

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**210913Orig1s000**

**CLINICAL PHARMACOLOGY**  
**REVIEW(S)**

# Office of Clinical Pharmacology Review

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|                                 |                                                                                                                                     |
|---------------------------------|-------------------------------------------------------------------------------------------------------------------------------------|
| <b>NDA or BLA Number</b>        | 213051                                                                                                                              |
| <b>Link to EDR</b>              | <a href="\\Cdsub1\evsprod\NDA213051\213051.enx">\\Cdsub1\evsprod\NDA213051\213051.enx</a>                                           |
| <b>Submission Date</b>          | 20 Mar 2019                                                                                                                         |
| <b>Submission Type</b>          | 505 (b)(1)                                                                                                                          |
| <b>Brand Name</b>               | Rybelsus (Proposed)                                                                                                                 |
| <b>Generic Name</b>             | Semaglutide                                                                                                                         |
| <b>Dosage Form and Strength</b> | Tablet; 3 mg, 7 mg and 14 mg                                                                                                        |
| <b>Route of Administration</b>  | Oral                                                                                                                                |
| <b>Proposed Indication</b>      | Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus                                    |
| <b>Applicant</b>                | Novo Nordisk                                                                                                                        |
| <b>Associated IND</b>           | IND-114464                                                                                                                          |
| <b>OCP Review Team</b>          | <i>Suryanarayana Sista, PhD; Mohammad (Abir) Absar, PhD; Justin Penzenstadler, PharmD, MS; Justin Earp, PhD; Manoj Khurana, PhD</i> |

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## 1. EXECUTIVE SUMMARY

This is an original NDA submitted by Novo Nordisk Inc. on March 20<sup>th</sup>, 2019, seeking marketing approval for oral semaglutide tablets as an adjunct to diet and exercise to improve glycemic control in adult patients with Type 2 diabetes mellitus (T2DM). Oral semaglutide tablets are proposed to be marketed under the tradename of RYBELSUS.

Semaglutide is a recombinant long-acting analogue of human glucagon-like peptide-1 (GLP-1) that selectively binds to and activates the GLP-1 receptor, a target receptor for native GLP-1. Semaglutide exhibits a 94% sequence homology to human GLP-1, an endogenous incretin hormone that stimulates insulin secretion and inhibits glucagon secretion from the pancreatic islets in a glucose-dependent manner.

Semaglutide is co-formulated with salcaprozate sodium, a small fatty-acid-derivate absorption enhancer (also called SNAC) for the tablet formulation. SNAC transiently increases the transcellular permeability of the gastric epithelium to semaglutide to facilitate absorption after oral administration. Mechanistic studies indicate that the absorption of semaglutide predominantly occurs in the stomach. Once absorbed, semaglutide is distributed, metabolized and eliminated in the same way irrespective of the route of administration. The systemic effect of semaglutide is therefore independent of the route of administration.

Through buffering actions, SNAC helps facilitate a high pH in the localized stomach environment beneath the tablet, thereby protecting semaglutide from degradation by gastric enzymes, whose action is most predominant at low pH. The presence of food results in greater dilution of SNAC and semaglutide and presents a barrier to establish a concentration gradient sufficient to permit enhanced absorption and protection against enzymatic degradation.

SNAC reportedly interacts with the plasma membrane of the gastric epithelium to promote absorption of semaglutide via the transcellular route. SNAC gets incorporated in and fluidizes model lipid membranes. The Applicant opines that despite its effects on the cell membrane of gastric mucosa, SNAC had no appreciable effect on tight junction complexes at the apical surface. The absorption enhancing effects of SNAC were transient, size dependent, reversible and require co-formulation.

In the phase 3a trials, oral semaglutide tablets were swallowed whole on an empty stomach with up to half a glass of water equivalent to 120 mL. At least 30 minutes had to lapse before the first meal or drink of the day and taking other oral medications.

The key issues addressed during the review of clinical pharmacology of oral semaglutide are summarized below:

- **Acceptability of the Proposed Dosage Regimen from Dose and Exposure-Response Perspective**
  - The proposed dosage regimen utilizing oral doses of 3 mg, 7 mg, and 14 mg semaglutide once daily is adequately supported by dose-response and exposure-response relationship in change in HbA1c after 26 weeks of treatment from safety/efficacy trials vis-à-vis the dose-response for safety. Further, with regards to the effect of body weight on apparent clearance, both 7 mg and 14 mg once-daily doses generated adequate systemic exposure over the typical body weight range of subjects with T2DM ensuring efficacy.
- **Optimal Dosing Conditions (time of fast prior to and after dosing, amount of water, meal)**
  - The results from the clinical pharmacology studies and two clinical studies (trials 3794 and 3957), support a recommended use for oral semaglutide tablet to be taken on an empty stomach and be swallowed whole with up to half a glass of water equivalent to 120 mL without splitting, crushing or chewing the tablet. After taking oral semaglutide, patients are recommended to wait at least 30 minutes before the first meal or drink of the day and taking other oral medications.

## 1.1 Recommendations

The Office of Clinical Pharmacology has reviewed the information contained in NDA 213051 and found it acceptable to support approval of oral Semaglutide in the T2DM population. Key review issues with specific recommendations and comments are summarized below:

| <b>Review Issues</b>                                                       | <b>Recommendations and Comments</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
|----------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Supportive evidence of effectiveness</b>                                | <p>The primary evidence of effectiveness for the proposed dosing regimen were obtained from data from 10 efficacy trials, which showed that oral semaglutide produced clinically relevant reductions in HbA1c that were dose-dependent and lasted through the duration of the trials.</p> <p>Clinically relevant dose-dependent sustained reduction in body weight was also observed across all phase 3a trials.</p>                                                                                                                                                                                              |
| <b>General dosing instructions</b>                                         | <p>Semaglutide oral tablets must be taken on an empty stomach after first waking up in the morning. Semaglutide oral tablets should be taken at least 30 minutes before the first food, beverage or other oral medications of the day with no more than half a glass of water (approximately 4 ounces). The tablet should be swallowed whole.</p> <p>The recommended starting dose is 3 mg once daily for 1 month. After 1 month on 3 mg, the dose should be increased to 7 mg once daily. If additional benefits are needed after at least one month on 7 mg, the dose may be increased to 14 mg once daily.</p> |
| <b>Dosing in patient subgroups</b>                                         | <p>No separate dose/dosing regimen is recommended in any patient subgroups due to intrinsic (age, sex, race, ethnicity, body weight, renal impairment, hepatic impairment) and extrinsic factors. Semaglutide does delay gastric emptying; therefore, caution should be exercised when oral medications are concomitantly administered with semaglutide.</p>                                                                                                                                                                                                                                                      |
| <b>Bridge between the “to-be-marketed” and clinical trial formulations</b> | <p>The to-be-marketed drug product formulation (Process 3) was used in all pivotal Phase 3 studies and in all the clinical pharmacology studies that evaluated drug-drug interactions.</p>                                                                                                                                                                                                                                                                                                                                                                                                                        |

## 1.2 Post-Marketing Requirements and Commitments

None.

## 2. SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT

### 2.1 Pharmacology and Clinical Pharmacokinetics

Semaglutide is a GLP-1 receptor agonist that selectively binds to and activates the GLP-1 receptor. A summary of the PK and PD characteristics of semaglutide is presented below.

The following is a summary of the clinical pharmacokinetics of oral semaglutide:

|                      |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
|----------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Absorption:</b>   | <ul style="list-style-type: none"><li>• Following oral administration, maximum concentration of semaglutide is reached 1-hour post-dose. Steady-state exposure is achieved following 4-5 weeks administration. In patients with type 2 diabetes, the mean population-PK estimated steady-state concentrations following once daily oral administration of 7 and 14 mg semaglutide were approximately 6.7 nmol/L and 14.6 nmol/L, respectively. Based on population pharmacokinetics (PK) estimates, semaglutide exposure increases in a dose-proportional manner. The Population-PK estimated absolute bioavailability of semaglutide to be approximately 0.4 - 1%, following oral administration.</li></ul> |
| <b>Distribution:</b> | <ul style="list-style-type: none"><li>• Semaglutide is extensively bound to plasma albumin (&gt;99%). The estimated volume of distribution of semaglutide following oral administration in healthy subjects is approximately 8 L.</li></ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| <b>Elimination:</b>  | <ul style="list-style-type: none"><li>• The elimination half-life of semaglutide is approximately 1-week. The clearance of semaglutide following oral administration in healthy subjects is approximately 0.04 L/h.</li><li>• The primary excretion routes of semaglutide-related material are via the urine and feces, with approximately 3% of the absorbed dose excreted in the urine as intact semaglutide.</li></ul>                                                                                                                                                                                                                                                                                    |
| <b>Metabolism:</b>   | <ul style="list-style-type: none"><li>• The primary route of elimination for semaglutide is metabolism following proteolytic cleavage of the peptide backbone and sequential beta-oxidation of the fatty acid side chain.</li></ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |

### 2.2 Dosing and Therapeutic Individualization

#### 2.2.1 General dosing

The proposed starting dose of RYBELSUS is as follows:

The recommended starting dose is 3 mg once daily for 1 month. After 1 month on 3 mg, the dose should be increased to 7 mg once daily. If additional glycemic control is needed after at least one month on 7 mg, the dose may be increased to 14 mg once daily.

Semaglutide oral tablets must be taken at least 30 minutes before the first food, beverage or other oral medications of the day with no more than half a glass of water (approximately 4 ounces). Other beverages (including mineral water), food, and some medications are likely to reduce the absorption of semaglutide. Waiting less than 30 minutes, or taking semaglutide with food, beverages (other than plain water) or other medications will lessen the effect of semaglutide by decreasing its absorption into the body. Remaining in a fast for more than 30 minutes after taking semaglutide is likely to increase the absorption. The tablet should be swallowed whole.

The dose-response relationship for HbA1c change from baseline following 26 weeks of treatment showed a non-linear dose-response relationship with an ED<sub>50</sub> value of approx. 6 mg with the steepest part of the curve ranging up to doses of 10 mg, following which the effect started to level off. The relationship was

adequately described by an  $E_{\max}$  model as indicated by the model shown as a line in Figure 1. The estimated model parameters for the dose-response model for HbA<sub>1c</sub> are provided in Table 1.

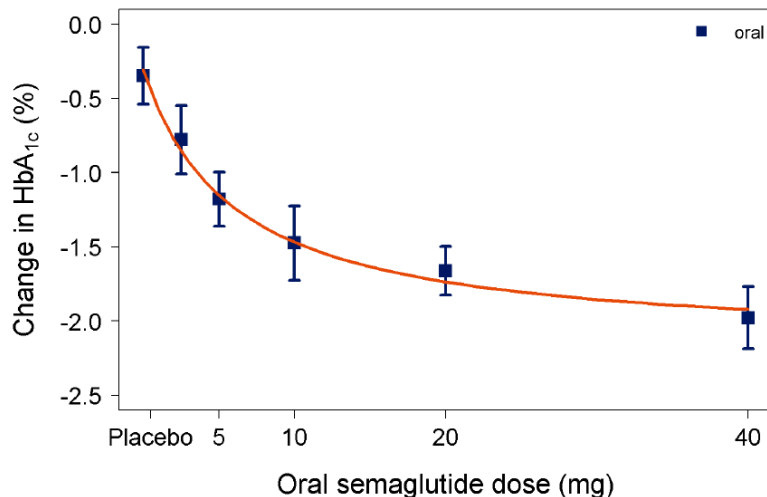


**Figure 1 HbA<sub>1c</sub> change from baseline versus oral maintenance dose of semaglutide**  
(Source: *Modelling Report Population PK and Exposure-Response Analysis, Figure 7, Page 32*)

**Table 1 Parameter estimates for the dose-response model for effects of oral semaglutide on HbA<sub>1c</sub>**

| Parameter         | Unit         | Estimate | Std. Error |
|-------------------|--------------|----------|------------|
| $E_0$             | (%-points)   | 0.30     | 0.09       |
| $E_{\max}$        | (%-points)   | 1.85     | 0.15       |
| $ED_{50}$         | (mg)         | 5.97     | 1.59       |
| $E_{\text{base}}$ | (1/%-points) | 0.2      | 0.1        |
| $I_{\text{base}}$ | (1/%-points) | 0.25     | 0.1        |

(Source: *Modelling Report Population PK and Exposure-Response Analysis, Table 15, Page 56*)

The proposed dosing regimen is supported by a dose-response analysis. For further details, see [Section 4.2.3](#).

## 2.2.2 Therapeutic individualization

No prospective dose adjustments based on patient factors are recommended. Semaglutide dosing should follow a titration scheme. Taking two 7 mg semaglutide tablets to achieve a 14 mg dose is not recommended. Patients treated with weekly 0.5 mg OZEMPIC (semaglutide) subcutaneous injection can be transitioned to 14 mg oral semaglutide by starting oral therapy 2 to -4 days following the last injection (see section 3.3.1, page 26). There is no equivalent dose of oral semaglutide for 1 mg OZEMPIC injection.

## 2.3 Outstanding Issues

None.

## 2.4 Summary of Labeling Recommendations

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

| Label Section                                                                           | Recommendation                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
|-----------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>2. DOSAGE AND ADMINISTRATION</b><br><b>2.1 Important Administration Instructions</b> | <ul style="list-style-type: none"> <li>Take TRADENAME at least 30 minutes before the first food, beverage, or medication of the day with no more than 4 ounces of plain water only [see Clinical Pharmacology (12.3)]. Other beverages (including mineral water), food, and some medications are likely to reduce the absorption of TRADENAME. Waiting less than 30 minutes, or taking TRADENAME with food, beverages (other than plain water) or other medications will lessen the effect of TRADENAME by decreasing its absorption. Remaining in a fast for more than 30 minutes after taking TRADENAME is likely to increase the absorption.</li> </ul>                                                   |
| <b>2.2 Recommended Dosage</b>                                                           | <ul style="list-style-type: none"> <li>Taking two 7 mg TRADENAME tablets to achieve a 14 mg dose is not recommended</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
| <b>2.3 Switching patients from OZEMPIC to TRADENAME</b>                                 | <ul style="list-style-type: none"> <li>Patients treated with weekly 0.5 mg OZEMPIC subcutaneous injection can be transitioned to 14 mg TRADENAME by starting oral therapy 2 to -4 days following the last injection. There is no equivalent dose of TRADENAME for 1 mg OZEMPIC.</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                   |
| <b>12 CLINICAL PHARMACOLOGY</b><br><b>12.1 Mechanism of Action</b>                      | (b) (4)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| <b>12.3 Pharmacokinetics</b>                                                            | <ul style="list-style-type: none"> <li>Population pharmacokinetics (PK) estimated semaglutide exposure to increase in a dose-proportional manner. In patients with type 2 diabetes, the mean population-PK estimated steady-state concentrations following once daily oral administration of 7 and 14 mg semaglutide were approximately 6.7 nmol/L and 14.6 nmol/L, respectively.</li> <li>Following oral administration, maximum concentration of semaglutide is reached 1-hour post-dose. Steady-state exposure is achieved following 4-5 weeks administration.</li> <li>Population-PK estimated absolute bioavailability of semaglutide to be approximately 1%, following oral administration.</li> </ul> |
| <b>12.3 Pharmacokinetics</b>                                                            | <ul style="list-style-type: none"> <li>Replace Figures 3 and 4 with one that also has vertical lines at 0.80 and 1.25 in addition to 1.00</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| <b>12.3 Pharmacokinetics</b>                                                            | (b) (4)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |

### 3. COMPREHENSIVE CLINICAL PHARMACOLOGY REVIEW

#### 3.1 Overview of the Product and Regulatory Background

The clinical development program for oral semaglutide comprised of 32 studies: 22 Phase 1 studies, 1 Phase 2 study, and 9 Phase 3 studies. A total of 8218 subjects participated in these clinical studies, including healthy volunteers (n = 1092), patients with renal impairment (n = 47), patients with hepatic impairment (n = 32) and T2DM patients (n=7047). In addition, clinical pharmacology information from 3 pharmacodynamic studies, 1 absorption, metabolism and elimination study and 1 QTc study for the subcutaneous semaglutide were used to support this program. Clinical pharmacology information were obtained from 6 of the 9 Phase 3 studies for oral semaglutide. These studies provide information supporting proof-of-concept as well as the definitive efficacy and safety of Rybelsus in the target population for the treatment of diabetes.

The regulatory history regarding these communications is summarized below:

| Dates       | Communication/Meeting Type                                | Key Communication Points                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
|-------------|-----------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 07 Jul 2014 | Type C Meeting Request                                    | To discuss with the Division, and reach consensus on the: <ul style="list-style-type: none"> <li>• Adequacy of the completed and ongoing oral semaglutide clinical pharmacology trials to support the initiation of phase 3 and submission of an NDA.</li> <li>• Adequacy of ongoing clinical drug-drug interaction and food interaction studies to support an NDA submission.</li> <li>• Adequacy of proposed plan to cross-reference to the subcutaneous semaglutide QT interval data to support an NDA submission</li> </ul> |
| 22 Sep 2014 | Agency's written feedback for the Type C Meeting Request  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| 27 Mar 2015 | End of Phase 2 (EOP2) Meeting Request                     | Applicant requested meeting to discuss the phase 3 development plans and requirements for NDA submission for oral semaglutide.                                                                                                                                                                                                                                                                                                                                                                                                  |
| 09 Jun 2015 | Preliminary Written Response                              | Agency issues preliminary written responses to the questions that the Applicant submitted in their 12 May 2015 meeting package for the EOP2 meeting.                                                                                                                                                                                                                                                                                                                                                                            |
| 11 Jun 2015 | EOP2 Meeting                                              | Applicant's additional clarifications discussed at the meeting.                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| 24 Jun 2015 | EOP2 Meeting minutes                                      | <i>*see below for Clinical Pharmacology related concerns raised by Agency and Applicant's response</i>                                                                                                                                                                                                                                                                                                                                                                                                                          |
| 24 Sep 2018 | Pre-NDA Meeting Request                                   | Applicant wanted to discuss the adequacy of the submission package for oral semaglutide.                                                                                                                                                                                                                                                                                                                                                                                                                                        |
| 27 Nov 2018 | Agency's written feedback for the Pre-NDA Meeting Request |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| 29 Nov 2018 | Pre-NDA Meeting                                           | Applicant's additional clarifications discussed at the meeting.                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| 10 Dec 2018 | Pre-NDA Meeting Minutes                                   | Based on the Agency's preliminary feedback, Novo Nordisk agreed to conduct a pharmacokinetic (PK) trial in addition to analyzing the effect of upper GI comorbidities on the systemic exposure of semaglutide through population PK in the phase 3 trial.                                                                                                                                                                                                                                                                       |

***\*Applicant's Clinical Pharmacology Related Question from May 12, 2015 Meeting Package and Agency's Preliminary Response from June 9, 2015:***

*The Applicant asked the Agency if it agreed that the proposed clinical pharmacology program was adequate to support the NDA submission and proposed indication. The Agency in its preliminary response responded that in general, the clinical pharmacology program of oral semaglutide tablets appeared reasonable to support a future NDA submission. The Agency, however, had a few comments for*

*the clinical pharmacology program of oral semaglutide tablets. The Agency's comments and Applicant's response are listed below:*

**Agency Comment #1:**

*If the clinically-tested formulation of the oral semaglutide tablets is different from the to-be marketed formulation of the oral semaglutide tablets, you need to address the bioequivalence issue between these formulations before submission of NDA for the oral semaglutide tablets.*

**Applicant's Response:**

*Novo Nordisk acknowledges that if the phase 3 formulation ("clinically tested formulation") is different from the to-be-marketed formulation then a bioequivalence trial may be required.*

**Agency Comment #2:**

*Trial NN9924-4154 tested the effect of food on the pharmacokinetics of the 5 mg and 10 mg oral semaglutide tablets. The oral semaglutide tablet strengths for the planned phase 3 trials are 3 mg, 7 mg, and 14 mg. Address the issue that the highest strength of a drug product intended to be marketed Industry "Food-Effect Bioavailability and Fed Bioequivalence Studies" (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070241.pdf>) for oral semaglutide tablets.*

**Applicant's Response:**

*The effect of food on absorption of semaglutide (10 mg) was pronounced with almost no semaglutide absorption (NN9924-4154). Similarly, exposure was significantly reduced if food was ingested 15 or 30 minutes after dosing compared to 2 hours after dosing (NN9924-3794). Conceivably, excessive amounts of food and/or liquid could result in excessive dilution of SNAC and thereby diminish its capacity to promote the absorption of semaglutide. As the amount of SNAC is the same in all tablet strengths it is not likely that the effect of food will be different at the 14 mg dose compared to the 10 mg dose, i.e., no absorption of semaglutide with food is expected with 14 mg oral semaglutide. As a consequence, Novo Nordisk proposes not to do a second food effect trial with 14 mg oral semaglutide.*

**Agency Comment #3:**

*Trial NN9924-4250 aims to study the potential interaction between oral semaglutide and transporters such as the Organic Anion Transporting Polypeptide 1B1 (OATP1B1) and the Breast Cancer Resistance Protein (BCRP) because the oral semaglutide absorption enhancer, SNAC, and its metabolites inhibit these transporters in vitro. Consider studying rosuvastatin instead of atorvastatin. The draft Guidance for Industry "Drug Interaction Studies – Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations" (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292362.pdf>) recommends rosuvastatin as a substrate of BCRP and OATP1B1, whereas the same guidance recommends atorvastatin as a substrate of OATP1B1.*

*Be consistent in reporting the plasma semaglutide concentrations in nmol/L or ng/mL scales throughout the trial reports and future regulatory submissions. For the ease of review effort, provide conversion factors for the nmol/L to ng/mL scale and vice versa.*

**Applicant's Response:**

*Novo Nordisk agrees to study rosuvastatin instead of atorvastatin in trial NN9924-4250.*

### 3.2 General Pharmacological and Pharmacokinetic Characteristics

Semaglutide is a white to almost white powder. Semaglutide is soluble in water (>100 g/L at pH 7 or above). Semaglutide immediate release tablets are to be made available at 3 mg, 7 mg and 14 mg strengths. The isoelectric point has been experimentally determined to be 5.4. The Semaglutide drug products are white to light yellow oval shaped tablets (b) (4) weighing approximately 401 to 412 mg depending on strength. The drug products are tablets intended for oral administration. The compositions of the 3 mg, 7 mg and 14 mg Semaglutide tablets are shown below in Table 2.

**Table 2 Compositions of drug products to be used in the phase 3 clinical trial expressed as "per tablet"**

| Component                       | Composition (mg/tablet) |             |              | Function            | Reference to standard |
|---------------------------------|-------------------------|-------------|--------------|---------------------|-----------------------|
|                                 | 3 mg tablet             | 7 mg tablet | 14 mg tablet |                     |                       |
| <b>Drug substance</b>           |                         |             |              |                     |                       |
| Semaglutide <sup>1</sup>        | 3                       | 7           | 14           | Active ingredient   | Novo Nordisk          |
| <b>Excipients</b>               |                         |             |              |                     |                       |
| SNAC                            | 300                     | 300         | 300          | Absorption enhancer | Novo Nordisk          |
| Cellulose, microcrystalline     | (b) (4)                 |             |              | (b) (4)             | Ph Eur, USP           |
| Povidone (b) (4)                |                         |             |              | Ph Eur, USP         |                       |
| Magnesium stearate <sup>2</sup> |                         |             |              | Ph Eur, USP         |                       |
| Gross weight                    | 400.7                   | 404.7       | 411.7        | N/A                 | N/A                   |

<sup>1</sup> The amounts of semaglutide are shown

(b) (4)

(b) (4)

<sup>2</sup> (b) (4)

(Source: Module 3.2.P.1 Description and Composition of the Drug Product, Table 1, Page 2)

#### 3.2.1 Mechanism of Action:

Glucagon-like peptide 1 is secreted from the L-cells of the lower gastrointestinal tract (primarily from the ileum and colon) following the ingestion of a carbohydrate- or fat-containing meal. GLP-1 positively modulates insulin release from the pancreatic islets in response to increases in plasma glucose. GLP-1 also suppresses glucagon secretion by direct action on pancreatic islet alpha cells, decreases gastric motility, and increases stomach acid secretion.

All these pharmacodynamic (PD) effects have been demonstrated in clinical studies employing exogenous GLP-1. The insulinotropic effect is glucose dependent, at glucose concentrations below approximately 4.5 mM, insulin secretion is not stimulated, thus minimizing the risk of relevant hypoglycemia. The slowing of gastric emptying together with a GLP-1 related increase in satiety (mediated through the central nervous system) may decrease body weight despite the insulinotropic effects.

The active, circulating form of GLP-1 in humans is GLP-1 (7-36)-amide. GLP-1 has a very short half-life in circulation (<2 minutes) mainly because of rapid N-terminal cleavage by the common, dipeptidyl peptidase-4 (DPP-4). Semaglutide is an enzymatically stable, long-acting GLP-1 analogue with a plasma half-life of 70-90 hours in minipigs.

Semaglutide activated GLP-1 receptor with an 8-fold lower potency than native GLP-1. The EC<sub>50</sub> for Semaglutide was 0.15 nM compared to an EC<sub>50</sub> of 0.018 for GLP-1.

The mechanism of action of semaglutide in reducing blood glucose is via stimulation of insulin secretion and lowering of glucagon secretion, both in a glucose-dependent manner. Another mechanism involved in the reduction of blood glucose is a minor delay in gastric emptying in the early postprandial phase.

### **3.2.2 Pharmacokinetics:**

A total of 30 completed clinical studies conducted in healthy volunteers and T2DM patients assessed the PK and PD of oral semaglutide. The PK of SNAC was also investigated in these studies.

#### **3.2.2.1 Absorption**

##### Semaglutide

The safety, tolerability and bioavailability of single escalating doses of oral semaglutide formulated with the absorption enhancing excipient SNAC was evaluated in Healthy Male Subjects. However, the plasma levels of semaglutide after i.v. administration approached the lower limit of quantification (LLOQ) of the analysis assay, and consequently absolute bioavailability of oral semaglutide could not be accurately assessed in healthy subjects. The  $t_{1/2}$  for semaglutide after i.v. administration was not available. The bioanalytical method used in this study was a luminescence oxygen channeling immunoassay (LOCI). Measurements with this assay were influenced by a matrix effect, which affected the assessment of the semaglutide plasma levels.

However, the relative oral bioavailability of a single oral dose of 10 mg semaglutide administered with 50 mL of water following an overnight fast of 10 hours and a post-dose fasting period of 5 hours was estimated to be 0.90% relative to s.c. administration, when only subjects with at least one quantifiable semaglutide plasma concentration were included. Due to the bioanalytical assay used (LOCI) in this study and due to the large number of healthy subjects with plasma levels of semaglutide approaching the LLOQ, the estimates of relative bioavailability should be interpreted with caution.

##### SNAC

When administered with semaglutide, SNAC is rapidly absorbed and eliminated. There is no accumulation of SNAC after multiple daily doses of oral semaglutide and the PK of SNAC appears similar after single and multiple dosing. Additionally, the PK of SNAC was comparable between healthy subjects and subjects with T2DM. Following 10 days of treatment with oral semaglutide (containing 300 mg SNAC) in subjects with T2DM, the geometric mean  $AUC_{0-24h}$  of SNAC was 1034 ng.hr/mL,  $C_{max}$  was 1038 ng/mL and median  $T_{max}$  was 0.3 hr.

##### Food Effect:

Absorption of semaglutide was considerably lower in the fed condition than in the fasting condition. Under fed condition, 14 out of 26 subjects had no concentration above the LLOQ of semaglutide (Section 3.3.5). Semaglutide exposure also tend to increase with increased post-dose fasting duration from 15 min to 120 min (Section 3.3.3). In addition, semaglutide exposure was lower when administered with 240 mL of water. Hence, the proposed dosing condition for semaglutide is to be administered under fasting condition with 120 mL (4 ounces) of water at least 30 min before the first food.

#### **3.2.2.2 Distribution**

The plasma protein binding for semaglutide was investigated to be >99% in humans in both healthy subjects and subjects with different stages of renal and hepatic impairment.

### 3.2.2.3 Metabolism

#### Semaglutide

In an in vitro study, following incubation of semaglutide with human neutral endopeptidase 24.11 (NEP), a total of 19 metabolites were structurally characterized. These metabolites are proposed to be products of initial NEP cleavage sites in the peptide backbone of semaglutide (4 metabolites were products from 1 proteolytic cleavage at one of the following sites: Ser18-Tyr19, Tyr19-Leu20, Glu27-Phe28, and Trp31-Leu32) and smaller peptides formed after additional proteolytic degradation.

In an in vivo mass balance study, following administration of a single SC dose of 0.5 mg [3H]-semaglutide to healthy subjects, 7, 22, and 7 components were detected in plasma, urine, and feces, respectively, of which components P4 in plasma and U22 in urine was identified as intact semaglutide. In plasma, metabolite P3B was identified as a peptide metabolite formed after proteolytic cleavage in semaglutide between Tyr19 and Leu20 and products P3C-I, P3C-II, and P3C-III were characterized as semaglutide isomers.

In urine, metabolite U6 and U7 was identified as the free Lys26 amino acid bound to the ADOLinker with di-butyric (C4) and di-hexanoic (C6) acid side chains, respectively, and are most likely formed after several proteolytic cleavages of the semaglutide peptide backbone and sequential beta-oxidation of the di-fatty acid side chain.

#### SNAC

Five major metabolites of SNAC were identified and quantified in plasma. The glucuronide metabolites (E1245, E1246 and E1247) accounted for most of the plasma exposure following a single dose; E1245, E1246 and E1247 accounted for in average 15.9%, 13.3% and 48.3%, respectively, of the AUCs of the total radioactivity. The  $\beta$ -oxidized metabolites E494 and E506 accounted for 1.4% and 7.9% of the AUC. Following a single dose, SNAC exposure accounted for only 5.1% of the total radioactivity exposure, indicating that SNAC is extensively metabolized.

### 3.2.2.4 Elimination

#### Semaglutide

The major excretion route of semaglutide-related materials was via the urinary (53% of administered dose) and fecal (18.6% of administered dose) routes. Approximately 3% of the dose was excreted as intact semaglutide in urine.

#### SNAC

The primary routes of elimination for SNAC were urine and feces. An average of 82.31% of the total radioactivity administered was recovered in the urine and 3.75% was recovered in the feces over 216 hours.

### 3.2.2.5 Single-Dose and Multiple-Dose Pharmacokinetics

#### Single-Dose Semaglutide PK

PK of semaglutide following single-dose administration in healthy subjects was reported in Study 3691. Four doses of semaglutide (2, 5, 10, and 20 mg) was administered with varying amount of SNAC (150, 300, 450 and 600 mg). With 300 mg SNAC, which is the SNAC content in the to-be-marketed formulations, semaglutide  $C_{max}$  increased less than dose-proportionally (the ratio of  $C_{max}$  from 2 mg to 10 mg semaglutide was 1.51) while  $AUC_{0-504h}$  increased higher than dose-proportionally (the ratio of  $AUC_{0-504h}$  from 2 mg to 10 mg semaglutide was 8.87). The variability (%CV) was high – ranging from 110% to 284% for  $C_{max}$  and 120% to 315% for  $AUC_{0-504h}$ . Note that (b) (4) semaglutide drug substance was used in this study while the to-be-marketed formulations were prepared using semaglutide produced from (b) (4).

### Single-Dose SNAC PK

Following single-dose administration of varying amount of SNAC formulated with semaglutide (as discussed above in Study 3691), the ratio of  $C_{max}$  from 150 mg to 600 mg SNAC was 3.06 and that of  $AUC_{0-5h}$  was 3.97. Following administration of 300 mg SNAC with 5 or 10 mg semaglutide, there appears to be no significant difference in SNAC exposure; however, a higher SNAC exposure was observed when administered with 2 mg semaglutide. The variability of SNAC  $C_{max}$  and  $AUC_{0-5h}$  ranged from 46% to 88% and from 23% to 51%, respectively.

### Multiple-Dose Semaglutide PK

In a multiple-dose study that evaluated 20 mg and 40 mg oral semaglutide administered to healthy subjects and subjects with T2DM, treatment ratio between 40 mg and 20 mg semaglutide calculated of the last three days of treatment was 1.89 for  $AUC_{0-24h,sema,SS}$  and 1.83 for  $C_{max,sema,SS}$ . The exposure of semaglutide was similar between healthy subjects and subjects with T2DM. For subjects treated with 40 mg semaglutide, the treatment ratios were 1.00 for both  $AUC_{0-24h,sema,SS}$  and  $C_{max,sema,SS}$ .  $T_{max}$  (median value: 2-2.5 hours) and  $t_{1/2}$  (geometric mean: 153-161 hours) were similar between healthy subjects and subjects with T2DM.

### Multiple-Dose SNAC PK:

SNAC did not accumulate from first day of treatment (day 0) to day 69. SNAC exposure was similar for healthy subjects and subjects with T2DM at the end of the treatment period. At steady-state,  $AUC_{0-24h,SNAC,SS}$ ,  $C_{max,SNAC,SS}$  and  $t_{max,SNAC,SS}$  for SNAC were similar between healthy subjects and subjects with T2DM. Compared to a placebo tablet with SNAC, the combination of semaglutide with SNAC showed a tendency towards a lower  $C_{max,SNAC,SS}$ , however,  $AUC_{0-24h,SNAC,SS}$  and  $t_{max,SNAC,SS}$  were similar between the two combinations.

### 3.2.2.6 Drug-Drug Interactions

#### Key results from in vitro studies:

In vitro studies showed semaglutide to have a low potential to inhibit or induce cytochrome P450 enzymes, and to inhibit drug transporters (P-gp, BCRP, OCT2, OAT1, OAT3). Semaglutide did partially inhibit OATP1B1 and OATP1B3, however the potential for clinically relevant interactions between semaglutide and OATP1B1/1B3 transporters is low.

#### Key results from in vivo studies:

The following key aspects were considered by the Applicant when selecting appropriate model drugs (victims) to investigate the potential of oral semaglutide as a perpetrator drug to affect exposure of other drugs:

- Drugs commonly used by subjects with T2D
- Drugs with a narrow therapeutic index
- Drugs with limited permeability and incomplete absorption (BCS class III), theoretically being most susceptible to the effect of enhanced absorption
- Drugs used as index transporter substrates, selected based on in vitro DDI results

The rationale for victim drug selection is provided in Table 3.

**Table 3 Drug-drug interaction: Rationale for victim drug selection – trials with oral semaglutide as potential perpetrator**

| Trial | Victim drug(s)<br>(indication)                                                | Rationale for victim drug selection                                                                                                                                                                                                                                                                                                                         |
|-------|-------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 4065  | <b>lisinopril</b><br>(hypertension)                                           | Lisinopril has low permeability (BCS class III), incomplete absorption and does not undergo metabolism (bioavailability ~25%). Therefore, lisinopril was considered an appropriate model drug for investigating the potential of SNAC in the oral semaglutide tablet to enhance absorption of other co-administered drugs.                                  |
| 4065  | <b>warfarin<sup>a</sup></b><br>(prevention of thrombosis and thromboembolism) | Warfarin is commonly used by subjects with T2D and was selected due to its narrow therapeutic index. Clinically relevant alterations in warfarin exposure can lead to increased risk of bleeding (higher exposure) or thromboembolic events (lower exposure). Hence, it was investigated if oral semaglutide alters warfarin exposures.                     |
| 4145  | <b>metformin</b><br>(type 2 diabetes)                                         | Metformin was selected because it is the most commonly used drug in the target population with T2D. Metformin has low permeability (BCS class III), incomplete absorption and does not undergo metabolism (bioavailability of 50%–60% for 850 mg metformin). Therefore, metformin may be susceptible to the absorption enhancing effect of SNAC.            |
| 4145  | <b>digoxin</b><br>(atrial fibrillation)                                       | Digoxin was selected due to its narrow therapeutic index. It was investigated if oral semaglutide alters digoxin exposures.                                                                                                                                                                                                                                 |
| 4249  | <b>ethylenestradiol/<br/>levonorgestrel</b><br>(oral contraceptive)           | A commonly used combination product with ethylenestradiol/levonorgestrel was selected to represent oral contraceptives.                                                                                                                                                                                                                                     |
| 4250  | <b>furosemide</b><br>(oedema and hypertension)                                | Initial <i>in vitro</i> data suggested SNAC may inhibit OAT1 and OAT3 transporters. Furosemide is an index victim substrate for OAT1 and OAT3 transporters <sup>25</sup> and was used to evaluate the potential for SNAC to alter plasma concentrations of such transporter substrates.                                                                     |
| 4250  | <b>rosuvastatin</b><br>(dyslipidaemia)                                        | Initial <i>in vitro</i> data suggested SNAC may inhibit BCRP and OATP1B1 transporters. Rosuvastatin is an index victim substrate for BCRP and OATP1B1 transporters <sup>8</sup> and was used to evaluate the potential for SNAC to alter plasma concentrations of such transporter substrates.                                                              |
| 4279  | <b>levothyroxine</b><br>(thyroid hormone replacement therapy)                 | Levothyroxine is a commonly prescribed thyroid hormone replacement drug with a narrow therapeutic index. It has similar dosing instructions as oral semaglutide, i.e. dosing before the first meal of the day and consequently it is important to understand the impact of oral semaglutide on levothyroxine absorption when dosing the two drugs together. |

<sup>a</sup> racemic mixture of S-warfarin and R-warfarin.

BCS: Biopharmaceutics Classification System

(Source: *Summary of Clinical Pharmacology, Table 3-8, Page 73*)

### **Drug interactions: Semaglutide**

The following observations were made when oral semaglutide was co-administered (i.e. taken at the same time) with other oral drugs (Figure 2):

- No effect on AUC and  $C_{max}$  was observed for lisinopril, S-warfarin and R-warfarin, digoxin, ethinylestradiol and levonorgestrel
- An increase in AUC but no effect on  $C_{max}$  was observed for metformin (+32%) and levothyroxine (+33%)
- An increase in AUC (+28%) and a decrease in  $C_{max}$  (-34%) was observed for furosemide
- An increase in both AUC (+41%) and  $C_{max}$  (+10%) was observed for rosuvastatin

The anticoagulating effect of warfarin, as measured by INR, was not affected when warfarin was co-administered with oral semaglutide. The estimated treatment ratio (with/without oral semaglutide) of the mean incremental AUC of INR and maximum INR response were:

- $iAUC_{INR, 0-144h}$ : 1.00 [0.93; 1.06] (90% CI)
- $INR_{max}$ : 0.98 [0.96; 1.01] (90% CI)

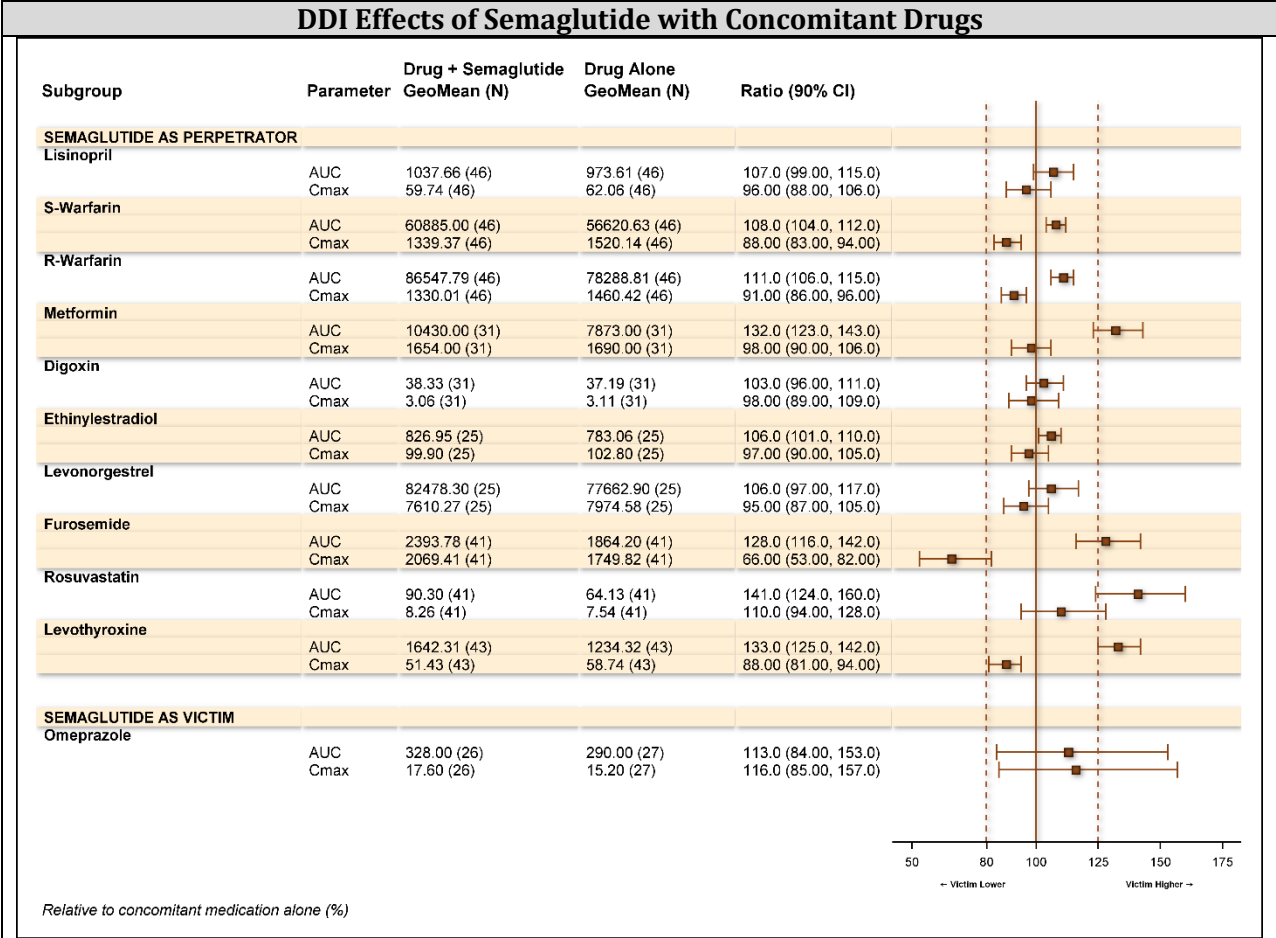


**Figure 2 Drug-Drug Interactions Between Semaglutide and Concomitant Medications**  
 (Source: FDA analysis of Applicant's data)

**Drug interactions: SNAC**

When co-administered with SNAC, no effect on systemic exposure was observed for lisinopril, warfarin, metformin, digoxin, ethinylestradiol, levonorgestrel, furosemide, rosuvastatin and levothyroxine. Probenecid and omeprazole had no effect on the systemic exposure of SNAC; however, cyclosporine increased the C<sub>max</sub> and AUC of SNAC by 41% and 31%, respectively (Figure 3).

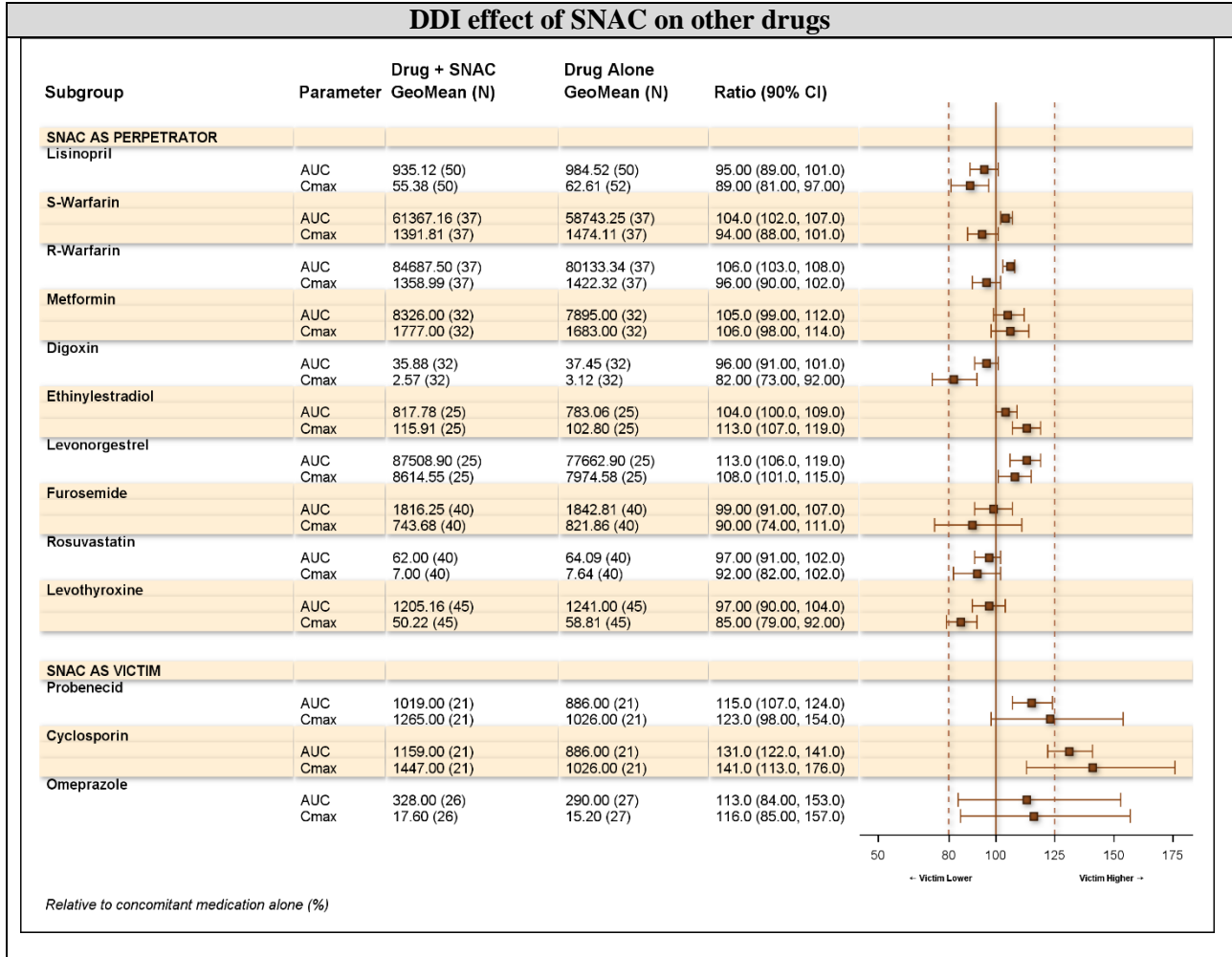


**Figure 3 Drug-drug interactions between SNAC and concomitant medications**

(Source: FDA analysis of Applicant's data)

### 3.2.2.7 Special Populations

#### 3.2.2.7.1 Renal Impairment

##### **Semaglutide:**

Semaglutide exposure did not exhibit any consistent patterns of increase or decrease with increasing renal impairment. The exposure of oral semaglutide was not affected by hemodialysis. The median  $t_{\max}$  was similar across renal function groups. As renal impairment increased, there was a slight increase in  $t_{1/2}$  (geometric mean  $t_{1/2}$  ranging 152–165 hours), except in the ESRD group (geometric mean  $t_{1/2}$  was 153 hours). The geometric mean  $t_{1/2}$  observed in subjects with renal impairment was not outside the range observed in other steady-state trials (geometric mean  $t_{1/2}$  ranging 139–174 hours). No statistically significant relationship between creatinine clearance (CLCR) and exposure ( $AUC_{0-24h}$  or  $C_{\max}$ ) across the renal function groups was observed. There was no statistically significant relationship between CLCR and  $C_{\max}$  of semaglutide.

##### **SNAC:**

SNAC exposure also did not exhibit any consistent patterns of increase or decrease with increasing renal impairment. The maximum increase in AUC was seen in subjects with severe renal impairment (49% higher AUC). The  $C_{\max}$  of SNAC was not affected by the degree of renal impairment. The median  $T_{\max}$  was similar across the renal function groups and ranged from 0.58 hours for subjects with mild renal impairment to 0.83 hours for ESRD subjects. The renal clearance ( $CL_R$ ) decreased with increasing degree of renal impairment. The estimated ratio of  $CL_R$  of SNAC in each of the renal impairment groups to that in the group with normal renal function ranged between 1.41 for subjects with mild renal impairment and 0.51 for subjects with severe renal impairment.

Exposure of SNAC metabolites increased with increasing degree of renal impairment, amounting up to 26-fold increase in metabolite E1246 exposure. Considering the safety margin established with non-clinical studies, such high exposure of SNAC metabolites does not pose to seem any safety concern. Refer to the non-clinical review by Dr. Elena Braithwaite for safety assessment of SNAC and its metabolites.

#### 3.2.2.7.2 Hepatic Impairment

##### **Semaglutide:**

Semaglutide exposure following 10 days of once daily dosing was similar across the hepatic function groups; no relationship was observed between  $AUC_{0-24h}$  or  $C_{\max}$  and the degree of hepatic function. The median  $t_{\max}$  of 1 to 1.5 hours was similar across the 4 hepatic function groups and no obvious trend in the geometric mean of  $t_{1/2}$  across the 4 hepatic function groups was observed. Statistically significant change in the exposure in relation to changes in the measured continuous hepatic laboratory parameters used in the Child-Pugh classification was not observed. The degree of hepatic function does not have a clinically relevant effect on semaglutide exposure.

##### **SNAC:**

Exposure of SNAC following 10 days of once daily dosing increased with increase in degree of hepatic impairment. The estimated ratio of mean  $AUC_{0-24h}$  and  $C_{\max}$  of SNAC ranged from 1.5 – 3.6, and 1.1 – 2.0 in the mild and severe hepatic impairment groups, respectively. Over the 10-day dosing, SNAC did not accumulate. The median  $t_{\max}$  of SNAC was 0.5 hours in all hepatic function groups, and a clear terminal phase was not observed for SNAC;  $t_{1/2}$  for SNAC could not be estimated. Renal clearance ( $CL_R$ ) of SNAC did not exhibit any apparent pattern according to changes in hepatic function. The ratio of the mean  $CL_R$  of SNAC in each of the hepatic impairment groups to that in the group with normal hepatic function ranged from 0.65 in the moderate hepatic impairment group to 1.20 in the severe hepatic impairment group. With decrease in hepatic function, the clearance decreased and ranged from 275.8 L/h in the group with normal hepatic function to 78.5 L/h in the severe hepatic impairment group.

### 3.2.2.7.3 Pediatric

Oral Semaglutide has not been studied in pediatric patients.

### 3.2.2.7.4 Effects of Age, Body Weight, Gender, Ethnicity and Race

PopPK analysis did not identify age, body weight, gender, ethnicity and race to have any clinically relevant impact on the pharmacokinetics of oral semaglutide.

## 3.2.3 Pharmacodynamics:

The pharmacodynamic properties of semaglutide were evaluated with the subcutaneous program (NDA 209637, see review by Dr. Wickramaratne Senarath Yapa in DARRTS, Reference ID: 4142722). The key PD properties are described below in section 3.2.3.1.

### 3.2.3.1 Pharmacodynamics of semaglutide in patients with T2DM

Pharmacodynamic effects of 1 mg SC semaglutide on glycodynamics at steady-state were demonstrated as follows:

An improvement in insulin secretion, during both the first (0-10 min) and second (10-120 min) phase insulin secretion, was observed following treatment with semaglutide when compared to placebo in patients with T2DM.

Following a meal stimulation test, there was a reduction in fasting glucose (22%), in AUC<sub>0-5 hr</sub> postprandial glucose (20-29%), and in the overall 24-hour glucose profile (22%) in patients with T2DM treated with semaglutide compared to placebo. Likewise, a reduction in fasting (8%), AUC<sub>0-5 hr</sub> postprandial (14-15%), and overall 24 hr profile (12%) glucagon was observed in patients with T2DM following semaglutide treatment compared to placebo. For insulin, an increase in fasting insulin was observed (30%) in patients treated with semaglutide compared to placebo, however no treatment effect of semaglutide when compared to placebo was evident for AUC<sub>0-5 hr</sub> postprandial insulin. For overall 24-hour insulin profile, the primary analysis revealed no treatment difference of semaglutide compared to placebo, however in a sensitivity analysis, which excluded patients who were non-compliant with meals, an 8-15% increase in insulin was observed after semaglutide treatment compared to placebo. Such observations for overall (primary analysis) and postprandial insulin are likely to be attributed to the lower postprandial demand for insulin in patients treated with semaglutide as a result of lower glucose concentrations and an increase in insulin sensitivity. In the Phase 3a studies, semaglutide treatment overall decreased insulin resistance (HOMA-IR indices) from baseline and throughout the trial.

Under hyperglycemic conditions, following an IV injection of arginine, an increase in insulin levels was observed during 0-10 min and 0-30 min periods following treatment with semaglutide compared to placebo (at end-of-treatment). The estimated treatment ratio (semaglutide/placebo) for mean change from baseline to end-of-treatment was 2.82 and 4.42 (significant) for the 0-10 min and 0-30 min time periods, respectively. The results suggest an improvement in maximal insulin secretory capacity in patients with T2DM treated with semaglutide when compared to placebo.

In patients with T2DM, an increase in insulin secretion rate with increasing plasma glucose levels (5-12 mmol/L) in a glucose-dependent manner was observed following treatment with semaglutide compared to placebo. For glucagon, a more pronounced glucose-dependent decrease in glucagon concentration was observed with increasing plasma glucose levels after treatment with semaglutide compared to placebo in patients with T2DM. Thereby, semaglutide improves insulin secretory response ( $\beta$ -cell responsiveness) and lowers glucagon secretion to elevated glucose concentrations in a glucose-dependent manner.

The insulin secretion rate-glucose concentration profile after semaglutide treatment in patients with T2DM was similar to that observed in healthy subjects (no treatment). The glucagon concentration-time profile for patients with T2DM was more similar to that of healthy subjects (no treatment) as compared to patients with T2DM treated with placebo.

Treatment with semaglutide (1 mg SC semaglutide at steady-state) did not compromise the overall counter-regulation of plasma glucose levels during hypoglycemia in patients with T2DM when compared to placebo. Semaglutide treatment compared to placebo did not alter the counterregulatory responses of increased glucagon and did not impair the reduction in C-peptide levels in patients with T2DM.

### 3.2.4 QT Prolongation:

#### Semaglutide:

The QTc prolongation effect of semaglutide were evaluated with the subcutaneous program (NDA 209637, see review by Dr. Chen in DARRTS, Reference ID: 4092903)

In brief, no significant QTc prolongation effect of semaglutide (0.5 mg, 1.0 mg, and 1.5 mg) was detected in this TQT study. The largest upper bounds of the 2-sided 90% CI for the mean difference between semaglutide (0.5 mg, 1.0 mg, and 1.5 mg) and placebo were below 10 ms, the threshold for regulatory concern as described in the ICH E14 guideline. The largest lower bound of the two-sided 90% CI for the  $\Delta\Delta\text{QTcF}$  for moxifloxacin was greater than 5 ms, and the moxifloxacin profile over time is adequately demonstrated in Figure 4.

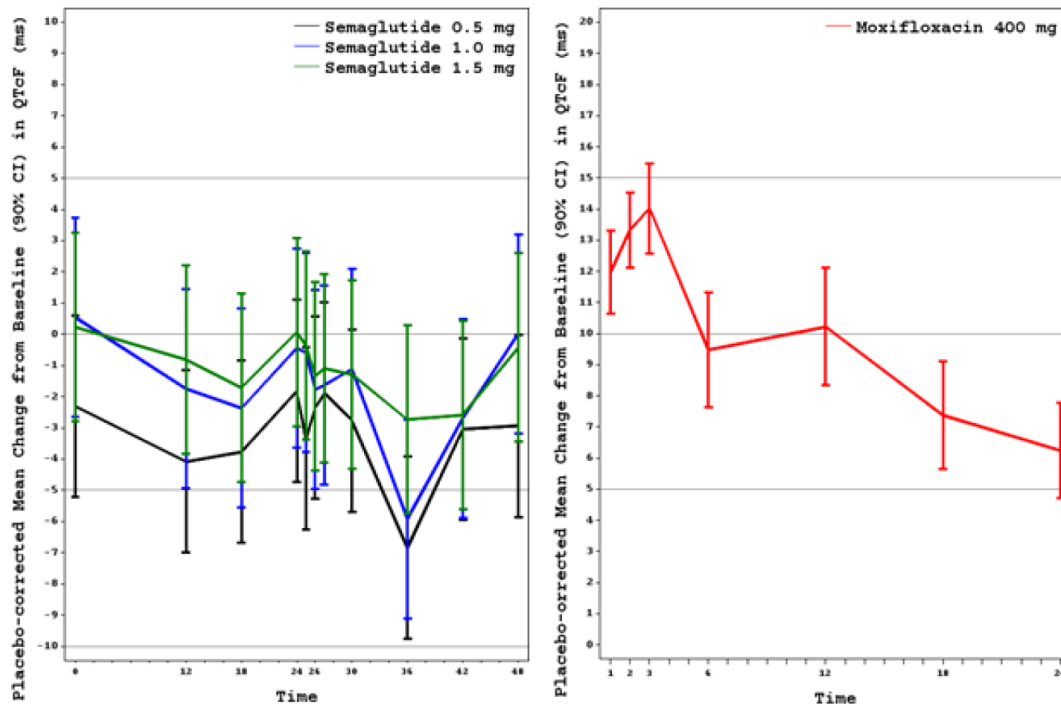


**Figure 4** Mean and 90% CI  $\Delta\Delta\text{QTcF}$  Time course

(Source: TQT Study Review by Dr. Chen, NDA 209637, Document ID 4092903 in DARRTS, Figure 5, Page 20)

### SNAC:

The QTc prolongation effect of SNAC were evaluated with the oral semaglutide program (*IND 114464, see review by Dr. Begum in DARRTS, Reference ID: 4373769*). QTc prolongation effect of SNAC was evaluated in a two-part study (a) part A was designed to inform the selection of SNAC dose to be used in part B, and (b) part B investigated the effect of SNAC (3.6 g) on cardiac repolarization in healthy subjects. Part A evaluated PK of SNAC and its metabolites (E494, E506, E1245, E1246 and E1247) at doses 1.2, 2.4 and 3.6 g.

No significant QTc prolongation effect of SNAC (3.6 g) was detected in this TQT study. The Agency reviewers compared SNAC with two placebo arms (Placebo 1 and Placebo 2) separately based on the study design. Using a conservative approach in the safety evaluation, the Agency interpreted the results based on the worse comparison with placebos in central tendency analysis. For QTcF primary analysis, results for both placebo 1 and placebo 2 were presented. For assay sensitivity analysis, only the smaller of the largest lower bound of comparison between moxifloxacin and placebos was presented. The largest upper bounds of the 2-sided 90% CI for the mean difference between SNAC and placebo 1 was 3.7 ms. The largest unadjusted 90% lower confidence interval is 10.5 ms. By considering Bonferroni multiple endpoint adjustment, the largest lower confidence interval is 9.9 ms, which indicates that at least 5 ms QTcF effect due to moxifloxacin can be detected from the study (Figure 5).

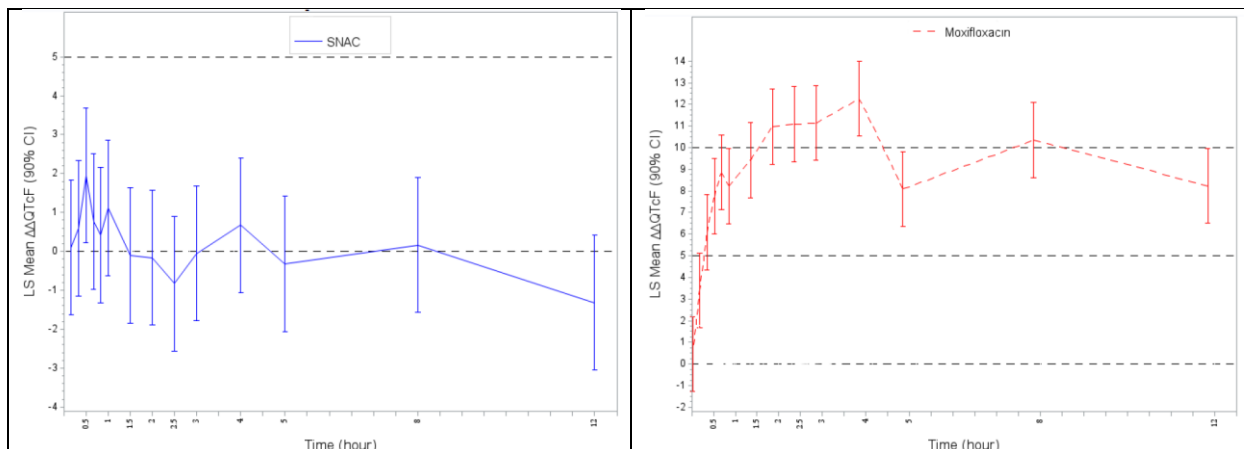


**Figure 5 Mean and 90% Unadjusted CI  $\Delta\Delta$ QTcF Timecourse (SNAC and Moxifloxacin)**

(Source: TQT Study Review by Dr. Begum, IND 114464, Document ID 4373769 in DARRTS, Figure 2, Page 7)

### 3.2.5 Immunogenicity:

In the oral semaglutide clinical development program, immunogenicity was assessed in three phase 1 trials (3692, 3991, 4140), one phase 2 trial (3790) and six phase 3 trials (PIONEER 1–5 and 9). In these trials, samples for antibody analysis were collected before start of dosing (baseline sample), during treatment (phase 2 and 3 trials only) and at the follow-up visit (after a suitable semaglutide wash out period).

A total of 22,343 samples from 2924 subjects treated with oral semaglutide were tested for antibodies. Only 14 of 2924 subjects (0.5%) tested positive for anti-semaglutide antibodies at any time point post-baseline. Anti-semaglutide in vitro neutralizing antibodies or anti-semaglutide antibodies with endogenous GLP-1 in vitro neutralizing effect at end-of-trial were not found in any subject. All subjects with treatment induced antibodies had a transient response with low levels of anti-semaglutide antibodies and at follow up were antibody negative. A few subjects had pre-existing antibodies which were not boosted following treatment with oral semaglutide, and the two antibody-positive follow-up samples were from subjects also positive at baseline.

Based on PK data in subjects that tested positive for anti-semaglutide antibodies, the plasma semaglutide concentrations were not influenced by the formation of anti-semaglutide antibodies. Efficacy of semaglutide in terms of reduction in HbA1c levels and safety as based on reported AEs in subjects were not influenced by the formation of anti-semaglutide antibodies.

The low immunogenicity observed with oral semaglutide is consistent with that reported with other approved GLP-1 analogs.

The acceptability of the immunogenicity data and associated analytical method is further deferred to the OBP review.

### 3.3 Clinical Pharmacology Questions

The clinical pharmacology review of this application pertained to addressing the following issues:

- a. Dose selection of semaglutide for Phase 3 trials
- b. Selection of SNAC as an absorption enhancer
- c. Dosing conditions for oral semaglutide tablets
  - i. time of fast prior to and after dosing
  - ii. amount of water to be administered with each tablet of semaglutide
  - iii. timing of meals related to semaglutide administration

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

The data presented in this NDA provides supportive evidence of effectiveness for oral semaglutide as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. Semaglutide exposures following oral administration were comparable to the exposure range observed following subcutaneous administration (Figure 6).

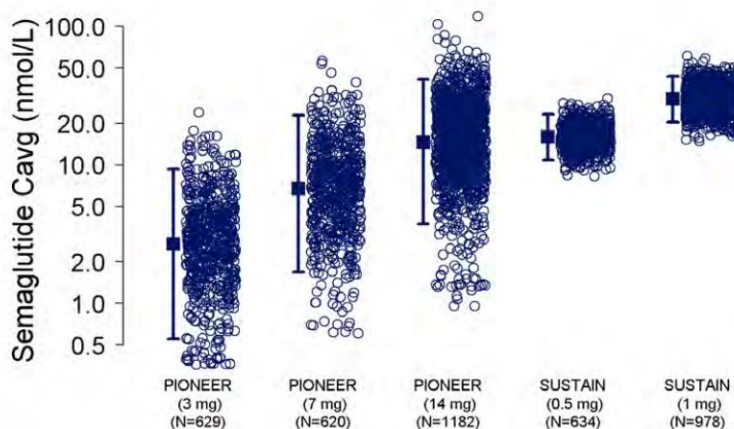


**Figure 6** Comparative Exposures of Semaglutide from Subcutaneous Dosing in SUSTAIN and Oral Dosing in PIONEER

(Source: Phase 3 Modelling Report, Figure 1-3, page 13)

#### 3.3.2. Why was SNAC used in the tablet formulation?

SNAC is an absorption enhancer that increases the oral bioavailability of semaglutide when formulated with semaglutide in a tablet form. SNAC is a small fatty acid derivative which is rapidly metabolized mainly via stepwise beta-oxidation of the side chain and the parent compound and its metabolites also undergo conjugation with glucuronic acid. Cytochrome P450 (CYP450) enzymes do not appear to be involved in the metabolism of SNAC. Five major metabolites, of which two were  $\beta$ -oxidized SNAC (E494 and E506) and three were the glucuronic acid conjugated forms of SNAC (E1245, E1246 and E1247), have been identified.

##### 3.3.2.1 How does SNAC exert its function?

SNAC, when co-formulated, protects semaglutide against enzymatic degradation in the stomach. Oral administration of therapeutic peptides such as GLP-1 analogues are challenged by poor absorption across the GI barrier and degradation by the proteolytic enzymes. SNAC exhibits a buffering action, which

likely helps facilitate a high pH in the localized stomach environment around the tablet and thereby confers protection of semaglutide from degradation by gastric enzymes. In addition, SNAC interacts with the plasma membrane of the gastric epithelium to promote absorption of semaglutide via transcellular route. The absorption enhancing effects of SNAC were transient, molecular size dependent, reversible and require co-formulation. Refer to the non-clinical review by Dr. Elena Braithwaite for additional details on the SNAC's mechanism of action in facilitating semaglutide absorption.

#### *3.3.2.2. On what basis was the SNAC content selected for the tablet formulation?*

A fixed amount of SNAC (300 mg) is used in all three strengths, i.e., 3 mg, 7 mg and 14 mg of semaglutide tablet. The amount of SNAC was selected based on results of Study 3691 which was a two-part, randomized, double-blind, placebo-controlled trial with single ascending doses of semaglutide. Healthy male subjects received oral semaglutide (2 – 20 mg) co-formulated with 150 – 600 mg SNAC or placebo with corresponding SNAC amounts. Study drugs were administered under fasting condition with 50 mL of water, and subjects were not allowed to eat until 5-hour post-dosing. Results showed that plasma semaglutide concentration was higher with 300 mg SNAC compared to 150 mg SNAC. However, increasing SNAC content from 300 mg to 600 mg did not result in a higher semaglutide exposure. Hence, 300 mg SNAC was selected for all the proposed semaglutide strengths and was used in all subsequent clinical studies. It is noted, however, that the concentration of semaglutide in all the samples of semaglutide 5 mg +SNAC 150 mg, and in a large number of samples for other three arms were below the LLOQ for semaglutide.

As shown in Figure 7, increasing SNAC content from 300 mg to 600 mg resulted in lower semaglutide exposure. Note that the data was highly variable (as shown in the inset) and 3 out of 11 subjects (27%) in the SNAC 300 mg arm vs 4 out of 10 subjects (40%) in the 600 mg arm did not have any measurable concentration above LLOQ at any timepoint. When subjects without any measurable concentration from both arms were excluded from analysis, no significant difference in semaglutide exposure was observed (Figure 8).

Considering the limited nature of the data and the imbalance in missing data between arms, it is difficult to draw any conclusion if semaglutide formulated with 300 mg or 600 mg SNAC would result in similar systemic exposure. Hence, the product label should clearly state that patients should not take two 7 mg tablet to account for one 14 mg tablet since two tablets would correspond to 600 mg SNAC. Similarly, patients should not split one 14 mg tablet to account for two 7 mg tablets.

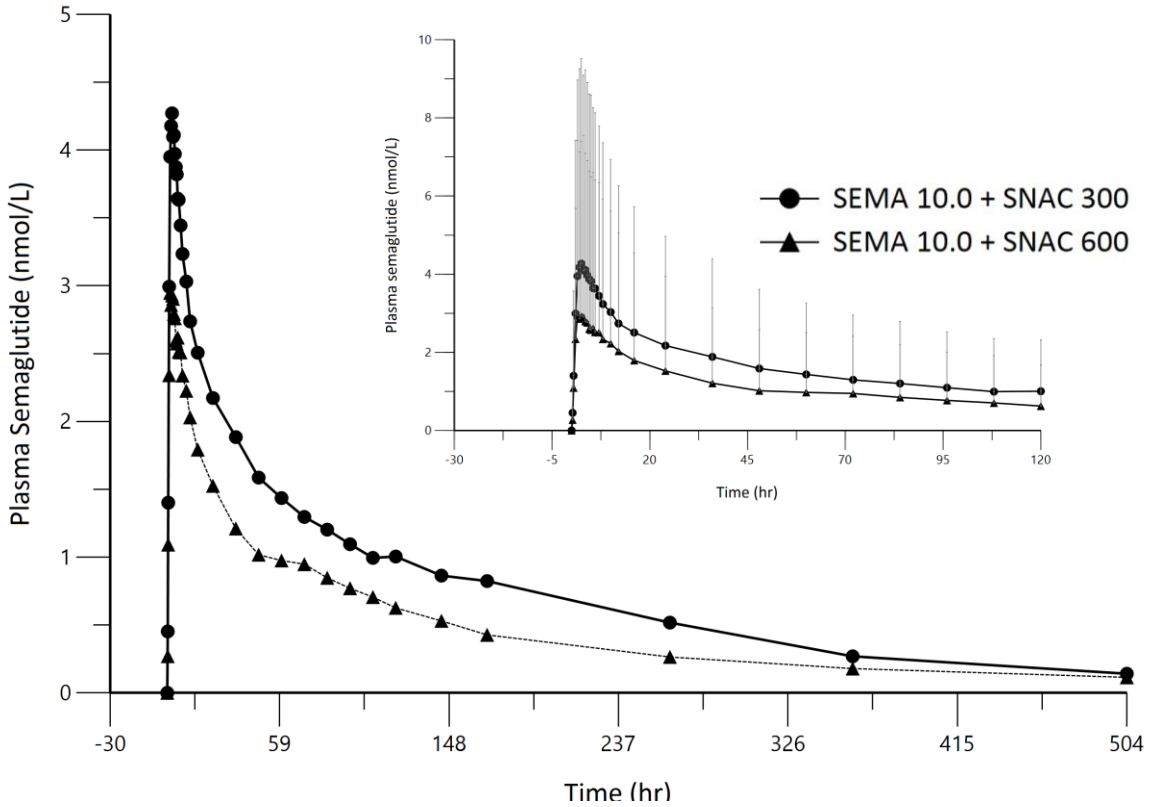


**Figure 7** Plasma concentration-time profile of oral semaglutide with varying amount of SNAC (Study 3691); (inset) plasma concentration time profile for 2 hr to demonstrate variability in semaglutide concentration

(Source: FDA analysis from Applicant's data submitted for Study 3691)

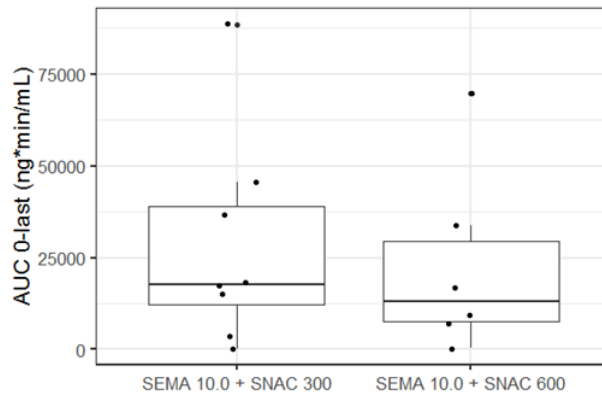


**Figure 8** Plasma semaglutide exposure following administration of 10 mg semaglutide formulated with 300 mg or 600 mg SNAC

(Source: FDA analysis from Applicant's data submitted for Study 3691)

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

Yes, the proposed general dosing regimen is appropriate for the general patient population for which the indication is being sought. However, there are some limitations of use for oral semaglutide as listed below:

- Oral semaglutide is not recommended as a first-line therapy for patients who have inadequate glycemic control on diet and exercise because of the uncertain relevance of rodent C-cell tumor findings to humans
- Oral semaglutide has not been studied in patients with a history of pancreatitis. Other antidiabetic therapies should be considered in patients with a history of pancreatitis
- Oral semaglutide is not indicated for use in patients with type 1 diabetes mellitus or for the treatment of patients with diabetic ketoacidosis, as it would not be effective in these settings

#### 3.3.3.1 Semaglutide Dose Selection

The Applicant conducted a randomized, partially-blinded, dose range, dose escalation, parallel design trial including 9 treatment arms in total; 7 oral semaglutide treatment arms, 1 oral placebo arm and 1 s.c. semaglutide arm. The oral semaglutide maintenance doses administered were once-daily 2.5 mg, 5 mg, 10 mg, 20 mg and 40 mg. The s.c. semaglutide maintenance dose administered was once-weekly 1.0 mg. Placebo was administered orally once-daily. The trial included 3 escalation schemes with oral semaglutide; in all 3 schemes, the maintenance dose was 40 mg. The schemes included were a standard dose escalation scheme (dose escalation every 4th week; referred to as 40 mg), a slow dose escalation scheme (dose escalation every 8th week; referred to as 40 mg S) and a fast dose escalation scheme (dose escalation every 2nd week; referred to as 40 mg F).

Mean steady-state semaglutide exposures following 2.5-40 mg oral semaglutide were in the range 2-50 nmol/L compared to approximately 30 nmol/L following 1 mg subcutaneous semaglutide dosed weekly (Figure 9).

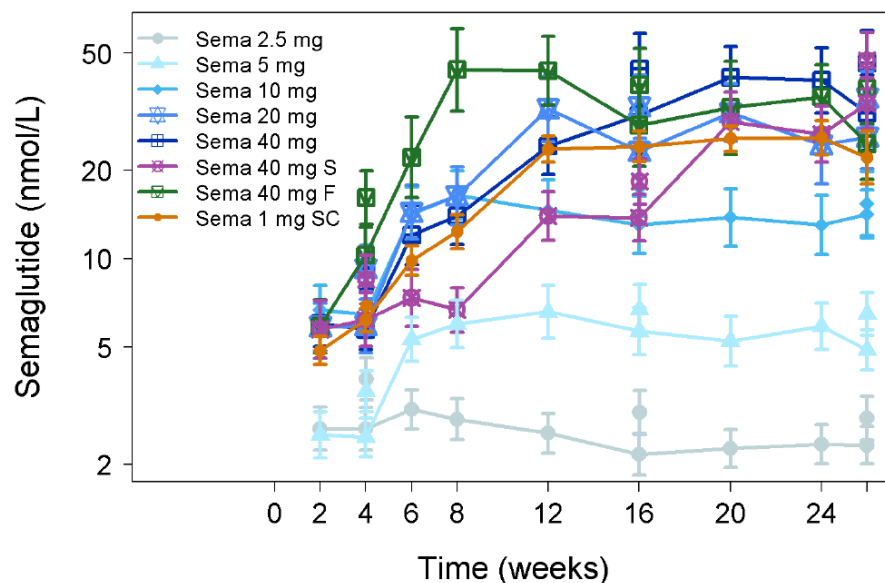


**Figure 9** Observed mean semaglutide exposure versus time for oral and s.c. dosing groups

(Source: Modelling Report - Oral Semaglutide NN9924 Population Pharmacokinetic and Exposure-Response analysis for Trial ID: NN9924-3790, figure on page 8)

Correlation of efficacy outcomes with oral semaglutide dose was performed for (a) change in HbA1c after 26 weeks of treatment, and (b) change in body weight after 26 weeks of treatment.

A dose-response relationship in change in HbA1c after 26 weeks of treatment with oral semaglutide showed an ED<sub>50</sub> value of approx. 6 mg and with the steepest part of the curve ranging up to doses of 10 mg after which the effects started to plateau, see Figure 10 (left panel).

Similarly, a dose-response relationship with an ED<sub>50</sub> value of approximately 15 mg was observed for change in body weight after 26 weeks of treatment with oral semaglutide. The steepest part of the curve ranged up to 20 mg, after which the effects started to plateau, see Figure 10 (right panel).

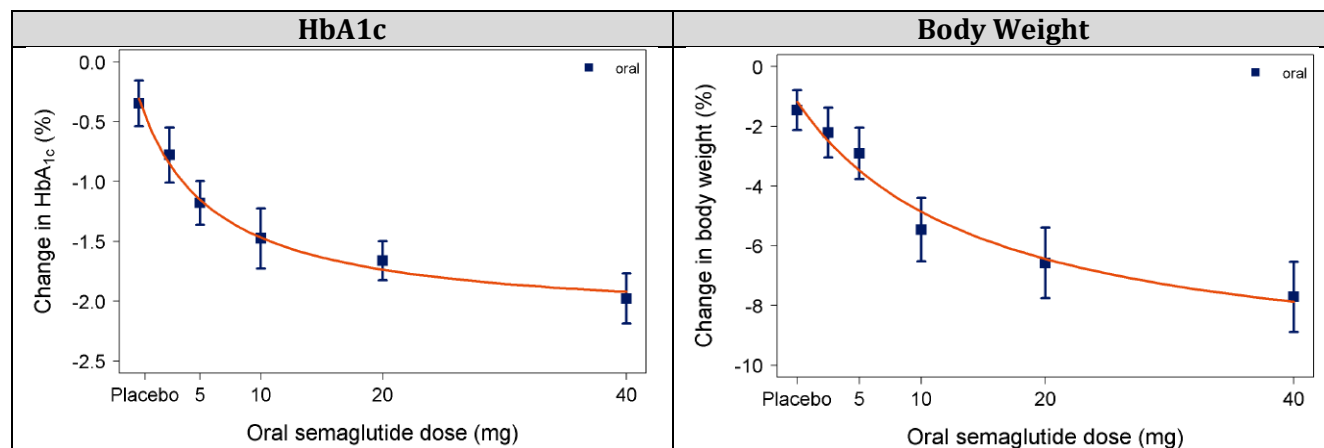


**Figure 10** Change from baseline versus oral maintenance dose of semaglutide for HbA1c (left panel) and body weight (right panel)

(Source: Modelling Report - Oral Semaglutide NN9924 Population Pharmacokinetic and Exposure-Response analysis for Trial ID: NN9924-3790, figure on page 9)

Based on the PK and PD data, the Applicant carried out simulations, and predicted mean exposures of 4.1 nmol/L, 9.5 nmol/L, and 19 nmol/L, respectively for oral doses of 3 mg, 7 mg, and 14 mg semaglutide once daily, respectively. The predicted mean HbA1c change from baseline for oral doses of 3 mg, 7 mg, and 14 mg semaglutide once daily are -0.95%, -1.35%, and -1.64 % for a similar population as was studied in the phase 2 trial, Study 3790 (Figure 11). All Phase 3 studies were conducted with once daily semaglutide 3 mg, 7 mg, and 14 mg doses using appropriate titration schemes.

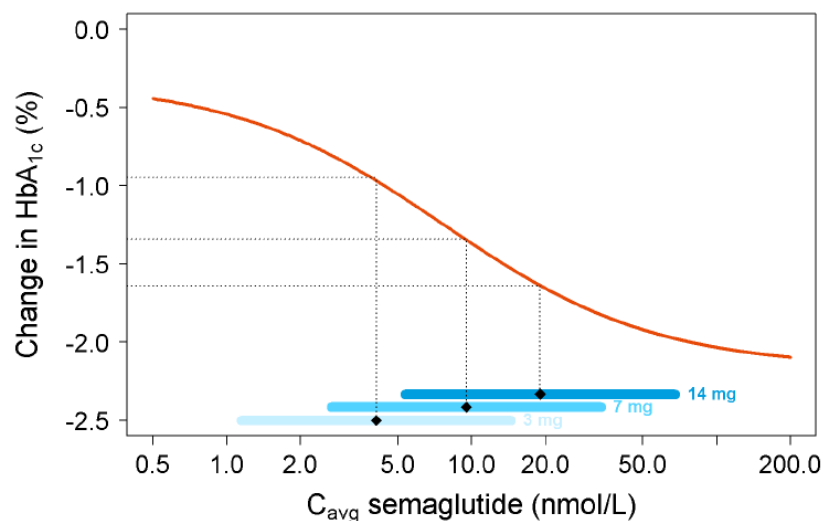


**Figure 11 Simulated effects on HbA<sub>1c</sub> change from baseline versus predicted average concentrations for phase 3a doses**

(Source: Modelling Report - Oral Semaglutide NN9924 Population Pharmacokinetic and Exposure-Response analysis for Trial ID: NN9924-3790, figure on page 10)

### 3.3.3.2 Selection of dosing condition

Oral semaglutide is proposed to be taken on an empty stomach and should be swallowed whole with up to half a glass of water equivalent to 120 mL without splitting, crushing or chewing the tablet. After taking oral semaglutide, patients should wait at least 30 minutes before the first meal or drink of the day and taking other oral medications. The proposed dosing conditions are based on the outcome from two clinical studies – 3794 and 3957.

Study 3794 was a multiple-dose, single-center, open-label, parallel-group, eight-armed, 2 x 4 factorial study in which healthy male subjects (n=151) were randomized to receive 10 mg oral semaglutide under fasting condition for 10 days. Subjects were to receive either 50 mL or 120 mL water at administration combined with post-dose fasting period of 15, 30, 60 or 120 minutes. The effect of water (50 mL vs 120 mL) was not statistically significant for AUC<sub>0-24h</sub> (p=0.541) or C<sub>max</sub> (p=0.676). However, the exposure of semaglutide increased with longer post-dose fasting (Figure 12).

As opposed to semaglutide, plasma concentration of SNAC decreased with increasing post-dose fasting with highest concentration achieved with 15 min post-dose fasting. Similar to semaglutide, SNAC exposure was not different between the two volumes of water (p=0.3957)

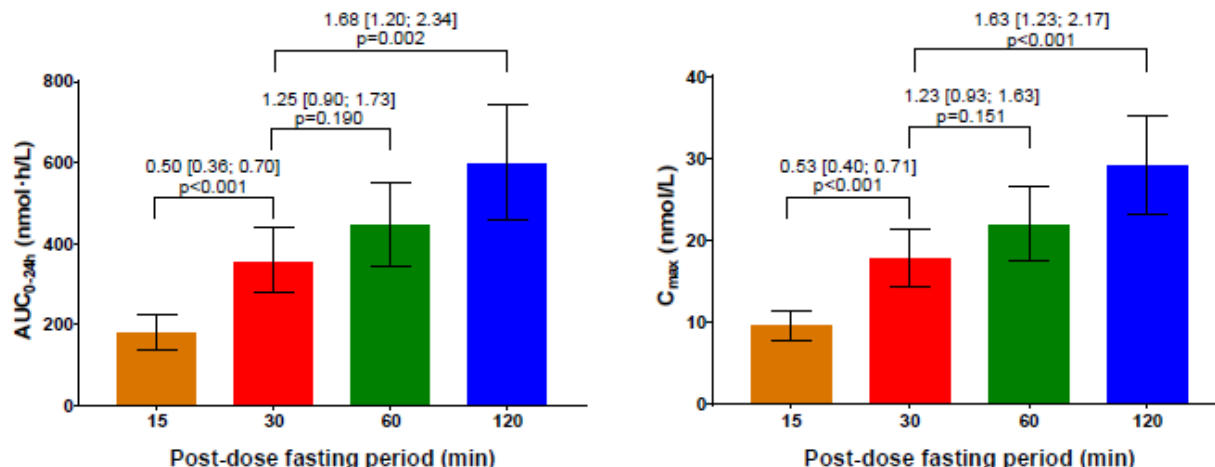


**Figure 12** Effect of post-dose fasting time on AUC<sub>0-24h</sub> (A) and C<sub>max</sub> (B) of semaglutide (Study 3794)

(Source: NDA 213051, Module 2.7.1. Summary of Biopharmaceutic Studies and Associated Analytical Methods)

Study 3957 was a single-center, randomized, open-label, cross-over study to investigate whether the volume of water administered with oral semaglutide (formulated with 300 mg SNAC) affects the pharmacokinetics of semaglutide. Healthy male subjects (n=26) received a single dose of 10 mg semaglutide with 50 mL or 240 mL water. Tablets and water were labeled with <sup>111</sup>Indium (<sup>111</sup>In) and <sup>99m</sup>Technetium (<sup>99m</sup>Tc), respectively. Subjects were dosed in the morning after a minimum of 8 hr of fasting; subjects continued to fast until 4-hour after dosing. A washout period of 2–5 weeks separated the two treatments.

Semaglutide exposure was higher following dosing with 50 mL water compared to that with 240 mL of water (Figure 13). C<sub>max</sub> were 7.7 nmol/L and 4.4 nmol/L and AUC<sub>0-24h</sub> were 117.2 nmol.h/mL and 46.4 nmol.h/mL when semaglutide was administered with 50 mL and 240 mL water, respectively. Hence, the proposed semaglutide dosing with 120 mL appears reasonable since semaglutide exposure was not significantly different while administered with either 50 mL or 120 mL whereas administration with 240 mL water resulted in lower plasma semaglutide concentration.

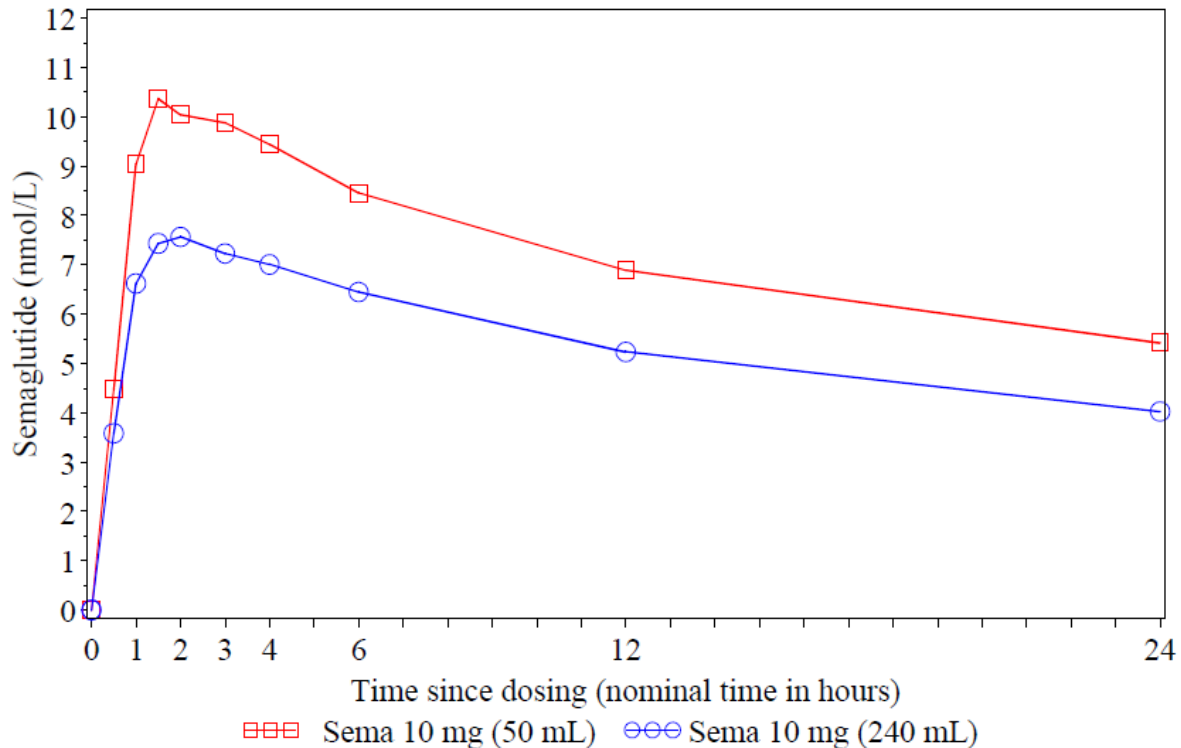


**Figure 13 Plasma semaglutide concentration following administration with 50 mL and 240 mL of water (Study 3957)**

(Source: NDA 213051, Module 5.3.3.4; CSR for Study 3957, Figure 11-2, Page 86)

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

Results from the clinical pharmacology trials and population PK analysis of data from phase 3 studies indicate that dose adjustment of oral semaglutide is not required for patients based on intrinsic factors of age, sex, body weight, race, ethnicity, upper GI disease, renal function or hepatic function. Other than body weight, which is the most influential covariate resulting in an inverse relationship between semaglutide exposure and body weight, the rest of the demographic covariates have little or no influence on exposure (Figure 14 and Figure 15). The exposure of semaglutide in moderate renal impairment from the dedicated Phase 1 study appeared to be 1.84 times that observed in subjects with normal renal function, however, there was considerable variability in the data (Figure 14). Semaglutide exposure in patients with moderate renal impairment in Phase 3 efficacy trials, however, were observed to be similar to that of patients with normal renal function (Figure 15).

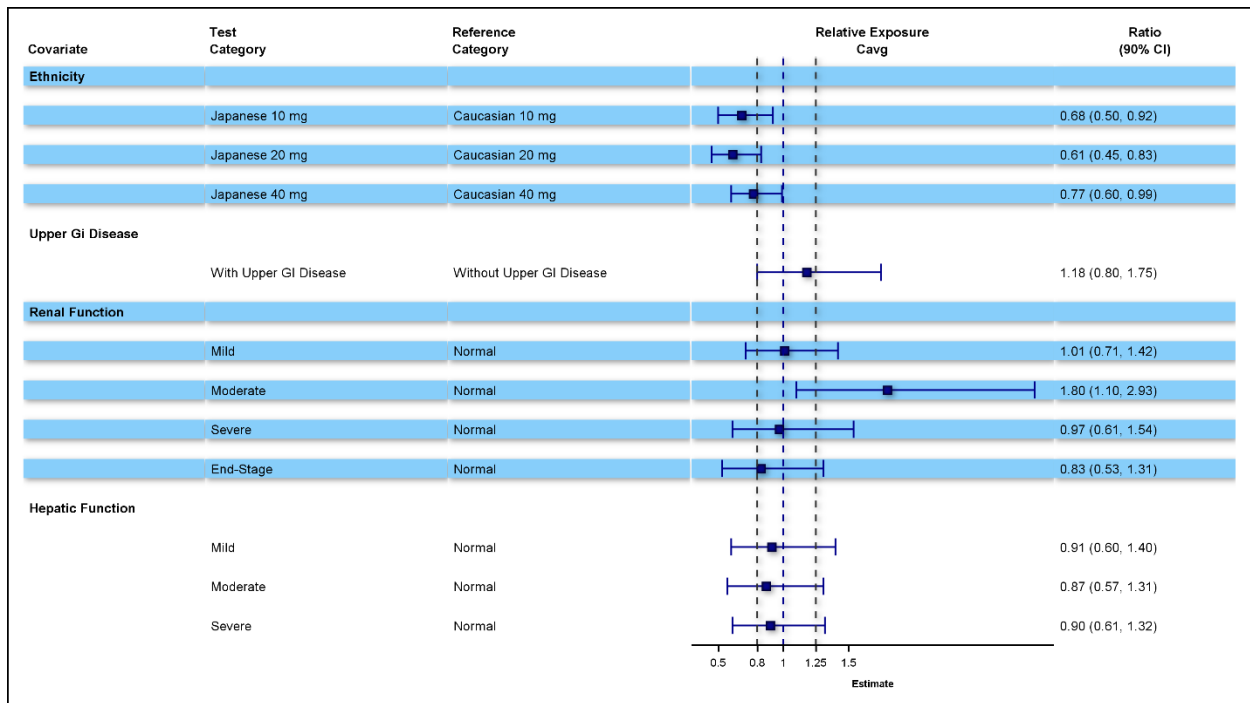


**Figure 14** Intrinsic factors: Covariate effects on the exposure of oral semaglutide – Phase 1 data

(Source: Reviewer generated plot)

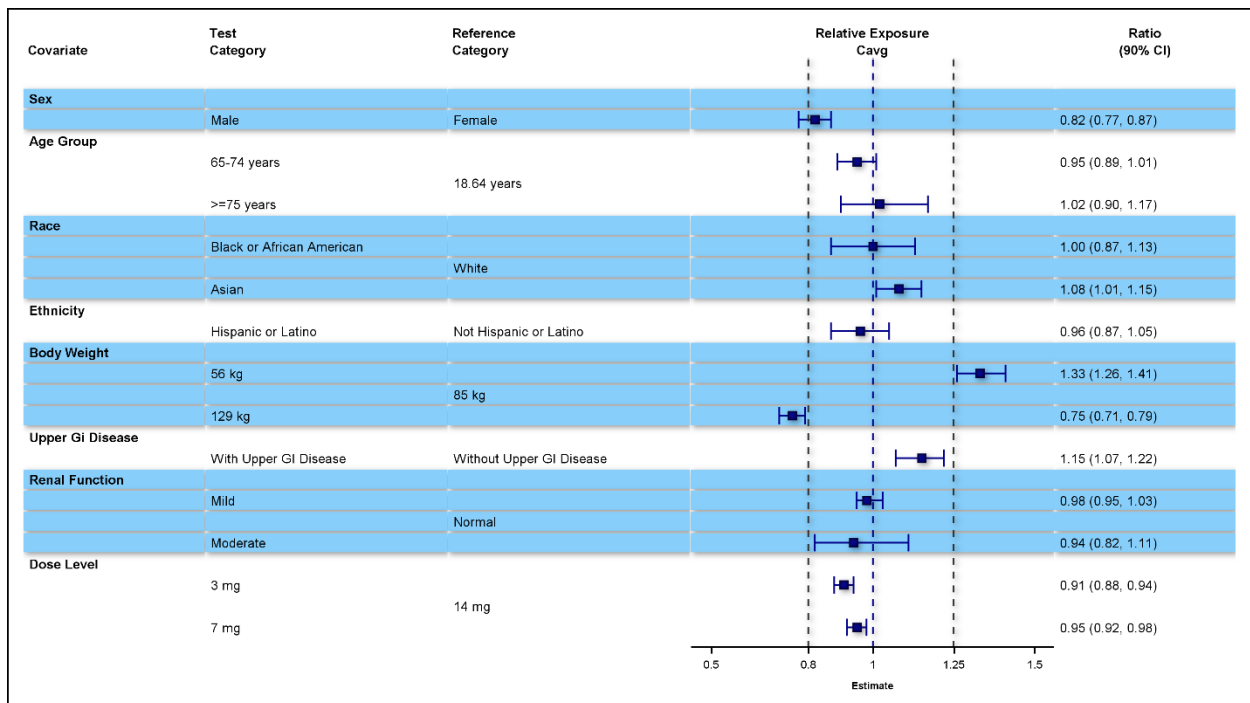


**Figure 15** Intrinsic factors: Covariate effects on the exposure of oral semaglutide – population PK analysis of Phase 3 data

(Source: Reviewer generated plot)

### 3.3.4.1 Hepatic Impairment

#### Semaglutide:

The Applicant conducted an open-label, multiple dose, parallel group trial to investigate the PK properties of semaglutide and SNAC in subjects with impaired hepatic function to assess whether there was a need to adjust the dose of oral semaglutide in subjects with hepatic impairment compared to subjects with normal hepatic function. The variability in semaglutide exposure was found to be very high after a single dose as some subjects had concentrations below the lower limit of quantification. A 10-day dosing regimen was therefore chosen to reduce the variability observed in exposure in a single dose setting and to avoid subjects without any measurable concentrations.

Following 10 days of once daily dosing of oral semaglutide, the exposure of semaglutide (AUC and  $C_{max}$ ) were similar across the 4 hepatic function groups, indicating that semaglutide exposure is not affected by the degree of hepatic function (Table 4).

#### SNAC:

Following 10 days of once daily dosing of oral semaglutide, the exposure of SNAC (AUC and  $C_{max}$ ) increased with a decrease in hepatic function (Table 4). The ratios of the estimated mean of  $AUC_{0-24h}$  of SNAC in each of the 3 hepatic impairment groups to that in the group with normal hepatic function ranged from 1.50 in the mild group to 3.64 in the severe group. The ratios of the estimated mean  $C_{max}$  of SNAC in each of the 3 hepatic impairment groups to that in the group with normal hepatic function ranged from 1.10 for the mild group to 2.00 for the severe group.

**Table 4 Statistical Analysis of PK Parameters for Semaglutide and SNAC in Hepatic Impaired Patients Compared to Healthy Matched Subjects**

| Group    | PK for Moiety      | AUC <sub>0-24</sub><br>(nmol·hr/L) | AUC <sub>0-24</sub> Ratio<br>90% CI | C <sub>max</sub><br>(nmol/L) | C <sub>max</sub> Ratio<br>90% CI |
|----------|--------------------|------------------------------------|-------------------------------------|------------------------------|----------------------------------|
| Normal   | <i>Semaglutide</i> | 244<br>(188, 317)                  |                                     | 12.9<br>(10.0, 16.6)         |                                  |
| Mild     |                    | 223<br>(140, 354)                  | 0.91<br>(0.60, 1.40)                | 11.8<br>(7.42, 18.9)         | 0.92<br>(0.60, 1.40)             |
| Moderate |                    | 211<br>(135, 329)                  | 0.87<br>(0.57, 1.31)                | 10.9<br>(6.86, 17.4)         | 0.85<br>(0.55, 1.30)             |
| Severe   |                    | 219<br>(143, 338)                  | 0.90<br>(0.61, 1.32)                | 11.4<br>(7.47, 17.3)         | 0.88<br>(0.61, 1.28)             |
| Group    | PK for Moiety      | AUC <sub>0-24</sub><br>(ng·hr/mL)  | AUC <sub>0-24</sub> Ratio<br>90% CI | C <sub>max</sub><br>(ng/mL)  | C <sub>max</sub> Ratio<br>90% CI |
| Normal   | <i>SNAC</i>        | 1069<br>(969, 1180)                |                                     | 1260<br>(1037, 1533)         |                                  |
| Mild     |                    | 1601<br>(1359, 1886)               | 1.50<br>(1.28, 1.74)                | 1382<br>(1029, 1855)         | 1.10<br>(0.83, 1.45)             |
| Moderate |                    | 2875<br>(2017, 4097)               | 2.69<br>(2.00, 3.62)                | 2399<br>(1740, 3309)         | 1.90<br>(1.40, 2.58)             |
| Severe   |                    | 3898<br>(2869, 5295)               | 3.64<br>(2.84, 4.68)                | 2525<br>(1193, 5344)         | 2.00<br>(1.10, 3.66)             |

(Source CSR for Study 4082, Tables 11-1 and 11-7, pages 103 and 114)

Since the Child-Pugh classification uses serum albumin, direct bilirubin and prothrombin time, among other parameters levels, to determine hepatic function, an association of semaglutide PK endpoints with the above 3 measured continuous parameters of hepatic function were analyzed statistically by the Applicant as recommended by the FDA and EMA for trials performed in hepatically impaired subjects. An evaluation of semaglutide exposure ( $AUC_{0-24h}$ ) as a function of the 3 parameters of hepatic function,

serum albumin, direct bilirubin and prothrombin time showed no obvious relationship for any of the 4 hepatic function groups.

#### 3.3.4.2 Renal Impairment

##### **Semaglutide:**

The effect of renal impairment on semaglutide exposure was evaluated in a multi-center, open-label, multiple-dose, parallel group study (Trial 4079) in which systemic exposure of semaglutide in subjects with mild, moderate, severe renal impairment and end stage renal disease (ESRD) was compared with that in subjects with normal renal function following a 10 day dosing regimen of oral semaglutide – 5 mg for 5 days followed by 10 mg for 5 days.

Semaglutide exposure was similar across the treatment arms. The ratios of the estimated mean of  $AUC_{0-24h}$  of semaglutide in each of the 4 renal impairment groups to that in the group with normal renal function varied from 1.37 in the mild group to 1.02 in the ESRD group. The ratios of the estimated mean  $C_{max}$  of semaglutide in each of the 4 renal impairment groups to that in the group with normal renal function ranged from 1.39 for the mild group to 1.06 for the ESRD group.

No consistent pattern in semaglutide exposure was observed when comparing the renally impaired groups to the group with normal renal function indicating that semaglutide exposure is not affected by the degree of renal function (Table 5).

##### **SNAC:**

In addition to semaglutide, impact of renal impairment on exposure to SNAC was also evaluated in Study 4079. Following 10 days of once daily dosing of oral semaglutide, SNAC exposure did not exhibit any consistent patterns of increase or decrease with increasing renal impairment (Table 5). The ratios of the estimated least squares mean in each of the 4 renal impairment groups to that in the group with normal renal function were 1.19, 1.30, 1.49 and 1.32 in the mild, moderate, severe and ESRD groups, respectively for  $AUC_{0-24h}$  of SNAC.

The ratios of the estimated least squares mean in each of the 4 renal impairment groups to that in the group with normal renal function were 0.94, 0.70, 1.06 and 0.79 in the mild, moderate, severe and ESRD groups, respectively for  $C_{max}$  of SNAC. Although exposure of SNAC metabolites increased with increasing degree of renal impairment, amounting up to 26-fold increase in metabolite E1246 exposure, this does not seem to pose any safety concern considering the safety margin established with non-clinical studies. Refer to the non-clinical review by Dr. Elena Braithwaite for safety assessment of SNAC and its metabolites.

**Table 5 Statistical Analysis of PK Parameters for Semaglutide and SNAC in Renal Impaired Patients Compared to Healthy Matched Subjects**

| Group     | PK for Moiety      | AUC <sub>0-24</sub><br>(nmol·hr/L) | AUC <sub>0-24</sub> Ratio<br>90% CI | C <sub>max</sub><br>(nmol/L) | C <sub>max</sub> Ratio<br>90% CI |
|-----------|--------------------|------------------------------------|-------------------------------------|------------------------------|----------------------------------|
| Normal    | <i>Semaglutide</i> | 259<br>(181, 370)                  |                                     | 13.8<br>(9.75, 19.6)         |                                  |
| Mild      |                    | 261<br>(204, 333)                  | 1.01<br>(0.71, 1.42)                | 13.6<br>(10.6, 17.3)         | 0.98<br>(0.70, 1.37)             |
| Moderate  |                    | 465<br>(280, 772)                  | 1.80<br>(1.10, 2.93)                | 25.5<br>(15.8, 41.1)         | 1.84<br>(1.15, 2.94)             |
| Severe    |                    | 252<br>(159, 401)                  | 0.97<br>(0.61, 1.54)                | 13.9<br>(8.69, 22.1)         | 1.00<br>(0.63, 1.59)             |
| End-Stage |                    | 215<br>(135, 340)                  | 0.83<br>(0.53, 1.31)                | 11.5<br>(7.33, 18.1)         | 0.83<br>(0.53, 1.30)             |
| Group     | PK for Moiety      | AUC <sub>0-24</sub><br>(ng·hr/mL)  | AUC <sub>0-24</sub> Ratio<br>90% CI | C <sub>max</sub><br>(ng/mL)  | C <sub>max</sub> Ratio<br>90% CI |
| Normal    | <i>SNAC</i>        | 1052<br>(948, 1167)                |                                     | 1053<br>(778, 1426)          |                                  |
| Mild      |                    | 1256<br>(1042, 1513)               | 1.19<br>(1.01, 1.42)                | 990<br>(658, 1491)           | 0.94<br>(0.63, 1.41)             |
| Moderate  |                    | 1370<br>(1110, 1691)               | 1.30<br>(1.08, 1.57)                | 741<br>(466, 1179)           | 0.70<br>(0.45, 1.10)             |
| Severe    |                    | 1564<br>(1315, 1861)               | 1.49<br>(1.26, 1.75)                | 1111<br>(638, 1935)          | 1.06<br>(0.64, 1.75)             |
| End-Stage |                    | 1388<br>(1175, 1640)               | 1.32<br>(1.13, 1.55)                | 829<br>(526, 1304)           | 0.79<br>(0.51, 1.22)             |

*(Source CSR for Study 4079, Tables 11-2 and 11-8, pages 110 and 126)*

A regression of Semaglutide exposure as a function of creatinine clearance showed that the slope was close to zero, indicating that the exposure of semaglutide was similar in all the renal groups evaluated (Figure 16).

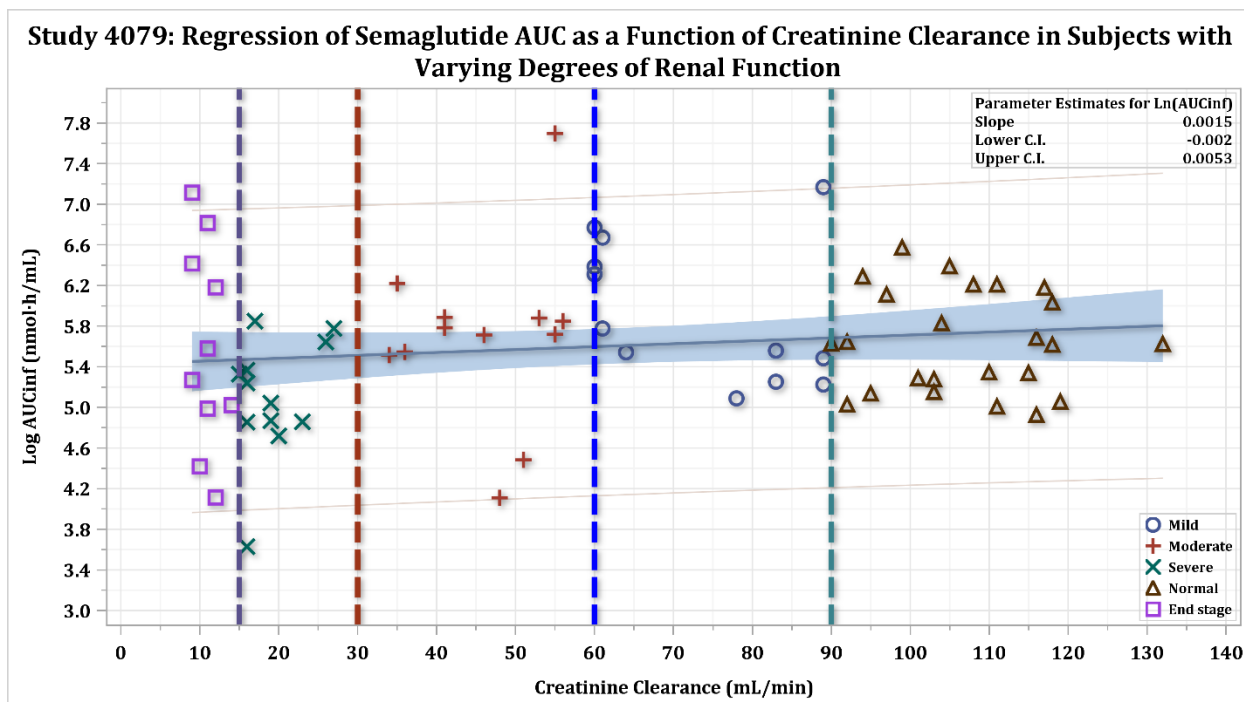


**Figure 16 Scatter plots for Semaglutide Exposure as a Function of Creatinine Clearance in Subjects with Varying Degrees of Renal Function**

(Source: Reviewer generated plot)

### 3.3.4.3 Upper Gastrointestinal Disease

#### Semaglutide:

The Applicant conducted an open-label, multiple dose, parallel group trial to investigate the PK, safety and tolerability of semaglutide and SNAC in T2DM subjects with upper GI disease compared to subjects without upper GI disease. According to the protocol, among the subjects in the group with upper GI disease that are used to evaluate the primary endpoint, at least 12 subjects were required to have chronic gastritis and at least 12 subjects were required to have GERD in order to include both diseases in the comparison to subjects without upper GI disease.

Multiple-dose administration (once daily dosing for 10 days) was selected as a substitute for single-dose administration to reduce the variability in semaglutide exposure and to avoid all PK measurements being below the lower limit of quantification (LLOQ) in the period 0 to 24 hours post dosing. Dose escalation with the first 5 days on 3 mg oral semaglutide was chosen to mitigate the risk of GI AEs as the most frequently reported AEs in clinical trials with oral semaglutide have been GI disorders such as nausea, vomiting, diarrhea, dyspepsia and constipation. Even though the highest therapeutic dose is 14 mg, it was judged as sufficient to administer 7 mg oral semaglutide in this trial to keep the trial duration as short as possible.

Following 10 days of once daily dosing of oral semaglutide, there was no statistically significant difference in exposure of semaglutide ( $AUC_{0-24h,sema,Day10}$  and  $C_{max,sema,Day10}$ ) between subjects with and without upper GI disease, however the exposure of semaglutide appeared to be slightly higher in subjects with upper GI disease compared to subjects without upper GI disease (Table 6).

### SNAC:

Following 10 days of once daily dosing of oral semaglutide, SNAC exposure ( $AUC_{0-24h,SNAC,SS}$  and  $C_{max,SNAC,SS}$ ) were similar between subjects with and without upper GI disease. The ratios of the estimated mean of  $AUC_{0-24h,SNAC,SS}$  and  $C_{max,SNAC,SS}$  for subjects with upper GI disease compared to subjects without upper GI disease were 1.06 and 1.08, respectively (Table 6).

**Table 6 Statistical Analysis of PK Parameters for Semaglutide and SNAC in Patients with Upper Gastrointestinal Disease Compared to Patients without Upper Gastrointestinal Disease**

| $AUC_{0-24, Day 10}$<br>(nmol·hr/L) |                          | $AUC_{0-24, Day 10}$ Ratio<br>90% CI | $C_{max}$<br>(nmol/L) |                          | $C_{max}$ Ratio<br>90% CI |
|-------------------------------------|--------------------------|--------------------------------------|-----------------------|--------------------------|---------------------------|
| With upper GI disease               | Without upper GI disease |                                      | With upper GI disease | Without upper GI disease |                           |
| <i>Semaglutide</i>                  |                          |                                      |                       |                          |                           |
| 144<br>(113, 183)                   | 122<br>(90, 166)         | 1.18<br>(0.80, 1.75)                 | 7.72<br>(6.01, 9.90)  | 6.63<br>(4.76, 9.23)     | 1.16<br>(0.77, 1.76)      |
| <i>SNAC</i>                         |                          |                                      |                       |                          |                           |
| 1095<br>(1013, 1185)                | 1035<br>(887, 1207)      | 1.06<br>(0.89, 1.26)                 | 1121<br>(871, 1442)   | 1039<br>(742, 1454)      | 1.08<br>(0.71, 1.65)      |

(Source CSR for Study 4267, Tables 11-1, 11-2, and 11-4, pages 79, 80, and 82)

#### 3.3.4.4 Ethnicity

Race and ethnicity do not appear to affect the PK of oral semaglutide. The effect of race and ethnicity on the PK of oral semaglutide was assessed by means of population PK analysis utilizing data from phase 3 trials. In addition, the PK of semaglutide was investigated in a clinical pharmacology trial in Japanese and Caucasian subjects.

#### PK in Japanese and Caucasian subjects

##### *Semaglutide*

Healthy Japanese and Caucasian subjects were administered 10, 20 and 40 mg oral semaglutide in a dose-escalation fashion, and the steady state PK properties of semaglutide were evaluated at each dose level. While the study was conducted with higher than proposed marketing doses, the dose range evaluated included the highest proposed marketing dose of oral semaglutide. The treatment periods included ‘Dose escalation period (Days 1–7)’, ‘Treatment period 1 (Days 8–35)’, ‘Treatment period 2 (Days 36–63)’ and ‘Treatment period 3 (Days 64–91)’.

Semaglutide exposure was lower in Japanese subjects at all investigated dose levels despite lower body weight in Japanese subjects compared to Caucasian subjects (Figure 17). The  $AUC_{0-24h,sema,SS}$  ratios (Japanese: Caucasian) were 0.68, 0.61 and 0.77 for the 10 mg, 20 mg and 40 mg oral semaglutide, respectively. The  $C_{max,sema,SS}$  ratios (Japanese: Caucasian) were 0.71, 0.65 and 0.79 for the 10 mg, 20 mg and 40 mg oral semaglutide, respectively (Table 7).

## SNAC

An evaluation of  $AUC_{0-24h,SNAC,SS}$  by the Applicant using a linear mixed model based on the log-transformed values, showed that on Day 63,  $AUC_{0-24h,SNAC,SS}$  in Japanese subjects was statistically significantly lower than that in Caucasian subjects. No statistically significant difference between the two race groups was found on Days 35 and 91.

Similarly,  $C_{max,SNAC,SS}$  evaluated by a linear mixed model based showed that on Day 63,  $C_{max,SNAC,SS}$  was statistically significantly lower in Japanese subjects than that in Caucasian subjects. No statistically significant difference between the two race groups was found on Days 35 and 91.

**Table 7 Statistical Analysis of PK Parameters for Semaglutide and SNAC in Japanese Subjects Compared to Caucasian Subjects**

| Dose               | $AUC_{0-24h,sema,SS}$<br>(nmol·hr/L) |                      | $AUC_{0-24h,sema,SS}$ Ratio<br>90% CI | $C_{max,sema,SS}$<br>(nmol/L) |                      | $C_{max}$ Ratio<br>90% CI |
|--------------------|--------------------------------------|----------------------|---------------------------------------|-------------------------------|----------------------|---------------------------|
|                    | Japanese                             | Caucasian            |                                       | Japanese                      | Caucasian            |                           |
| <i>Semaglutide</i> |                                      |                      |                                       |                               |                      |                           |
| <b>10 mg</b>       | 374<br>(301, 464)                    | 551<br>(444, 684)    | 0.68<br>(0.50, 0.92)                  | 19.1<br>(15.3, 23.7)          | 26.8<br>(21.5, 33.4) | 0.71<br>(0.52, 0.97)      |
| <b>20 mg</b>       | 676<br>(544, 839)                    | 1105<br>(890, 1372)  | 0.61<br>(0.45, 0.83)                  | 34.7<br>(27.9, 43.3)          | 53.5<br>(43.0, 66.6) | 0.65<br>(0.48, 0.89)      |
| <b>40 mg</b>       | 1184<br>(992, 1414)                  | 1544<br>(1290, 1848) | 0.77<br>(0.60, 0.99)                  | 60.3<br>(50.6, 71.9)          | 76.4<br>(63.9, 91.4) | 0.79<br>(0.61, 1.01)      |
| <i>SNAC</i>        |                                      |                      |                                       |                               |                      |                           |
| Dose               | $AUC_{0-24h,SNAC,SS}$<br>(ng·hr/mL)  |                      | $AUC_{0-24h,SNAC,SS}$ Ratio<br>90% CI | $C_{max,SNAC,SS}$<br>(ng/mL)  |                      | $C_{max}$ Ratio<br>90% CI |
|                    | Japanese                             | Caucasian            |                                       | Japanese                      | Caucasian            |                           |
| <b>Day 35</b>      | 1246<br>(1102, 1408)                 | 1476<br>(1306, 1669) | 0.84<br>(0.71, 1.00)                  | 1475<br>(1108, 1964)          | 1643<br>(1234, 2187) | 0.90<br>(0.60, 1.35)      |
| <b>Day 63</b>      | 1180<br>(1044, 1334)                 | 1463<br>(1294, 1653) | 0.81<br>(0.68, 0.96)                  | 987<br>(742, 1314)            | 1683<br>(1264, 2241) | 0.59<br>(0.39, 0.88)      |
| <b>Day 91</b>      | 1340<br>(1186, 1515)                 | 1542<br>(1363, 1746) | 0.87<br>(0.73, 1.03)                  | 1083<br>(813, 1442)           | 1602<br>(1193, 2149) | 0.68<br>(0.45, 1.02)      |

(Source CSR for Study 4140, Tables 11-2, 11-4, and 11-10, pages 108, 111, and 127)

Dose proportionality evaluation of semaglutide showed that in Japanese and Caucasian subjects, semaglutide exposure increased less than 2-fold when the dose was doubled (Figure 17). There was no interaction between race and dose in the analyses of dose-proportionality ( $p = 0.1968$  for  $AUC_{0-24h,sema}$ ;  $p = 0.3323$  for  $C_{max,sema,SS}$ ) indicating no differences in dose-proportionality between Japanese and Caucasian subjects.  $T_{max}$  and  $t_{1/2}$  were also similar in Japanese and Caucasian subjects.

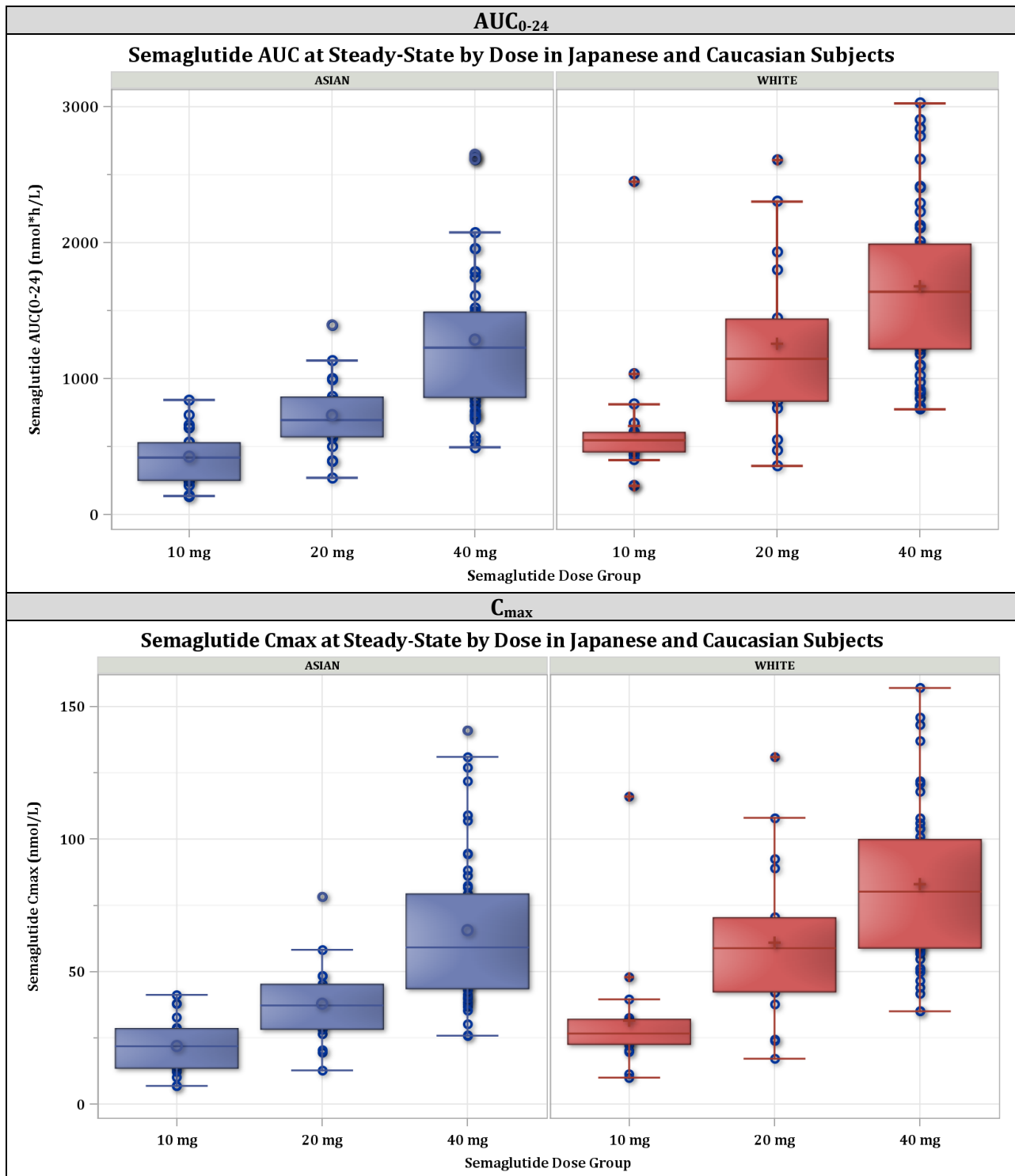


**Figure 17** Semaglutide AUC<sub>0-24</sub> (top panel) and C<sub>max</sub> (bottom panel) at Steady-State Following Oral Dosing of 10, 20 and 40 mg Semaglutide in Japanese and Caucasian Subjects

(Source: Reviewer generated plot)

### Population PK analysis

The population available for PopPK analyses in the phase 3 trials were predominantly White (67%). Asian subjects comprised 26% of the population, and 6.5% were Black or African American. Non-Hispanic or non-Latino ethnicity constituted 85% of the subjects. Mean  $C_{avg}$  in Asian subjects and Black or African American subjects compared to White subjects showed that the 90% CIs were within the [0.80-1.15]-limits (Figure 15). Similarly, the 90% CI of the mean  $C_{avg}$  in Hispanic/Latino subjects, relative to non-Hispanic/Non-Latino subjects, was within the [0.80–1.25]-limits.

### **3.3.5 Are there clinically relevant food-drug or drug-drug interactions and what is the appropriate management strategy?**

#### **3.3.5.1 Food-Drug Interaction**

Effect of food on the PK of semaglutide was studied in a single-center, randomized, open-labeled, multiple-dose, parallel group study in healthy subjects (n=78). Subjects were randomized 1:1:1 to three treatment arms (fed, fasting and reference). All subjects received 5 mg oral semaglutide for 5 days followed by 10 mg oral semaglutide for 5 days. Subjects in the fed group fasted for 10 hours overnight after which they received a high-fat, high-calorie meal followed by administration of semaglutide with 240 mL of water and 4-hour post-dose fasting period. Subjects in the fasting group fasted 10-hour overnight followed by administration of semaglutide with 240 mL water and a 4-hour post-dose fasting period. In the reference group, subjects fasted 6-hour overnight followed by administration of semaglutide with 120 mL water and 30 min post-dose fasting.

Semaglutide exposure was almost negligible in the fed group; very low exposure slightly above the LLOQ was observed in 12 subjects; 14 out of 26 subjects had no concentration above the LLOQ, and only one subject had exposure levels comparable to the other groups. The exposure to semaglutide ( $AUC_{0-24h}$  and  $C_{max}$  on Day 10) could only be evaluated in the fasting and reference conditions (Figure 18). SNAC exposure was generally comparable between fed and fasting condition; estimated ratios of  $AUC_{0-24h}$  and  $C_{max}$  on Day 10 were 0.85 and 0.75, respectively (Figure 19). As a result of the low semaglutide exposure in the fed group, patients are advised to take oral semaglutide on an empty stomach.

Exposure in the fasting group was in general higher compared to that in the reference group even though reference group received semaglutide tablet with 120 mL of water (semaglutide exposure was supposed to be higher when administered with 120 mL water compared to 240 mL). However, it was noted that the post-dose fasting period was higher in the fasting group (e.g., 4 hr) vs 30 min in the reference group. Since semaglutide exposure appears to increase with increasing post-dose fasting duration (Figure 12), this perhaps explains the higher exposure observed with the fasting group compared to the reference group.

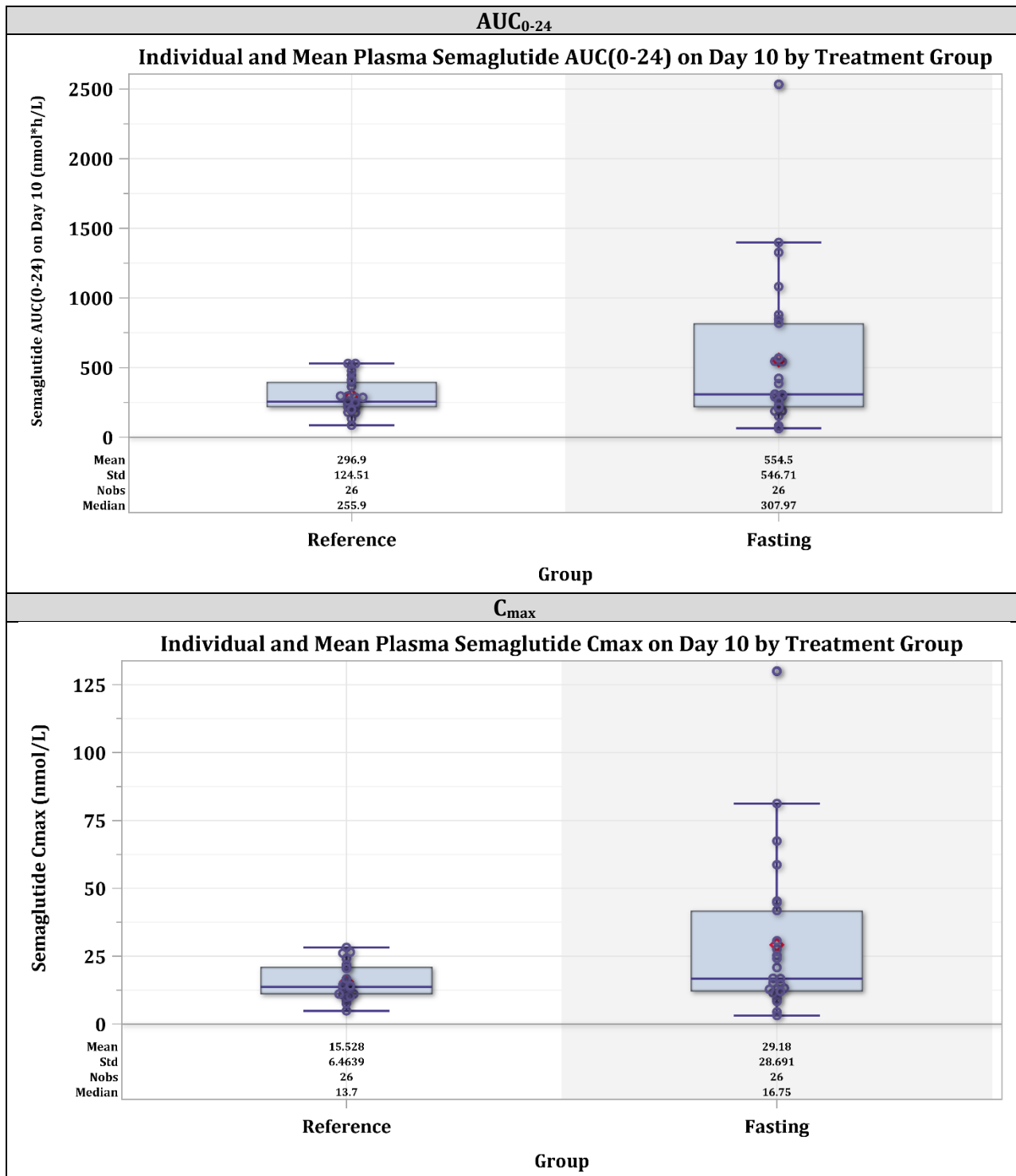


**Figure 18 Semaglutide AUC<sub>0-24</sub> (top panel) and C<sub>max</sub> (bottom panel) at Steady-State Following Oral Dosing of Semaglutide Under Fasting (with 240 mL Water) and Reference (with 120 mL Water) Conditions**

*(Source: Reviewer generated plot)*

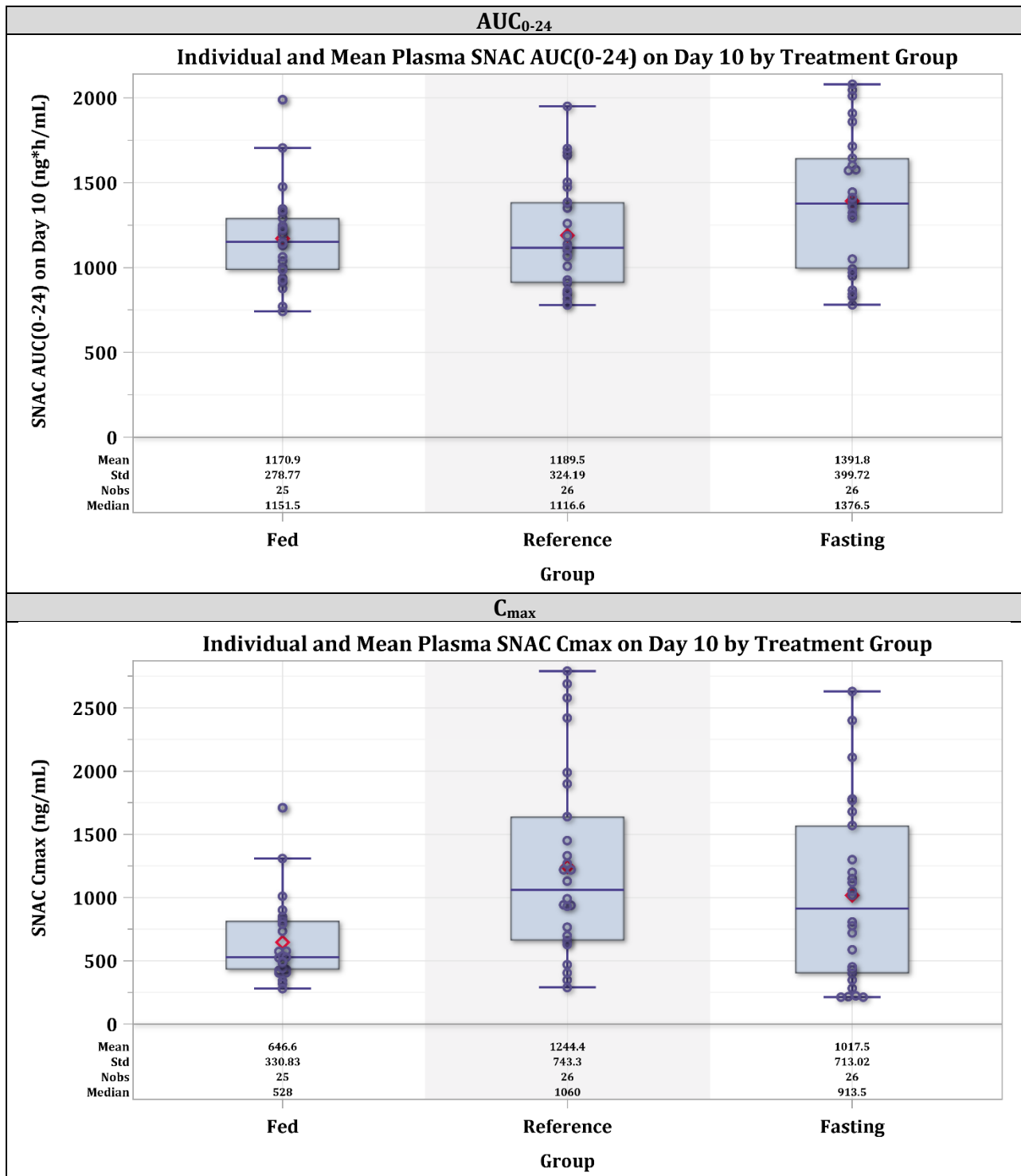


**Figure 19** SNAC AUC<sub>0-24</sub> (top panel) and C<sub>max</sub> (bottom panel) at Steady-State Following Oral Dosing of Semaglutide Under Fasting (with 240 mL Water) and Reference (with 120 mL Water) Conditions

(Source: Reviewer generated plot)

### 3.3.5.2 Drug-Drug Interactions

*Oral semaglutide was investigated as a perpetrator drug in trials 4065, 4145, 4249, 4250 and 4279, and as a victim drug when co-administered with omeprazole in a parallel group trial design in trial 4141. Probenecid and cyclosporine were evaluated as perpetrator drugs when co-administered with SNAC in crossover trial 4394.*

#### 3.3.5.2.1. Effect of semaglutide on other drugs:

Semaglutide causes a delay of gastric emptying and thereby has the potential to impact the absorption of other oral medications. In addition, SNAC alters the gastric environment to protect semaglutide in stomach and hence might also affect the absorption of other drugs administered orally. Five drug-drug interaction (DDI) studies were conducted with semaglutide to assess the impact of semaglutide on the PK of concomitantly administered drugs, as shown in Table 8.

**Table 8 Summary of trials investigating drug-drug interactions**

| Trial ID<br>Perpetrator/<br>victim drug<br>Duration <sup>a</sup> | Primary objective                                                                                                                                                                                           | Trial design                                | Treatment <sup>b</sup>                                                  | Exposed<br>subjects               | Sex<br>Age (min-max) <sup>c</sup><br>BMI (min-<br>max) <sup>c</sup> |
|------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------|-------------------------------------------------------------------------|-----------------------------------|---------------------------------------------------------------------|
| 4065<br>Lisinopril and<br>warfarin<br>56 days (SS)               | To investigate the effect of oral semaglutide dosed at steady state on the PK exposure of lisinopril and warfarin                                                                                           | Open-label, one-sequence cross-over         | Oral semaglutide 20 mg<br>Lisinopril 20 mg<br>Warfarin 25 mg            | 52 healthy subjects               | M and F<br>18–75 years<br>20.0–29.9 kg/m <sup>2</sup>               |
| 4145<br>Metformin and<br>digoxin<br>55 days (SS)                 | To investigate the effect of oral semaglutide dosed at steady state on the PK exposure of metformin and digoxin                                                                                             | Open-label, one-sequence cross-over         | Oral semaglutide 20 mg<br>Metformin 850 mg<br>Digoxin 500 µg            | 32 healthy subjects               | M and F<br>18–75 years<br>20.0–29.9 kg/m <sup>2</sup>               |
| 4249<br>Oral<br>contraception<br>58 days (SS)                    | To investigate the effect of oral semaglutide dosed at steady state on the PK exposure of ethylenestradiol and levonorgestrel                                                                               | Open-label, one-sequence cross-over         | Oral semaglutide 14 mg<br>ethylenestradiol /levonorgestrel 0.03/0.15 mg | 25 healthy postmenopausal females | F<br>≥45 years<br>20.0–29.9 kg/m <sup>2</sup>                       |
| 4250<br>Furosemide<br>and<br>rosuvastatin<br>47 days (SS)        | To investigate the effect of oral semaglutide dosed at steady state on the PK exposure of furosemide and rosuvastatin                                                                                       | Open-label, one-sequence cross-over         | Oral semaglutide 14 mg<br>Furosemide 40 mg<br>Rosuvastatin 20 mg        | 41 healthy subjects               | M and F<br>18–65 years<br>20.0–29.9 kg/m <sup>2</sup>               |
| 4279<br>Levothyroxine<br>and placebo<br>100 days (SS)            | To investigate the effect of oral semaglutide dosed at steady state on the PK exposure of levothyroxine and to investigate if semaglutide PK is influenced by co-administration with multiple other tablets | Open-label, one-sequence cross-over         | Oral semaglutide 14 mg<br>Levothyroxine 600 µg<br>Placebo (5 tablets)   | 45 healthy subjects               | M and F<br>18–50 years<br>20.0–29.9 kg/m <sup>2</sup>               |
| 4141<br>Omeprazole<br>10 days                                    | To investigate the effect of omeprazole on the PK of oral semaglutide                                                                                                                                       | Randomised, open-label, parallel group      | Oral semaglutide 10 mg<br>Omeprazole 40 mg                              | 54 healthy subjects               | M and F<br>18–75 years<br>18.5–29.9 kg/m <sup>2</sup>               |
| 4394<br>Probenecid and<br>ciclosporin<br>SD                      | To investigate the effect of probenecid and ciclosporin on the PK of SNAC after administration of oral semaglutide                                                                                          | Randomised, open-label, 3-period cross-over | Oral semaglutide 3 mg<br>Probenecid 500 mg<br>Ciclosporin 600 mg        | 21 healthy subjects               | M and F<br>18–64 years<br>18.5–29.9 kg/m <sup>2</sup>               |

<sup>a</sup> planned duration of treatment; <sup>b</sup> does not include doses used in dose escalation; <sup>c</sup> both inclusive and based on inclusion criteria.

BMI: body mass index; F: female; M: male; PK: pharmacokinetics; SD: single dose; SS: steady state.

(Source: *Module 2.7.2 Summary of Clinical Pharmacology, Table 1-4, Page 24*)

The DDI trials followed open-label, one-sequence, cross-over, steady-state trial design. Oral semaglutide and victim drug were co-administered (i.e. taken at the same time). The trials also included a period with co-administration of SNAC-alone and victim drug. Identical tablet formulation containing SNAC without semaglutide were administered to investigate if SNAC affected the PK of the co-administered drug. Trial 4279 in addition investigated the effect of the presence of multiple other tablets in the stomach on the PK of semaglutide. Trial 4394 investigated SNAC as a victim drug. A general study design where semaglutide and SNAC were assessed as perpetrator drugs is presented in Figure 20.

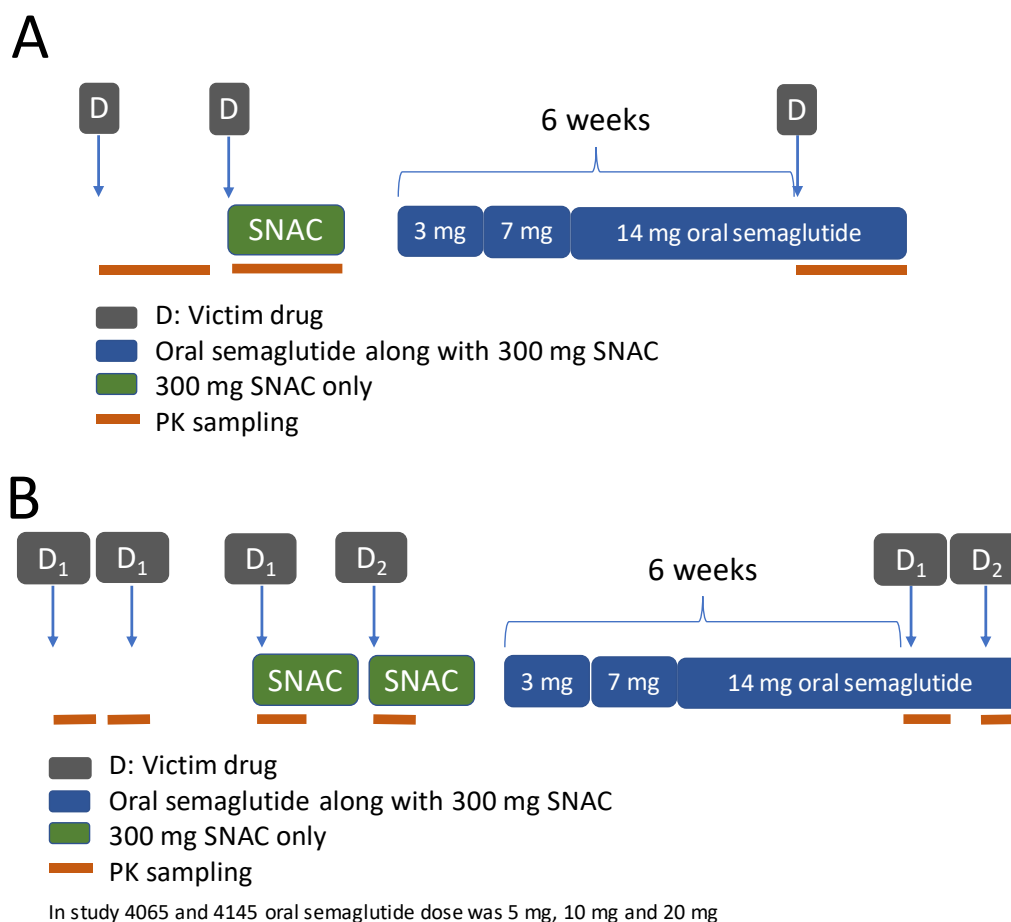


**Figure 20** General study design to investigate the effect of oral semaglutide/SNAC on other drugs: single victim drug (A); multiple victim drugs (B)

Source: Reviewer generated plot

In these DDI trials, semaglutide did not affect the absorption of orally administered medications to any clinically relevant degree. Therefore, no dose adjustment is required when these orally administered medications are taken with semaglutide. When a single dose of levothyroxine 600 ug was concurrently administered with semaglutide, the total exposure (AUC) of thyroxine (adjusted for endogenous levels) was increased by 33%. Maximum exposure ( $C_{max}$ ) was unchanged. Monitoring of thyroid parameters should be considered when treating patients with oral semaglutide at the same time as levothyroxine. Due to semaglutide's gastric delaying properties, dosing instructions should be followed when taking other oral medications. Table 9 summarizes the outcome of semaglutide as a perpetrator, and Table 10 summarizes the outcome of SNAC as a perpetrator in these DDI studies.

**Table 9 Semaglutide as a Perpetrator on Commonly Administered Drugs**

| Interacting Moieties                                                                | PK for Moiety              | AUC <sub>inf</sub> (ng·hr/mL)        | AUC <sub>inf</sub> Ratio<br>90% CI | C <sub>max</sub> (ng/mL)          | C <sub>max</sub> Ratio<br>90% CI |
|-------------------------------------------------------------------------------------|----------------------------|--------------------------------------|------------------------------------|-----------------------------------|----------------------------------|
| <b>Lisinopril + Semaglutide</b>                                                     | <b>Lisinopril</b>          | 1037.66<br>(971.44, 1108.39)         | 1.07<br>(0.99 – 1.15)              | 59.74<br>(55.25, 64.60)           | 0.96<br>(0.88 – 1.06)            |
| <b>Lisinopril Alone</b>                                                             |                            | 973.61<br>(911.48, 1039.98)          |                                    | 62.06<br>(57.39, 67.11)           |                                  |
| <i>(Source CSR for Study 4065, Table 14.2.3, page 214)</i>                          |                            |                                      |                                    |                                   |                                  |
| <b>Warfarin + Semaglutide</b>                                                       | <b>R-Warfarin</b>          | 86548<br>(83706, 89486)              | 1.11<br>(1.06 – 1.15)              | 1330<br>(1267, 1396)              | 0.91<br>(0.86 – 0.96)            |
| <b>Warfarin Alone</b>                                                               |                            | 78289<br>(75718, 80947)              |                                    | 1460<br>(1392, 1533)              |                                  |
| <i>(Source CSR for Study 4065, Table 14.2.24, page 251)</i>                         |                            |                                      |                                    |                                   |                                  |
| <b>Warfarin + Semaglutide</b>                                                       | <b>S-Warfarin</b>          | 60885<br>(58989, 62842)              | 1.08<br>(1.04, 1.12)               | 1339<br>(1270, 1413)              | 0.88<br>(0.83, 0.94)             |
| <b>Warfarin Alone</b>                                                               |                            | 56621<br>(54858, 58440)              |                                    | 1520<br>(1441, 1603)              |                                  |
| <i>(Source CSR for Study 4065, Table 14.2.10, page 228)</i>                         |                            |                                      |                                    |                                   |                                  |
| <b>Warfarin + Semaglutide</b>                                                       | <b>INR<sub>max</sub></b>   |                                      |                                    | 1.83 <sup>a</sup><br>(1.79, 1.88) | 0.98<br>(0.96 – 1.01)            |
| <b>Warfarin Alone</b>                                                               |                            |                                      |                                    | 1.86 <sup>a</sup><br>(1.82, 1.91) |                                  |
| <i>(Source CSR for Study 4065, Tables 14.2.123 and 14.2.126, pages 371 and 374)</i> |                            |                                      |                                    |                                   |                                  |
| <b>Metformin + Semaglutide</b>                                                      | <b>Metformin</b>           | 10430<br>(7382, 8397)                | 1.32<br>(1.23 – 1.43)              | 1654<br>(1543, 1774)              | 0.98<br>(0.90 – 1.06)            |
| <b>Metformin Alone</b>                                                              |                            | 7873<br>(7382, 8397)                 |                                    | 1690<br>(1576, 1812)              |                                  |
| <i>(Source CSR for Study 4145, Tables 11-2 and 11-12, pages 105 and 123)</i>        |                            |                                      |                                    |                                   |                                  |
| <b>Digoxin + Semaglutide</b>                                                        | <b>Digoxin</b>             | 38.33<br>(36.11, 40.69)              | 1.03<br>(0.96 – 1.11)              | 3.06<br>(2.81, 3.33)              | 0.98<br>(0.89 – 1.09)            |
| <b>Digoxin Alone</b>                                                                |                            | 37.19<br>(35.03, 39.48)              |                                    | 3.11<br>(2.86, 3.39)              |                                  |
| <i>(Source CSR for Study 4145, Tables 11-7 and 11-16, pages 113 and 129)</i>        |                            |                                      |                                    |                                   |                                  |
| <b>OC + Semaglutide</b>                                                             | <b>Ethinylestradiol</b>    | 827 <sup>b</sup><br>(796, 859)       | 1.06<br>(1.01 – 1.10)              | 99.9 <sup>c</sup><br>(93.9, 106)  | 0.97<br>(0.90 – 1.05)            |
| <b>OC Alone</b>                                                                     |                            | 783 <sup>b</sup><br>(754, 813)       |                                    | 103 <sup>c</sup><br>(96.6, 109)   |                                  |
| <i>(Source CSR for Study 4249, Tables 11-1 and 11-5, pages 95 and 108)</i>          |                            |                                      |                                    |                                   |                                  |
| <b>OC + Semaglutide</b>                                                             | <b>Levonorgestrel</b>      | 82478 <sup>b</sup><br>(76060, 89438) | 1.06<br>(0.97 – 1.17)              | 7610 <sup>c</sup><br>(7107, 8254) | 0.95<br>(0.87 – 1.05)            |
| <b>OC Alone</b>                                                                     |                            | 77663 <sup>b</sup><br>(71620, 84216) |                                    | 7975 <sup>c</sup><br>(7353, 8649) |                                  |
| <i>(Source CSR for Study 4249, Tables 11-3 and 11-8, pages 102 and 113)</i>         |                            |                                      |                                    |                                   |                                  |
| <b>Furosemide + Semaglutide</b>                                                     | <b>Furosemide</b>          | 2393<br>(2199, 2605)                 | 1.28<br>(1.16 – 1.42)              | 557<br>(462, 671)                 | 0.66<br>(0.53 – 0.82)            |
| <b>Furosemide Alone</b>                                                             |                            | 1864<br>(1712, 2029)                 |                                    | 847<br>(703, 1021)                |                                  |
| <i>(Source CSR for Study 4250, Tables 11-1 and 11-5, pages 96 and 108)</i>          |                            |                                      |                                    |                                   |                                  |
| <b>Rosuvastatin + Semaglutide</b>                                                   | <b>Rosuvastatin</b>        | 90<br>(81, 100)                      | 1.41<br>(1.24 – 1.60)              | 8.26<br>(7.25, 9.42)              | 1.10<br>(0.94 – 1.28)            |
| <b>Rosuvastatin Alone</b>                                                           |                            | 64<br>(58, 71)                       |                                    | 7.54<br>(6.61, 8.60)              |                                  |
| <i>(Source CSR for Study 4250, Tables 11-3 and 11-10, pages 103 and 116)</i>        |                            |                                      |                                    |                                   |                                  |
| <b>Levothyroxine + Semaglutide</b>                                                  | <b>Total T<sub>4</sub></b> | 1642 <sup>d</sup><br>(1555, 1734)    | 1.33<br>(1.25 – 1.42)              | 51 <sup>e</sup><br>(48, 55)       | 0.88<br>(0.81 – 0.94)            |
| <b>Levothyroxine Alone</b>                                                          |                            | 1234 <sup>d</sup><br>(1169, 1303)    |                                    | 59 <sup>e</sup><br>(55, 62)       |                                  |
| <i>(Source CSR for Study 4279, Tables 11-1 and 11-2; pages 95 and 98)</i>           |                            |                                      |                                    |                                   |                                  |

<sup>a</sup>Ratio, no units; <sup>b</sup>pg·hr/mL; <sup>c</sup>pg/mL; <sup>d</sup>nmol·hr/L; <sup>e</sup>nmol/L

**Table 10 SNAC as a Perpetrator on Commonly Administered Drugs**

| Interacting Moieties                                                                | PK for Moiety              | AUC <sub>inf</sub> (ng·hr/mL)        | AUC <sub>inf</sub> Ratio<br>90% CI | C <sub>max</sub> (ng/mL)          | C <sub>max</sub> Ratio<br>90% CI |
|-------------------------------------------------------------------------------------|----------------------------|--------------------------------------|------------------------------------|-----------------------------------|----------------------------------|
| <b>Lisinopril + Semaglutide</b>                                                     | <b>Lisinopril</b>          | 935.12<br>(885.46, 987.56)           | 0.95<br>(0.89 – 1.01)              | 55.38<br>(51.13, 59.98)           | 0.89<br>(0.81 – 0.97)            |
| <b>Lisinopril Alone</b>                                                             |                            | 984.52<br>(932.24, 1039.73)          |                                    | 62.48<br>(57.69, 67.67)           |                                  |
| <i>(Source CSR for Study 4065, Table 14.2.6, page 217)</i>                          |                            |                                      |                                    |                                   |                                  |
| <b>Warfarin + Semaglutide</b>                                                       | <b>R-Warfarin</b>          | 57072<br>(49804, 65402)              | 0.73<br>(0.62 – 0.85)              | 928<br>(797, 1080)                | 0.64<br>(0.53 – 0.76)            |
| <b>Warfarin Alone</b>                                                               |                            | 78612<br>(68600, 90085)              |                                    | 1454<br>(1249, 1693)              |                                  |
| <i>(Source CSR for Study 4065, Table 14.2.27, page 254)</i>                         |                            |                                      |                                    |                                   |                                  |
| <b>Warfarin + Semaglutide</b>                                                       | <b>S-Warfarin</b>          | 39404<br>(33976, 45699)              | 0.69<br>(0.58 – 0.83)              | 944<br>(806, 1104)                | 0.62<br>(0.52, 0.75)             |
| <b>Warfarin Alone</b>                                                               |                            | 56704<br>(48893, 65764)              |                                    | 1512<br>(1292, 1770)              |                                  |
| <i>(Source CSR for Study 4065, Table 14.2.15, page 233)</i>                         |                            |                                      |                                    |                                   |                                  |
| <b>Warfarin + Semaglutide</b>                                                       | <b>INR<sub>max</sub></b>   |                                      |                                    | 1.44 <sup>a</sup><br>(1.38, 1.51) | 0.77<br>(0.73 – 0.81)            |
| <b>Warfarin Alone</b>                                                               |                            |                                      |                                    | 1.88 <sup>a</sup><br>(1.79, 1.96) |                                  |
| <i>(Source CSR for Study 4065, Tables 14.2.123 and 14.2.126, pages 371 and 374)</i> |                            |                                      |                                    |                                   |                                  |
| <b>Metformin + Semaglutide</b>                                                      | <b>Metformin</b>           | 8326<br>(7918, 8755)                 | 1.05<br>(0.99 – 1.12)              | 1777<br>(1661, 1901)              | 1.06<br>(0.98 – 1.14)            |
| <b>Metformin Alone</b>                                                              |                            | 7895<br>(7508, 8302)                 |                                    | 1683<br>(1572, 1800)              |                                  |
| <i>(Source CSR for Study 4145, Tables 11-4 and 11-14, pages 108 and 126)</i>        |                            |                                      |                                    |                                   |                                  |
| <b>Digoxin + Semaglutide</b>                                                        | <b>Digoxin</b>             | 35.88<br>(34.25, 37.60)              | 0.96<br>(0.91 – 1.01)              | 2.57<br>(2.32, 2.84)              | 0.82<br>(0.73 – 0.92)            |
| <b>Digoxin Alone</b>                                                                |                            | 37.45<br>(35.74, 39.24)              |                                    | 3.12<br>(2.82, 3.45)              |                                  |
| <i>(Source CSR for Study 4145, Tables 11-9 and 11-18, pages 117 and 132)</i>        |                            |                                      |                                    |                                   |                                  |
| <b>OC + Semaglutide</b>                                                             | <b>Ethinylestradiol</b>    | 818 <sup>b</sup><br>(787, 814)       | 1.04<br>(1.00 – 1.09)              | 116 <sup>c</sup><br>(111, 121)    | 1.13<br>(1.07 – 1.19)            |
| <b>OC Alone</b>                                                                     |                            | 783 <sup>b</sup><br>(754, 814)       |                                    | 103 <sup>c</sup><br>(98.4, 107)   |                                  |
| <i>(Source CSR for Study 4249, Tables 11-2 and 11-6, pages 98 and 110)</i>          |                            |                                      |                                    |                                   |                                  |
| <b>OC + Semaglutide</b>                                                             | <b>Levonorgestrel</b>      | 87509 <sup>b</sup><br>(83270, 91963) | 1.13<br>(1.06 – 1.19)              | 8615 <sup>c</sup><br>(8163, 9091) | 1.08<br>(1.01 – 1.15)            |
| <b>OC Alone</b>                                                                     |                            | 77663 <sup>b</sup><br>(73901, 81616) |                                    | 7975 <sup>c</sup><br>(7556, 8416) |                                  |
| <i>(Source CSR for Study 4249, Tables 11-4 and 11-9, pages 105 and 115)</i>         |                            |                                      |                                    |                                   |                                  |
| <b>Furosemide + Semaglutide</b>                                                     | <b>Furosemide</b>          | 1816<br>(1693, 1949)                 | 0.99<br>(0.91 – 1.07)              | 744<br>(626, 883)                 | 0.90<br>(0.74 – 1.11)            |
| <b>Furosemide Alone</b>                                                             |                            | 1842<br>(1717, 1977)                 |                                    | 822<br>(692, 976)                 |                                  |
| <i>(Source CSR for Study 4250, Tables 11-2 and 11-6, pages 98 and 110)</i>          |                            |                                      |                                    |                                   |                                  |
| <b>Rosuvastatin + Semaglutide</b>                                                   | <b>Rosuvastatin</b>        | 62<br>(59, 65)                       | 0.97<br>(0.91 – 1.02)              | 7.00<br>(6.36, 7.70)              | 0.92<br>(0.82 – 1.02)            |
| <b>Rosuvastatin Alone</b>                                                           |                            | 64<br>(61, 67)                       |                                    | 7.64<br>(6.95, 8.40)              |                                  |
| <i>(Source CSR for Study 4250, Tables 11-4 and 11-11, pages 105 and 118)</i>        |                            |                                      |                                    |                                   |                                  |
| <b>Levothyroxine + Semaglutide</b>                                                  | <b>Total T<sub>4</sub></b> | 1205 <sup>d</sup><br>(1133, 1281)    | 0.97<br>(0.90 – 1.04)              | 50 <sup>e</sup><br>(47, 54)       | 0.85<br>(0.79 – 0.92)            |
| <b>Levothyroxine Alone</b>                                                          |                            | 1241 <sup>d</sup><br>(1167, 1319)    |                                    | 59 <sup>e</sup><br>(55, 63)       |                                  |
| <i>(Source CSR for Study 4279, Tables 11-6, page 113)</i>                           |                            |                                      |                                    |                                   |                                  |

<sup>a</sup>Ratio, no units; <sup>b</sup>pg·hr/mL; <sup>c</sup>pg/mL; <sup>d</sup>nmol·hr/L; <sup>e</sup>nmol/L

### 3.3.5.2.2 Effect of other drugs on PK of oral semaglutide and SNAC

- a. Semaglutide and SNAC were evaluated as a victim drug and excipient, respectively, in an interaction with omeprazole in Study 4141. Omeprazole, a proton pump inhibitor (PPI) is used to reduce gastric acid production. Nonclinical data suggest that the solubility of SNAC is pH dependent and that its mode of action involves buffering of the acidic pH locally. The absorption enhancing effects of SNAC may be affected by increases in gastric pH. The intended population for treatment with oral semaglutide is subjects with T2DM who are commonly treated with PPIs. The Applicant chose omeprazole to represent PPI compounds because it is one of the most widely prescribed PPIs.
- b. In vitro data suggest that SNAC is primarily metabolized by UGT2B7. SNAC and/or the SNAC metabolites are substrates of BCRP, OAT1, OAT3 and MRP2. The effect of inhibitor of UGT enzymes or the transporters on SNAC exposure were evaluated by co-administering with probenecid (inhibitor of UGD enzymes, OAT1 and OAT3) and cyclosporin (inhibitor of BCRP and MRP2) in crossover trial 4394.

### 3.3.5.2.2.1 Semaglutide as a victim drug

The dosing scheme for the two trials where semaglutide was evaluated as a victim drug are shown in Figure 21:

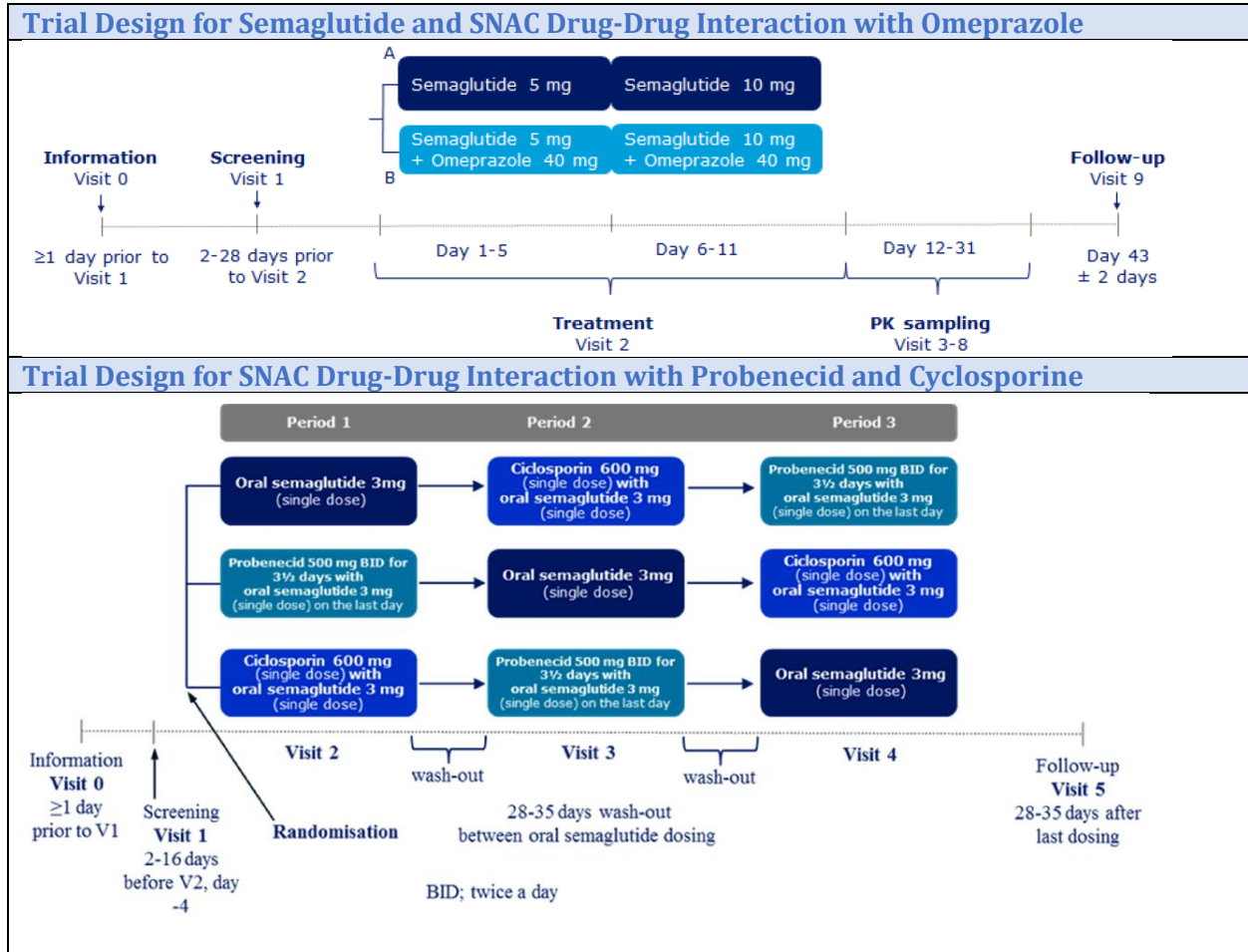


Figure 21 Trial Designs for Semaglutide as Victim Drug and SNAC as Victim Excipient

Table 11 summarizes the outcome of semaglutide as victim drug and SNAC as victim excipient in these two DDI studies.

**Table 11 PK of semaglutide as victim drug and SNAC as victim excipient**

| Interacting Moieties                                                      | PK for Moiety | AUC <sub>0-24</sub> (ng·hr/mL) | AUC <sub>0-24</sub> Ratio<br>90% CI | C <sub>max</sub> (ng/mL)          | C <sub>max</sub> Ratio<br>90% CI |
|---------------------------------------------------------------------------|---------------|--------------------------------|-------------------------------------|-----------------------------------|----------------------------------|
| Semaglutide +<br>Omeprazole                                               | Semaglutide   | 328 <sup>a</sup><br>(265, 407) | 1.13<br>(0.88 – 1.45)               | 17.6 <sup>b</sup><br>(14.1, 21.8) | 1.16<br>(0.90 – 1.49)            |
| Semaglutide Alone                                                         |               | 290 <sup>a</sup><br>(235, 358) |                                     | 15.2 <sup>b</sup><br>(12.3, 18.8) |                                  |
| <i>(Source CSR for Study 4141, Tables 11-1 and 11-2, pages 82 and 83)</i> |               |                                |                                     |                                   |                                  |
| Semaglutide +<br>Omeprazole                                               | SNAC          | 1284<br>(1169, 1410)           | 1.14<br>(1.02 – 1.27)               | 986<br>(768, 1267)                | 0.96<br>(0.72 – 1.29)            |
| Semaglutide Alone                                                         |               | 1129<br>(1029, 1238)           |                                     | 1028<br>(804, 1314)               |                                  |
| <i>(Source CSR for Study 4141, Tables 11-4 and 11-5, pages 86 and 87)</i> |               |                                |                                     |                                   |                                  |
| Interacting Moieties                                                      | PK for Moiety | AUC <sub>0-t</sub> (ng·hr/mL)  | AUC <sub>0-t</sub> Ratio<br>90% CI  | C <sub>max</sub> (ng/mL)          | C <sub>max</sub> Ratio<br>90% CI |
| Semaglutide +<br>probenecid                                               | SNAC          | 1019<br>(959, 1083)            | 1.15<br>(1.07 – 1.24)               | 1266<br>(1046, 1582)              | 1.23<br>(0.98 – 1.54)            |
| Semaglutide Alone                                                         |               | 885<br>(833, 941)              |                                     | 1027<br>(848, 1242)               |                                  |
| <i>(Source CSR for Study 4394, Tables 11-1, page 77)</i>                  |               |                                |                                     |                                   |                                  |
| Semaglutide +<br>Cyclosporin                                              | SNAC          | 1059<br>(1091, 1231)           | 1.31<br>(1.22 – 1.41)               | 1447<br>(1195, 1751)              | 1.41<br>(1.13 – 1.76)            |
| Semaglutide Alone                                                         |               | 885<br>(833, 941)              |                                     | 1027<br>(848, 1242)               |                                  |
| <i>(Source CSR for Study 4394, Tables 11-1, page 77)</i>                  |               |                                |                                     |                                   |                                  |

<sup>a</sup>nmol·h/L; <sup>b</sup>nmol/L

### 3.3.6 Is the to-be-marketed formulation the same as the clinical trial formulation, and if not, are there bioequivalence data to support the to-be-marketed formulation?

Several formulations and strengths of oral semaglutide were developed and used in clinical trials. These processes used (b) (4) (manufacturing process I), and (b) (4) (manufacturing processes II and III). Drug product made using manufacturing process III was used in all pivotal safety/efficacy trials as well as several clinical pharmacology DDI trials. Differences in the processes are outlined in Table 12. The composition of the semaglutide drug products used in pivotal safety/efficacy trials and some clinical pharmacology DDI trials are the same as the to-be marketed formulations of the drug product (Table 13).

The manufacturing process for the formulation that was used in late Phase 1 trials, Phase 2 trial and all Phase 3 trials, including clinical pharmacology Phase 1 trials conducted during the Phase 2 / Phase 3 development phase (Formulation B) has remained unchanged apart from scale up. Scale up to larger batch sizes was performed (b) (4) (Table 14). All other critical parameters remained unchanged.

**Table 12 Semaglutide Trial Products, Manufacturing Process and Associated Clinical Trials**

| Strength (mg/tablet)              | 2            | 2.5 | 3   | 5 | 7   | 10 | 14  | 20 | 40 |
|-----------------------------------|--------------|-----|-----|---|-----|----|-----|----|----|
| (b) (4) manufacturing process I   |              |     |     |   |     |    |     |    |    |
| <b>Trial</b>                      | <b>Phase</b> |     |     |   |     |    |     |    |    |
| 3691 <sup>a, b</sup>              | 1/clinpharm  | X   |     | X |     | X  |     | X  |    |
| 3692 <sup>b</sup>                 | 1/clinpharm  | X   |     | X |     | X  |     |    |    |
| (b) (4) manufacturing process II  |              |     |     |   |     |    |     |    |    |
| <b>Trial</b>                      | <b>Phase</b> |     |     |   |     |    |     |    |    |
| 3991                              | 1/clinpharm  |     |     | X |     | X  |     | X  | X  |
| 3957                              | 1/clinpharm  |     |     |   |     | X  |     |    |    |
| 3794                              | 1/clinpharm  |     |     |   |     | X  |     |    |    |
| 4247 <sup>c</sup>                 | 1/clinpharm  |     | N/A |   | N/A |    | N/A |    |    |
| 3790                              | 2            | X   |     | X |     | X  |     | X  | X  |
| 4065                              | 1/clinpharm  |     |     | X |     | X  |     | X  |    |
| 4082                              | 1/clinpharm  |     |     | X |     | X  |     | X  |    |
| 4140                              | 1/clinpharm  |     |     | X |     | X  |     | X  | X  |
| 4141                              | 1/clinpharm  |     |     | X |     | X  |     |    |    |
| 4145                              | 1/clinpharm  |     |     | X |     | X  |     | X  |    |
| 4154                              | 1/clinpharm  |     |     | X |     | X  |     |    |    |
| 4079                              | 1/clinpharm  |     |     | X |     | X  |     |    |    |
| (b) (4) manufacturing process III |              |     |     |   |     |    |     |    |    |
| <b>Trial</b>                      | <b>Phase</b> |     |     |   |     |    |     |    |    |
| 4249                              | 1/clinpharm  |     | X   |   | X   |    | X   |    |    |
| 4250                              | 1/clinpharm  |     | X   |   | X   |    | X   |    |    |
| 4267                              | 1/clinpharm  |     | X   |   | X   |    |     |    |    |
| 4279                              | 1/clinpharm  |     | X   |   | X   |    | X   |    |    |
| 4394                              | 1/clinpharm  |     | X   |   |     |    |     |    |    |
| 4221                              | 3a           |     | X   |   | X   |    | X   |    |    |
| 4222                              | 3a           |     | X   |   | X   |    | X   |    |    |
| 4223                              | 3a           |     | X   |   | X   |    | X   |    |    |
| 4224                              | 3a           |     | X   |   | X   |    | X   |    |    |
| 4233                              | 3a           |     | X   |   | X   |    | X   |    |    |
| 4234                              | 3a           |     | X   |   | X   |    | X   |    |    |
| 4257                              | 3a           |     | X   |   | X   |    | X   |    |    |
| 4280                              | 3a           |     | X   |   | X   |    | X   |    |    |
| 4281                              | 3a           |     | X   |   | X   |    | X   |    |    |
| 4282                              | 3a           |     | X   |   | X   |    | X   |    |    |

<sup>a</sup> In all trials except trial 3691, tablets were formulated with 300 mg SNAC. In trial 3691, tablets were formulated with 150 mg, 300 mg, 450 mg or 600 mg SNAC; <sup>b</sup> Tablet formulation (b) (4)

(b) (4): Tablets contained only SNAC. Clinpharm: clinical pharmacology; N/A: not applicable

(Source Module 2.7.1 Summary of Biopharmaceutic Studies and Associated Analytical Methods. Table 1-1, page 10)

**Table 13 Overview of Clinical Formulations – Late Phase 1 to Phase 3 and Commercial Scale**

| Development phase           | Late phase 1        | Phase 2 <sup>a</sup> | Phase 3 <sup>a</sup> | Commercial use |
|-----------------------------|---------------------|----------------------|----------------------|----------------|
| <b>Formulation</b>          | <b>B</b>            |                      |                      |                |
| <b>Component</b>            | Content (mg/tablet) |                      |                      |                |
| Semaglutide                 | 5, 10, 20 or 40     | 2.5, 5, 10, 20 or 40 | 3, 7 or 14           | 3, 7 or 14     |
| Salcaprostate sodium        | 300                 | 300                  | 300                  | 300            |
| Cellulose, microcrystalline | (b) (4)             |                      |                      |                |
| Povidone                    | (b) (4)             |                      |                      |                |
| Magnesium stearate          | (b) (4)             |                      |                      |                |

<sup>a</sup> Including clinical pharmacology phase 1 trials conducted during the phase 2 / phase 3 development phase.

(Source Module 3.2.P.2.2 Drug Product. Table 2, page 5)

**Table 14 Overview of Process Changes During Scale-Up**

(b) (4)

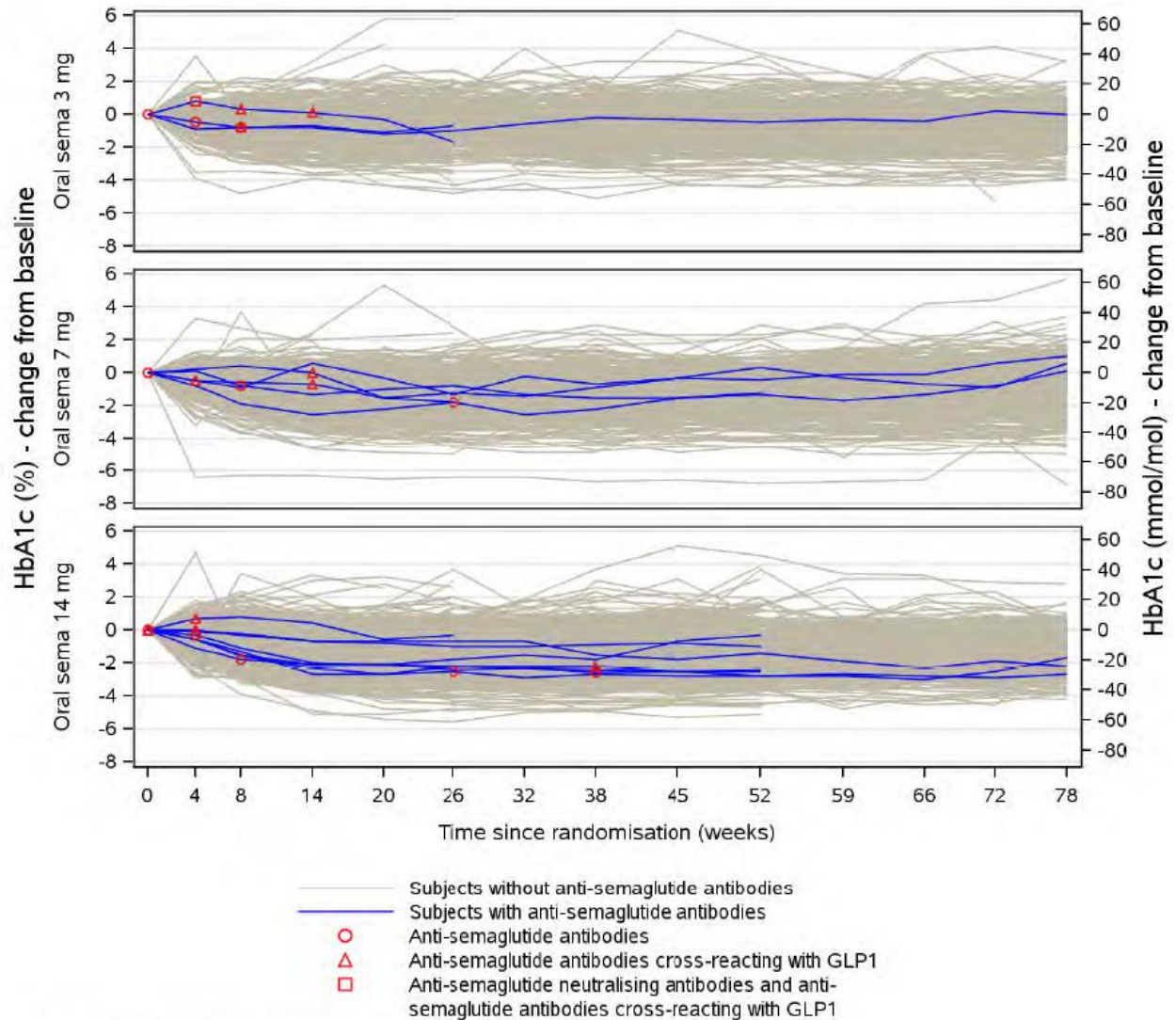
### **3.3.7 What were the immunogenicity findings?**

Overall, the low immunogenicity observed with oral semaglutide is consistent with that reported with other GLP-1 analogues with high homology to the human GLP-1 amino acid backbone.

There was a low percentage (0.5%) of subjects that tested positive for anti-semaglutide antibodies at any time point post-baseline. One subject who had anti-semaglutide antibodies with in vitro neutralizing effect at a single visit during treatment was antibody negative at follow-up. Anti-semaglutide antibodies with endogenous GLP-1 in vitro neutralizing effect was not found in any subject. All subjects who had treatment induced antibodies had a transient response with low levels of anti-semaglutide antibodies and at follow up were antibody negative. A few subjects had pre-existing antibodies which were not boosted following treatment with oral semaglutide, and the two antibody-positive follow-up samples were from subjects also positive at baseline.

Based on PK data in subjects that tested positive for anti-semaglutide antibodies, the plasma semaglutide concentrations were not influenced by the formation of anti-semaglutide antibodies. Efficacy of semaglutide in terms of reduction in HbA1c levels (Figure 22) and safety as based on reported AEs in subjects were not influenced by the formation of anti-semaglutide antibodies.

The low immunogenicity observed with oral semaglutide is consistent with that reported with other approved GLP-1 analogs. The data presented in this NDA application appears to suggest that the immunogenicity risk of oral semaglutide is low and for subjects with anti-semaglutide antibody formation, the benefit/risk ratio remains favorable.



Observed data from the on-treatment observation period.  
 Solid lines (grey and blue) represent observed levels of change from baseline in HbA1c at each visit by subject.  
 Red symbols represent visit where a given subject is tested positive for the indicated anti-semaglutide antibody and type of anti-semaglutide antibody.

**Figure 22 Spaghetti Plot of HbA1c Change from Baseline by Occurrence of Antibodies – Pioneer 1-5 And 9 - On-Treatment**

(Source Module 5.3.5.3 Integrated Summary of Immunogenicity. Figure 4-3, page 44)

## 4. APPENDICES

**Table 15 Tabular Listing of Phase 1 studies Providing Clinical Pharmacology Data**

| Summary of trials investigating PK              |                                                                                                                                                                                                                                                     |                                                                                       |                                                                                                                                                                             |                                                          |                                                                                                          |
|-------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------|----------------------------------------------------------------------------------------------------------|
| Trial ID                                        | Primary objective                                                                                                                                                                                                                                   | Trial design                                                                          | Treatment <sup>b</sup>                                                                                                                                                      | Exposed subjects                                         | Sex<br>Age (min-max) <sup>c</sup><br>BMI (min-max) <sup>c</sup>                                          |
| 3691<br>Single ascending dose (FHD) SD          | Part 1: To assess the safety and tolerability of oral semaglutide in healthy male subjects<br>Part 2: To further explore safety, tolerability and exposure of oral semaglutide in addition to bioavailability compared to semaglutide s.c. and i.v. | Randomised double-blind, sequential cohort<br>Randomised double-blind, parallel group | Oral semaglutide 2, 5, 10, 15, and 20 mg, and placebo with SNAC <sup>d</sup><br>Oral semaglutide 2, 5, 10 mg, placebo, semaglutide s.c. 0.4 mg, and semaglutide i.v. 0.1 mg | 84 healthy subjects<br>107 healthy subjects <sup>e</sup> | M<br>18–50 years<br>18.5–27.5 kg/m <sup>2</sup>                                                          |
| 3692<br>Multiple ascending dose 1 10 weeks (SS) | To assess the safety and tolerability of multiple daily doses of oral semaglutide                                                                                                                                                                   | Randomised, partially double-blind, semi-sequential                                   | Oral semaglutide 5, 10, 2x10 mg and semaglutide s.c. 0.5 mg                                                                                                                 | 96 healthy subjects                                      | M<br>18–60 years<br>21–30 kg/m <sup>2</sup>                                                              |
| 3991<br>Multiple ascending dose 2 10 weeks (SS) | To assess the safety and tolerability of multiple doses of once-daily oral semaglutide and SNAC in a tablet formulation in healthy subjects and subjects with T2D                                                                                   | Randomised double-blind, semi-sequential                                              | Oral semaglutide 20 and 40 mg, and placebo                                                                                                                                  | 84 healthy subjects<br>23 subjects with T2D              | M<br>18–64 years<br>Healthy:<br>20–30 kg/m <sup>2</sup><br>Subjects with T2D:<br>20–37 kg/m <sup>2</sup> |
| 4140<br>Caucasian/<br>Japanese<br>13 weeks (SS) | To assess and compare the PK of oral semaglutide at steady state between healthy male Japanese and Caucasian subjects.                                                                                                                              | Randomised double-blind, parallel                                                     | Oral semaglutide 10, 20 and 40 mg                                                                                                                                           | 24 healthy subjects<br>24 healthy Japanese subjects      | M<br>20–55 years<br>20–25 kg/m <sup>2</sup>                                                              |
| 3794<br>Dosing conditions 10 days               | To compare the PK of semaglutide after 10 days of oral semaglutide treatment at 8 different dosing conditions                                                                                                                                       | Randomised open-label, parallel                                                       | Oral semaglutide 10 mg                                                                                                                                                      | 158 healthy subjects                                     | M<br>18–55 years<br>18.5–30.0 kg/m <sup>2</sup>                                                          |
| 4154<br>Food effect 10 days                     | To compare PK of semaglutide after treatment with oral semaglutide in fed and fasting conditions                                                                                                                                                    | Randomised open-label, parallel                                                       | Oral semaglutide 10 mg                                                                                                                                                      | 78 healthy subjects                                      | M and F<br>18–75 years<br>18.5–29.9 kg/m <sup>2</sup>                                                    |
| 3957<br>Pharmacokinetic SD                      | To investigate whether the volume of water administered with oral semaglutide affects the location of tablet erosion                                                                                                                                | Randomised open-label, two-period, two-sequence cross-over                            | Oral semaglutide 10 mg                                                                                                                                                      | 26 healthy subjects                                      | M<br>18–64 years<br>18.5–30.0 kg/m <sup>2</sup>                                                          |
| NN9535-3789<br>AME<br>Semaglutide SD            | To investigate absorption, metabolism and excretion in human subjects after a single s.c. administration of [ <sup>3</sup> H]-semaglutide                                                                                                           | Open-label, single-group                                                              | [ <sup>3</sup> H]-semaglutide s.c. 0.5 mg                                                                                                                                   | 7 healthy subjects                                       | M<br>45–64 years<br>20–30 kg/m <sup>2</sup>                                                              |
| ERP23<br>AME SNAC SD                            | To determine the metabolism of SNAC and elimination of <sup>14</sup> C-labeled compounds in humans                                                                                                                                                  | Open-label, single-group                                                              | [ <sup>14</sup> C]-SNAC oral 2.25 g / 90,000 USP heparin units containing 100 μCi <sup>14</sup> C-SNAC                                                                      | 9 healthy subjects                                       | M<br>19–45 years                                                                                         |

<sup>a</sup> single dose or planned duration of treatment; <sup>b</sup> does not include doses used in dose escalation; <sup>c</sup> both inclusive and based on inclusion criteria; <sup>d</sup> 2 mg semaglutide with 300 mg SNAC, 5 mg semaglutide with 150 mg or 300 mg SNAC, 10 mg semaglutide with 300 or 600 mg SNAC, 15 mg semaglutide with 450 mg SNAC, 20 mg semaglutide with 600 mg SNAC and placebo with 150, 300, 450 or 600 mg SNAC; <sup>e</sup> pooled group consisting of 36 subjects from part 1 of the trial.

AME: absorption, metabolism and elimination; BMI: body mass index; F: female; FHD: first human dose; i.v.: intravenous; M: male; PK: pharmacokinetics; s.c.: subcutaneous; SD: single dose; SS: steady state.

| Summary of trials investigating PK in special populations |                                                                                                       |                            |                        |                                                                                                                                             |                                                                 |
|-----------------------------------------------------------|-------------------------------------------------------------------------------------------------------|----------------------------|------------------------|---------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------|
| Trial ID                                                  | Primary objective                                                                                     | Trial design               | Treatment <sup>b</sup> | Exposed subjects                                                                                                                            | Sex<br>Age (min-max) <sup>c</sup><br>BMI (min-max) <sup>c</sup> |
| 4079<br>Renal impairment 10 days                          | To compare PK properties in subjects with normal renal function to subjects with renal impairment     | Open-label, parallel group | Oral semaglutide 10 mg | 24 subjects with normal renal function and 47 subjects with renal impairment (12 mild, 12 moderate and 12 severe and 11 subjects with ESRD) | M and F<br>18–85 years<br>18.5–40.0 kg/m <sup>2</sup>           |
| 4082<br>Hepatic impairment 10 days                        | To compare PK properties in subjects with normal hepatic function to subjects with hepatic impairment | Open-label, parallel group | Oral semaglutide 10 mg | 24 subjects with normal hepatic function and 32 subjects with hepatic impairment (12 mild, 12 moderate and 8 severe)                        | M and F<br>18–85 years<br>18.5–40.0 kg/m <sup>2</sup>           |
| 4267<br>Upper GI disease 10 days                          | To investigate if upper GI disease influences PK properties in subjects with T2D                      | Open-label, parallel group | Oral semaglutide 7 mg  | 55 subjects with T2D (36 with upper GI disease and 19 without upper GI disease)                                                             | M and F<br>18–80 years<br>18.5–39.9 kg/m <sup>2</sup>           |

<sup>a</sup> planned duration of treatment; <sup>b</sup> does not include doses used in dose escalation; <sup>c</sup> both inclusive and based on inclusion criteria.

BMI: body mass index; ESRD: end-stage renal disease; F: female; GI: gastrointestinal; M: male; PK: pharmacokinetics.

### Summary of trials investigating drug-drug interactions

| Trial ID                                                     | Primary objective                                                                                                                                                                                           | Trial design                                | Treatment <sup>b</sup>                                                   | Exposed subjects                  | Sex<br>Age (min-max) <sup>c</sup><br>BMI (min-max) <sup>c</sup> |
|--------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------|--------------------------------------------------------------------------|-----------------------------------|-----------------------------------------------------------------|
| 4065<br>Perpetrator/<br>victim drug<br>Duration <sup>a</sup> |                                                                                                                                                                                                             |                                             |                                                                          |                                   |                                                                 |
| Lisinopril and warfarin<br>56 days (SS)                      | To investigate the effect of oral semaglutide dosed at steady state on the PK exposure of lisinopril and warfarin                                                                                           | Open-label, one-sequence cross-over         | Oral semaglutide 20 mg<br>Lisinopril 20 mg<br>Warfarin 25 mg             | 52 healthy subjects               | M and F<br>18–75 years<br>20.0–29.9 kg/m <sup>2</sup>           |
| 4145<br>Metformin and digoxin<br>55 days (SS)                | To investigate the effect of oral semaglutide dosed at steady state on the PK exposure of metformin and digoxin                                                                                             | Open-label, one-sequence cross-over         | Oral semaglutide 20 mg<br>Metformin 850 mg<br>Digoxin 500 µg             | 32 healthy subjects               | M and F<br>18–75 years<br>20.0–29.9 kg/m <sup>2</sup>           |
| 4249<br>Oral contraception<br>58 days (SS)                   | To investigate the effect of oral semaglutide dosed at steady state on the PK exposure of ethyleneestradiol and levonorgestrel                                                                              | Open-label, one-sequence cross-over         | Oral semaglutide 14 mg<br>ethyleneestradiol /levonorgestrel 0.03/0.15 mg | 25 healthy postmenopausal females | F<br>≥45 years<br>20.0–29.9 kg/m <sup>2</sup>                   |
| 4250<br>Furosemide and rosuvastatin<br>47 days (SS)          | To investigate the effect of oral semaglutide dosed at steady state on the PK exposure of furosemide and rosuvastatin                                                                                       | Open-label, one-sequence cross-over         | Oral semaglutide 14 mg<br>Furosemide 40 mg<br>Rosuvastatin 20 mg         | 41 healthy subjects               | M and F<br>18–65 years<br>20.0–29.9 kg/m <sup>2</sup>           |
| 4279<br>Levothyroxine and placebo<br>100 days (SS)           | To investigate the effect of oral semaglutide dosed at steady state on the PK exposure of levothyroxine and to investigate if semaglutide PK is influenced by co-administration with multiple other tablets | Open-label, one-sequence cross-over         | Oral semaglutide 14 mg<br>Levothyroxine 600 µg<br>Placebo (5 tablets)    | 45 healthy subjects               | M and F<br>18–50 years<br>20.0–29.9 kg/m <sup>2</sup>           |
| 4141<br>Omeprazole<br>10 days                                | To investigate the effect of omeprazole on the PK of oral semaglutide                                                                                                                                       | Randomised, open-label, parallel group      | Oral semaglutide 10 mg<br>Omeprazole 40 mg                               | 54 healthy subjects               | M and F<br>18–75 years<br>18.5–29.9 kg/m <sup>2</sup>           |
| 4394<br>Probenecid and ciclosporin<br>SD                     | To investigate the effect of probenecid and ciclosporin on the PK of SNAC after administration of oral semaglutide                                                                                          | Randomised, open-label, 3-period cross-over | Oral semaglutide 3 mg<br>Probenecid 500 mg<br>Ciclosporin 600 mg         | 21 healthy subjects               | M and F<br>18–64 years<br>18.5–29.9 kg/m <sup>2</sup>           |

<sup>a</sup> planned duration of treatment; <sup>b</sup> does not include doses used in dose escalation; <sup>c</sup> both inclusive and based on inclusion criteria.

BMI: body mass index; F: female; M: male; PK: pharmacokinetics; SD: single dose; SS: steady state.

### Summary of trials investigating pharmacodynamics

| Trial ID                                           | Primary objective                                                                                                             | Trial design                                    | Treatment <sup>b</sup>             | Exposed subjects                                                                                                         | Sex<br>Age (min-max) <sup>c</sup><br>BMI (min-max) <sup>c</sup> |
|----------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------|------------------------------------|--------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------|
| NN9535-3635<br>Beta-cell function<br>13 weeks (SS) | To evaluate the effects of semaglutide in steady state on first and second phase insulin secretion in subjects with T2D       | Randomised, double-blind, parallel group        | Semaglutide s.c. 1.0 mg<br>Placebo | 75 subjects with T2D (treated with diet/exercise and/or metformin)<br>12 healthy subjects (not exposed to trial product) | M and F<br>18–64 years<br>20.0–35.0 kg/m <sup>2</sup>           |
| NN9535-3684<br>Hypoglycaemia<br>13 weeks (SS)      | To investigate the effect of semaglutide compared with placebo on glucagon response during hypoglycaemia in subjects with T2D | Randomised, double-blind, two-period cross-over | Semaglutide s.c. 1.0 mg<br>Placebo | 38 subjects with T2D (treated with metformin)                                                                            | M and F<br>18–64 years<br>20.0–35.0 kg/m <sup>2</sup>           |
| NN9535-3685<br>Energy intake<br>13 weeks (SS)      | To compare the effect of semaglutide and placebo on ad libitum energy intake                                                  | Randomised, double-blind, two-period cross-over | Semaglutide s.c. 1.0 mg<br>Placebo | 30 subjects with obesity                                                                                                 | M and F<br>≥18 years<br>30–45 kg/m <sup>2</sup>                 |

<sup>a</sup> planned duration of treatment; <sup>b</sup> does not include doses used in dose escalation; <sup>c</sup> both inclusive and based on inclusion criteria.

BMI: body mass index; F: female; M: male; s.c.: subcutaneous; SS: steady state.

### Summary of trials investigating cardiac repolarisation

| Trial ID                                        | Primary objective                                                                                                                                                                                                | Trial design                                                                                                     | Treatment <sup>b</sup>                                            | Exposed subjects                           | Sex<br>Age (min-max) <sup>c</sup><br>BMI (min-max) <sup>c</sup> |
|-------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------|--------------------------------------------|-----------------------------------------------------------------|
| NN9535-3652<br>QTc Semaglutide<br>16 weeks (SS) | To confirm that treatment with semaglutide does not result in an unacceptable prolongation in cardiac repolarisation compared to placebo                                                                         | Randomised, double-blind, parallel group with a nested cross-over design                                         | Semaglutide s.c. 0.5, 1.0, 1.5 mg, moxifloxacin and placebo       | 168 healthy subjects                       | M and F<br>18–55 years<br>20–30 kg/m <sup>2</sup>               |
| 4247<br>QTc SNAC<br>SD                          | Part A: To assess safety and tolerability of three different supra-therapeutic doses of SNAC<br>Part B: To confirm that SNAC does not cause an unacceptable prolongation of the QTc interval compared to placebo | Randomised, partially double-blind, sequential cohort<br>Randomised, partially double-blind, 4-period cross-over | SNAC 1.2, 2.4, and 3.6 g<br>SNAC 3.6 g, moxifloxacin, and placebo | 36 healthy subjects<br>48 healthy subjects | M<br>18–55 years<br>18.5–28.0 kg/m <sup>2</sup>                 |

<sup>a</sup> single dose or planned duration of treatment; <sup>b</sup> does not include doses used in dose escalation; <sup>c</sup> both inclusive and based on inclusion criteria.

BMI: body mass index; F: female; M: male; QTc: corrected QT interval; SD: single dose; SS: steady state.

**Summary of trials included in the population PK and exposure-response analyses**

| Trial ID<br>PIONEER #<br>Duration <sup>a</sup> | Primary objective                                                                                                                                                                                                                                                                       | Trial design                                       | Treatment                                                                     | Randomised subjects                                              | Sex<br>Age (min-max) <sup>b</sup><br>HbA <sub>1c</sub> (min-max) <sup>b</sup> |
|------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------|-------------------------------------------------------------------------------|------------------------------------------------------------------|-------------------------------------------------------------------------------|
| 4233<br>PIONEER 1<br>26 weeks                  | To compare the effects of three dose levels of once-daily oral semaglutide (3, 7 and 14 mg) vs once-daily placebo on glycaemic control in subjects with T2D treated with diet and exercise only.                                                                                        | Randomised, double-blind, parallel group           | Oral semaglutide 3, 7 and 14 mg<br>Placebo                                    | 703 subjects with T2D                                            | M and F<br>≥18 years<br>(Japan: ≥20 years, Algeria: ≥19 years)<br>7.0–9.5%    |
| 4223<br>PIONEER 2<br>52 weeks                  | To compare the effect of once-daily dosing of 14 mg oral semaglutide versus 25 mg empagliflozin, both in combination with metformin, on glycaemic control in subjects with T2D                                                                                                          | Randomised, open-label, parallel group             | Oral semaglutide 14 mg<br>Empagliflozin 25 mg                                 | 822 subjects with T2D                                            | M and F<br>≥18 years<br>7.0–10.5%                                             |
| 4222<br>PIONEER 3<br>78 weeks                  | To compare the effect of once-daily dosing of three dose levels (3 mg, 7 mg and 14 mg) of oral semaglutide versus sitagliptin 100 mg once-daily, both in combination with metformin with or without sulfonylurea, on glycaemic control in subjects with T2D                             | Randomised, double-blind, parallel group           | Oral semaglutide 3, 7 and 14 mg<br>Sitagliptin 100 mg                         | 1864 subjects with T2D                                           | M and F<br>≥18 years<br>(Japan: ≥20 years)<br>7.0–10.5%                       |
| 4234<br>PIONEER 5<br>26 weeks                  | To compare the effect of once-daily dosing of 14 mg oral semaglutide versus placebo, both in combination with metformin and/or sulfonylurea, basal insulin alone or metformin in combination with basal insulin on glycaemic control in subjects with T2D and moderate renal impairment | Randomised, double-blind, parallel-group           | Oral semaglutide 14 mg<br>Placebo                                             | 324 subjects with T2D and moderate renal impairment <sup>c</sup> | M and F<br>≥18 years<br>7.0–9.5%                                              |
| 4280<br>PIONEER 8<br>52 weeks                  | To compare the effect of once-daily dosing of three dose levels of oral semaglutide (3, 7 and 14 mg) versus placebo on glycaemic control in subjects with T2D treated with insulin.                                                                                                     | Randomised, double-blind, parallel-group           | Oral semaglutide 3, 7 and 14 mg<br>Placebo                                    | 731 subjects with T2D                                            | M and F<br>≥18 years<br>(Japan: ≥20 years)<br>7.0–9.5%                        |
| 4281<br>PIONEER 9<br>52 weeks                  | To assess the dose-response relationship of once-daily dosing of three dose levels (3, 7 and 14 mg) of oral semaglutide versus placebo as monotherapy on glycaemic control in Japanese subjects with T2D.                                                                               | Randomised, partially double-blind, Parallel-group | Oral semaglutide 3, 7 and 14 mg<br>Placebo<br>Liraglutide 0.9 mg (open-label) | 243 Japanese subjects with T2D                                   | M and F<br>≥20 years<br>6.5–9.5%                                              |

<sup>a</sup>planned duration of treatment, <sup>b</sup>both inclusive and based on inclusion criteria; <sup>c</sup>based on eGFR as per Chronic Kidney Disease Epidemiology Collaboration formula (CKD-EPI).

F: female; M: male.

(Source Module 2.7.2 Summary of Clinical Pharmacology, Tables 1-2 – 1-7, pp 21- 28)

## 4.1 Appendix - Summary of Bioanalytical Method Validation

### 4.1.1 How are parent drug and relevant metabolites of semaglutide identified and what are the analytical methods used to measure them in plasma and other matrices?

Semaglutide was quantified in human plasma and human urine using validated liquid chromatography and tandem mass spectrometry (LC-MS/MS) methods. Validation methods reported below are based on the LC-MS/MS method and the reported PK of semaglutide in the Clinical Pharmacology review is based on concentrations determined with the LC-MS/MS method. Concentration of semaglutide in Study NN9924-3691 (safety, tolerability and bioavailability of oral semaglutide) was determined using a validated GLP-like Luminescent Oxygen Channeling Immunoassay (LOCI) method. The LOCI assay was found to be influenced by a matrix effect, which could have affected the measured semaglutide plasma levels in study 3691.

An alternative assay for semaglutide bioanalysis was therefore developed based on LC-MS/MS and used in all subsequent trials with semaglutide concentration assessment. No matrix effects were observed for the LC-MS/MS assay at validation or during routine bioanalysis. All the trials also included incurred sample reanalysis. Earlier validation of the LCMS/MS assay in plasma had a LLOQ of 1.94 nmol/L (assay range: 1.94 –194 nmol/L). Subsequently a more sensitive assay was developed to support PK evaluations. The optimized had a lower LLOQ of 0.729 nmol/L (assay range: 0.729 –60.8 nmol/L).

Validation assessments for the LC-MS/MS method for quantification of semaglutide in human plasma and human urine are reported below.

#### **LC-MS/MS Method:**

An LC-MS/MS (electrospray ionization, positive MRM mode) was used to analyze plasma Semaglutide in all trials, except trial 3691 using plasma protein precipitation. The assay was developed and validated by (b) (4). The initial assay (assay range: 1.94 – 194 nmol/L) was used in a multiple-dose safety, tolerability PK study of semaglutide (trial 3692). The quadruple charged molecular ion m/z 1029.5 and its fragment ion m/z 136.3 were the most intense and selective ions and were chosen for quantification. The internal standard for the assay was either a structural analogue of semaglutide (NNC0113-0000-0679) or a stable isotope labelled analogue of semaglutide (NNC0113-0000-4168) (m/z: 1106.6 → 123.2 and m/z: 1033.5 → 136.3, respectively). K<sub>3</sub>EDTA-plasma was used for preparing and sampling unknown samples, calibrators and quality controls. A weighted linear regression fitting was used to calculate plasma sample concentrations.

Urine concentrations of semaglutide were analyzed by LC-MS/MS using an assay similar to the plasma assay. Triton™ X-100 was added to the urine samples to prevent non-specific binding of semaglutide to the containers (urine/1% Triton™ X-100 9/1 v/v). The assay was also developed and validated by (b) (4).

### 4.1.2 What was the performance of bioanalytical methods for Semaglutide?

Summary of the assay validation for semaglutide is presented in Table 16.

**Table 16 Summary of Semaglutide PK Assay Validation (LC-MS/MS) in Human Plasma**

| Assay             | Matrix                             | Parameter                    | Results                          | Validation study ID (location)                                   |  |
|-------------------|------------------------------------|------------------------------|----------------------------------|------------------------------------------------------------------|--|
| LC-MS/MS          | K <sub>2</sub> EDTA Plasma         | Range                        | 1.94 – 194 nmol/L                | AA91659 (M 5.3.1.4)                                              |  |
|                   |                                    | Regression                   | Linear weighted 1/x              | AA91659 (M 5.3.1.4)                                              |  |
|                   |                                    | <u>Accuracy</u>              |                                  |                                                                  |  |
|                   |                                    | LLOQ                         | 1.94 nmol/L: 97.3% – 119.6%      | AA91659 (M 5.3.1.4)                                              |  |
|                   |                                    | QC Low                       | 5.83 nmol/L: 95.8% – 105.3%      |                                                                  |  |
|                   |                                    | QC Mid                       | 30.4 nmol/L: 93.8% - 104.3%      |                                                                  |  |
|                   |                                    | QC High                      | 156 nmol/L: 97.6% - 102.2%       |                                                                  |  |
|                   |                                    | <u>Precision</u>             |                                  |                                                                  |  |
|                   |                                    | LLOQ                         | 1.94 nmol/L: 6.0% - 18.1%        | AA91659 (M 5.3.1.4)                                              |  |
|                   |                                    | QC Low                       | 5.83 nmol/L: 5.7% - 14.4%        |                                                                  |  |
|                   |                                    | QC Mid                       | 30.4 nmol/L: 3.7% - 12.2%        |                                                                  |  |
|                   |                                    | QC High                      | 156 nmol/L: 3.9% - 7.8%          |                                                                  |  |
|                   |                                    | Dilution                     | Dilution 1:20 within acceptance  | AA91659 (M 5.3.1.4)                                              |  |
|                   |                                    | Sensitivity                  | LLOQ = 1.94 nmol/L               | AA91659 (M 5.3.1.4)                                              |  |
|                   |                                    | Plasma Stability             | 24 hours at room temperature     | AA91659 (M 5.3.1.4)                                              |  |
|                   |                                    |                              | 582 days at -20°C                | AA91659 (M 5.3.1.4) and AA95112 (M 5.3.1.4)                      |  |
|                   |                                    |                              | 322 days at -80°C                | AA95112 (M 5.3.1.4)                                              |  |
|                   |                                    | Freeze/thaw plasma stability | 3 cycles at -20°C and at -80°C   | AA91659 (M 5.3.1.4)                                              |  |
|                   |                                    | Whole blood stability        | 2 hours at room temperature      | AA91659 (M 5.3.1.4)                                              |  |
|                   |                                    | <u>Interference</u>          |                                  |                                                                  |  |
| Matrix            | No impact                          | AA91659 (M 5.3.1.4)          |                                  |                                                                  |  |
| SNAC              | No impact                          | AA91659 (M 5.3.1.4)          |                                  |                                                                  |  |
| Haemolytic plasma | Minor impact of haemolysis at LLOQ | AA91659 (M 5.3.1.4)          |                                  |                                                                  |  |
| ISR               | Within acceptance in all trials    |                              |                                  |                                                                  |  |
| LC-MS/MS          | K <sub>2</sub> EDTA Plasma         | Range                        | 0.729 – 60.8 nmol/L              | AA95860 (M 5.3.1.4), CA11388 (M 5.3.1.4) and ZZ44775 (M 5.3.1.4) |  |
|                   |                                    | Regression                   | Linear weighted 1/x <sup>2</sup> | AA95860 (M 5.3.1.4), CA11388 (M 5.3.1.4) and ZZ44775 (M 5.3.1.4) |  |
|                   |                                    | <u>Accuracy<sup>a</sup></u>  |                                  |                                                                  |  |
|                   |                                    | LLOQ                         | 0.729 nmol/L: 85.2% - 96.5%      | AA95860 (M 5.3.1.4)                                              |  |
|                   |                                    | QC Low                       | 2.19 nmol/L: 89.5% - 95.0%       |                                                                  |  |
|                   |                                    | QC Mid                       | 9.73 nmol/L: 88.7% - 95.3%       |                                                                  |  |
|                   |                                    | QC High                      | 48.6 nmol/L: 88.0% - 91.5%       |                                                                  |  |
|                   |                                    | LLOQ                         | 0.729 nmol/L: 96.1%              | CA11388 (M 5.3.1.4)                                              |  |
|                   |                                    | QC Low                       | 2.19 nmol/L: 98.9%               |                                                                  |  |
|                   |                                    | QC Mid                       | 9.73 nmol/L: 98.6%               |                                                                  |  |
|                   |                                    | QC High                      | 48.6 nmol/L: 96.3%               |                                                                  |  |
|                   |                                    | LLOQ                         | 0.729 nmol/L: 95.1% - 107.7%     | ZZ44775 (M 5.3.1.4)                                              |  |
|                   |                                    | QC Low                       | 2.19 nmol/L: 90.0% - 100.1%      |                                                                  |  |
|                   |                                    | QC Mid                       | 9.73 nmol/L: 96.6% - 99.1%       |                                                                  |  |
|                   |                                    | QC High                      | 48.6 nmol/L: 90.4% - 101.4%      |                                                                  |  |
|                   |                                    | <u>Precision<sup>a</sup></u> |                                  |                                                                  |  |

| Assay | Matrix | Parameter                    | Results                        | Validation study ID (location)                                         |
|-------|--------|------------------------------|--------------------------------|------------------------------------------------------------------------|
|       |        | LLOQ                         | 0.729 nmol/L: 5.1% - 12.1%     | AA95860 (M 5.3.1.4)                                                    |
|       |        | QC Low                       | 2.19 nmol/L: 3.6% - 10.0%      |                                                                        |
|       |        | QC Mid                       | 9.73 nmol/L: 3.0% - 15.3%      |                                                                        |
|       |        | QC High                      | 48.6 nmol/L: 2.7% - 12.7%      |                                                                        |
|       |        | LLOQ                         | 0.729 nmol/L: 4.8%             | CA11388 (M 5.3.1.4)                                                    |
|       |        | QC Low                       | 2.19 nmol/L: 2.7%              |                                                                        |
|       |        | QC Mid                       | 9.73 nmol/L: 2.2%              |                                                                        |
|       |        | QC High                      | 48.6 nmol/L: 3.6%              |                                                                        |
|       |        | LLOQ                         | 0.729 nmol/L: 9.4% - 12.5%     | ZZ44775 (M 5.3.1.4)                                                    |
|       |        | QC Low                       | 2.19 nmol/L: 5.9% - 9.9%       |                                                                        |
|       |        | QC Mid                       | 9.73 nmol/L: 2.9% - 4.7%       |                                                                        |
|       |        | QC High                      | 48.6 nmol/L: 4.3% - 7.3%       |                                                                        |
|       |        | Dilution                     | Dilution 1:5 within acceptance | AA95860 (M 5.3.1.4)                                                    |
|       |        | Sensitivity                  | LLOQ = 0.729 nmol/L            | AA95860 (M 5.3.1.4) and<br>CA11388 (M 5.3.1.4)                         |
|       |        | <u>Recovery</u>              |                                |                                                                        |
|       |        | Semaglutide                  | 45.6-50.1%                     | CA23034 (M 5.3.1.4)                                                    |
|       |        | IS (b) (4)                   | 55.1%                          | CA23034 (M 5.3.1.4)                                                    |
|       |        | Plasma Stability             | 72 hours at room temperature   | AA95860 (M 5.3.1.4) and<br>CA12337 (M 5.3.1.4)                         |
|       |        |                              | 1021 days at -20°C             | AA95860 (M 5.3.1.4),<br>CA11388 (M 5.3.1.4) and<br>CA17145 (M 5.3.1.4) |
|       |        |                              | 351 days at -80°C              | AA95860 (M 5.3.1.4) and<br>CA17145 (M 5.3.1.4)                         |
|       |        | Freeze/thaw plasma stability | 7 cycles at -20°C              | AA95860 (M 5.3.1.4) and<br>CA17145 (M 5.3.1.4)                         |
|       |        |                              | 2 cycles at -80°C              | AA95860 (M 5.3.1.4)                                                    |
|       |        | Whole blood stability        | 2 hours at room temperature    | AA95860 (M 5.3.1.4)                                                    |
|       |        | <u>Interference</u>          |                                |                                                                        |
|       |        | Matrix                       | No impact                      | AA95860 (M 5.3.1.4) and<br>CA11388 (M 5.3.1.4)                         |
|       |        | SNAC                         | No impact                      | AA95860 (M 5.3.1.4) and<br>CA11388 (M 5.3.1.4)                         |
|       |        | Atorvastatin                 | No impact                      | CA17145 (M 5.3.1.4)                                                    |
|       |        | Digoxin                      | No impact                      | CA17145 (M 5.3.1.4)                                                    |
|       |        | Metformin                    | No impact                      | CA17145 (M 5.3.1.4) and<br>AA98749 (M 5.3.1.4)<br>(trial NN9924-3991)  |
|       |        | Warfarin                     | No impact                      | CA17145 (M 5.3.1.4)                                                    |
|       |        | Lisinopril                   | No impact                      | CA17145 (M 5.3.1.4)                                                    |
|       |        | Omeprazole                   | No impact                      | CA17145 (M 5.3.1.4)                                                    |
|       |        | Ethinylestradiol             | No impact                      | AA96048 (M 5.3.1.4)<br>(trial NN9535-3819)                             |
|       |        | Levonorgestrel               | No impact                      | AA96048 (M 5.3.1.4)<br>(trial NN9535-3819)                             |
|       |        | Acetaminophene               | No impact                      | AA98749 (M 5.3.1.4)<br>(trial NN9924-3991) and<br>CA24615 (M 5.3.1.4)  |

| Assay                        | Matrix                       | Parameter              | Results                          | Validation study ID (location)                 |
|------------------------------|------------------------------|------------------------|----------------------------------|------------------------------------------------|
|                              |                              | Acetylsalicylic acid   | No impact                        | AA98749 (M 5.3.1.4)<br>(trial NN9924-3991)     |
|                              |                              | Rosuvastatin           | No impact                        | CA24615 (M 5.3.1.4)                            |
|                              |                              | Furosemide             | No impact                        | CA24615 (M 5.3.1.4)                            |
|                              |                              | Levothyroxine          | No impact                        | CA24615 (M 5.3.1.4)                            |
|                              |                              | Liothyronine           | No impact                        | CA24615 (M 5.3.1.4)                            |
|                              |                              | Probenecid             | No impact                        | CA24615 (M 5.3.1.4)                            |
|                              |                              | Ciclosporin            | No impact                        | CA24615 (M 5.3.1.4)                            |
|                              |                              | Haemolytic plasma      | No impact assay valid            | AA95860 (M 5.3.1.4) and<br>CA11388 (M 5.3.1.4) |
|                              |                              | Hyperlipaemic plasma   | No impact assay valid            | CA23034 (M 5.3.1.4)                            |
|                              |                              | Type 2 diabetic plasma | No impact assay valid            | CA23034 (M 5.3.1.4)                            |
|                              |                              | ESRD patient plasma    | No impact assay valid            | CA17145 (M 5.3.1.4)                            |
|                              |                              | ISR                    | Within acceptance in all trials  |                                                |
| LC-<br>MS/MS                 | Urine <sup>b</sup>           | Range                  | 0.729 – 60.8 nmol/L              | CA11773 (M 5.3.1.4)                            |
|                              |                              | Regression             | Linear weighted 1/x <sup>2</sup> | CA11773 (M 5.3.1.4)                            |
|                              |                              | <u>Accuracy</u>        |                                  |                                                |
|                              |                              | LLOQ                   | 0.729 nmol/L: 103.2%             | CA11773 (M 5.3.1.4)                            |
|                              |                              | QC Low                 | 2.19 nmol/L: 102.7%              |                                                |
|                              |                              | QC Mid                 | 9.73 nmol/L: 99.1%               |                                                |
|                              |                              | QC High                | 48.6 nmol/L: 99.1%               |                                                |
|                              |                              | <u>Precision</u>       |                                  |                                                |
|                              |                              | LLOQ                   | 0.729 nmol/L: 4.6%               | CA11773 (M 5.3.1.4)                            |
|                              |                              | QC Low                 | 2.19 nmol/L: 3.9%                |                                                |
|                              |                              | QC Mid                 | 9.73 nmol/L: 3.0%                |                                                |
|                              |                              | QC High                | 48.6 nmol/L: 2.9%                |                                                |
|                              |                              | Dilution integrity     | Dilution 1:5 within acceptance   | CA11773 (M 5.3.1.4)                            |
|                              |                              | Sensitivity            | LLOQ = 0.729 nmol/L              | CA11773 (M 5.3.1.4)                            |
|                              |                              | <u>Recovery</u>        |                                  |                                                |
|                              |                              | Semaglutide            | 61.5–63.6%                       | CA23034 (M 5.3.1.4)                            |
|                              |                              | IS (b) (4)             | 59.2%                            | CA23034 (M 5.3.1.4)                            |
| Urine Stability              | 24 hours at room temperature | CA11773 (M 5.3.1.4)    |                                  |                                                |
|                              | 225 days at -20°C            | CA11773 (M 5.3.1.4)    |                                  |                                                |
|                              | 105 days at -80°C            | CA17145 (M 5.3.1.4)    |                                  |                                                |
| Freeze/thaw plasma stability | 3 cycles at -20°C            | CA11773 (M 5.3.1.4)    |                                  |                                                |
|                              | 2 cycles at -80°C            | CA11773 (M 5.3.1.4)    |                                  |                                                |
| <u>Interference</u>          |                              |                        |                                  |                                                |
| Matrix                       | No impact                    | CA11773 (M 5.3.1.4)    |                                  |                                                |
| ISR                          | Not relevant <sup>c</sup>    |                        |                                  |                                                |
| LOCI                         | EDTA<br>Plasma               | Range                  | 0.500 – 50.0 nmol/L              | 207163 (M 5.3.1.4)                             |
|                              |                              | Regression             | SPL Weighted 1/y <sup>2</sup>    | 207163 (M 5.3.1.4)                             |
|                              |                              | <u>Accuracy</u>        |                                  |                                                |
|                              |                              | ~LLOQ                  | 0.588 nmol/L: 78.0%              | 207163 (M 5.3.1.4)                             |
|                              |                              | QC Low                 | 1.74 nmol/L: 81.4%               |                                                |
|                              |                              | QC Mid                 | 9.30 nmol/L: 85.9%               |                                                |
|                              |                              | QC High                | 23.4 nmol/L: 87.5%               |                                                |

| Assay | Matrix | Parameter                    | Results                                                          | Validation study ID (location) |
|-------|--------|------------------------------|------------------------------------------------------------------|--------------------------------|
|       |        | <u>Precision</u>             |                                                                  |                                |
|       |        | ~LLOQ                        | 0.588 nmol/L: 10.1%                                              | 207163 (M 5.3.1.4)             |
|       |        | QC Low                       | 1.74 nmol/L: 4.68%                                               |                                |
|       |        | QC Mid                       | 9.30 nmol/L: 4.53%                                               |                                |
|       |        | QC High                      | 23.4 nmol/L: 4.05%                                               |                                |
|       |        | Dilution                     | Dilution 1:2, 1:4, 1:16, 1:60, 1:150 and 1:600 within acceptance | 207163 (M 5.3.1.4)             |
|       |        | Sensitivity                  | LLOQ = 0.500 nmol/L                                              | 207163 (M 5.3.1.4)             |
|       |        | Plasma Stability             | 24 hours at room temperature and at 4°C                          | 207163 (M 5.3.1.4)             |
|       |        |                              | 12 months (365 days) at -20°C                                    | 209082 (M 5.3.1.4)             |
|       |        | Freeze/thaw plasma stability | 5 cycles at -20°C                                                | 207163 (M 5.3.1.4)             |
|       |        | <u>Interference</u>          |                                                                  |                                |
|       |        | Haemolytic plasma            | Sensitive to haemolysis in samples                               | 207163 (M 5.3.1.4)             |
|       |        | ISR                          | Within acceptance (samples from trial NN9924-3691)               | 210190 (M 5.3.1.4)             |

<sup>a</sup> Assay validated using analogue Internal Standard (b) (4), assay validated using stable labelled Internal Standard (b) (4) and assay validated using stable labelled Internal Standard and automatic sample preparation (b) (4).

<sup>b</sup> Matrix defined as urine/1% Triton X-100 (9/1 v/v) (Assay range corresponds to 0.810 – 67.6 nmol/L in urine);

<sup>c</sup> Semaglutide concentrations below assay LLOQ in all samples. ISR not carried out.

ESRD: End Stage Renal Disease; LLOQ: Lower limit of quantification; ISR: Incurred Sample Reproducibility.

(Source Module 2.7.1 Summary of Biopharmaceutical Studies and Associated Analytical Methods. Table 1-5, pp 16- 19)

#### 4.1.3. What analytical methods were used to measure the concentration of SNAC and its relevant metabolites?

SNAC was analyzed in plasma by LC-MS/MS (electrospray ionization, negative multiple-reaction monitoring (MRM) mode), initially using on-line solid phase extraction (SPE) later using plasma protein precipitation for sample preparation. The assays were developed and validated by (b) (4). The molecular ion m/z 278.1 and its fragment ion m/z 118.1 were the most intense and selective ions and were chosen for quantification. A structural analogue of SNAC (NNC0113-0000-3341) or a stable isotope labelled analogue of SNAC (NNC0113-0000-4196) was used as assay internal standard (m/z: 249.1 → 135.3, respectively m/z: 282.2 → 121.2). Unknown samples, calibrators and quality controls were sampled or prepared in K3EDTA plasma. The plasma sample concentrations were calculated using a weighted linear regression fitting.

In one study (ERP-23), SNAC was analyzed in plasma by LC-MS/MS (electrospray ionization, positive MRM mode) using SPE for sample preparation. The assays were developed and validated by (b) (4)

Summary of the assay validation for SNAC is presented in Table 17.

**Table 17 Bioanalytical method validation summary for SNAC**

| Validation method                 | (b) (4)                                                                   |
|-----------------------------------|---------------------------------------------------------------------------|
| Matrix (anticoagulant)            | Human plasma (K <sub>2</sub> EDTA)                                        |
| Sample volume                     | 50 µL                                                                     |
| Analytical method/detection       | Solid phase extraction/LC-MS/MS                                           |
| Internal standard                 | NNC 0113-0000-3341 and NNC0113-0000-4196                                  |
| Validated range                   | 5.0 to 2000 ng/mL                                                         |
| Calibration model                 | Linear regression                                                         |
| Weighting factor                  | 1/x <sup>2</sup>                                                          |
| Quantitation method               | Peak area ratio                                                           |
| Recovery                          | 93.7% to 100.6%                                                           |
| Intra-run accuracy (%Theoretical) | 94.0% to 105.1%                                                           |
| Intra-run precision (%CV)         | 1.7% to 5.8% (LLOQ)                                                       |
| Inter-run accuracy (%Theoretical) | 95.6% to 103.6%                                                           |
| Inter-run precision (%CV)         | 2.7% to 4.3%                                                              |
| Freeze-thaw stability             | Three cycles at -20°C and -80°C                                           |
| Long-term stability               | 496 days at -20°C and 85 days at -80°C; 124 days at -20°C in human plasma |
| Short-term stability              | 24 hours at RT                                                            |
| Study                             | TO BE INCLUDED                                                            |

(Source NDA 213051, Module 2.7.1 Summary of Biopharmaceutic Studies and Associated Analytical Methods; Module 5.3.1.4 Study Report AA89946)

## 4.2 Pharmacometrics Assessment

### 4.2.1 Executive Summary

The Applicant submitted 5 population PK analyses to support this supplemental NDA. The SC/IV and clinical pharmacology PO analyses are on file and not reviewed in detail. The phase II analysis provided information that was superseded by phase III data. Finally, a population PK and E-R analysis was conducted for SNAC.

The phase III population PK/PD model used pooled data from 6 PIONEER studies to characterize PK and Exposure Response relationships in this population. The analysis was prespecified, had negligible analysis deviations, and minimal missing data. The model was built using previous knowledge from SC, IV, and clinical pharmacology modeling of PO data, which allowed robust estimation of individual level and population absolute bioavailability. All standard model qualification procedures were followed, including goodness of fit plots, visual predictive checks, and sensitivity analyses. Based on review of the model qualification tables and plots, I find the resulting PK model to adequately individual level exposure estimates and draw inferences in covariate-exposure relationships.

Oral semaglutide follows dose proportional kinetics, has approximately a week half-life, and accumulates 12-fold at steady state. This drug has high intra-patient and between-patient variability in bioavailability. In a controlled setting (clinical pharmacology trials), the estimated single dose, within subject variability was estimated at 137%. The between subject variability was estimated to be 53% CV. Within-patient steady state concentrations were less variable due to the accumulating effect: the steady state exposure variability was estimated at 33% within the same patient over multiple observation. Albeit more variable, semaglutide 14 mg daily provides exposure similar to that of 0.5 mg weekly of the subcutaneous formulation.

In clinical pharmacology studies for PO semaglutide, the oral bioavailability was estimated to be 0.795% (95% CI: 0.736-0.864%). In phase III studies, the oral bioavailability was estimated to be 0.471% (95% CI: 0.443 – 0.498%). This effect was hypothesized to be caused by decreased patient adherence to the required dosing conditions (as dosing in clinical pharmacology trials was supervised). In addition, trough plasma concentrations tended to decrease with respect to time for most randomized arms. Taken together, it appears the patients included in this analysis did not typically follow optimal dosing conditions, and their adherence to the prescribed dosing conditions degraded with time.

Most studied patient characteristics did not have significant effects on the average plasma levels of semaglutide, including sex, age, race, ethnicity, upper GI disease, and renal function. However, body weight was identified as a potential covariate warranting dose adjustment. Patients with body weights less than 70 kg had approximately twice the exposure of patients with body weight less than 110 kg. After considering the large variability in PK and shape of the exposure-response curve, dose-adjustment for weight is not necessary.

The applicant conducted Exposure-Response relationships for the cumulative of nausea and vomiting (the most common AEs), however, the relationship is confounded by the increased number dose titrations occurring in the 14 mg dose. Empirical time-to-event graphs indicate nausea and vomiting occurs mostly during titration and has an incidence rate (as defined as time to first event) near placebo 30 days post-titration. No other remarkable dose-response relationships were identified in an exploratory analysis for all high level MedDRA AEs occurring in more than 50 patients.

Drug exposure was related to change from baseline in HbA1c and was well described by an  $E_{max}$  model with a Hill coefficient of 1. The half-maximal exposure correlated roughly to the 7mg dose. Due to the

between-subject variability in plasma exposures, it is expected that many patients may get suboptimal exposure.

#### 4.2.2 Population PK Analysis

##### **PK Data:**

PK sampling was performed in 6 out of 10 phase 3a trials in the PIONEER program. The trials contributing PK data are summarized in Table 18. All subjects were instructed to take oral semaglutide in the morning after an overnight fast and at least 30 minutes before the first meal of the day or other oral medication, and with 4 oz or less of water. Oral semaglutide tablets were taken with up to half a glass of water (~120 mL), and tablets were taken whole. Samples with semaglutide content below the lower limit of quantification (9% of PK samples) were included as LLOQ/2, per the M2 method.

**Table 18 Summary of phase 3a trials contributing data to population PK and exposure response of oral semaglutide**

| Trial ID                      | Population <sup>1</sup>      | HbA <sub>1c</sub> at screening | Background treatment                                                                              | Dose (mg)    | Comparator treatment             | Treatment duration <sup>2</sup> (weeks) |
|-------------------------------|------------------------------|--------------------------------|---------------------------------------------------------------------------------------------------|--------------|----------------------------------|-----------------------------------------|
| <b>PIONEER 1 (trial 4233)</b> | Global                       | 7.0–9.5% (53-80 mmol/mol)      | Diet and exercise                                                                                 | 3 or 7 or 14 | Placebo                          | 26                                      |
| <b>PIONEER 2 (trial 4223)</b> | Global                       | 7.0–10.5% (53-91 mmol/mol)     | Metformin                                                                                         | 14           | SGLT-2 inhibitor (Empagliflozin) | 52                                      |
| <b>PIONEER 3 (trial 4222)</b> | Global                       | 7.0–10.5% (53-91 mmol/mol)     | Metformin alone or in combination with SU                                                         | 3 or 7 or 14 | DPP-4 inhibitor (Sitagliptin)    | 78                                      |
| <b>PIONEER 5 (trial 4234)</b> | Global with renal impairment | 7.0-9.5% (53-80 mmol/mol)      | Metformin or SU with/without metformin or basal insulin with/without metformin                    | 14           | Placebo                          | 26                                      |
| <b>PIONEER 8 (trial 4280)</b> | Global                       | 7.0–9.5% (53-80 mmol/mol)      | Basal insulin alone or Basal and bolus insulin or Premixed insulin, all with or without metformin | 3 or 7 or 14 | Placebo                          | 52 <sup>3</sup>                         |
| <b>PIONEER 9 (trial 4281)</b> | Japanese only                | 6.5%–9.5% (48–80 mmol/mol)     | Diet and exercise <sup>4</sup>                                                                    | 3 or 7 or 14 | Placebo or Liraglutide           | 52                                      |

<sup>1</sup> Age ≥ 18 years, for Japanese subjects: Age ≥ 20 years; <sup>2</sup>Treatment duration includes dose escalation (every 4 weeks 3→7→14 mg) and excludes follow-up period; <sup>3</sup>Includes initial 26-week period with restricted insulin dosing followed by 26-week period with freely adjustable insulin; <sup>4</sup>Subjects in PIONEER 9 could be treated with OAD monotherapy (Metformin, SU, glinide, alpha-glucosidase inhibitor, DPP-4i or SGLT2i) at up to half-maximum dose. Pre-trial OAD was discontinued at screening.

DPP-4: dipeptidyl peptidase-4 inhibitor; OAD: oral antidiabetic; SGLT-2: sodium/glucose cotransporter 2 inhibitor; SU: sulfonylurea

(Source: Table 4-1 of Phase 3 Modelling Report)

Trough PK sampling was planned for all subjects randomized to oral semaglutide, except for PIONEER 3 in which PK sampling was planned for approximately 50% of subjects randomized to oral semaglutide comprising all subjects from North America, Germany and Japan. Data from all 6 trials were included in the population PK analysis. The number of subjects included for PK sampling in each trial is provided in

Table 19. Pioneer 2 included samples taken approximately 25 minutes after dose to capture  $C_{max}$ . Pioneer 9 included a sample taken 60-90 minutes post dose at week 26.

**Table 19** Number of subjects with PK sampling during treatment with oral semaglutide for PIONEER

| Trial     | Week 4 | Week 8 | Week 14 | Week 26 | Week 38 | Week 52 | Week 78 | Total |
|-----------|--------|--------|---------|---------|---------|---------|---------|-------|
| PIONEER 1 | 463    | 460    | 469     | 451     | -       | -       | -       | 525   |
| PIONEER 2 | 372    | -      | -       | 347     | -       | 331     | -       | 410   |
| PIONEER 3 | 561    | 514    | 565     | 541     | 522     | 512     | 489     | 341   |
| PIONEER 5 | 143    | 140    | 136     | 129     | -       | -       | -       | 163   |
| PIONEER 8 | 493    | -      | 470     | 462     | 442     | 441     | -       | 546   |
| PIONEER 9 | 137    | -      | 139     | 1382    | 138     | 138     | -       | 146   |

(Source: Table 4-2 of Phase 3 Modelling Report)

### Methods

The model used for PK evaluation was pre-specified in a model analysis plan, finalized prior to database lock, with minor exceptions as follows:

- A more simplistic modelling approach was not required to describe the data
- The fraction of PK data below the LLOQ (9% of PK samples) was considered non-negligible and the data were included as LLOQ/2 in the model. A sensitivity analysis explored the use of the M1 and M3 method for inclusion of observations below the LLOQ. The M2 method was preferred as M3 had very long run times and didn't change parameter estimates.
- The log-normal error model was found to overestimate the residual error and was replaced by a proportional error model.

A pharmacometric model previously built<sup>1</sup> using IV and SC data was used to model the disposition of oral semaglutide central Vd, peripheral Vd, intercompartmental clearance, and drug clearance. Fixing the disposition PK model using previously estimated parameter values from IV and SC dosing and allowed estimation of the apparent bioavailability of oral semaglutide.

The phase 3a data did not contain data informative to the absorption of oral semaglutide. Therefore, the semaglutide absorption rate constant ( $k_a$ ) was set to a value of  $2 \text{ h}^{-1}$  obtained from a PK model based on full PK profiles from clinical pharmacology trials in normoglycemic and T2D subjects (Novo Nordisk, data on file<sup>2</sup>). The sensitivity of the model to assumptions about the was determined by a sensitivity analysis. Between-subject variability (log-normal; without correlation between parameters) was estimated for F. No between-subject variability was included for  $k_a$ . The model was estimated using a proportional error model was used to describe the residual variability. Models were estimated using first order conditional estimation with interaction (FOCE+I).

A full covariate model (FCM) approach was used to determine point estimates and confidence intervals for potential effects of patient demographics on semaglutide plasma exposure. All prespecified covariate-

<sup>1</sup> Novo Nordisk, Data-on-File: <https://link.springer.com/article/10.1007%2Fs13300-019-0581-y>

parameter relationships were added to the base model at once and estimated. This “full model” was used to illustrate covariate effects in a forest plot. A reduced model was determined by examining individual covariate effects on parameters and excluding those without statistical and clinical relevance. A covariate was considered to not have a relevant impact on the exposure of semaglutide if the 90% CI was entirely within the [0.80–1.25]-limits. A stepwise method was not used. No multiplicity correction was applied.

This “reduced model” was considered final and used for complete model qualification. Model qualification included inspection of goodness of fit plots, visual predictive checks, and sensitivity analyses.

### **Results**

A total of 10,681 PK observations from 2,349 subjects were assessed during semaglutide treatment and evaluated for inclusion in the population PK dataset. Only 154 observations (1%) and 4 subjects were excluded due to inadequate dosing history according to pre-specified criteria. The final population PK dataset comprised 10,527 observations from 2,345 subjects.

The base, full and reduced PK models of oral semaglutide were successfully estimated using 2-compartment PK models in which the entire disposition part (including covariates on CL, Q, V<sub>c</sub> and V<sub>p</sub>) and the absorption rate constant (k<sub>a</sub>) were fixed to values obtained previously, as discussed above.

The shrinkage estimate for bioavailability, which was the main estimated PK parameter, was low (3.5%) and in accordance with the general target of less than 20–30% (Table 20).

**Table 20 Parameter Estimates for the Reduced Population Pharmacokinetic Model**

|                                            | Estimate               | CI95%<br>Lower | CI95%<br>Upper | RSE<br>(%) |
|--------------------------------------------|------------------------|----------------|----------------|------------|
| Absorption rate constant (k <sub>a</sub> ) | 2.09                   | Fixed          | Fixed          | Fixed      |
| Clearance (CL)                             | 0.039 L/h              | Fixed          | Fixed          | Fixed      |
| Central volume (V <sub>c</sub> )           | 3.59 L                 | Fixed          | Fixed          | Fixed      |
| Inter-compartmental clearance (Q)          | 0.304 L/h              | Fixed          | Fixed          | Fixed      |
| Peripheral volume (V <sub>p</sub> )        | 4.1 L                  | Fixed          | Fixed          | Fixed      |
| Body weight exponent on clearance          | 1.01                   | Fixed          | Fixed          | Fixed      |
| Body weight exponent on volume             | 0.923                  | Fixed          | Fixed          | Fixed      |
| Bioavailability (F) Percent                | 0.471                  | 0.00443        | 0.00498        | 2.99       |
| IIV On Bioavailability (% CV)              | 84.3 (3.48% Shrinkage) |                |                |            |
| Sex factor on F                            | 0.814                  | 0.76           | 0.868          | 3.38       |
| Asian factor on F                          | 1.1                    | 1.02           | 1.19           | 4.02       |
| Body weight factor on F                    | 0.374                  | 0.229          | 0.519          | 19.8       |
| Upper GI disease factor on F               | 1.13                   | 1.04           | 1.22           | 3.93       |
| Trial effect of PIONEER2                   | 0.6                    | 0.559          | 0.642          | 3.57       |
| Trial effect of PIONEER 3                  | 0.758                  | 0.651          | 0.866          | 7.22       |
| Proportional residual error                | 0.454                  | 0.444          | 0.465          | 1.17       |

(Source: 8-7 of the Phase 3 Modelling Report)

A forest plot with estimated means and CIs for dose-normalized exposures relative to a reference subject profile is shown in Table 21. The influence of a single covariate was investigated while adjusting for remaining covariates, and the result from the full model, including all pre-specified covariates, is presented. Body weight was the most influential covariate resulting in lower exposures with higher body weights and vice versa. Males had slightly lower exposure compared to females with

a 90% CI just outside the [0.80-1.25]-limits. The other covariates tested (age group, race, ethnicity, upper GI disease and renal function) were all within the [0.80-1.25]-limits. The between-subject variability of exposure (in terms of CV%) was 96%, of which 18.1% was explained by inclusion of covariates in the model.

**Table 21 Forest plot of covariate effects on the exposure of oral semaglutide.**

| Covariate        | Test category             | Reference category       | Relative Exposure $C_{avg}$ | Ratio [90% CI]   |
|------------------|---------------------------|--------------------------|-----------------------------|------------------|
| Sex              | Male                      | Female                   |                             | 0.82 [0.77;0.87] |
| Age group        | 65-74 years               | 18-64 years              |                             | 0.95 [0.89;1.01] |
|                  | >= 75 years               |                          |                             | 1.02 [0.90;1.17] |
| Race             | Black or African American | White                    |                             | 1.00 [0.87;1.13] |
|                  | Asian                     |                          |                             | 1.08 [1.01;1.15] |
| Ethnicity        | Hispanic or Latino        | Not Hispanic or Latino   |                             | 0.96 [0.87;1.05] |
| Body weight      | 56 kg                     | 85 kg                    |                             | 1.33 [1.26;1.41] |
|                  | 129 kg                    |                          |                             | 0.75 [0.71;0.79] |
| Upper GI disease | With Upper GI disease     | Without Upper GI disease |                             | 1.15 [1.07;1.22] |
| Renal function   | Mild                      | Normal                   |                             | 0.98 [0.95;1.03] |
|                  | Moderate                  |                          |                             | 0.94 [0.82;1.11] |
| Dose level       | 3 mg                      | 14 mg                    |                             | 0.91 [0.88;0.94] |
|                  | 7 mg                      |                          |                             | 0.95 [0.92;0.98] |

(Source: Phase 3 Modelling Report, Figure 5-7, page 47)

There was considerable overlap in exposure between 14 mg oral semaglutide and 0.5 mg subcutaneous semaglutide. Treatment with 0.5 mg SC (556 subjects) resulted in average plasma concentrations with geometric mean of 15.9 nmol/L (5-95% quantiles; 10.8 – 23.1 nmol/L). Treatment with 14 mg PO (1182 subjects) resulted in average plasma concentrations with a geometric mean of 14.6 nmol/L, but with much higher variability (5-95% quantiles; 3.7 – 41.3 nmol/L).

The applicant's diagnostic plots for the base model are shown below in Figure 23 and visual predictive check in Figure 24.

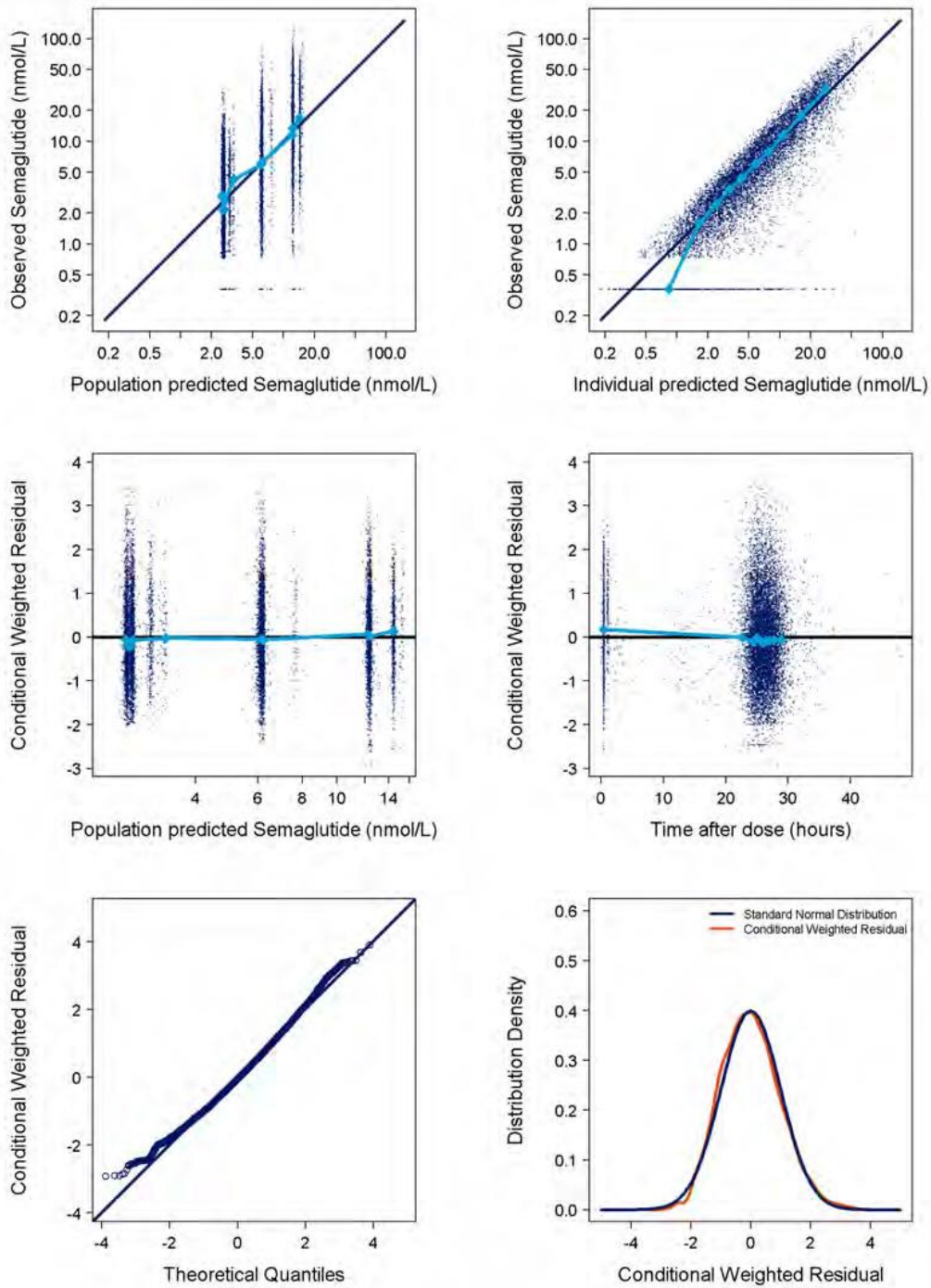


**Figure 23 Residual Goodness of Fit Plots for the Reduced Model**

(Source: Figure 8.5 of the Phase 3 Modelling Report)

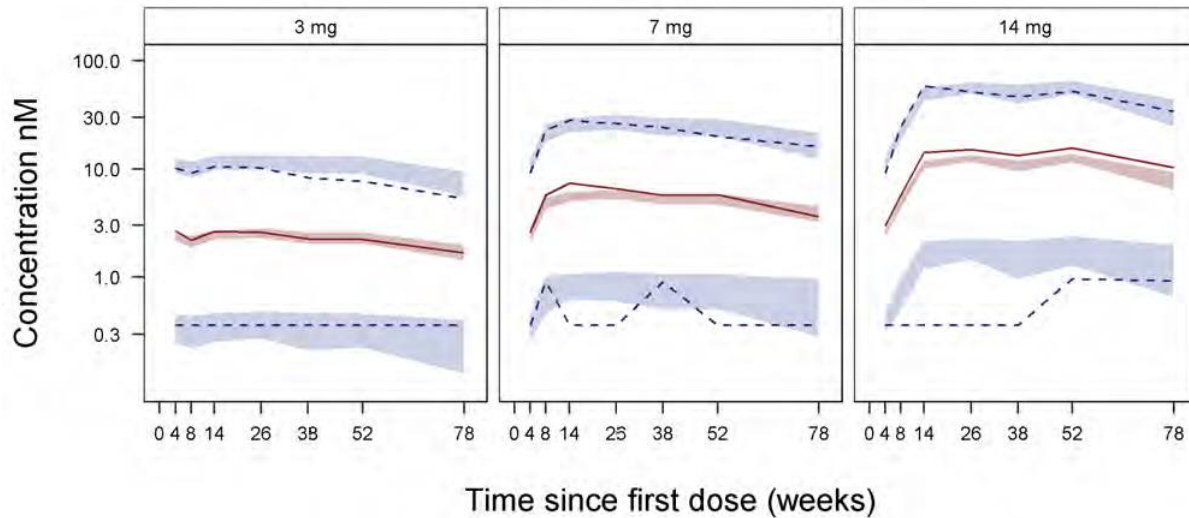


**Figure 24 Visual Predictive Check**  
 (Source: Figure 8.7 of the Phase 3 Modelling Report)

**Reviewer's Analysis and Comments:**

Of the 6 studies included in this meta-analysis, all but two (study 4223, 4281) sampled only trough PK samples. In Study 4281, only about 15% of all samples were drawn around  $C_{max}$  (Figure 25 Panel A). In study 4223, all samples were drawn after dosing. Each patient had multiple trough samples occurring throughout treatment (Figure 25, Panel B).

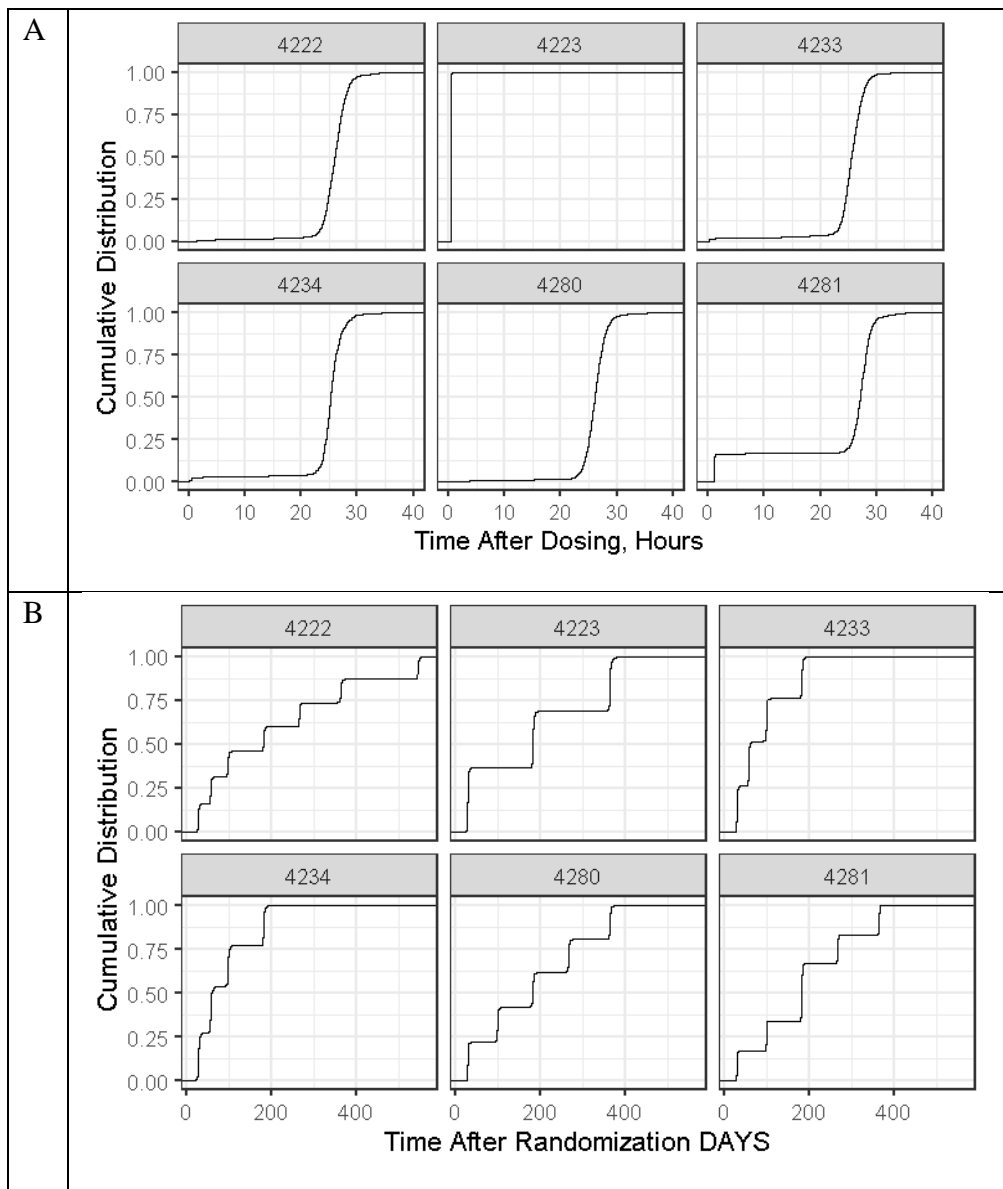


**Figure 25 Empirical Cumulative Distribution Plots for PK Observations Vs. Time After Dosing and Time After Randomization**

(Source: Reviewer's Independent Analysis)

Using volume and clearance parameter estimates from the IV and SC model, the elimination half-life ( $k$ ) is approximately 4.3 days. The following equation estimates an oral semaglutide accumulation ratio of 4.8:

$$AR = \frac{1}{1 - e^{-\left(\frac{CL}{V}\right) \cdot \tau}}$$

In a highly accumulating drug, the absorption and distribution phase resulting from individual drug administration has little consequence to the total average exposure of the drug (Figure 26). Therefore, uncertainty in patient-level estimates of the absorption and distribution phase are less important to

accurately predict patient-level average plasma concentrations. For this reason, the sparse, trough only, pharmacokinetic sampling strategy, is sufficient to characterize individual level  $C_{avg}$ .

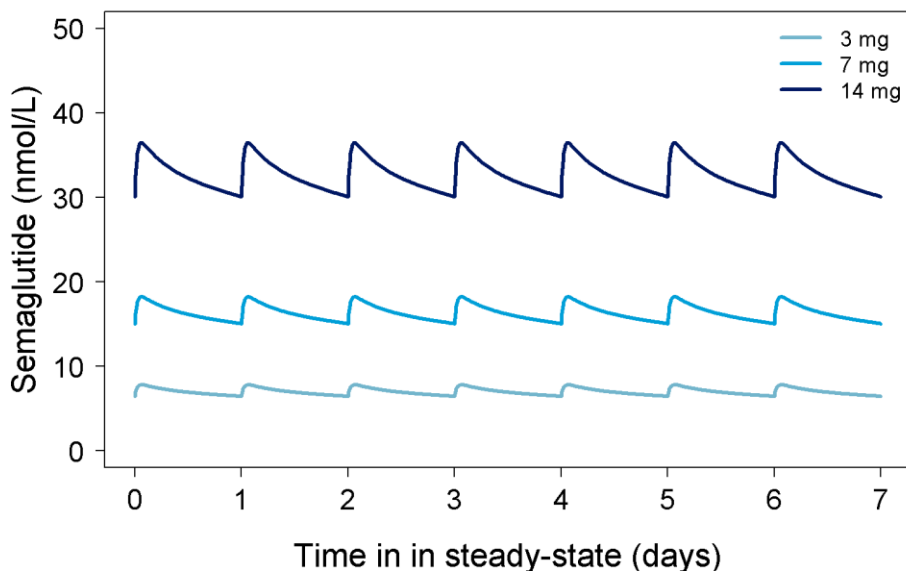


**Figure 26 Simulated Concentration Versus Time Profiles for a Typical Patient at Steady State In Clinical Pharmacology Trials**

(Source: Figure 5-6; clinical pharmacology meta-analysis modelling report)

The standard goodness of fit plots (Figure 23, above) did not indicate any model heteroscedasticity with respect to time, prediction, or covariates. Per the NONMEM covariance step output (Table 20), all parameters included in the final model were estimated with reasonable certainty. The Applicant conducted a series of sensitivity analyses to investigate if the parameter estimates of the full model are robust towards assumptions regarding, 1) implementation of fixed parameter values, 2) handling of values below LLOQ, and 3) differences across trials. The parameter estimates for the covariate effects on exposure were in general robust towards different model elements. The VPC (Figure 24) reasonably predicted the data. It is expected that the covariate model should have minimal impact on post-hoc estimates of steady state exposure.

The model fits were acceptable for determination of PK covariates and use in an exposure-response model. There were no trends in the conditional weighted residuals versus neither semaglutide concentration nor time. The individual bioavailability estimates appeared to be approximately log-normal distributed and the random effect estimate for between-subject variability were approximately log-normal distributed, as seen from QQ-plot.

The visual predictive check showed that the reduced model was able to reproduce the median and the 5<sup>th</sup> and 95<sup>th</sup> percentiles of the observed concentrations. At the highest dose level (14 mg), the median model predictions were slightly lower than the observed concentrations. The 5<sup>th</sup> and 95<sup>th</sup> percentiles on the other hand, were well captured by the model.

Most importantly, the n-shrinkage for bioavailability was at 3.5%, which is below the 20-30% threshold for interpreting covariate-parameter relationships. It is expected that individual POST-HOC estimates of exposure will be robust towards covariate model misspecification.

Lastly, the Applicant utilized a structural model and parameter estimates from previous SC, IV, and rich PO sampling studies (data on file). As discussed previously, this is a reasonable approach given the trough-only study design. However, this reviewer tested these assumptions by independently modeling the data without utilizing this prior knowledge. The data alone supported a one compartment model with between subject variability only on clearance.

This reviewer conducted additional sensitivity analyses to evaluate how different assumptions under the base model, final covariate model, and a mis-specified covariate model, and a data-driven only model may affect individual estimates of exposure (Figure 27). Because of the low n-shrinkage and reasonable assumptions, the post-hoc exposure estimates were comparable to the Applicant’s two compartment model.

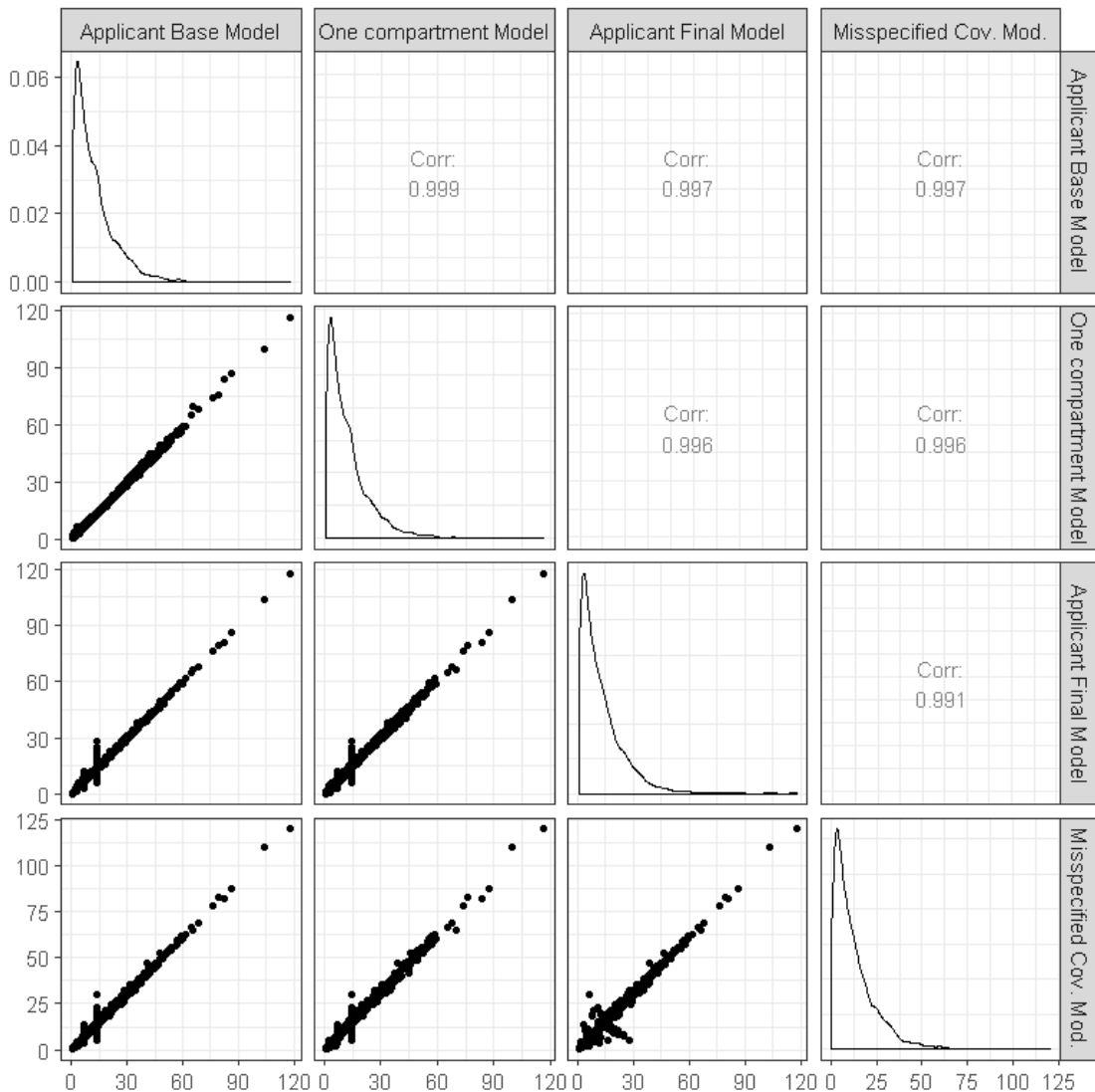


**Figure 27 Correlation Matrix of Post-Hoc Average Plasma Concentration Estimates Between Different Models**

(Source: Reviewer’s Independent Analysis. The “One compartment Model” corresponds to a model built by the reviewer using a parsimonious approach. The “Mis-specified Cov. Mod.” corresponds to an extremely mis specified covariate model, where all covariate-parameter relationships were inverted and/or made 1.5-2x more extreme.)

In summary, post-hoc exposure estimates were relatively invariant towards covariate model misspecification and a different (e.g. 1 compartment) model. The developed population PK model was qualified and found suitable for descriptive. Deviations from expected results were minor and without practical implications.

**What is the impact of selected covariates on semaglutide exposure following oral administration?**

The structural population PK model, built from rich SC and IV data, suggests plasma clearance follows a power model with an exponent of approximately 1. These relationships were carried over by “FIX-ing” the parameter estimates in the oral model. Additionally, the oral model indicated bioavailability also scales with weight, with an exponent of approximately 0.3. This is well reflected in individual post-hoc estimates (Figure 28), and in observed data (not shown).

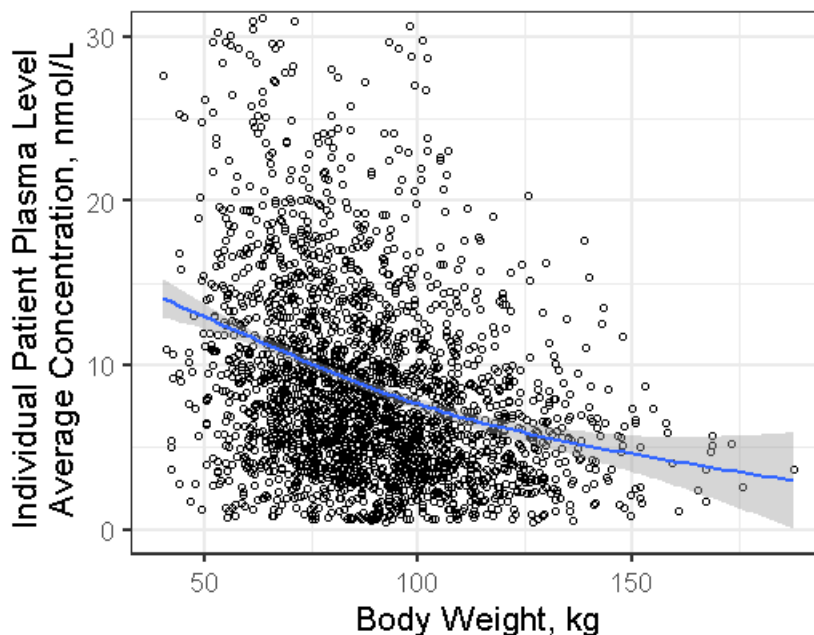


**Figure 28 Scatterplot of Average Plasma Level Versus Body Weight, with a Loess Overlay**

*(Source: Reviewer’s Independent Analysis. Note: The individual data points have gaussian noise added to protect proprietary data.)*

Despite the highly significant correlation, accounting for all covariates, including weight, only reduces the between subject variability in average plasma level from 96% (from applicant base model) to 84% (from applicant final model) in Figure 29 below.

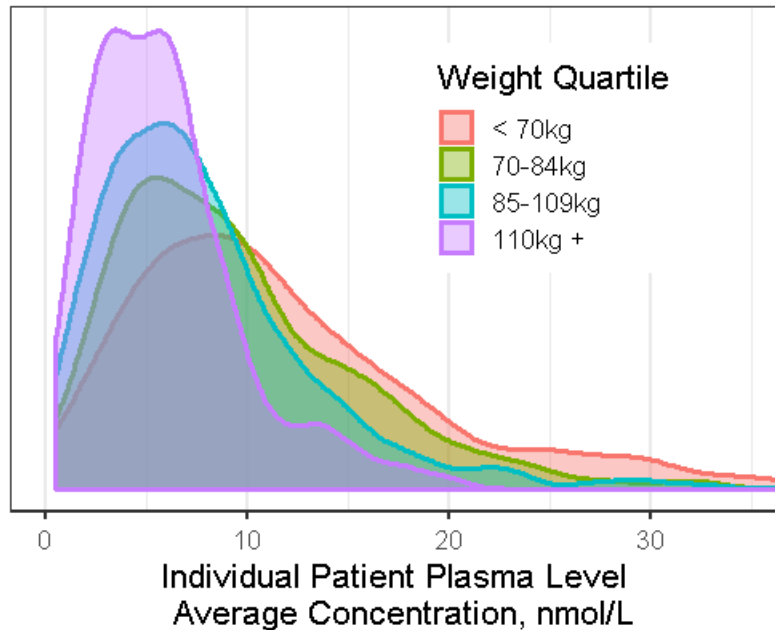


**Figure 29** Smoothed Density Plots of Predicted Average Patient Plasma Level At Steady State Treatment of 7mg Oral Semaglutide, Daily, Faceted by Dose

(Source: Reviewer's Independent Analysis)

**What is the impact of offsite dosing on semaglutide exposure following oral administration?**

Overall, across clinical pharmacology trials, the absolute bioavailability was estimated to be approximately 1%. In the phase 3a trials, the estimated apparent bioavailability was approximately 0.4% (parameter table, above); corresponding to approximately half of the estimated absolute bioavailability from clinical pharmacology trials. This was likely due to the difference between on-site dosing with monitored compliance of dosing and dosing conditions and home-dosing, as previously observed.

Further, a decline of plasma levels can be observed within each trial and dose level. This shows how fleeting patient compliance can affect drug therapy (Figure 30).

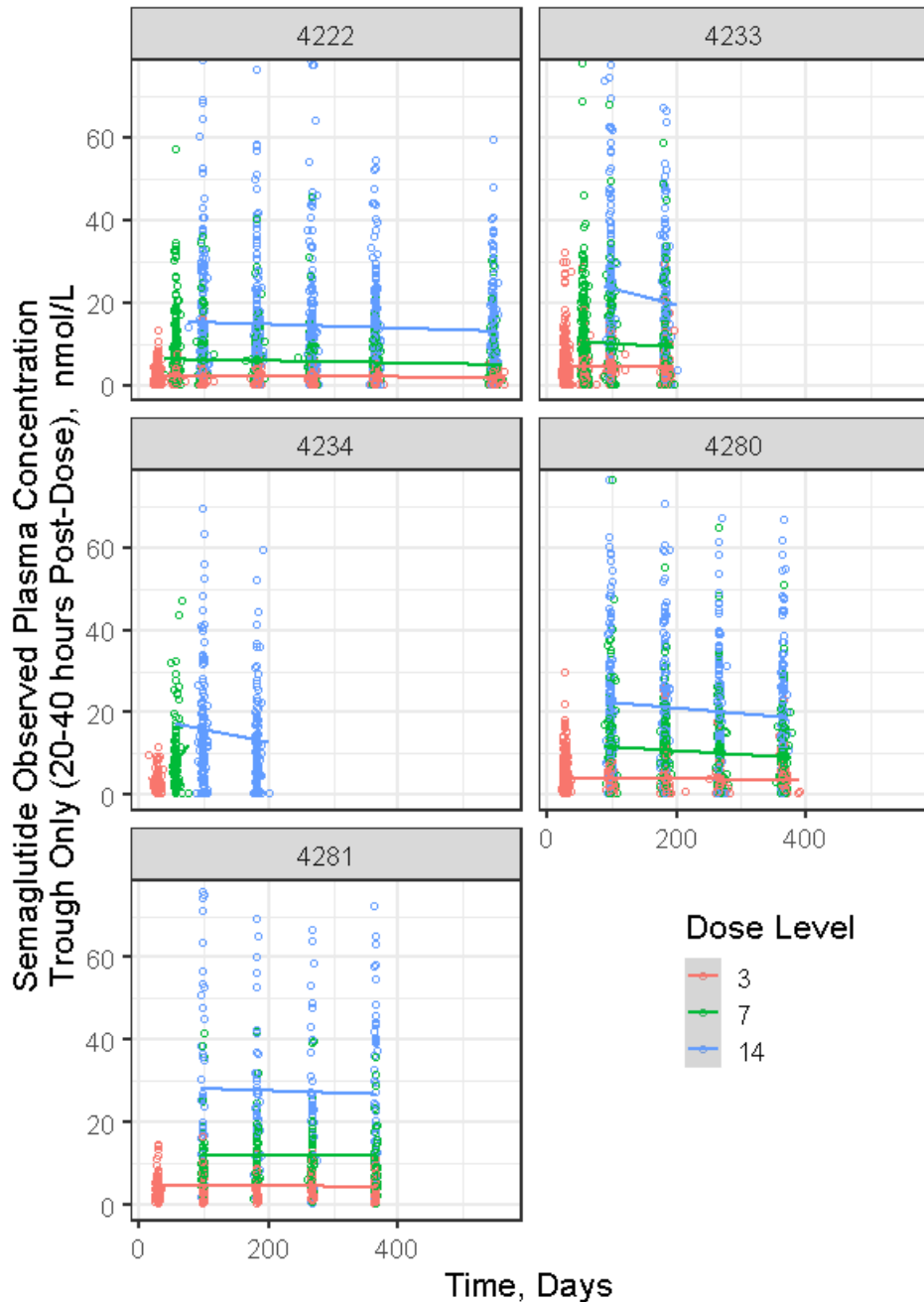


**Figure 30 Semaglutide Plasma Observations Vs. Time, Faceted by Dose and Study**  
 (Source: Reviewer's Independent Analysis, Using the Phase III dataset)

The Applicant justified the apparent decline in exposures as being confounded by different study designs, as study 4222 (PIONEER 3) has lower overall exposures. However, inspection of individual weighted residuals indicates the model systematically underpredicts early exposures by approximately 10% and overpredicts later exposures by 10%, regardless of randomized dose or study (Figure 31). One exception was study 4281, conducted in Japan. The clinical significance of this finding is unclear. Of note, the treatment effect throughout all studies is not fleeting.

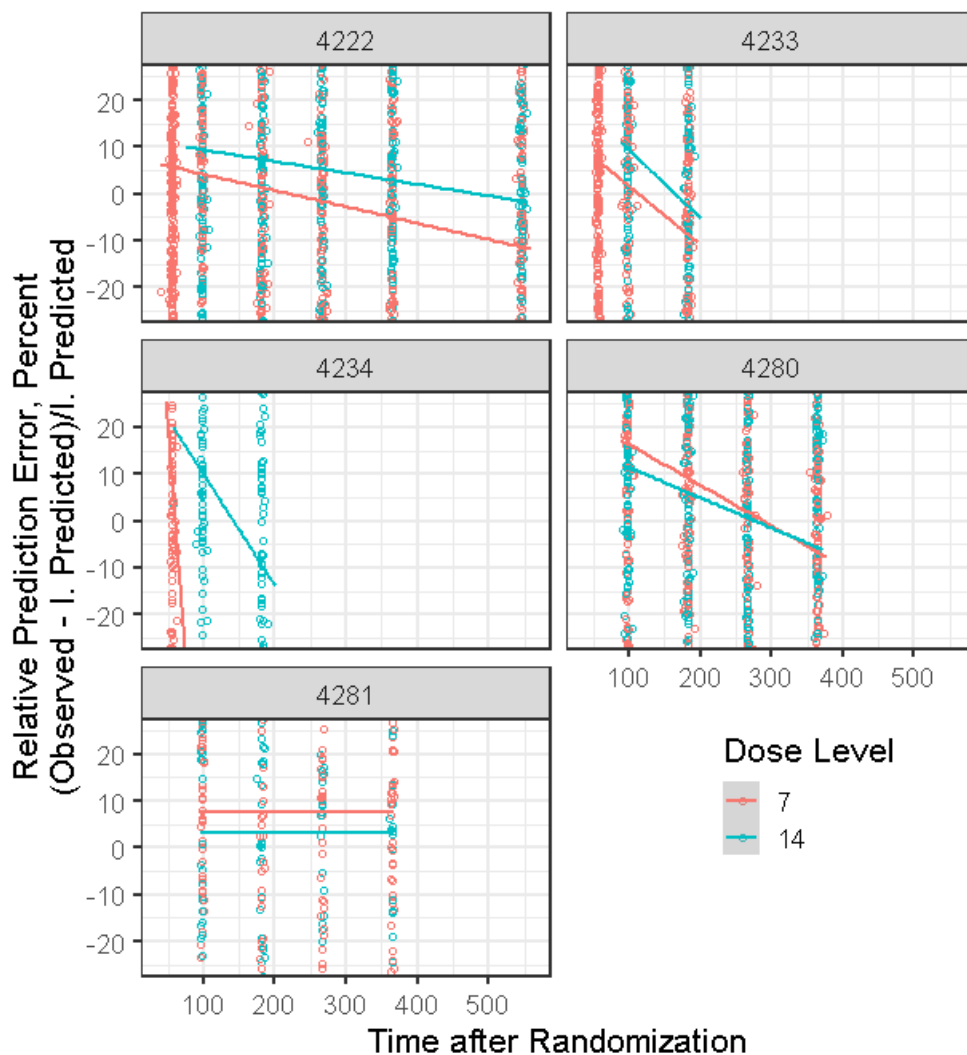


**Figure 31 Model Prediction Error Versus Time after Randomization**

(Source: Reviewer's Independent Analysis, using the NONMEM output from the Applicant's final model. Solid lines represent linear model fit. Only Trough Concentrations are included in this analysis)

**Other Comments:**

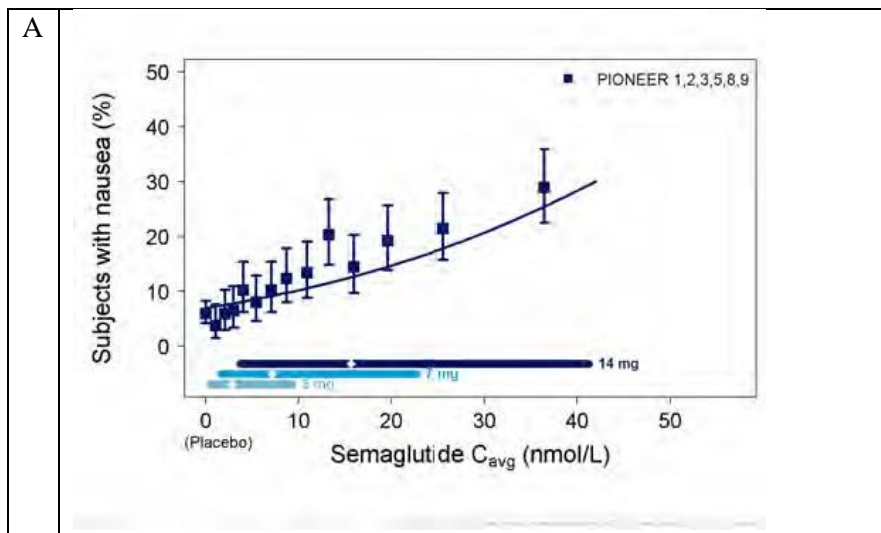
- The NONMEM control file and dataset used to support the two-compartment disposition model were supplied and are acceptable.
- Major deviations from the analysis plan were independently vetted by conducting sensitivity analyses.
- The data used to support the absorption rate was supplied, but not needed to verify acceptability. Accurate estimation of the absorption rate is not critical to determining individual exposure levels because there is both substantial drug accumulation and sparse (trough) PK sampling. Nonetheless, the Applicant conducted sensitivity analyses to confirm low-sensitivity of the model to  $K_a$  estimate. FDA reviewers reproduced these independently.

### 4.2.3 Dose- and Exposure- Response Analysis for Safety

The Applicant conducted a series of exposure-response analyses for complaints of nausea and vomiting. The measure of exposure used in exposure-response models was the average steady-state concentration ( $C_{avg}$ ) based on the individual parameter estimates using the reduced PK model, as described above. The estimands for nausea and vomiting were defined as proportion of subjects reporting the respective event starting during the initial 26 weeks of treatment. The relationship of exposure and safety estimands was modelled using a logistic relationship. The model was validated by overlaying observed data split into quantiles (mean + 95% CI), with model prediction.

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The analysis by the Applicant suggests that nausea (Figure 32, panel A) and vomiting (Figure 32, panel B) is related to drug exposure, and thus, may occur less with lower doses.



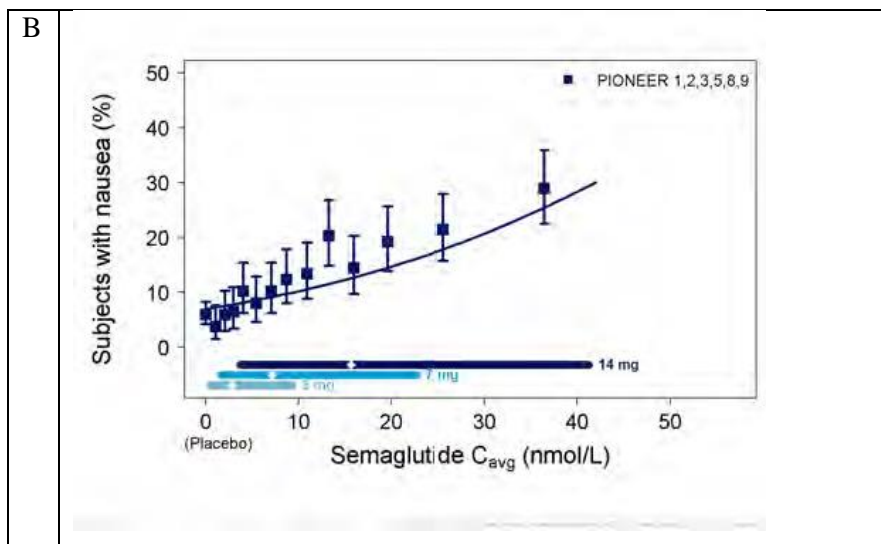


**Figure 32 Exposure-Response Analysis for Nausea and Vomiting**  
 (Source: Figure 5-19, Panel A and Panel D from Applicant's Phase III meta-analysis POP PK Report)

The Applicant's logistic regression identified the presence of renal impairment, concomitant oral antidiabetic drugs, insulin, gender (female), and nationality (Hispanic) significant positive predictors of nausea and vomiting reporting regardless of treatment. For details on adverse event reports and subgroups, refer to the medical and statistical reviews.

**Reviewer's Analysis and Comments:**

The titration of the drug confounds the exposure-response relationship, as more dose titrations occur in subjects with higher  $C_{avg}$  (owing to a higher final dose). The confounding effect of multiple dose titrations can be visualized by plotting the applicant's estimands versus time using Kaplan-Meier methods (Figure 33). Rapid increases in fraction of patients reporting N/V symptoms occur at dose titration periods, at approximately 0, 30, and 60 days post randomization. Due to this confounding, the exposure-response analysis proposed by the Applicant is difficult to interpret. However, a dose response analysis, as above, provides insights into the nature of gastrointestinal side effects. Approximately 10% of subjects undergoing dose-titration, regardless of titration step, experience side effects. After the initial titration period, the accumulation rate of new patients reporting nausea and vomiting is similar between all treatment arms, including placebo.

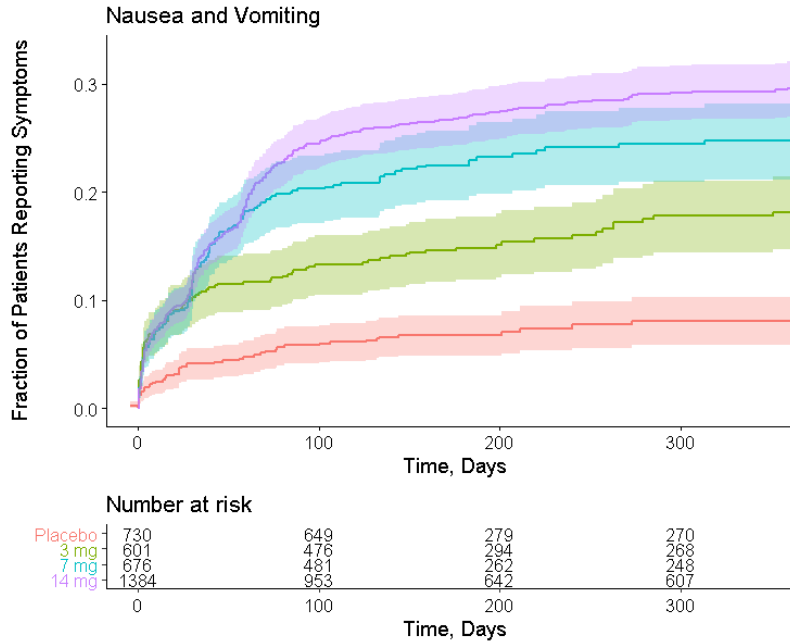


**Figure 33** Kaplan-Mayer Plot of Cumulative Prevalence of Patients Reporting Nausea or Vomiting

(Source: Reviewer's Independent Analysis. A time-to-first event dataset was built from the integrated summary of safety (ISS) dataset. Only the first event per subject, with the high-level MedDRA term "Nausea and vomiting symptoms" was included in the analysis.)

One should not assume that all gastrointestinal adverse reactions are related to dose titration and transient. For example, hypomotility, diarrhea, dyspepsia, and gas complaints accumulate without regard to titration, and continue to accumulate faster than placebo throughout the observation period (Figure 34 Panel A and B. diarrhea, dyspepsia, and gas adverse event plots not shown).

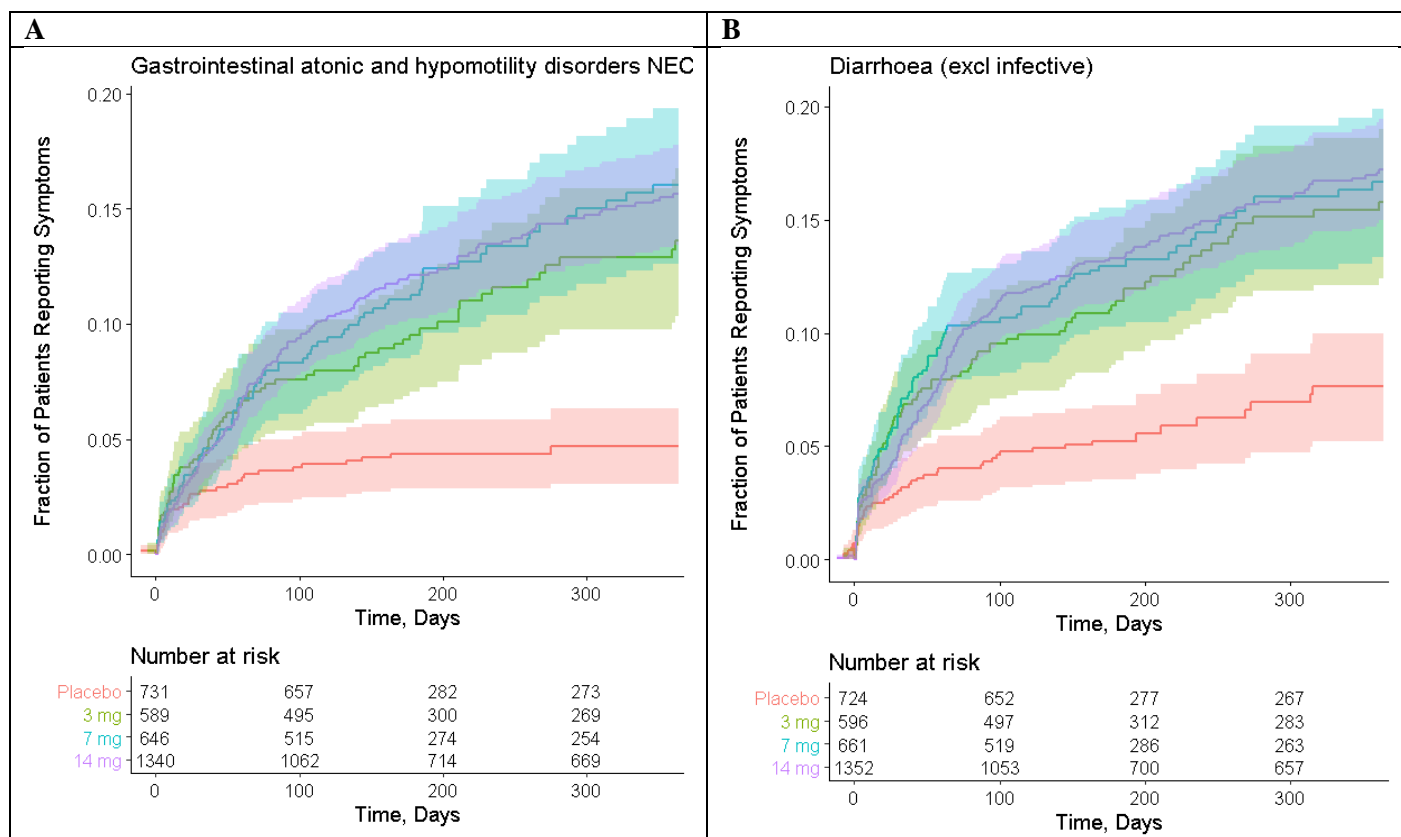


**Figure 34** Kaplan-Meier Plot of Cumulative Prevalence of Patients Reporting Nausea or Vomiting

(Source: Reviewer's Independent Analysis. A time-to-first event dataset was built from the integrated summary of safety (ISS) dataset. Only the first event per subject, with the high-level MedDRA term in the title was included in the analysis.)

Among all GI complaints investigated (nausea, vomiting, hypomotility, diarrhea, dyspepsia, and gas), dose reduction is unlikely to reduce the complaint. In addition, the occurrence of nausea and vomiting symptoms are only associated with recent dose titration.

Finally, an exploratory dose-response for all other adverse events was conducted by the reviewer. A cox-proportional hazards model with a linear effect of DOSE on the log-odds of the occurrence of an event was assumed. The model was stratified by trial to account for differences in study design and demographics. For subjects with multiple events, only the time to the first event was analyzed. Only unique low-level MedDRA term with an incidence of greater than ~0.5% was included in the analysis. There were no findings inconsistent with our current understanding of GLP-1 pharmacology (Figure 35).

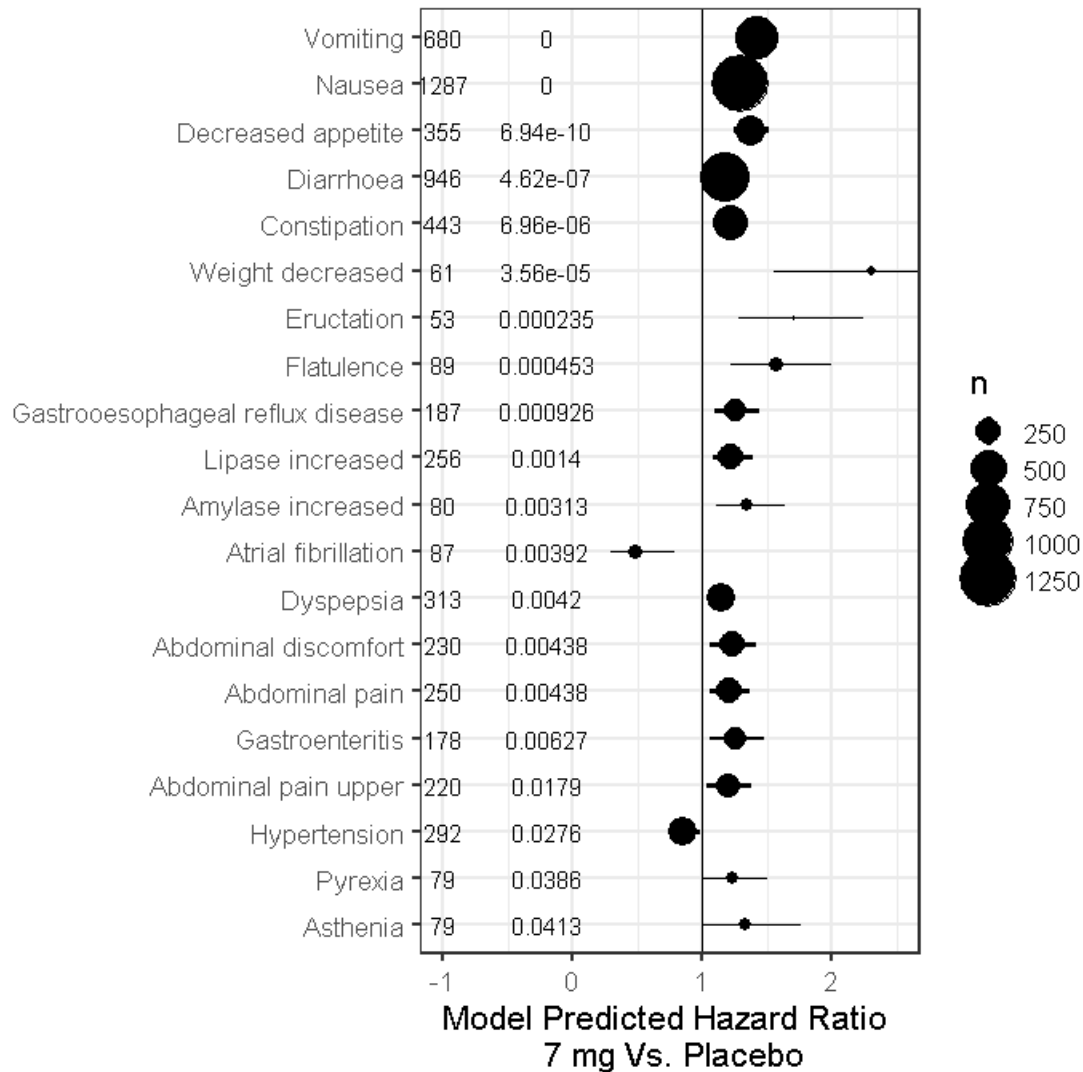


**Figure 35 Forest Plot of Model Predicted Hazard Ratios Between 7mg Oral Semaglutide and Placebo**

(Source: Reviewer’s Independent Analysis. Error bars represent asymptotic 95% confidence intervals for the estimate. P-values are not adjusted for multiplicity. Only adverse reactions with greater than 50 individuals reported were included in this analysis.)

This model should be considered exploratory and interpreted with caution. Seventy-five adverse events made the criteria for analysis; and the p-values presented here are not corrected for multiplicity. Secondly, the assumption that log-odds of an adverse event increases linearly with dose is not correct, as shown with the nausea, vomiting, and other GI events in the plots above.

#### 4.2.4 Exposure- Response Analysis for Efficacy

##### **Data**

The exposure-response population was the full analysis set for those subjects on semaglutide treatment who were scheduled for PK assessment or subjects treated with placebo in PIONEER 1, 2,3,5, 8 and 9. A total of 3003 subjects were included, 572 subjects on placebo were included in the model, with semaglutide plasma concentration set to 0 nmol/L.

##### **Methods**

Change from baseline in HbA1c were the primary endpoints for efficacy exposure-response analysis. A change from baseline in body weight model was not reviewed as it is not pertinent to the proposed indication. The NLS function in R was used to build the model. The model was qualified using standard residual plots, quantile plots of observed data overlaid on the mean model, and subgroups overlaid (e.g. by dose, trial, and demographic subgroups), and by evaluation of the parameter estimates and their uncertainties.

Three sensitivity analyses were conducted for the model of change from baseline in HbA1c: a complete case analysis, including only data obtained at week 26, while subjects are on treatment without use of any rescue medication, a treatment policy analysis aiming at reflecting the results from the primary statistical analysis for HbA1c in the PIONEER trials (those with missing data or drop outs incurred a penalty in addition to data imputation), and an observed PK analysis, where observed PK data was summarized for each individual subject and used instead of model-predicted exposure.

Subjects who did not contribute data to the population PK model were assigned predicted  $C_{avg}$  values based on their demographic characteristics. For subjects who did not have an observation of HbA1c while on treatment without rescue medication, a predicted value for the change from baseline obtained from the MMRM model was used in the analysis.

The exposure-response model for HbA1c change from baseline at Week 26, the starting model was an  $E_{max}$  model without Hill coefficient, with HbA1c at baseline included as a covariate model for  $E_{max}$  (centered on 8%-points), motivated by previous exposure-response models developed based on phase 2 data with oral semaglutide and SUSTAIN data with semaglutide SC.

The Applicant overlaid the model fit to observed data for HbA1c change from baseline by all of the key covariates included in the dataset. Covariates were explored graphically and tested for significance using reductions of the objective function value.

##### **Results**

The  $E_{max}$  model without hill coefficient adequately described data with a clear saturation in effect at high exposures and therefore, no further exploration of the model structure was performed. There were no significant differences in the model between the sensitivity analyses (Figure 36).

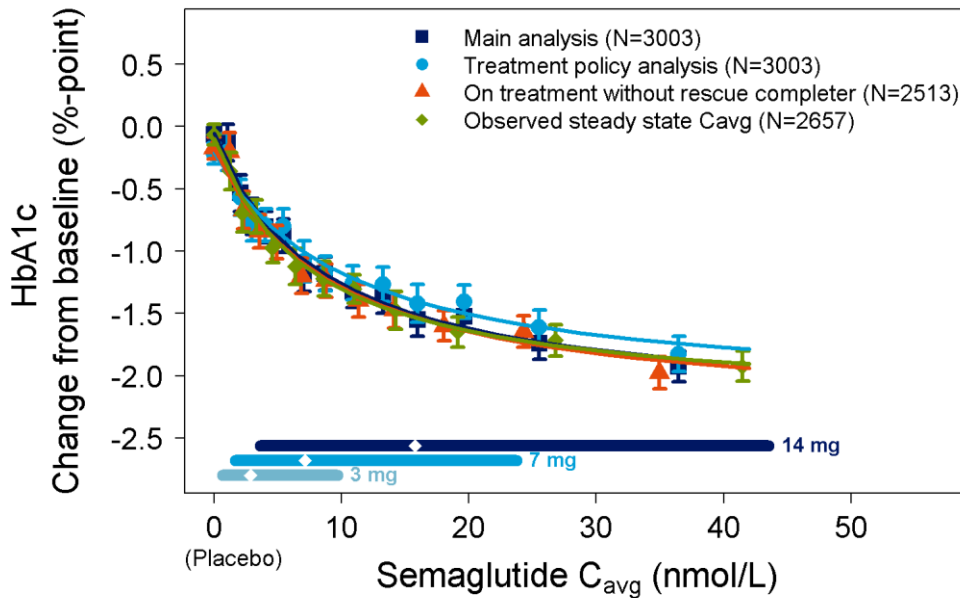
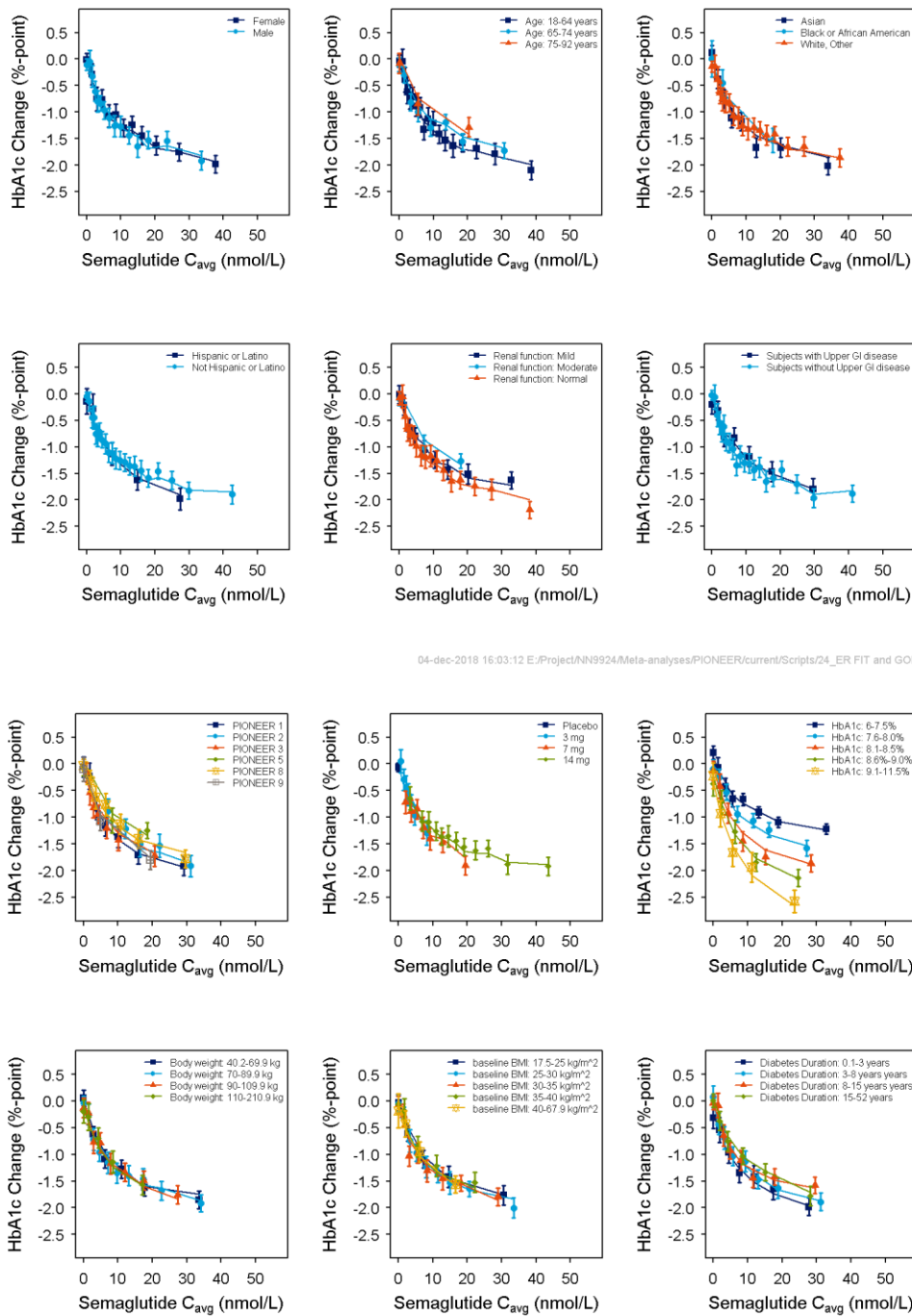


**Figure 36 Base Exposure-Response model of HbA1c Change from Baseline with Sensitivity Analyses Overlaid**

(Source: Figure 8-16 from Phase 3 Meta-Analysis)

With increasing semaglutide exposure, a larger HbA1c change from baseline was seen in subjects with higher baseline HbA1c, and in subjects with shorter diabetes duration. The exposure-response relationship for HbA1c was similar in males and females and across subgroups of body weight, BMI, age, race, ethnicity, renal function and upper GI disease. The Applicant’s final model fit the observed data (Figure 37) for all relevant subgroups. Parameter estimates from the dose-response model of HbA1c change from baseline are shown in Table 22.



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**Figure 37 Model fit to observed data for HbA1c change from baseline by trial, dose, HbA1c baseline, body weight baseline, BMI, diabetes duration, sex, age group, race, ethnicity, renal function and presence of upper GI disease**

(Source: Figure 8-11 of the Phase III Population PK Report)

Data are mean HbA1c response values with 95% CI obtained after 26 weeks of treatment versus exposure expressed as quantiles of C<sub>avg</sub> (plus placebo at C<sub>avg</sub> of 0 nmol/L). The lines through data represent mean model predictions for each exposure quantile. Data from PIONEER 1, 2, 3, 5, 8, 9.

It was claimed that larger effects appeared in semaglutide mono therapy (PIONEER 1 and 9) or treatment with 1-2 OADs (PIONEER 2 and 3) compared to the trials with insulin background treatment (PIONEER 8) and moderate renal impairment (PIONEER 5) (Figure 38).

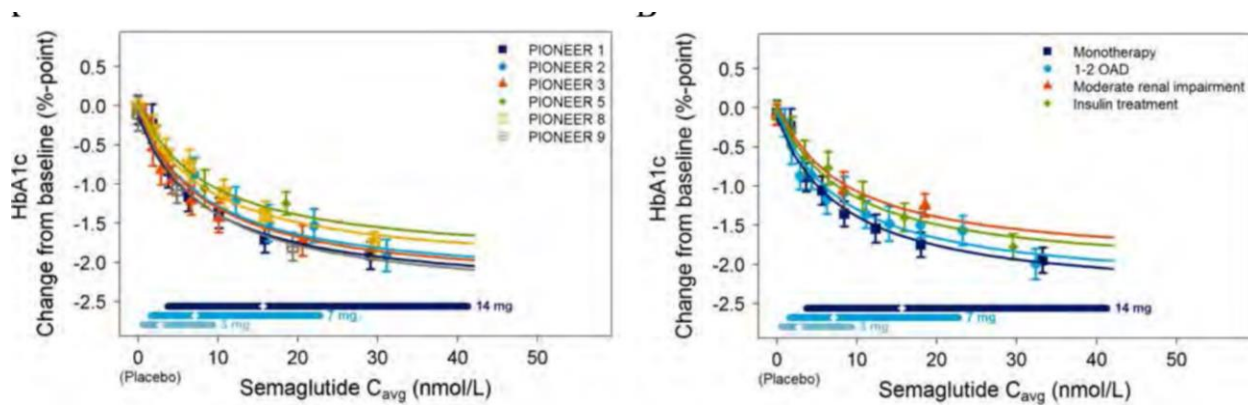


**Figure 38 HbA1c change from baseline versus semaglutide exposure stratified by trial (Left) and by population (Right)**

(Source: Figure 5-15 From Phase 3 Meta-Analysis)

**Table 22 Parameter estimates from the dose-response model of HbA1c change from baseline**

| Parameter                                | Unit                  | Estimate | 95% CI lower bound | 95% CI upper bound | RSE (%) |
|------------------------------------------|-----------------------|----------|--------------------|--------------------|---------|
| $E_{max}$                                | %-points              | -2.304   | -2.508             | -2.117             | 4.3     |
| $EC_{50}$                                | nM                    | 8.321    | 6.753              | 10.321             | 10.8    |
| Placebo                                  | %-points              | -0.179   | -0.256             | -0.103             | 21.8    |
| Emax covariate: HbA1c baseline           | 1/(%-points)          | 0.273    | 0.208              | 0.341              | 12.3    |
| Emax covariate: 1-2 OAD                  | -                     | -0.068   | -0.129             | -0.001             | 48.2    |
| Emax covariate: Moderate renal           | -                     | -0.105   | -0.210             | 0.006              | 52.2    |
| Emax covariate: Insulin treatment        | -                     | -0.126   | -0.200             | -0.047             | 30.7    |
| Placebo covariate: HbA1c baseline        | (%-points)/(%-points) | -0.218   | -0.285             | -0.150             | 15.7    |
| Placebo covariate: log diabetes duration | (%-points)/log(years) | 0.088    | 0.063              | 0.113              | 14.5    |
| Residual standard error                  | %-points              | 0.838    | NA                 | NA                 | NA      |

CI: confidence interval, RSE: relative standard error

(Source: Table 8-21 From Phase 3 Meta-Analysis)

### Reviewer’s Analysis and Comments

The model was independently verified by the reviewer. The qualification procedures provided by the Applicant indicate there is no bias in model predictions for all patient subgroups. However, certain covariates on  $E_{max}$  (Renal impairment, insulin treatment, and concomitant OAD) were not distributed across trials, so they are potentially confounded by differences in study populations. In addition, the PIONEER studies 4222 and 4223 with OAD did not have placebo arms, so the entire exposure-response curve could not be informed ( $E_{max}$  and placebo effect). For this reason, these covariates should be interpreted with caution or left out of the model. Nonetheless, inclusion of these covariates are of little

consequence, as the estimand of OAD, renal impairment, and insulin treatment on the maximum treatment effect are small (0.068 – 0.126% less reduction in HbA1c).

In the model building run-log, it was noted that adding BMI caused a large reduction in the objective function value (OFV, -2 times the log likelihood) to the model was significant but left out of the model as it did not explain the variability. I independently verified this by plotting this data faceted by BMI category. The Applicant's residual plots (residual vs prediction and residual vs  $C_{avg}$ ) indicate good model fit. Observed data as quantiles, for each subgroup, overlaid on mean prediction plots also indicate a good fit for all subgroups. In an independent analysis, no trends in residuals with respect to covariates were detected (Figure 39, Figure 40).

In conclusion, this exposure response model indicates change from baseline in week 26 HbA1c is related to drug exposure in a sigmoidal fashion, where therapeutic benefit rapidly increases until the half maximal benefit, around 6-8 mg of semaglutide daily. The benefit continues to increase but reaches an asymptotic limit of approximately 2.3 points reduction in HbA1c. Subjects with higher baseline HbA1c tend to have better response to treatment, and those with longer diabetes duration tend to receive less therapeutic benefit in the study regardless of treatment (e.g. the placebo and treatment effect were smaller).

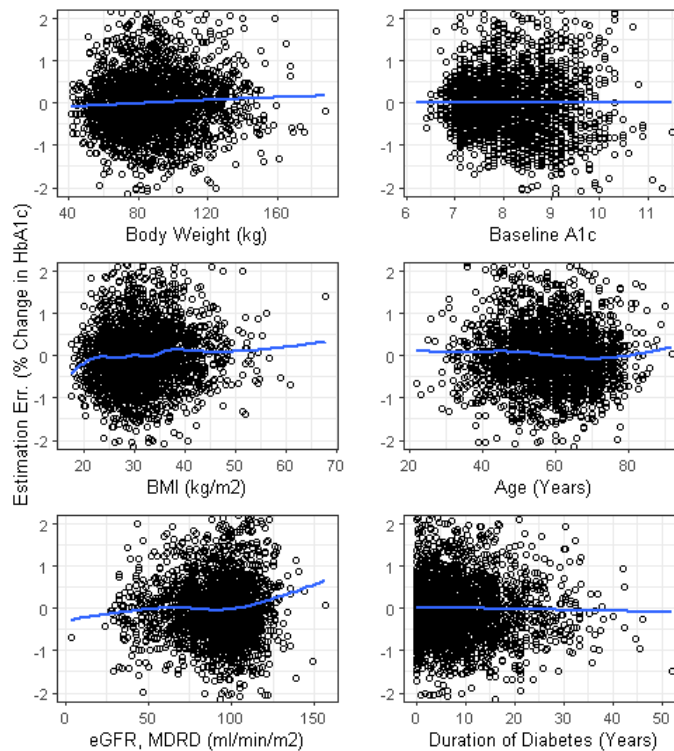


**Figure 39 Model Residual Error Versus Continuous Covariates**

(Source: Reviewer's Independent Analysis Using Final HbA1c Model. Blue line represents a LOESS fit with span parameter of 0.75 )

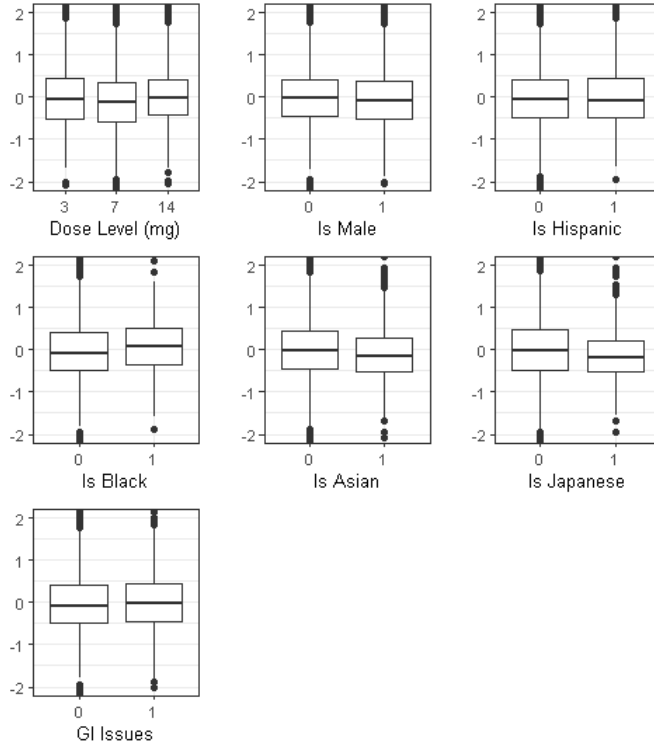


**Figure 40 Model Residual Error Versus Discrete Covariate**  
 (Source: Reviewer's Independent Analysis Using Final HbA1c Model)

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