3.3.5 Was there PK bridging between to-be-marketed product and clinical trial product?

Yes, the applicant conducted the pivotal PK comparability trial (Trial 4590) to bridge the proposed to-be-marketed product (single-dose prefilled pen-injector and formulation D) to the clinical product (multi-dose cartridge pen-injector and formulation B). See the Regulatory Background (section 3.1) for the bridging objective and trial design in Appendix (4.2.1).

The BE of semaglutide was assessed in a Phase 1, randomized, open-label trial comparing semaglutide PK following the proposed dosing regimen with the TBM product versus clinical

product in subject with overweight or obesity (Trial 4590). Dose-escalation was introduced to mitigate potential GI AEs with 2.4 mg dosing. The primary endpoint was the semaglutide AUC and Cmax, and the secondary endpoint was change in body weight (see trial design in Appendix).

Results of analysis indicates that the BE of semaglutide was demonstrated between the TBM and clinical product (Table 3). There was no apparent difference in body weight change (Figure 10) with the two products.

Table 3 Statistical analysis for semaglutide BE assessment
(Source; Table 11-1, CSR, Trial 4590)

	FAS	N	Estimate	95% CI	90% CI
AUC, 0-168h (nmol*h/L)					
Mean					
Semaglutide D, DV3396	33	29	14572	[13937 ; 15236]	
Semaglutide B, PDS290	31	30	13827	[13234 ; 14446]	
Treatment ratio					
Semaglutide D, DV3396 / Semaglutide B, PDS290			1.0539		[1.0003 ; 1.1104]
Cmax (nmol/L)					
Mean					
Semaglutide D, DV3396	33	29	118	[112 ; 125]	
Semaglutide B, PDS290	31	30	102	[96.8 ; 108]	
Treatment ratio					
Semaglutide D, DV3396 / Semaglutide B, PDS290			1.1556		[1.0800 ; 1.2365]

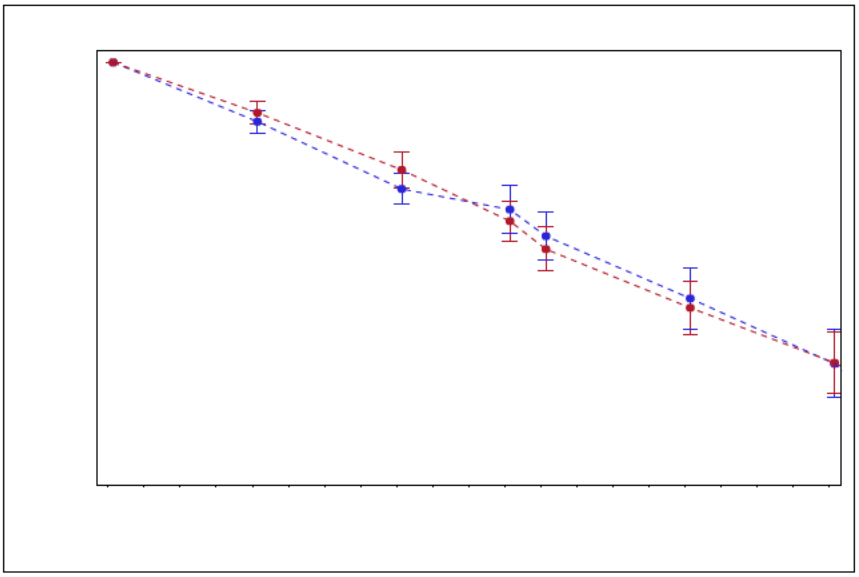


Figure 10 Change in body weight (% from baseline) during the treatment (red symbol for TBM product and blue symbol for clinical product)

The on-site inspection for the bioanalytical and clinical trial sites (Trial 4590) was requested to the Office of Study Integrity and Surveillance (OSIS). The OSIS determined that the inspection was not warranted for the sites as the Office of Regulatory Affairs and OSIS inspected the clinical and bioanalytical sites recently.

4. APPENDICES

4.1 Summary of Bioanalytical Method Validation

Semaglutide concentrations in human plasma were quantified using plasma protein precipitation followed by LC-MS/MS assays.

In general, the bioanalytical methods (Table 4) were acceptable refering guidelines in the guidance (https://www.fda.gov/media/70858/download).

Table 4 Summary of bioanalytical method validation
(Source; Appendix 16.2.9, CSR, Trial 4459)

Analyte		Semaglutide	
Matrix (Anticoagulant)		Human plasma (K_3EDTA)	
Preservative		N/AP	
SOP Number		SOP SM1-385A	
Assay Method		LC-MS/MS method following protein precipitation	
Detector		Applied Biosystems/MDS SCIEX API QTrap® 5500	
Assay Volume Required		0.10 mL	
Standard Curve Range		0.729 – 60.8 nmol/L (3.00 – 250 ng/mL)	
Regression Type		Linear (1/concentration^2)	
Quantification Method		Peak Area Ratio	
Quality Control Samples		Precision (%)	Accuracy (%)
Between-run (Watson runs 2, 3, 4)	LLOQ (QC 3)	6.8	100.2
	QC 9	3.9	99.9
	QC 40	3.3	99.7
	QC 200	3.3	98.0
Within-run (Watson run 3)	LLOQ (QC 3)	4.8	96.1
	QC 9	2.7	98.9
	QC 40	2.2	98.6
	QC 200	3.6	96.3
Selectivity		No interference, 10 matrix lots investigated	
Sensitivity		Within acceptance	
Matrix Effect		Within acceptance, 7 matrix lots investigated	
Carry-over		Within acceptance	
Stress test		No cross-well contamination	
Interference in haemolysed matrix		No interference observed	
Impact of haemolysis		No impact on precision and accuracy observed	
Processed Sample Integrity		Demonstrated for up to 172 hours at 5°C	
Performance of Acquity UPLC Iclass Binary Solvent Manager		Not demonstrated	
Stability of Semaglutide N15 C13 (IS):			
Short-term stability in solution		Demonstrated at room temperature for at least: • 20 hours at 1.20 mg/mL (as delivered by Sponsor) • 20 hours in methanol / water / formic acid (80:20:0.2 v/v/v) at 12.0 µg/mL • 29 hours in BSA / water (0.5:100 w/v) at 150 ng/mL	
Long-term stability in solution		Demonstrated at -20°C for at least 65 days in methanol / water / formic acid (80:20:0.2 v/v/v) at 12.0 µg/mL	
Stability of Semaglutide:			
Long-term stability in matrix		Demonstrated at -20°C for at least 463 days in matrix (at low QC, high QC and DQC level)	
Batch Size		Up to (b) (4) injections	

4.2 Summary of Individual Clinical Pharmacology Studies

4.2.1. Trial 4590 – Pivotal PK bridging trial for the TBM product compared to clinical product

Title: A trial to demonstrate bioequivalence between semaglutide formulation D with the DV3396 pen-injector and formulation B with the PDS290 pen-injector in subjects with overweight or obesity.

Objective:

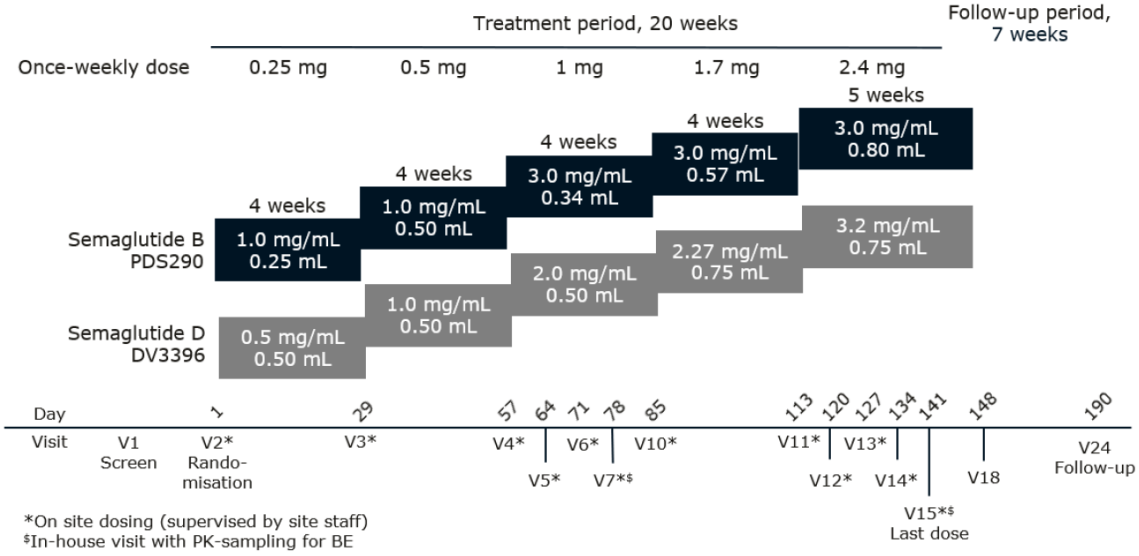
Primary objective:

- To demonstrate bioequivalence between s.c. administrations of the semaglutide formulation used with the DV3396 pen-injector and the semaglutide formulation used with the PDS290 pen-injector for the semaglutide 2.4 mg dose.

Secondary objectives:

- To demonstrate bioequivalence between s.c. administrations of the semaglutide formulation used with the DV3396 pen-injector and the semaglutide formulation used with the PDS290 pen-injector for the semaglutide 1.0 mg dose.
- To investigate changes in body weight following s.c. once-weekly doses of the semaglutide formulation used with DV3396 pen-injector and the formulation used with PDS290 pen-injector in subjects with overweight or obesity.

Figure 11 Trial design (Trial 4590)
(Source; Figure 9-1, CSR)



Major trial results:

- Semaglutide BE of 2.4 mg once weekly with TBM product was demonstrated referencing that of clinical product (primary endpoints, Table 4)
- Semaglutide BE of 1.0 mg once weekly with TBM product was demonstrated referencing that of clinical product (secondary endpoints)

Table 5 Statistical analysis for semaglutide BE assessment
(Source; Table 11-2, CSR, Trial 4590)

	FAS	N	Estimate	95% CI	90% CI
AUC, 0-168h (nmol*h/L)					
Mean					
Semaglutide D, DV3396	33	33	5729	[5500 ; 5968]	
Semaglutide B, PDS290	31	31	5532	[5303 ; 5770]	
Treatment ratio					
Semaglutide D, DV3396 / Semaglutide B, PDS290			1.0357		[0.9860 ; 1.0879]
Cmax (nmol/L)					
Mean					
Semaglutide D, DV3396	33	33	46.3	[43.4 ; 49.3]	
Semaglutide B, PDS290	31	31	42.0	[39.3 ; 44.9]	
Treatment ratio					
Semaglutide D, DV3396 / Semaglutide B, PDS290			1.1014		[1.0202 ; 1.1891]

- Semaglutide PK was proportional between 1.0 and 2.4 mg
- There was no significant difference between products in body weight change from baseline at the end of treatment (secondary PD endpoints)

Table 6 Statistical analysis for semaglutide BE assessment
(Source; Table 11-7, CSR, Trial 4590)

	FAS	N	Estimate	SE	95% CI	p-value
Body weight, relative change from baseline (%)						
Mean						
Semaglutide D, DV3396	33	30	-9.3	0.8		
Semaglutide B, PDS290	31	30	-9.0	0.8		
Treatment difference						
Semaglutide D, DV3396 - Semaglutide B, PDS290			-0.3		[-2.5 ; 2.0]	0.8148

- Ctrough concentrations were proportional to doses

Table 7 Semaglutide trough values - descriptive statistics
(Source; Table 16.2.5.1, CSR)

	Pre-dose	Sema 0.25 mg	Sema 0.5 mg	Sema 1 mg	Sema 1.7 mg	Sema 2.4 mg
Number of subjects	64	64	63	64	64	60
Semaglutide D, DV3396						
N	33	33	33	33	33	30
N<LLOQ	33	0	0	0	0	0
Mean (SD)	0.00 (0.00)	6.00 (1.14)	12.94 (2.42)	25.33 (5.77)	44.91 (13.00)	63.82 (24.83)
Geometric mean (CV)	. (.)	5.90 (18.4)	12.74 (18.3)	24.73 (22.6)	42.87 (33.9)	60.75 (30.3)
Median	0.00	5.69	12.60	24.20	41.20	59.50
Min ; Max	0.00 ; 0.00	3.91 ; 8.83	8.73 ; 19.00	12.90 ; 43.20	12.40 ; 77.20	36.60 ; 176.00
Semaglutide B, PDS290						
N	31	31	30	31	31	30
N<LLOQ	31	1	0	0	0	0
Mean (SD)	0.00 (0.00)	5.40 (1.71)	12.23 (2.57)	24.15 (4.34)	40.73 (12.96)	62.72 (14.03)
Geometric mean (CV)	. (.)	4.89 (64.0)	11.98 (20.6)	23.78 (17.9)	38.19 (41.1)	61.31 (21.7)
Median	0.00	5.39	11.60	23.60	42.10	61.10
Min ; Max	0.00 ; 0.00	0.36 ; 9.30	8.27 ; 19.30	16.50 ; 32.70	14.00 ; 65.20	40.90 ; 105.00

N: Number of subjects with available data, LLOQ: Lower limit of quantification, SD: Standard deviation
CV: Coefficient of variation in %
Trough values are measured after each 4 weeks of treatment.
* Pre-dose sample taken prior to first dosing.

4.2.2. Trial 4455 – PD assessment

Title: Effect of semaglutide 2.4 mg once weekly on gastric emptying in subjects with obesity

Objectives:

Primary objective:

- To compare the effect of semaglutide s.c. 2.4 mg once-weekly and placebo on gastric emptying

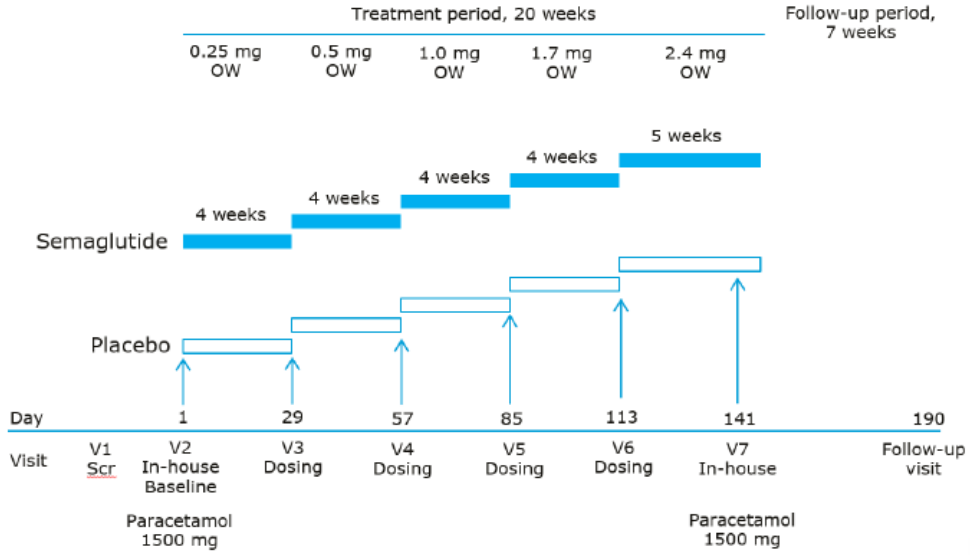
Secondary objectives:

- To compare the effect of semaglutide s.c. 2.4 mg once-weekly and placebo on *ad libitum* energy intake
- To compare the effect of semaglutide s.c. 2.4 mg once-weekly and placebo on appetite using Visual Analogue Scale

Exploratory objective

- To compare the effect of semaglutide s.c. 2.4 mg once-weekly and placebo on control of eating using Control of Eating Questionnaire

Figure 12 Trial design (Trial 4455)
(Source, Figure 9-1, CSR, Trial 4455)



Treatment period is 20 weeks from first to last dose (total of 21 weekly doses). Follow-up period is 7 weeks after last dose. Randomisation 1:1. OW: once weekly

Major trial results:

- There was no significant impact of semaglutide 2.4 mg once weekly on paracetamol PK following adjustment of body weight.
- Body weight was reduced as expected with semaglutide treatment.
- Semaglutide 2.4 mg once weekly reduced energy intake and appetite. However, secondary and exploratory endpoints were estimated using patient-reported outcome scales and control of eating questionnaire, respectively, and their results may not be adequate to support labeling due to exploratory nature of assessment.

Trial flow chart

	Screening		Pre-treatment	Randomisation	Treatment						Follow-up		
Visit	0	1	2		3	4	5	6	7 (D1)	7 (D2)	8	7X[a]	8X[b]
Study day			-1	1	29	57	85	113	141	142	190		
Visit window (Days)		2-28 days before V2	±0	±0	±2	±2	±2	±2	±1	±1	±4		
SUBJECT RELATED INFORMATION AND ASSESSMENTS													
Informed consent	X[c]												
Inclusion criteria		X	X[d]										
Exclusion criteria		X	X[d]										
Eligibility criteria			X										
Randomisation				X									
Randomisation criteria				X									
Discontinuation criteria			X	X	X	X	X	X	X	X			
Concomitant illness		X											
Concomitant medication		X	X	X	X	X	X	X	X	X	X	X	X
Demography[e]		X											
Medical history		X											
Pregnancy test[f]		X	X		X	X	X	X	X		X	X	X
Pregnancy test (Serum HCG)		X							X			X	
Pregnancy test (Urine HCG)			X		X	X	X	X			X		X
Childbearing potential		X											
Tobacco and nicotine products use[g]		X											
EFFICACY													
Body measurements													
Height		X											
Body weight		X		X					X		X	X	X
BMI		X											
Meal Test													
Meal test - Standard meal[h]				X[i]						X			
Meal test - Ad libitum meal				X[i]						X			
Appetite VAS[j]				X[i,l]						X[l]			
Appeal VAS[k]				X[i]						X			
Clinical outcome assessments (COA)													
Control of eating questionnaire[m]			X						X[i]				
Meal test profiles													
Serum paracetamol				X[i,l]						X[i]			
SAFETY													
Adverse event		X	X	X	X	X	X	X	X	X	X	X	X
Screen for alcohol													
Urine alcohol screen		X	X						X[i]			X	
Screen for drugs													
Urine drugs screen		X	X						X[i]			X	
ECG[n]													
12-lead ECG, single recording		X							X[i]			X	
Biochemistry		X							X[i]			X	
Glucose metabolism													
Glucose, plasma		X[m]											
HbA1c		X											
Physical examination		X							X[i]			X	
Vital signs													
Systolic blood pressure		X	X		X	X	X	X	X[i]		X	X	X
Diastolic blood pressure		X	X		X	X	X	X	X[i]		X	X	X
Pulse		X	X		X	X	X	X	X[i]		X	X	X
Body temperature		X	X						X[i]		X	X	X
Haematology													
Leukocytes		X							X[i]			X	
Thrombocytes		X							X[i]			X	
Haemoglobin Blood		X							X[i]			X	
OTHER ASSESSMENTS													
PK sampling													
Semaglutide plasma				X[i]	X[i]	X[i]	X[i]	X[i]	X[i]			X	
TRIAL MATERIAL													
Drug accountability				X	X	X	X	X	X			X	
Administration of trial product				X	X	X	X	X	X				
Dispensing visit				X	X	X	X	X	X				
REMINDERS													
Hand out directions for use[o]				X									
Training in trial product, pen-handling[o]		X		X	X								
Hand out dose reminder card[o]				X									
Hand out and instruct in Diary				X	X	X	X	X		X			
Collect diary					X	X	X	X	X		X	X	X
Hand out ID card		X											
Attend visit fasting		X	X	X					X	X			
Sign-off case-book													X
End of Trial													X

a Visit 7X, day 1 will be performed as soon as possible after discontinuation Control of Eating Questionnaire (COEQ) and trial product will not be administered
b Visit 8X will be performed 49 days after last trial product administration
c The informed consent must be obtained before any trial related procedures Date of informed consent will be recorded in the CRF (case report form) at visit 1
d Confirmation that the subject is eligible for continuation in the trial This is not a repeat of assessment but a review of results from screening
e Demography consists of age, sex, ethnicity and race (according to local regulation)
f Pregnancy tests only to be performed in females of child-bearing potential
g Smoking is defined as smoking at least one cigarette or equivalent daily
h A standardised energy fixed breakfast meal with regular macronutrient composition and 1500 mg paracetamol (for gastric emptying assessment) Subjects will be instructed that paracetamol is not allowed within 72 h prior to standardised meal test
I Prior to dosing
J Visual analogue scales for appetite (hunger, fullness, satiety, prospective food consumption, thirst, nausea and well-being)
K Visual analogue scales for appeal (taste, visual appearance and overall pleasantness)
L Pre-meal samples/assessments to be taken fasting
M Must be taken in a fasting state
N Overall interpretation will be collected
O Hand out of dose reminder card and direction for use as well as training in pen-handling can be repeated as necessary throughout the trial

Table 8 Gastric emptying – endpoints derived from paracetamol concentration profiles after standardized meal - descriptive statistics
(source; Table 14.21., CSR, Trial 4455)

	Sema 2.4 mg	Placebo
Number of subjects	36	36
AUC paracetamol, 0-5h (ug*h/mL)		
Visit 2 (Day 1), baseline		
N	36	36
Mean (SD)	39.8 (11.4)	42.0 (9.10)
Geometric mean (CV)	38.5 (26.3)	41.1 (21.2)
Median	36.8	41.6
Min ; Max	26.6 ; 69.1	29.3 ; 70.2
Visit 7 (Day 142), steady state of treatment		
N	35	35
Mean (SD)	47.6 (15.1)	46.0 (10.7)
Geometric mean (CV)	45.7 (29.2)	44.9 (22.3)
Median	42.9	43.7
Min ; Max	31.1 ; 84.0	32.9 ; 71.4
AUC paracetamol, 0-1h (ug*h/mL)		
Visit 2 (Day 1), baseline		
N	36	36
Mean (SD)	11.3 (3.45)	12.2 (3.53)
Geometric mean (CV)	10.9 (29.8)	11.8 (28.6)
Median	10.6	11.2
Min ; Max	6.36 ; 21.3	7.24 ; 20.7
Visit 7 (Day 142), steady state of treatment		
N	35	35
Mean (SD)	13.3 (5.01)	13.8 (3.97)
Geometric mean (CV)	12.5 (38.3)	13.2 (30.4)
Median	12.2	13.4
Min ; Max	5.55 ; 26.0	6.28 ; 24.2
Cmax paracetamol, 0-5h (ug/mL)		
Visit 2 (Day 1), baseline		
N	36	36
Mean (SD)	16.4 (4.56)	17.3 (5.03)
Geometric mean (CV)	15.8 (28.5)	16.6 (28.3)
Median	16.1	16.5
Min ; Max	9.37 ; 26.5	10.7 ; 32.0
Visit 7 (Day 142), steady state of treatment		
N	35	35
Mean (SD)	19.1 (6.81)	20.6 (6.69)
Geometric mean (CV)	18.0 (35.4)	19.6 (32.1)
Median	17.3	19.9
Min ; Max	10.3 ; 34.2	10.7 ; 40.5
tmax paracetamol, 0-5h (h)		
Visit 2 (Day 1), baseline		
N	36	36
Mean (SD)	0.51 (0.24)	0.50 (0.22)
Geometric mean (CV)	0.46 (45.1)	0.46 (46.5)
Median	0.50	0.50
Min ; Max	0.22 ; 1.50	0.25 ; 1.00
Visit 7 (Day 142), steady state of treatment		
N	35	35
Mean (SD)	0.48 (0.18)	0.46 (0.15)
Geometric mean (CV)	0.45 (41.3)	0.44 (35.8)
Median	0.50	0.50
Min ; Max	0.25 ; 0.77	0.25 ; 0.78

4.2.3. Trial 4153 – Phase 2 Dose-finding trial; Investigation of safety and efficacy of once-daily semaglutide in obese subjects without diabetes mellitus

Title: A 52-week, randomized, double-blind, placebo-controlled, sixteen-armed, parallel group, multi-center, multinational trial with liraglutide 3.0 mg as active comparator.

Objectives:

Primary objective:

- To assess and compare the dose-response of five doses of once-daily semaglutide versus placebo in inducing and maintaining weight loss after 52 weeks in obese subjects without diabetes mellitus

Secondary objectives:

- To compare the effect of once-daily semaglutide versus once-daily liraglutide 3.0 mg in inducing and maintaining weight loss after 52 weeks in obese subjects without diabetes mellitus
- To compare the effects of once-daily semaglutide to placebo and once-daily liraglutide 3.0 mg on:
  - Glucose metabolism
  - Cardiovascular risk factors
  - Change in antihypertensive and lipid-lowering medical treatment
  - Compliance with dietary counselling
  - Patient reported weight-related quality of life (QoL) and general health status
- To compare the safety and tolerability of five dose levels of once-daily semaglutide with placebo and once-daily liraglutide 3.0 mg in obese subjects without diabetes mellitus.
- To compare effect of dose escalation every 2 weeks versus that of dose escalation every 4 weeks for two dose levels of once-daily semaglutide after 52 weeks in obese subjects without diabetes mellitus.
- To compare tolerability of dose escalation every 2 weeks versus that of dose escalation every 4 weeks for two dose levels of once-daily semaglutide in obese subjects without diabetes mellitus.
- To examine criteria for identifying early responders that predict weight loss after 52 weeks.

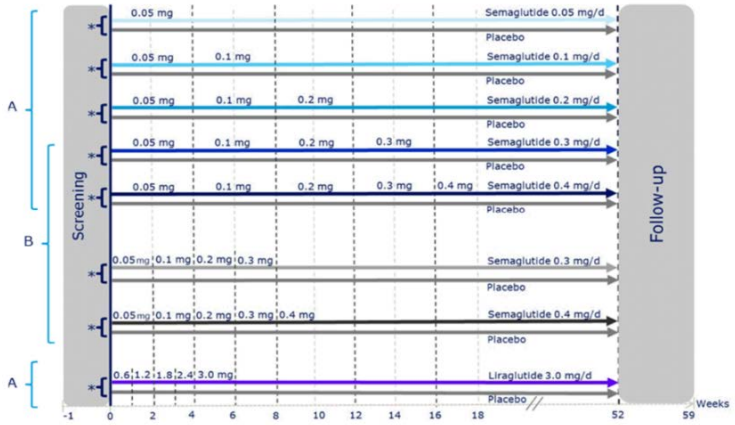


Figure 13 Trial design (Trial 4153)

(Source; Figure 9-1, CSR)

Major efficacy primary endpoints and safety:

- Overall, there was a decrease in **body weight (%)** with increasing dose from baseline at week 52, with a small deviation around the semaglutide 0.2 mg and 0.3 mg dose levels (estimated means: -5.99%, -8.62%, -11.60%, -11.17%, and -13.84% in the semaglutide 0.05 mg, 0.1 mg, 0.2 mg, 0.3 mg, and 0.4 mg arms, respectively, -11.38% and -16.29% in the semaglutide 0.3 mg F and semaglutide 0.4 mg F arms, respectively, -7.76% in the liraglutide 3.0 mg arm, and -2.29% in the pooled placebo arm) (Figure 5, left)
- During the 52 weeks of treatment, semaglutide was generally safe and well tolerated in subjects with obesity without diabetes, and overall, the safety and tolerability profile was consistent with other GLP-1 Ras (Figure 14)

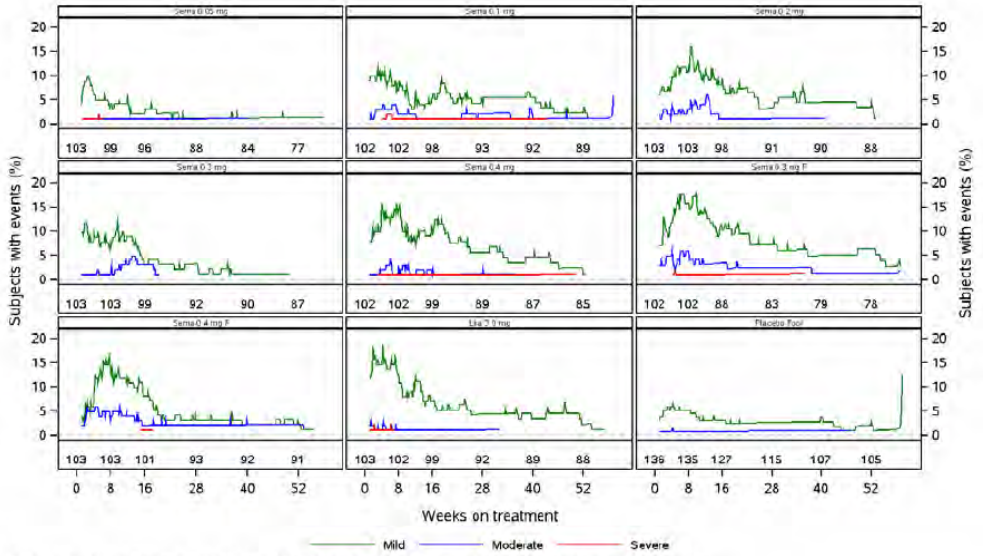


Figure 14 Subjects with adverse events of nausea by treatment, day and severity (Trial 4153)
(Source; Figure 12-9, CSR)

4.3. Pharmacometrics Review

4.3.1 Synopsis from the modeling report: Population PK and E-R analysis of Trial 4153 (Phase 2)

The aim of trial was to support the dose selection for the Phase 3 trials.

The following key questions were addressed with indication of the high-level results:

1. PK-questions:

a. What is the impact of covariates on semaglutide exposure?

Baseline body weight was the most important covariate for semaglutide exposure showing decreased exposure with increasing body weight

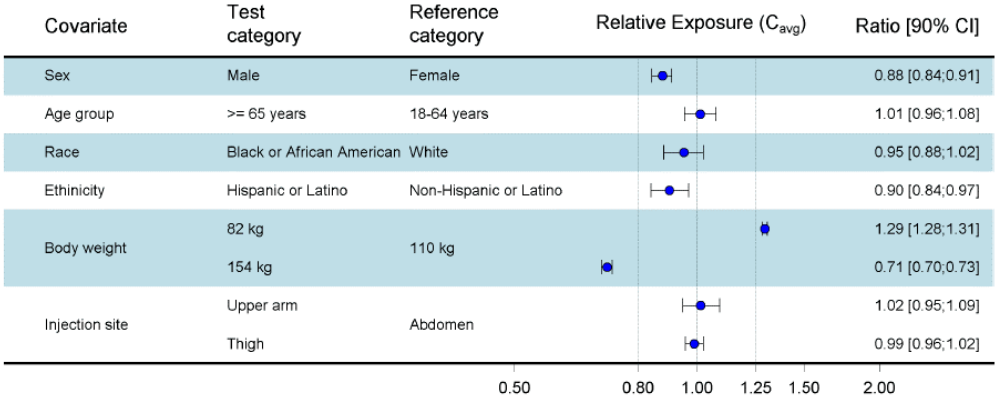


Figure 15 Forest plot of covariate analysis for semaglutide exposure expressed as steady-state dose-normalized average semaglutide concentrations relative to a reference subject (Trial 4153)
(Source; Figure S1)

b. Does semaglutide pharmacokinetics indicate dose proportionality in the studied dose range?

Semaglutide exposure was proportional to the dose.

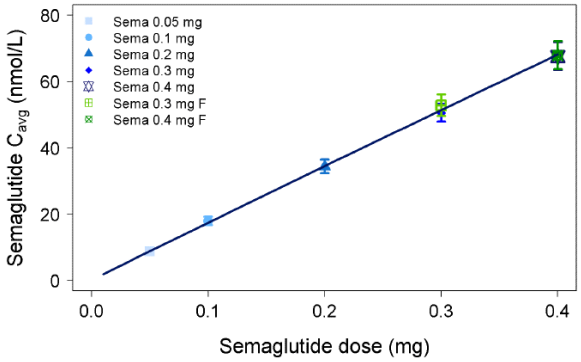


Figure 16 Semaglutide exposure versus dose (Trial 4153)
Treatment arms with fast dose escalation are designated 0.3 mg F and 0.4 mg F, respectively. Exposure (C_{avg}) increase by doubling the dose was estimated to 1.98[1.93–2.02]$_{95\% CI}$. Data from trial 4153.
(Source; Figure S2)

c. Does anti-semaglutide antibody status affect semaglutide exposure?

No semaglutide antibodies were detected in the Phase 2 trial; hence effects on semaglutide exposure could not be investigated.

2. Exposure-response questions:

What are the characteristics of the exposure-response relationship for:

a. **Change in body weight from baseline to week 52?**
b. **The proportion (%) of subjects with weight loss of ≥ 5% at 52 weeks?**
c. **The proportion (%) of subjects with weight loss of ≥ 10% at 52 weeks?**

The exposure-response relationship for BW %-change from baseline until end of treatment (week 52) showed a consistently increased weight loss at increasing exposure (Figure 17). The BW response started to level-off at high exposures and the concentration providing half-maximal effect (EC_{50}) was estimated at 54.6 nmol/L.

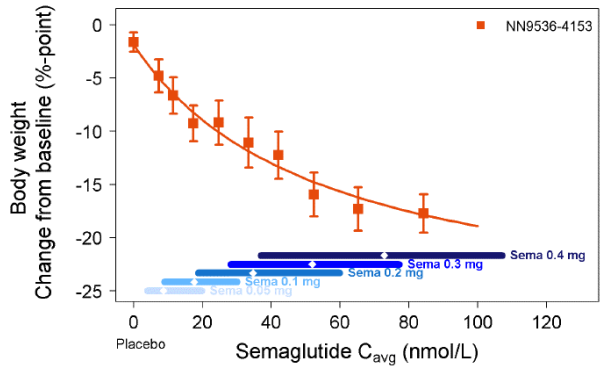


Figure 17 Body weight change from baseline versus exposure of semaglutide (Trial 4153).
(Source; Figure S3)

The proportions of subjects reaching 5% and 10% weight loss increased with increasing semaglutide exposure (Figure 18). At the median concentration obtained with 0.4 mg semaglutide (approximately 70 nmol/L), more than 90% of the subjects reached at least 5% weight loss and more than 80% reached at least 10% weight loss.

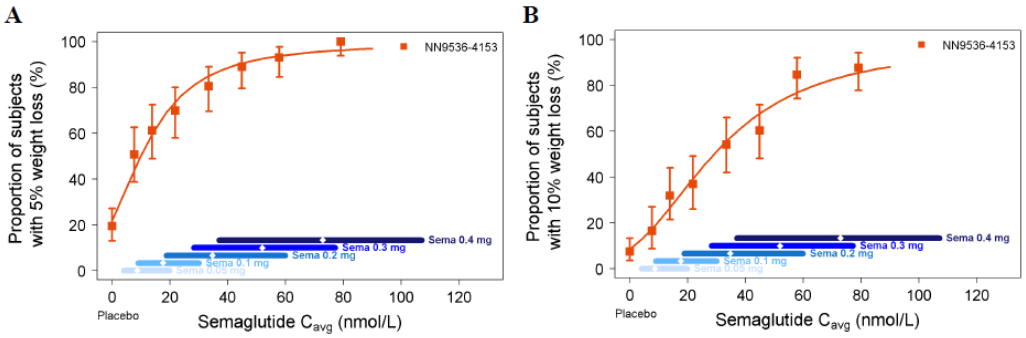


Figure 18 Proportions of subjects reaching at least 5 % (A) and 10% (B) weight loss versus semaglutide exposure (Trial 4153)
(Source; Figure S4)

3. What are the characteristics of the exposure-response relationship for

a. Premature discontinuations due to GIAEs?

The proportion of subjects discontinuing the trial due to GI adverse events increased slightly with semaglutide exposure. The proportion appeared to be higher in males compared to females and was independent of age group and body weight across the exposure range.

b. Occurrence of GIAEs (of any degree), being nausea, vomiting, diarrea and constipation?

The proportions of subjects reporting nausea, vomiting, diarrea or constipation increased slightly with increasing exposure.

- The proportion of subjects reporting nausea appeared higher in females compared to males and was independent of age group and baseline body weight across the exposure range.
- The proportion of subjects reporting vomiting was independent of sex, age group and baseline body weight across the exposure range.
- The proportion of subjects reporting diarrea was independent of sex, age group and baseline body weight across the exposure range.
- The proportion of subjects reporting constipation appeared higher in elderly compared to young subjects and was independent of sex and baseline body weight across the exposure range.

- **Occurrence of nausea over time?**

  During early weeks of treatment, the exposure-response relationship for nausea exhibited a steep increase in the proportion at increasing exposure. Over time the slope of the exposure-response curve gradually decreased indicating tolerance development.

c. Occurrence of moderate and severe GIAEs?

- The proportion of subjects reporting moderate or severe GIAEs of any kind increased with increasing exposure independently of sex, age group and baseline BW.
- How does the occurrence of GI adverse events in the population with obesity compare to subjects with type 2 diabetes (T2D) dosed either daily or weekly, at comparable exposure levels?

Exposure-response relations were similar across trials for GIAE endpoints although proportions of subjects reporting nausea, vomiting, diarrea, constipation and GIAEs of any kind at a given exposure level were higher in subjects with obesity (trial 4153) compared to subjects with T2D (trial NN9535-4191 and SUSTAIN trials). In spite of this, the proportions of subjects discontinuing treatment were similar across trials.

d. Change in pulse rate from baseline to week 52?

The change of resting pulse rate from baseline until end of trial was independent of semaglutide exposure.

Comparing exposure and exposure-response between populations and dosing regimens

Simulation of exposure and comparison of results from trial 4153 to SUSTAIN data with OW dosing in T2D and to data from trial NN9535-4191 with OD dosing in T2D showed the following:

- Semaglutide 2.4 mg dosed OW is predicted to provide similar Cmax values as 0.4 mg semaglutide dosed OD in subjects with obesity
- The relationship between exposure and baseline BW was similar for subjects with obesity dosed OD (trial 4153) and subjects with T2D dosed either OW (SUSTAIN trials) or OD (trial NN9535-4191).
- Larger reduction in body weight was observed in subjects with obesity compared to subjects with T2D across the exposure ranges, likely due to different populations (e.g. age and BMI) with different background treatment.
- Exposure-response relations for GIAEs were similar across trials although the proportions of subjects reporting GIAEs at a given exposure level appeared to be higher in subjects with obesity compared to subjects with T2D. In spite of this, the proportions of subjects discontinuing treatment due to GIAEs were similar across trials.

Exposure-response rationale for phase 3 dose selection

Data from the current trial (4153) and from trial NN9535-4191 (semaglutide OD in T2D) and the data from semaglutide OW in T2D indicate that there are no additional benefits from daily dosing compared to weekly dosing, neither during dose escalation nor in the maintenance period evaluated by body weight loss, GIAE reporting and treatment discontinuation.

Moving from OD to OW dosing with the proposed 2.4 mg OW regimen is estimated to provide lower average plasma concentrations with Cmax values that will not exceed those obtained in trial 4153.

Moreover, the BW loss and proportions of subjects reporting GIAEs and subjects discontinuing treatment due to GIAEs appear to be similar across subgroups of subjects

defined by sex and baseline BW. The smaller BW loss obtained with 2.4 mg semaglutide OW compared to 0.4 mg OD was estimated to approximately 1 %-point. This difference is due to a slightly lower weekly dose (2.4 mg OW versus 0.4 mg OD, corresponding to a total weekly dose of 2.8 mg). With respect to tolerability, it is predicted that both the proportion of subjects reporting GIAEs and proportion of subjects discontinuing treatment due to GIAEs will be approximately 2%-point lower with 2.4 mg semaglutide OW compared to 0.4 mg OD.

Reviewer's comment: *The modeling and simulation was submitted as part of EOP2 meeting background material, and the dose-selection rationale using the modeling and simulation was acceptable.*

4.3.2 Synopsis from the modeling report: a meta-analysis of Phase 3 data

This report presents the population pharmacokinetics (PK) and exposure-response analyses for phase 3 trials of semaglutide administered by subcutaneous injection for weight management. The meta-analyses were based on data from two trials; STEP 1 (trial id: NN9536-4373) and STEP 2 (trial id: NN9536-4374). STEP 1 investigated the effect and safety of semaglutide 2.4 mg once weekly in subjects with overweight or obesity, while STEP 2 investigated effect and safety of semaglutide 2.4 mg once-weekly in subjects with overweight or obesity and type 2 diabetes (T2D). The following key questions are addressing dose-proportionality of semaglutide at weekly doses up to 2.4 mg, covariate effects on semaglutide exposures and the exposure-response characteristics of weight loss as well as gastrointestinal (GI) adverse effects, with indication of high-level results:

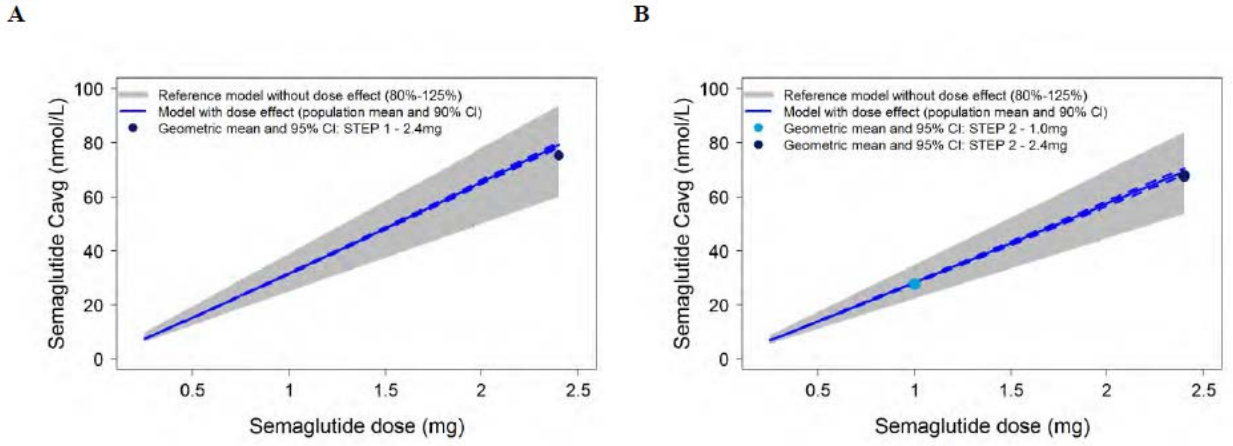
PK questions:

1. Does population PK indicate dose proportionality?

In a model-based analysis, the 90% CI for a model with dose-dependent apparent clearance was within the 0.80‑1.25 range for the reference model without dose-dependent apparent clearance (Figure 19) and hence, dose-proportionality for semaglutide was indicated up to 2.4 mg once weekly.

Figure 19 Dose proportionality plots for semaglutide exposure in STEP 1 (A) and STEP 2 (B)

(Source; Figure 1-1)

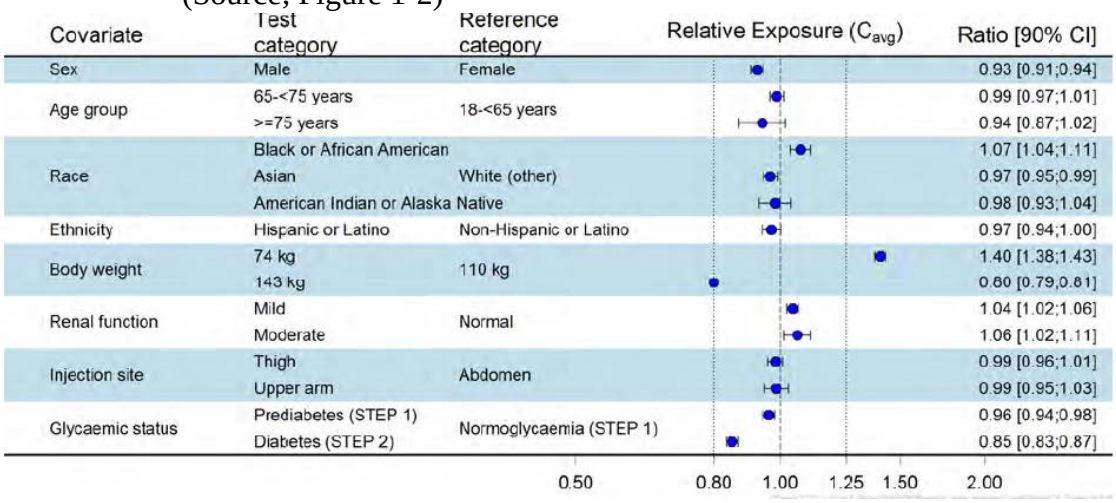


The line represent mean and dotted lines 90% CI of Cavg versus dose from the model with dose-dependency of apparent clearance and the shaded area represents the 80-125% exposure range for a model, assuming dose-proportionality. Data from trials STEP 1 and STEP 2. The geometric mean of the individual estimated Cavg at steady state at the maintenance dose of 2.4 mg in STEP 1 **A)** and at the maintenance doses of 1.0 mg and 2.4 mg in STEP 2 **B)** are superimposed over the Cavg versus dose from the model assuming dose proportionality.

2. What is the impact of covariates on semaglutide exposure?

Body weight was the most important covariate for semaglutide exposure showing decreased exposure with increasing body weight (Figure 20). Other investigated covariates (sex, age, race, ethnicity, renal function, injection site and glycemic status) were of no or minor importance for the exposure of semaglutide.

Figure 20 Forest plot of covariate effects for semaglutide exposure
(Source; Figure 1-2)



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).

Exposure-response questions:

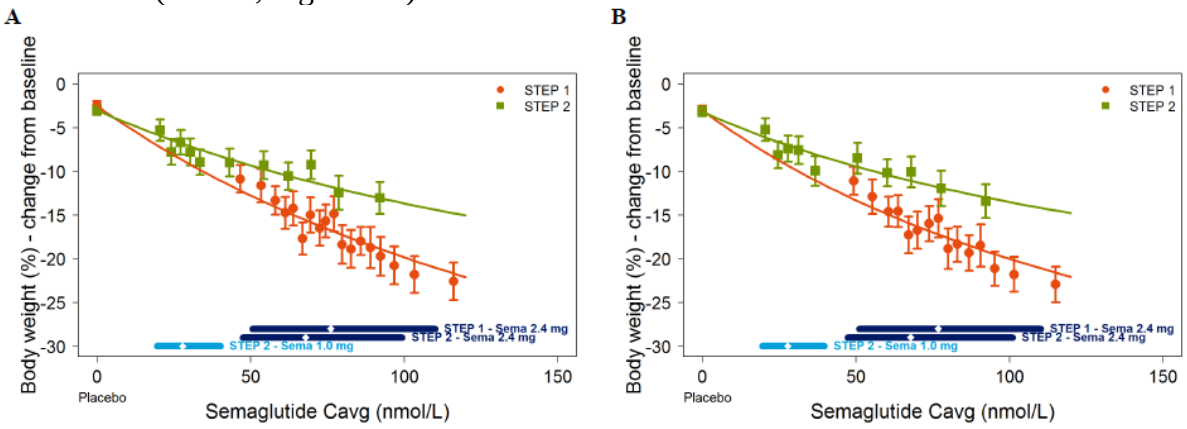
3. What is the exposure-response relationship of semaglutide for

a) Weight loss?

For all subjects randomized to semaglutide treatment, the weight loss increased in an exposure dependent manner (Figure 21A). The exposure-response relationship for the completers (Figure 21B) was comparable to the primary analysis that was based on the full analysis set. This was as expected, especially since more than 80% of subjects completed on-treatment.

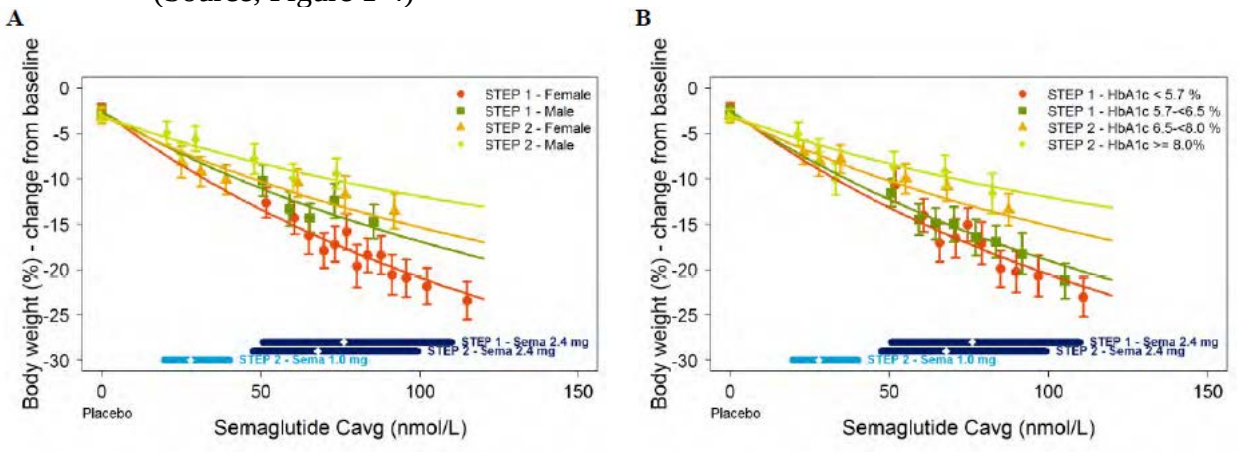
A larger weight loss in STEP 1 as compared to STEP 2 was observed at a given exposure level (Figure 21).

Figure 21 Body weight change from baseline by trial versus semaglutide exposure for all randomized subjects (A) and for subjects completing 68 weeks on-treatment with measurable semaglutide concentrations in active treatment arms (B)
(Source; Figure 1-3)



Factors contributing to this weight loss difference appeared to include gender distribution and baseline HbA_{1c} levels (i.e. glycemic status) between the two trials. Covariates sex (Figure 22A) and baseline HbA_{1c} levels (Figure 22B) were compared across trials in the same plots, showing that the weight loss increased in an exposure-dependent manner within all subgroups.

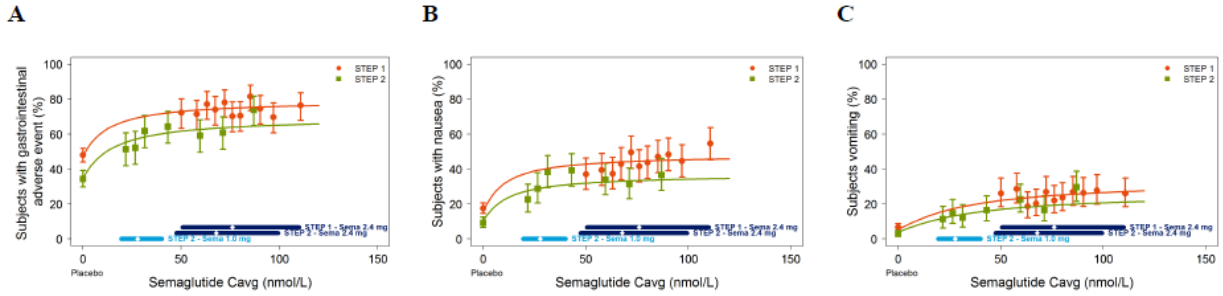
Figure 22 Body weight change from baseline by trial versus semaglutide exposure for all randomized subjects stratified by sex (A) and baseline HbA_{1c} (B)
(Source; Figure 1-4)



b) Gastrointestinal adverse events?

The exposure-response analyses showed that the proportion of subjects reporting gastrointestinal adverse events of any kind, nausea or vomiting at any time during semaglutide treatment increased to a minor extent with increasing semaglutide exposure in both STEP 1 and STEP 2 (Figure 23). Moreover, the proportion of subjects reporting gastrointestinal adverse events appeared to plateau so that it was almost constant over the studied exposure range for the 2.4 mg once-weekly semaglutide dose, likely due to the dose-escalation regimen used in both trials.

Figure 23 Proportion of subjects reporting gastrointestinal adverse events of any kind (A), nausea (B) or vomiting (C) at any time during semaglutide treatment versus exposure
(Source; Figure 1-5)



4. Do the population PK and exposure-response analyses support the recommended treatment dose overall and across relevant subgroups?

Exposure-response analysis of weight loss indicated that the response overall and across subgroups increased substantially over the entire exposure range obtained with 1.0 mg and 2.4 mg semaglutide (Figure 21 and Figure 22). Moreover, data indicate that the proportions of subjects attaining 10% or 15% weight loss increased substantially over the entire exposure range obtained with 1.0 and 2.4 mg semaglutide (Figure 24). Consequently, larger weight loss can be obtained with 2.4 mg semaglutide as opposed to 1.0 mg in line with the results of the statistical efficacy analysis in STEP 2.

Contrary to this, the proportion of subjects reporting nausea and vomiting adverse events appeared to plateau and hence, remained almost constant over the studied exposure range Figure 23. Thus, based on exposure data the additional benefit of greater weight loss with 2.4 mg compared to 1.0 mg semaglutide is associated with only marginally increased risk in terms of GI adverse events, likely due to the dose escalation regimen used in both trials. Therefore, the weight loss benefit and the risk of GI adverse events was concluded to be favorable for semaglutide 2.4 mg across the exposure range for the 2.4 mg dose and increasingly so towards the higher end of the investigated exposure range as illustrated in Figure 24.

Figure 24 Exposure-response based benefit-risk evaluation
(Source; Figure 1-6)

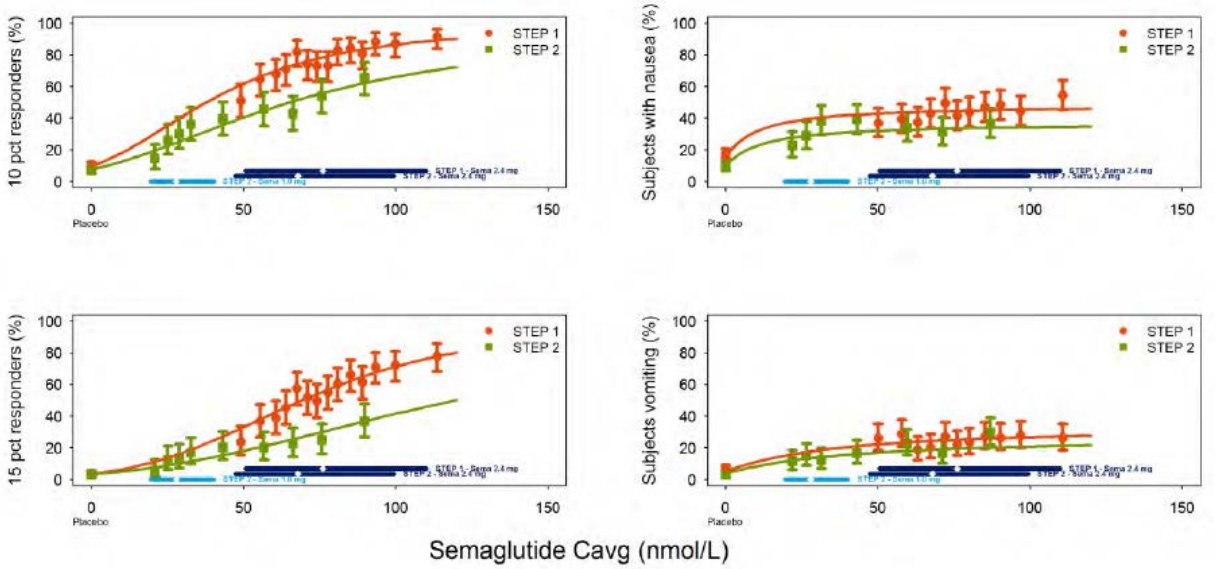


Table 9 Overview of trials designs
(Source; Table 4-1, Modeling report)

	Trial 4373 (STEP 1)	Trial 4374 (STEP 2)
Clinical stage	Phase 3	Phase 3
BMI criteria	Overweight (BMI≥ 27 kg/m^2) with weight-related comorbidities or obesity (BMI≥ 30 kg/m^2)	Overweight (BMI≥ 27 kg/m^2)
Glycaemic status	Normoglycaemic or Prediabetes[3]	Type 2 diabetes
Age criteria	≥18 years	≥18 years
Sex criteria	Male and female	Male and female
Prior antidiabetic treatment	None	Diet and exercise alone or up to 3 OADs[4]
Lifestyle intervention	Diet and exercise	Diet and exercise
4-weekly dose escalation steps (mg/week)	0.25, 0.5, 1.0, 1.7, 2.4	0.25, 0.5, 1.0 or 0.25, 0.5, 1.0, 1.7, 2.4
Maintenance dose (mg/week)	2.4	1.0 or 2.4
Treatment duration (weeks)[1]	68 weeks	68 weeks
Number of subjects planned for PK sampling	1300	800
Sparse PK sampling weeks[2]	2, 4, 8, 12, 28, 52, 68	4, 8, 12, 28, 52, 68

[1]Including dose escalation period. [2]Follow-up samples week 75 will not be included due to anticipated exposures below LLOQ. [3]HbA_{1c}<6.5%. [4]Metformin, sulfonylurea, SGLT2 inhibitor and/or glitazone. BMI: body mass index. OAD: oral antidiabetic.

A standard one-compartment structural model with first-order absorption and elimination was used to describe the semaglutide PK.

Clinically relevant covariates (e.g., sex, age, race, body weight, renal function, injection site and glycemic status) were investigated. The models were evaluated by the typical measures of goodness-of-fit and model diagnostics.

Exposure-weight loss was based on an Emax model with covariates. Exposure-GI AEs was based on logistic regression model.

Table 10 Parameter estimate from the reduced final model of semaglutide PK
(Source; Table 8-9, Modeling report)

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

Table 11 Parameter estimate from the final E-R model of body weight change
(Source; Table 8-15, Modeling report)

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 12 Parameter estimate from the final E-GI AEs model
(Source; Table 8-15, Modeling report)

GI effects of any kind

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

Nausea

Parameter	Estimate	SE
Emax	1.631	0.179
EC50 (nmol/L)	7.721	6.394
E0	-1.377	0.097
STEP 2 cov	-0.214	0.107
Male cov	-0.775	0.099
BW cov	0.000	0.002
Race (Black or African American) cov	-0.493	0.172
Race (Asian) cov	-0.552	0.123
Race (American Indian or Alaska Native) cov	-1.387	0.549

Vomiting

Parameter	Estimate	SE
Emax	2.192	0.327
EC50 (nmol/L)	18.175	11.623
E0	-2.616	0.148
STEP 2 cov	-0.085	0.134
Male cov	-0.857	0.126
BW cov	0.008	0.003

Reviewer's Comment: *The applicant's population PK, and E-R models generally appear acceptable for characterizing covariate effects of semaglutide PK.*

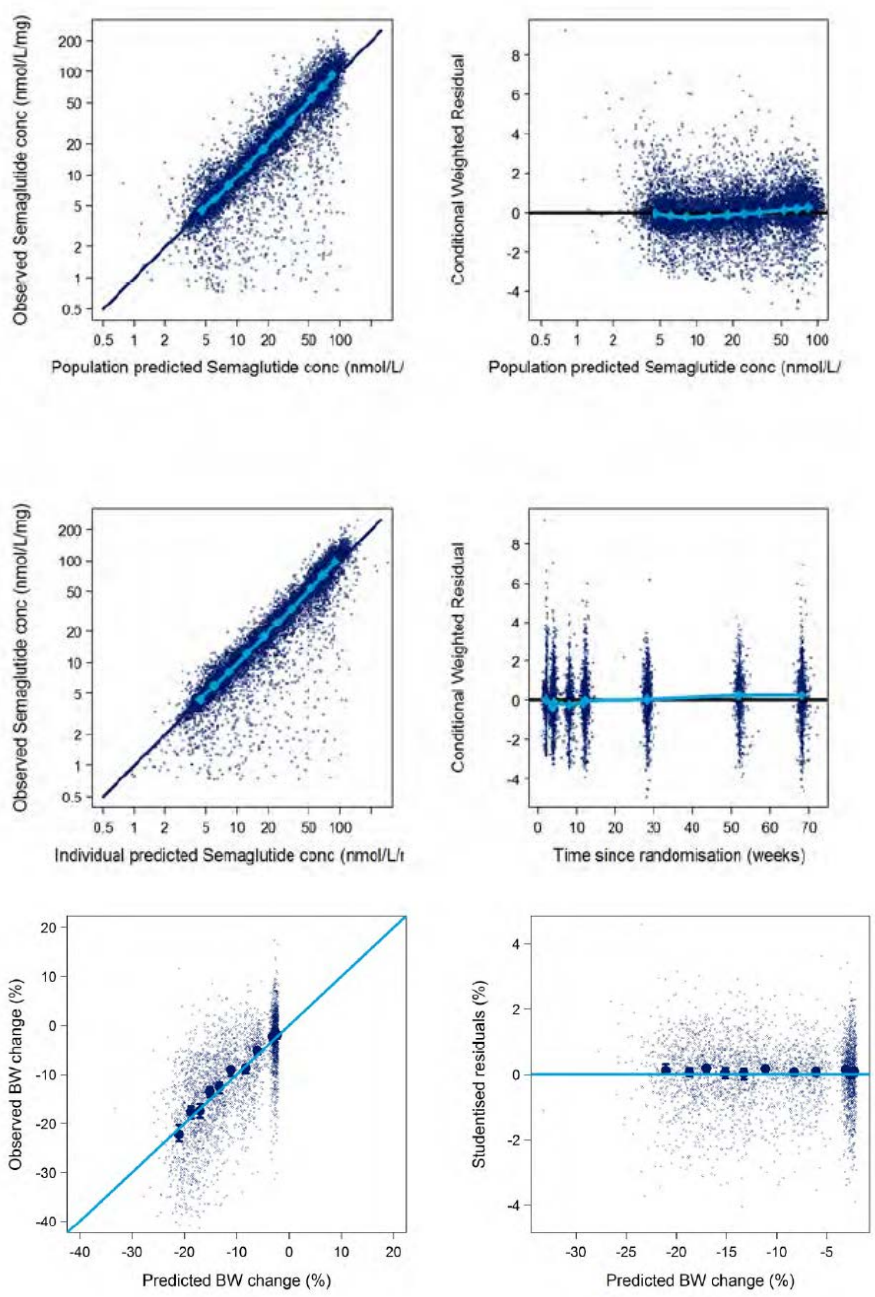


Figure 25 Standard goodness of fit diagnostics; the reduced final PK model (first and second rows) and exposure-body weight change model (third row)

4.3. Formulation composition of semaglutide

Table 13 Composition of drug products

Compound	Quantity per ml	Function	Reference to standard
Active substance			
Semaglutide	0.5 mg 1.0 mg 2.0 mg 2.27 mg 3.2 mg	Drug substance	Novo Nordisk A/S
Excipients			
Disodium phosphate, dihydrate	1.42 mg	(b) (4)	USP, Ph. Eur.
Sodium chloride	8.25 mg		USP, JP, Ph. Eur.
Hydrochloric acid	q.s[a]	pH adjustment	USP, JP, Ph. Eur.
Sodium hydroxide	q.s[a]	pH adjustment	USP, JP, Ph. Eur.
Water for injections	(b) (4)		USP, JP, Ph. Eur.

[a] To reach pH 7.4

Source: Table 1, Module 2.3.P.1, eCTD

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