

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

213051Orig1s000

OTHER REVIEW(S)

MEMORANDUM
REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum: September 3, 2019
Requesting Office or Division: Division of Metabolism and Endocrinology Products (DMEP)
Application Type and Number: NDA 213051
Product Name and Strength: Rybelsus (semaglutide) tablet, 3 mg, 7 mg, and 14 mg
Applicant/Sponsor Name: Novo Nordisk Inc. (Novo)
FDA Received Date: August 30, 2019
OSE RCM #: 2019-643-1
DMEPA Safety Evaluator: Ariane O. Conrad, PharmD, BCACP, CDE
DMEPA Team Leader: Hina Mehta, PharmD

1 PURPOSE OF MEMORANDUM

Novo Nordisk submitted revised labels and labeling for Rybelsus on August 30, 2019. We reviewed the revised labels and labeling for Rybelsus (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.^a

2 CONCLUSION

The Applicant implemented all of our recommendations and we have no additional recommendations at this time.

^a Conrad A. Label and Labeling Review for Rybelsus (NDA 213051). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 Aug 2 MON DD. RCM No.: 2019-643.

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/s/

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09/03/2019 03:18:47 PM

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09/04/2019 09:57:17 AM

INTRODUCTION

DMEP consulted DPMH on April 8, 2019, to provide input for appropriate labeling of the pregnancy and lactation subsections of NDA 213051 for Rybelsus, [semaglutide oral tablets formulated with an absorption enhancer, salcaprozate sodium (SNAC).] to comply with the Pregnancy and Lactation Labeling Rule (PLLR) format.

REGULATORY HISTORY AND BACKGROUND

- Ozempic [semaglutide, a human glucagon-like peptide-1 (GLP-1) receptor agonist], for injection was approved on December 5, 2017.
- On March 20, 2019, Novo Nordisk, Inc. submitted a NDA for Rybelsus, a semaglutide oral tablet via the 505 (b) 2 pathway, which contains a novel absorption enhancer, SNAC. This product is indicated as an adjunct to diet and exercise to improve glycemic control in adults with T2DM and as an adjunct to standard treatment of cardiovascular risk factors to reduce the risk of myocardial infarction or stroke in adults with T2DM and high cardiovascular risk.
- The Applicant proposes dosing as a once daily oral tablet.
- The original submission included a review of the literature and a summary of the pharmacovigilance database regarding pregnancy, lactation and effects on fertility for semaglutide.
- At the time of the original consultation, DPMH proposed to attend the labeling meeting and provide recommendations for PLLR language but did not plan to provide a written review. A previous written DPMH review for Ozempic (semaglutide for injection), NDA 209637 was to be the basis for the labeling recommendations. Labeling recommendations similar to those proposed for the previous semaglutide injection product were provided prior to the first labeling meeting. The language for labeling that was approved are reproduced below from the 2019 Ozempic label¹. Minor modifications in the language for the first sentence of section 8.1 Risk Summary are proposed by DPMH to update the language as follows:

Available data with TRADENAME use in pregnant women are insufficient to evaluate for a drug-associated risk of major birth defects, miscarriage or other adverse maternal or fetal outcomes.

OZEMPIC LABEL¹

Highlights of Prescribing Information (HPI)

.....**USE IN SPECIFIC POPULATIONS**.....
Females and Males of Reproductive Potential: Discontinue OZEMPIC in women at least 2 months before a planned pregnancy due to the long washout period for semaglutide (8.3).

¹ Approved label for Ozempic, dated 4/9/2019

Full Prescribing Information

8 Use in Specific Populations

8.1 Pregnancy

Risk Summary

There are limited data with semaglutide use in pregnant women to inform a drug-associated risk for adverse developmental outcomes. There are clinical considerations regarding the risks of poorly controlled diabetes in pregnancy (*see Clinical Considerations*). Based on animal reproduction studies, there may be potential risks to the fetus from exposure to semaglutide during pregnancy. OZEMPIC should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

In pregnant rats administered semaglutide during organogenesis, embryofetal mortality, structural abnormalities and alterations to growth occurred at maternal exposures below the maximum recommended human dose (MRHD) based on AUC. In rabbits and cynomolgus monkeys administered semaglutide during organogenesis, early pregnancy losses and structural abnormalities were observed at below the MRHD (rabbit) and ≥ 5 -fold the MRHD (monkey). These findings coincided with a marked maternal body weight loss in both animal species (*see Data*).

The estimated background risk of major birth defects is 6–10% in women with pre-gestational diabetes with an HbA_{1c} >7 and has been reported to be as high as 20–25% in women with a HbA_{1c} >10. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Clinical Considerations

Disease associated maternal and fetal risk

Poorly controlled diabetes during pregnancy increases the maternal risk for diabetic ketoacidosis, preeclampsia, spontaneous abortions, preterm delivery, stillbirth and delivery complications. Poorly controlled diabetes increases the fetal risk for major birth defects, stillbirth, and macrosomia related morbidity.

Data

Animal Data

In a combined fertility and embryofetal development study in rats, subcutaneous doses of 0.01, 0.03 and 0.09 mg/kg/day (0.1-, 0.4-, and 1.1-fold the MRHD) were administered to males for 4 weeks prior to and throughout mating and to females for 2 weeks prior to mating, and throughout organogenesis to Gestation Day 17. In parental animals, pharmacologically mediated reductions in body weight gain and food consumption were observed at all dose levels. In the offspring, reduced growth and fetuses with visceral (heart blood vessels) and skeletal (cranial bones, vertebra, ribs) abnormalities were observed at the human exposure.

In an embryofetal development study in pregnant rabbits, subcutaneous doses of 0.0010, 0.0025 or 0.0075 mg/kg/day (0.03-, 0.3-, and 2.3-fold the MRHD) were administered throughout organogenesis from Gestation Day 6 to 19. Pharmacologically mediated reductions in maternal body weight gain and food consumption were observed at all dose levels. Early pregnancy losses and increased incidences of minor visceral (kidney, liver) and skeletal (sternbra) fetal abnormalities were observed at ≥ 0.0025 mg/kg/day, at clinically relevant exposures.

In an embryofetal development study in pregnant cynomolgus monkeys, subcutaneous doses of 0.015, 0.075, and 0.15 mg/kg twice weekly (1.0-, 5.2-, and 14.9-fold the MRHD) were administered throughout organogenesis, from Gestation Day 16 to 50. Pharmacologically mediated, marked initial maternal body weight loss and reductions in body weight gain and food consumption coincided with the occurrence of sporadic abnormalities (vertebra, sternbra, ribs) at ≥ 0.075 mg/kg twice weekly ($>5X$ human exposure).

In a pre- and postnatal development study in pregnant cynomolgus monkeys, subcutaneous doses of 0.015, 0.075, and 0.15 mg/kg twice weekly (0.7-, 3.3-, and 7.2-fold the MRHD) were administered from Gestation Day 16 to 140. Pharmacologically mediated marked initial maternal body weight loss and reductions in body weight gain and food consumption coincided with an increase in early pregnancy losses and led to delivery of slightly smaller offspring at ≥ 0.075 mg/kg twice weekly ($\geq 3X$ human exposure).

8.2 Lactation

Risk Summary

There are no data on the presence of semaglutide in human milk, the effects on the breastfed infant, or the effects on milk production. Semaglutide was present in the milk of lactating rats, however, due to species-specific differences in lactation physiology, the clinical relevance of these data are not clear (*see Data*). The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for OZEMPIC and any potential adverse effects on the breastfed infant from OZEMPIC or from the underlying maternal condition.

Data

In lactating rats, semaglutide was detected in milk at levels 3-12 fold lower than in maternal plasma.

8.3 Females and Males of Reproductive Potential

Discontinue OZEMPIC in women at least 2 months before a planned pregnancy due to the long washout period for semaglutide [*see Use in Specific Populations (8.1)*].

On August 13, 2019, the DPMH reviewer was advised by the Pharmacology-Toxicology (PT) team, of the Division's concerns regarding the high concentration of the novel excipient SNAC, in the milk of lactating rats. More details were provided at a telecon with this reviewer and the PT team later that day. On August 14, 2019, the DPMH team (team leader Tamara Johson, MD and reviewer Jane Liedtka, MD) met with the division (including PT, clinical pharmacology and

clinical) and changes to the proposed lactation language were discussed. The need for a possible PMR for a lactation study was also discussed. DPMH advised DMEP that following consultation with upper management on August 19, 2019, final labeling recommendations and a decision as to whether a lactation study was needed as a PMR would be provided.

REVIEW

Nonclinical Experience

See above for nonclinical data for semaglutide. The division PT team proposed to add the following information about SNAC to the animal data for section 8.1 for NDA 213051.

In a pre- and postnatal development study in pregnant Sprague Dawley rats, salcaprozate sodium (SNAC), an excipient in TRADENAME, was administered orally at 1,000 mg/kg/day (32-fold a clinical 300 mg dose based on BSA) on gestation days 7 through 24 or lactation day 20. Statistically significant increases in gestation length and the number of stillbirths, and decreases in pup viability were observed in the F1 generation descended from SNAC-treated rats when compared to F1 generation rats descended from controls.

See nonclinical review by Federica Basso, PhD for further details.

DPMH had previously reviewed Ozempic², a semaglutide for injection at the time of the original submission for approval in 2017. See that review for the previous human experience with regard to the active moiety semaglutide.

DMEP also provided the following information regarding SNAC:

- The rat lacteal study showed that SNAC can accumulate in the breast milk after a single maternal administration on lactation day 10. Mean SNAC concentrations in rat breast milk could reach levels 12-fold higher than maternal plasma but ratios ranged between 0.982 – 18.1-fold (please see table below).

² DPMH review of Ozempic(semaglutide) injection, NDA 209637. Jane Liedtka, MD, September 6, 2017. DARRTS Reference ID 4148940.

Table 12 Concentrations of SNAC in the plasma, blood and milk of lactating female rats following a single oral administration of ¹⁴C-SNAC at a nominal dose level of 500 mg/kg (Group B)

Animal Number	Timepoint (hours)	Ratio					
		Milk : Plasma		Milk : Blood		Plasma : Blood	
		Individual	Mean ± SD	Individual	Mean ± SD	Individual	Mean ± SD
201F	1	(b) (4)	1.60 ± 0.946	(b) (4)	2.57 ± 1.61	(b) (4)	1.59 ± 0.061
202F							
203F							
204F	2	(b) (4)	2.69 ± 1.35	(b) (4)	4.54 ± 2.35	(b) (4)	1.68 ± 0.038
205F							
206F							
207F	4	(b) (4)	7.22 ± 0.836	(b) (4)	12.6 ± 1.90	(b) (4)	1.73 ± 0.067
208F							
209F							
210F	8	(b) (4)	12.1 ± 5.80	(b) (4)	21.4 ± 10.4	(b) (4)	1.77 ± 0.014
211F							
212F							
213F	24	(b) (4)	10.0 ± 3.15	(b) (4)	17.0 ± 4.93	(b) (4)	1.70 ± 0.110
214F							
215F							

- SNAC plasma concentrations were not measured in the pups in the lacteal study. In a pre- and post-natal study, pups born to SNAC-treated mothers had an increased incidence of stillbirths and decreases in pup viability that exceeded ranges observed in historical controls. Discussion with the PT reviewer revealed that milk was not present in the stomachs of the rat pups that died, so mortality was not due to SNAC exposure via milk. We understand that it is difficult to determine how much pup exposure will occur through maternal milk; however, we are concerned because:
 - General toxicology studies show that SNAC causes mortality at C_{max} values greater than 1,000,000 ng/mL. Since SNAC accumulates in the milk of lactating rats, neonates may achieve higher SNAC plasma concentrations than the mother.
 - The main enzyme responsible for detoxifying SNAC (UGT2B7) is not fully developed in neonates and their capacity to detoxify this compound may be reduced.
 - Maternal exposure to SNAC can vary greatly. While toxicokinetic parameters were not measured for the pre- and post-natal study, other mechanistic toxicology studies in rats show that C_{max} values can vary 23-fold within a dosing group after repeated administration. So, it is unclear how much SNAC would be found in the milk of nursing mothers clinically. Therefore, the 32-fold safety margin we calculated using body surface area may not be very meaningful.
 - SNAC concentrations found in milk continued to accumulate up to 24 hours after a single exposure. We are not sure if SNAC would accumulate further after repeated administration. SNAC does not accumulate in humans after oral administration.

The division proposed adding the following to the language for section 8.2

SNAC and/or its metabolites were excreted in milk of lactating rats following administration at 1,000 mg/kg on lactation day 10. Levels of SNAC in milk were approximately 12-fold higher than those found in maternal blood based on C_{max}.

Higher SNAC plasma levels may occur in neonates and infants, given that activity of UGT2B7, the major enzyme involved in SNAC clearance, is lower in infants compared to adults. SNAC caused inhibition of cellular respiration in adult rats at >30-times the clinical C_{max}.

The division proposed adding the following to the language for section 13.2

SNAC caused inhibition of cellular respiration leading to mortality in rats at >30- and 96-times the clinical C_{max}, respectively. In mechanistic studies, a single dose of SNAC resulted in adverse clinical signs (lethargy, abnormal respiration, ataxia, abnormal body posture and reduced activity, body tone and reflexes), marked increases in lactate levels and decreases in glucose levels in the plasma and cerebrospinal fluid, and reduced heart and liver ATP levels. In a 13-week mechanistic study, slight increases in lactate levels in the cerebrospinal fluid were observed at >8x the clinical C_{max}. These findings are consistent with inhibition of cellular respiration.

Further information regarding SNAC includes

- SNAC is currently available in a marketed ‘medical food’ in the US where 1,000 mcg vitamin B₁₂ is formulated with 100 mg SNAC as EligenB12³. The amount of SNAC present at the maximum recommended dose for EligenB12 is 200 mg, which is less than the 300 mg/day dose proposed in Rybelsus®; therefore, SNAC has not been used in a marketed product at the proposed level. EligenB12 has been on the market since at least 2016. Medical foods do not have to undergo premarket review or approval, making them similar to dietary supplements. SNAC has “generally regarded as safe” (GRAS) status.⁴
- The FDA designation of EligenB12 as a medical food was based on 2 limited drug trials, including a pharmacokinetics study of oral formulations in 20 healthy men, and an efficacy and tolerability comparison of EligenB12 with the current FDA-approved IM formulation in 48 patients for 3 months.⁵ Adverse events associated with the product in the two small studies performed prior to marketing included constipation, diarrhea, nausea, fatigue, headache, back pain, and upper respiratory tract infection.
- Pediatric patients may especially be at risk for decreased detoxification of SNAC. At birth, it is estimated that UGT2B7 operates at approximately 3-10% of its maximal activity in adults and its maturation profile can vary significantly (Badee, Fowler⁶ et al. 2019). Therefore, pediatric patients might be at a greater risk of adverse events due to immature detoxifying enzymes.

³ EligenB12 Fact Sheet <https://www.emisphere.com/wp-content/uploads/2017/01/Eligen-B12-Fact-Sheet-FINAL-12.3.14.pdf>

⁴ Twarog C et al. Intestinal Permeation Enhancers for Oral Delivery of Macromolecules: A Comparison between Salcaprozate Sodium (SNAC) and Sodium Caprate (C10). *Pharmaceutics*. 2019; 11(2) 78.

⁵ Smith L et al. Cyanocobalamin/Salcaprozate Sodium: A Novel Way to Treat Vitamin B12 Deficiency and Anemia. *Hematol Oncol Pharm*. 2016;6(2):42-45.

⁶ Badee, J. et al. The Ontogeny of UDP-glucuronosyltransferase Enzymes, Recommendations for Future Profiling Studies and Application Through Physiologically Based Pharmacokinetic Modelling. *Clin Pharmacokinet*. 2019; 58(2): 189-211.

Discussion of the Need for a PMR for a Lactation Study

There are no published data on Rybelsus or SNAC levels in human milk or of exposure in breastfed infants. Animal studies indicate that SNAC and/or its metabolites was detected in the milk of lactating rats up to 12-fold the maternal blood concentration based on C_{max}. When a drug is present in animal milk, it is likely that the drug will also be present in human milk. Higher SNAC plasma levels may occur in neonates and infants, given that activity of UGT2B7, the major enzyme involved in SNAC clearance, is lower in infants compared to adults. Based on findings in animals, it is possible that SNAC will be present in human milk and that an infant may be at risk for harm. DPMH recommends including information about possible exposure to SNAC in the risk summary for subsection 8.2. See DPMH Proposed Rybelsus (semaglutide) Oral Tablet Labeling for details.

Rybelsus is indicated for a condition that would be expected to be seen commonly in females of reproductive potential and increased use may be expected with a new oral route of administration. Since there are concerns based on animal studies, that the drug may accumulate in human milk, DPMH recommends a PMR for the applicant to conduct a milk only lactation study.

RECOMMENDATIONS

1. DPMH recommends a PMR for a milk only lactation study in women receiving Rybelsus using a validated assay to assess concentrations of semaglutide and salcaprozate sodium (SNAC) in breast milk.
2. DPMH proposes the following language for Rybelsus (semaglutide) oral tablet PLLR labeling. DPMH met again with the DMEP team to discuss labeling and the PMR for a lactation study on August 28, 2019. DPMH refers to the final NDA action for final labeling.

DPMH Proposed Rybelsus (semaglutide) oral tablet Pregnancy and Lactation Labeling

HIGHLIGHTS OF PRESCRIBING INFORMATION

-----USE IN SPECIFIC POPULATIONS-----

- Pregnancy: May cause fetal harm (8.1).
- Lactation: Breastfeeding not recommended (8.2).
- Females and Males of Reproductive Potential: Discontinue TRADENAME in women at least 2 months before a planned pregnancy due to the long washout period for semaglutide (8.3).

FULL PRESCRIBING INFORMATION

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Available data with TRADENAME use in pregnant women are insufficient to evaluate for a drug-associated risk of major birth defects, miscarriage or other adverse maternal or fetal outcomes. There are clinical considerations regarding the risks of poorly controlled diabetes in pregnancy (*see Clinical Considerations*). Based on animal reproduction studies, there may be potential risks to the fetus from exposure to TRADENAME during pregnancy. TRADENAME should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

In pregnant rats administered semaglutide during organogenesis, embryofetal mortality, structural abnormalities and alterations to growth occurred at maternal exposures below the maximum recommended human dose (MRHD) based on AUC. In rabbits and cynomolgus monkeys, early pregnancy losses and structural abnormalities, which did not resemble the abnormalities in rats, were observed at exposures ≥ 0.3 -fold the MRHD (rabbit) and ≥ 10 -fold the MRHD (monkey). These findings coincided with a marked maternal body weight loss in both animal species (*see Data*).

The estimated background risk of major birth defects from women with uncontrolled pre-gestational diabetes (Hemoglobin A_{1C} >7) is 6 to 10%. The major birth defect rate has been reported to be as high as 20 to 25% in women with a Hemoglobin A_{1C} >10. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Clinical Considerations

Disease-associated maternal and/or embryo/fetal risk

Poorly controlled diabetes in pregnancy increases the maternal risk for diabetic ketoacidosis, pre-eclampsia, spontaneous abortions, preterm delivery, and delivery complications. Poorly controlled diabetes increases the fetal risk for major birth defects, still birth, and macrosomia related morbidity.

Data

Animal Data

In a combined fertility and embryofetal development study in rats, subcutaneous doses of 0.01, 0.03 and 0.09 mg/kg/day (0.2-, 0.7-, and 2.1-fold the MRHD) were administered to males for 4 weeks prior to and throughout mating and to females for 2 weeks prior to mating, and throughout organogenesis to Gestation Day 17. In parental animals, pharmacologically mediated reductions in body weight gain and food consumption were observed at all dose levels. In the offspring, reduced growth and fetuses with visceral (heart blood vessels) and skeletal (cranial bones, vertebra, ribs) abnormalities were observed at the human exposure.

In an embryofetal development study in pregnant rabbits, subcutaneous doses of 0.0010, 0.0025 or 0.0075 mg/kg/day (0.06-, 0.6-, and 4.4-fold the MRHD) were administered from Gestation Day 6 throughout organogenesis to Gestation Day 19. Pharmacologically mediated reductions in maternal body weight gain and food consumption were observed at all dose levels. Early pregnancy losses and increased incidences of minor visceral (kidney, liver) and skeletal (sternebra) fetal abnormalities were observed at ≥ 0.0025 mg/kg/day, at clinically relevant exposures.

In an embryofetal development study in pregnant cynomolgus monkeys, subcutaneous doses of 0.015, 0.075, and 0.15 mg/kg twice weekly (1.9-, 9.9-, and 29-fold the MRHD) were administered from gestation day 16 to 50. Pharmacologically mediated, marked initial maternal body weight loss and reductions in body weight gain and food consumption coincided with the occurrence of sporadic abnormalities (vertebra, sternebra, ribs) at ≥ 0.075 mg/kg twice weekly ($>9X$ human exposure).

In a pre- and postnatal development study in pregnant cynomolgus monkeys, subcutaneous doses of 0.015, 0.075, and 0.15 mg/kg twice weekly (1.3-, 6.4-, and 14-fold the MRHD) were administered from Gestation Day 16 to 140. Pharmacologically mediated marked initial maternal body weight loss and reductions in body weight gain and food consumption coincided with an increase in early pregnancy losses and led to delivery of slightly smaller offspring at ≥ 0.075 mg/kg twice weekly ($>6X$ human exposure).

Salcaprozate sodium (SNAC), an absorption enhancer in TRADENAME, crosses the placenta and reaches fetal tissues in rats. In a pre- and postnatal development study in pregnant Sprague Dawley rats, SNAC was administered orally at 1,000 mg/kg/day ((approximately 39-fold the MRHD based on mg/body surface area) on gestation day 7 through lactation day 20. An increase in gestation length, an increase in the number of stillbirths and a decrease in pup viability were observed.

8.2 Lactation

Risk Summary

There are no data on the presence of semaglutide in human milk, the effects on the breastfed infant, or the effects on milk production. Semaglutide was present in the milk of lactating rats. SNAC and/or its metabolites concentrated in the milk of lactating rats. When a substance is present in animal milk, it is likely that the substance will be present in human milk (*see Data*). There are no data on the presence of SNAC in human milk. Since the activity of UGT2B7, an

enzyme involved in SNAC clearance, is lower in infants compared to adults, higher SNAC plasma levels may occur in neonates and infants. Because of the potential for serious adverse reactions in the breastfed infant due to possible accumulation of SNAC from breastfeeding and because there are alternative formulations of semaglutide that can be used during lactation, advise patients that breastfeeding is not recommended during treatment with TRADENAME.

Data

In lactating rats, semaglutide was detected in milk at levels 3-12 fold lower than in maternal plasma. SNAC and/or its metabolites were detected in milk of lactating rats following a single maternal administration on lactation day 10. Levels of and its metabolites in milk were approximately 2-12 fold higher than those found in maternal plasma.

8.3 Females and Males of Reproductive Potential

Discontinue TRADENAME at least 2 months before a planned pregnancy due to the long washout period for semaglutide [*see Use in Specific Populations (8.1)*].

17 PATIENT COUNSELING INFORMATION

Pregnancy

Advise a pregnant woman of the potential risk to a fetus. Advise women to inform their healthcare provider if they are pregnant or intend to become pregnant [*see Use in Specific Populations (8.1)*].

Lactation

Advise females not to breastfeed during treatment with TRADENAME [*see Use in Specific Populations (8.2)*].

Females and Males of Reproductive Potential

Discontinue TRADENAME at least 2 months before a planned pregnancy due to the long washout period for semaglutide [*see Use in Specific Populations (8.3)*].

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/s/

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**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy**

PATIENT LABELING REVIEW

Date: August 28, 2019

To: Lisa Yanoff, MD
Acting Director
**Division of Metabolism and Endocrinology Products
(DMEP)**

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)

Marcia Williams, PhD
Team Leader, Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Maria Nguyen, MSHS, BSN, RN
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Samantha Bryant, PharmD, BCPS
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: Review of Patient Labeling: Medication Guide (MG)

Drug Name (established name): TRADENAME (semaglutide)

Dosage Form and Route: tablets, for oral use

Application Type/Number: NDA 213051

Applicant: Novo Nordisk, Inc.

1 INTRODUCTION

On March 20, 2019, Novo Nordisk, Inc., submitted for the Agency's review a New Drug Application (NDA) 213051 TRADENAME (semaglutide) tablets, for oral use. The proposed indication is for treatment as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Metabolism and Endocrinology Products (DMEP) on April 8, 2019, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for TRADENAME (semaglutide) tablets, for oral use.

2 MATERIAL REVIEWED

- Draft TRADENAME (semaglutide) tablets MG received on March 20, 2019, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on August 26, 2019.
- Draft TRADENAME (semaglutide) Prescribing Information (PI) received on March 20, 2019, revised by the Review Division throughout the review cycle, and received by DMPP on August 26, 2019.
- Approved OZEMPIC (semaglutide) injection, for subcutaneous use, labeling dated December 5, 2017.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss.

In our collaborative review of the MG we:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20

- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the MG is consistent with the approved labeling where applicable.

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

4 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

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DMPP-OPDP review of semaglutide (TRADENAME) NDA 213051 MG

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**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion**

*****Pre-decisional Agency Information*****

Memorandum

Date: August 28, 2019

To: Peter Franks, Regulatory Project Manager
Division of Metabolism and Endocrinology Products (DMEP)

Monika Houstoun, Associate Director for Labeling, (DMEP)

From: Samantha Bryant, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Twyla Thompson, Acting Team Leader, OPDP

Subject: OPDP Labeling Comments for semaglutide tablets, for oral use

NDA: 213051

In response to DMEP's consult request dated April 5, 2019, OPDP has reviewed the proposed product labeling (PI), Medication Guide, and carton and container labeling for the original NDA submission for semaglutide tablets, for oral use.

PI and Medication Guide: OPDP's comments on the proposed labeling are based on the draft PI received by electronic mail from DMEP (Peter Franks) on August 23, 2019, and are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review will be completed, and comments on the proposed Medication Guide will be sent under separate cover.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling received by electronic mail from DMEP on August 27, 2019, and we do not have any comments.

Thank you for your consult. If you have any questions, please contact Samantha Bryant at (301) 348-1711 or Samantha.Bryant@fda.hhs.gov.

44 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

SAMANTHA E BRYANT
08/28/2019 09:31:47 AM

Clinical Inspection Summary

Date	8/14/2019
From	Cynthia F. Kleppinger, M.D., Senior Medical Officer Min Lu, M.D., M.P.H., Acting Team Leader Kassa Ayalew, M.D., M.P.H., Branch Chief Good Clinical Practice Assessment Branch (GCPAB) Division of Clinical Compliance Evaluation (DCCE) Office of Scientific Investigations (OSI)
To	Andreea (Ondina) Lungu, M.D., Clinical Reviewer Mitra Rauschecker, M.D., Clinical Team Leader Peter Franks, M.S., Regulatory Project Manager Division of Metabolism and Endocrinology Products (DMEP)
NDA	213051; 213182; 209637/s003
Applicant	Novo Nordisk Inc.
Drug	Semaglutide
NME	Yes
Therapeutic Classification	Antidiabetic Agents, Non-Insulin (3031400)
Proposed Indication	As an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus and to reduce the risk of major adverse cardiovascular events
Consultation Request Date	4/26/2019
Summary Goal Date	8/15/2019
Action Goal Date	9/20/2019
PDUFA Date	9/20/2019

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The inspection for this new drug application (NDA) consisted of five domestic and five foreign clinical sites covering three studies.

In general, based on the inspections of the ten clinical sites, the inspectional findings support validity of data as reported by the sponsor under this NDA.

All classifications are considered preliminary until the final communication letter is sent to the inspected entity. An inspection summary addendum will be generated if conclusions change upon receipt and review of the pending Establishment Inspection Reports.

II. BACKGROUND

Novo Nordisk submitted an original new drug application (NDA 213051) for Rybelsus® (semaglutide) tablets indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes. If approved, this would be the first glucagon-like peptide-1 (GLP-1) receptor agonist in a pill form.

Novo Nordisk is also seeking an indication for Rybelsus® to reduce the risk of major adverse cardiovascular events (cardiovascular death, nonfatal myocardial infarction or non-fatal stroke) in adults with type 2 diabetes mellitus and established cardiovascular disease (b) (4)

The NDA to support this indication was also filed on March 20, 2019 and has an NDA number of 213182. The once-a-week injectable form of semaglutide was approved in December 2017 and is sold as Ozempic®. Outcome data was also submitted to NDA 209637/S-003.

Inspections were requested for three studies:

NN9924-4221 A trial investigating the cardiovascular safety of oral semaglutide in subjects with type 2 diabetes – PIONEER 6

This was a randomized, double-blind, placebo-controlled, multinational, multi-center, cardiovascular outcomes trial (CVOT) designed to assess the cardiovascular safety of oral semaglutide versus placebo when added to standard-of-care in subjects with type 2 diabetes at high risk of cardiovascular events. The primary endpoint is time from randomization to first occurrence of a MACE composite endpoint consisting of: cardiovascular death, non-fatal myocardial infarction or non-fatal stroke.

The trial was conducted at 214 sites in 21 countries. A total of 3418 subjects were screened, 3183 subjects were randomized, and 3172 subjects completed the study. The trial began January 17, 2017 and concluded September 25, 2018, with database lock as of November 2, 2018.

NN9924-4222 Efficacy and long-term safety of oral semaglutide versus sitagliptin in subjects with type 2 diabetes – PIONEER 3

The trial was a 78-week, randomized, double-blind, double-dummy, active-controlled, trial with four arms comparing the efficacy and safety of oral semaglutide 3 mg, 7 mg and 14 mg once-daily with sitagliptin 100 mg once-daily. Randomized trial product was given with metformin alone or in combination with a sulphonylurea. The primary endpoint was change from baseline to Week 26 in HbA1c.

The trial was conducted at 206 sites in 14 countries. There were 2463 subjects screened, 1864 subjects randomized, and 1566 subjects completed the trial. The trial began February 15, 2016 and concluded March 28, 2018. Database lock was May 29, 2018.

NN9924-4233 A 26-week, randomized, double-blind, placebo-controlled trial to investigate the efficacy and safety of oral semaglutide vs placebo in subjects with type 2 diabetes mellitus treated with diet and exercise only – PIONEER 1

This was a randomized, double-blind, placebo-controlled multinational, multi-center efficacy and safety trial with a 26-week treatment period (including an 8-week dose escalation period) and a 5-week follow-up period. Eligible subjects had to have been treated with diet and exercise for at least 30 days and not received anti-diabetic medication at least 90 days prior to screening. The primary endpoint was change from baseline to Week 26 in HbA1c.

The trial was conducted at 93 sites in 9 countries. In total, 1006 subjects were screened, 703 subjects were randomized, and 663 subjects completed the trial. The trial began September 20, 2016 and concluded December 8, 2017. Database lock was January 30, 2018.

III. RESULTS (by Site):

NOTE: Site inspections focused on review of informed consent documents (ICDs), institutional review board (IRB)/ ethics committee (EC) correspondences, 1572s/investigator agreements, financial disclosures, training records, CVs and licenses, delegation of duties, monitoring logs and reports, inclusion/exclusion criteria, enrollment logs, subject source documents including medical history records, drug accountability, concomitant medication records, and adverse event reports. Source records were compared to the sponsor's data line listings that were submitted with the application.

1. Freddy Goldberg Eliaschewitz, M.D.

Avenida Angélica, 2162 Higienópolis São Paulo, Sao Paulo 01228-200, Brazil

Study: NN9924-4221

Site Number: 160

Study: NN9924-4222

Site Number: 480

Dates of inspection: August 5 – 9, 2019

For Study NN9924-4221, there were 116 subjects screened and 101 subjects enrolled into the study; 99 subjects completed the study. (The study ended at the site before all subjects completed all study visits due to the sponsor closing the study for meeting the required number of subjects with endpoint criteria). Two subjects died. There were 45 subject records reviewed.

For Study NN9924-4222, there were 35 subjects screened and 23 subjects enrolled into the study; 23 subjects completed the study (one subject ended treatment with the study drug early due to a serious adverse event but remained in the study). There were 35 subject records reviewed.

All enrolled subjects had corresponding source study records and signed informed consents. The records were organized and legible. Source documents were compared against the sponsor data line listings. No discrepancies were noted. The primary endpoint was verifiable. There was no under-reporting of adverse events.

The full Establishment Inspection Report was not available for review. Preliminary inspection results were communicated by the FDA ORA field investigator.

The inspection revealed adequate adherence to the regulations and the investigational plan. There were no objectionable conditions noted and no Form FDA-483, Inspectional Observations, issued.

2. Yasushi Fukushima, M.D.
3-3-11 Nihombashi, Chuo-ku, Tokyo 103-0027, Japan

Study: NN9924-4233
Site Number: 804

Dates of inspection: July 22 – 26, 2019

There were 20 subjects screened and 20 subjects enrolled into the study; 19 subjects completed the study. One subject discontinued the study drug early due to an adverse event (Subject (b) (6)) but completed the subsequent study visits and procedures. There were 20 subject records reviewed.

All enrolled subjects had corresponding source study records and signed informed consents. The records were organized and legible. Additionally, the site had visit notes that supplemented the study records that were printed and signed/dated by the investigator (showing his review date) and placed in the study binders. These notes were generated electronically and showed the name of the investigator who entered the information but not an electronic signature and date/time stamp, although this information was available in the electronic medical records system and confirmed. Source documents were compared against the sponsor data line listings. Minor discrepancies were noted (one transcription error [blood pressure] and one example where a hypoglycemic episode was not reported [Subject (b) (6)]). The primary endpoint was verifiable. There was no under-reporting of adverse events.

The full Establishment Inspection Report was not available for review. Preliminary inspection results were communicated by the FDA ORA field investigator.

The inspection revealed adequate adherence to the regulations and the investigational plan. There were no objectionable conditions noted and no Form FDA-483, Inspectional Observations, issued.

3. Satoshi Inoue, M.D., Ph.D.
4-12-11 Kasuga Suita-shi, Osaka 565-0853, Japan

Study: NN9924-4233
Site Number: 806

Dates of inspection: July 29 – August 2, 2019

There were 33 subjects screened and 29 subjects enrolled into the study; 27 subjects completed the study. Two subjects discontinued the study drug early due to adverse events but completed their subsequent study visits and procedures. There were 33 subject records reviewed.

All enrolled subjects had corresponding source study records and signed informed consents. The records were organized and legible. Source documents were compared against the sponsor data line listings. No discrepancies were noted. The primary endpoint was verifiable. There was no under-reporting of adverse events.

The full Establishment Inspection Report was not available for review. Preliminary inspection results were communicated by the FDA ORA field investigator.

The inspection revealed adequate adherence to the regulations and the investigational plan. There were no objectionable conditions noted and no Form FDA-483, Inspectional Observations, issued.

4. Adriana Gabriela Onaca, M.D.
Republicii nr. 32 Oradea, Bihor 410025, Romania

Study: NN9924-4222
Site Number: 209

Study: NN9924-4221
Site Number: 532

Dates of inspection: July 29 – August 8, 2019

For Study NN9924-4222, there were 18 subjects screened and 18 subjects enrolled into the study; 15 subjects completed the study. There were 18 subject records reviewed.

For Study NN9924-4221, there were 25 subjects screened and 25 subjects enrolled into the study; 25 subjects completed the study. There were 25 subject records reviewed.

All enrolled subjects had corresponding source study records and signed informed consents. The records were organized and legible. Source documents were compared against the sponsor data line listings. A few minor discrepancies were noted (such as lack of source for a waist

circumference and one missing lab report). The primary endpoint was verifiable as well as all secondary endpoints. There was no under-reporting of adverse events. There were no MACE events for PIONEER 6.

The full Establishment Inspection Report was not available for review. Preliminary inspection results were communicated by the FDA ORA field investigator.

The inspection revealed adequate adherence to the regulations and the investigational plan. There were no objectionable conditions noted and no Form FDA-483, Inspectional Observations, issued.

5. Plamen Popivanov, M.D.

**University Multi-Profile Hospital for Active Treatment (UMHAT) Aaleksandrovskaa,
UMHAT Aleksandrovska, 1 Sv. Georgi Sofiyiski Str., Sofia 1431, Bulgaria**

Study: NN9924-4233

Site Number: 102

Dates of inspection: July 22 – 24, 2019

There were 20 subjects screened and 12 subjects enrolled into the study; 11 subjects completed the study. Subject ^{(b) (6)} was lost to follow-up. There were 12 subject records reviewed. A translator was present throughout the inspection.

Dr. Popivanov has been at the site since 1980. He allocates approximately 5-10% of his resources to clinical trials; 30% to associate professorship at the hospital university; and 60% to medical practice. Subjects were recruited within the hospital network and physician referrals.

The ^{(b) (4)} was the ethics committee of record.

All enrolled subjects had corresponding source study records and signed informed consents. The records were organized and legible. Source documents were compared against the sponsor data line listings. A couple minor discrepancies were noted (two eCRF transcription errors with the subject surveillance questionnaire). The primary endpoint was verifiable. There was no under-reporting of adverse events.

The full Establishment Inspection Report was submitted for review.

The inspection revealed adequate adherence to the regulations and the investigational plan. There were no objectionable conditions noted and no Form FDA-483, Inspectional Observations, issued.

6. Jeanne-Elyse Cedeño, M.D.
1601 North Palm Ave. Suite 102, Pembroke Pines, FL 33026
Study: NN9924-4233
Site Number: 753

Dates of inspection: May 22 – 30, 2019

There were 15 subjects screened and 11 subjects enrolled into the study; 10 subjects completed the study. One subject (Subject (b) (6)) was lost to follow-up. There were seven subject records reviewed.

This study was conducted by Dr. Cedeño at Family Clinical Trials. The site was established for research in 2010 by Dr. Cedeño, and the site is also utilized for her private practice where she practices as a family physician. The subjects for this study were either patients of Dr. Cedeño or a local referring physician.

(b) (4) was the IRB of record.

All enrolled subjects had corresponding source study records and signed informed consents. The records were organized and legible. Source documents were compared against the sponsor data line listings. Discrepancies were noted (as discussed below). The primary endpoint was verifiable. There was no under-reporting of adverse events.

The full Establishment Inspection Report was submitted for review.

At the conclusion of the inspection, a Form FDA-483, Inspectional Observations, was issued for failure to prepare or maintain adequate and accurate case histories with respect to observations and data pertinent to the investigation and informed consent. Specifically, the protocol required Patient Reported Outcome (PRO) questionnaires be completed and transcribed into the electronic data capture system (EDC). Each subject was required to be administered a PRO questionnaire at Visit 2 (Randomization), Visit 5 (During Treatment Phase), and Visit 8 (End of Treatment). A total of 62 questions were to be answered at Visit 1 and Visit 8; and 60 questions were to be answered at Visit 5. Of the 10 subjects that completed the study, there were a total of 1951 answers completed in the questionnaires. Each entry was transcribed by the Study Coordinators to the EDC. However, when comparing 100% of the source documents to the eCRF records, a total of 96 discrepancies were observed across 7 of the 10 subjects.

OSI Reviewer Comment: The monitoring plan was risk-based and did not include 100% data verification. The total percentage of discrepancies compared to datapoints total is low. Of the 1951 answers, 96 (4.9%) had discrepancies between the source document and the CRF. Except for the PRO data, there were no other discrepancies during the data verification comparing source and EDC data.

Dr. Cedeno responded to the inspectional observations with acknowledgement of the discrepancies. The root cause for the observation was the entry of responses from a Spanish PRO

questionnaire into an English eCRF. The alignment of the response choices, horizontally for the Spanish PRO and vertically for the eCRF, caused confusion. Additionally, no adequate quality control (QC) process was in place. A second quality review of all data has been implemented and includes a verified signature confirming the review took place for all ongoing trials.

Although regulatory violations were noted as described above, they are unlikely to significantly impact primary safety and efficacy analyses. Data from this site appear acceptable.

7. Charles Lovell, M.D.
142 W. York St., Suite 905, Norfolk, VA 23510-2015

Study: NN9924-4221
Site Number: 812

Study: NN9924-4233
Site Number: 735

Dates of inspection: July 29 – August 2, 2019

For Study NN9924-4221, there were 26 subjects screened and 22 subjects enrolled into the study; 21 subjects completed the study. There were 9 subject records reviewed.

For Study NN9924-4233, there were 4 subjects screened and 2 subjects enrolled into the study; one subject completed the study. There were 4 subject records reviewed.

All enrolled subjects had corresponding source study records and signed informed consents. The records were organized and legible. Source documents were compared against the sponsor data line listings. No discrepancies were noted. The primary endpoint was verifiable. There was no under-reporting of adverse events. It was noted that the cholesterol laboratory units were provided in mmol/L in the data line listing; however, the source records were reported using mg/dL. These cholesterol laboratory test results had to be verified manually by converting mg/dL to mmol/L using methods provided from internet searches.

The full Establishment Inspection Report was not available for review. Preliminary inspection results were communicated by the FDA ORA field investigator.

The inspection revealed adequate adherence to the regulations and the investigational plan. There were no objectionable conditions noted and no Form FDA-483, Inspectional Observations, issued.

8. Ildiko Lingvay, M.D.
5323 Harry Hines Blvd, Suite G4.100, Dallas, TX 75390-9302

Study: NN9924-4221

Site Number: 862

Study: NN9924-4222
Site Number: 856

Dates of inspection: July 1 – 12, 2019

For Study NN9924-4221, there were 25 subjects screened and 23 subjects enrolled into the study; 23 subjects completed the study. There were 23 subject records reviewed.

For Study NN9924-4222, there were 25 subjects screened and 13 subjects enrolled into the study; 9 subjects completed the study. Four subjects did not return for the final visit. There were 25 subject records reviewed.

All enrolled subjects had corresponding source study records and signed informed consents. The records were organized and legible. Source documents were compared against the sponsor data line listings. No discrepancies were noted. The primary endpoint was verifiable. There was no under-reporting of adverse events.

The full Establishment Inspection Report was not available for review. Preliminary inspection results were communicated by the FDA ORA field investigator.

The inspection revealed adequate adherence to the regulations and the investigational plan. There were no objectionable conditions noted and no Form FDA-483, Inspectional Observations, issued.

9. Zeeshan Shaikh
5900 Chimney Rock Road, Suite X, Houston, TX 77081

Study: NN9924-4222
Site Number: 879

Dates of inspection: July 11 – 19, 2019

There were 28 subjects screened and 19 subjects enrolled into the study; 18 subjects completed the study. There were 12 subject records reviewed. Of note, one of the subjects was a transfer from another site in May 2017.

Dr. Zeeshan Shaikh works at SW Clinical Trials Research. She was on extended vacation in Pakistan and not present during the inspection. The research coordinators involved with the study were no longer employed at the firm. The study closed a year ago at the site and the documents had to be retrieved from storage. The Office Manager provided the documents and was in touch with Dr. Shaikh regarding any questions during the inspection.

All enrolled subjects had corresponding source study records and signed informed

consents. The records were organized and legible. Source documents were compared against the sponsor data line listings. No discrepancies were noted. The primary endpoint was verifiable. There was no under-reporting of adverse events.

The full Establishment Inspection Report was not available for review. Preliminary inspection results were communicated by the FDA ORA field investigator.

The inspection revealed adequate adherence to the regulations and the investigational plan. There were no objectionable conditions noted and no Form FDA-483, Inspectional Observations, issued.

10. Eileen M. Palace, Ph.D.

3500 N. Causeway Blvd. Suite 1145, Metairie, LA 70002

Study: NN9924-4222

Site Number: 870

Study: NN9924-4233

Site Number: 727

Dates of inspection: June 10 – 13, 2019

For Study NN9924-4222, there were 28 subjects screened and 24 subjects enrolled into the study; 14 subjects completed the study (eight subjects withdrew consent, one was lost to follow-up and one terminated early). There were 28 subject records reviewed.

For Study NN9924-4233, there were 7 subjects screened and 5 subjects enrolled into the study; 3 subjects completed the study (one subject withdrew consent and one terminated early). There were 7 subject records reviewed.

Although Dr. Palace was the Principal Investigator at the site, she is a family therapist and not a physician; all the study procedures were done by her sub-investigator who was a physician. After the study closed at the site, the sub-investigator died. Dr. Palace then closed her site to clinical research and transferred all study files to the sponsor. The sponsor arranged to have the records shipped for review by the FDA ORA inspector. Dr. Palace and a sponsor representative were available for any questions.

None of the subjects were patients at the site and all were seen by private physicians for their medical care. All enrolled subjects had corresponding study records and signed informed consents. The records were organized and legible. Source documents were compared against the sponsor data line listings. No discrepancies were noted. The primary endpoint was verifiable. There was no under-reporting of adverse events.

The full Establishment Inspection Report was not available for review. Preliminary inspection results were communicated by the FDA ORA field investigator.

The inspection revealed adequate adherence to the regulations and the investigational plan. There were no objectionable conditions noted and no Form FDA-483, Inspectional Observations, issued.

{See appended electronic signature page}

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/s/

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LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	August 2, 2019
Requesting Office or Division:	Division of Metabolism and Endocrinology Products (DMEP)
Application Type and Number:	NDA 213051
Product Name and Strength:	Rybelsus (semaglutide) tablet, 3 mg, 7 mg, and 14 mg
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Novo Nordisk Inc. (Novo)
FDA Received Date:	March 20, 2019
OSE RCM #:	2019-643
DMEPA Safety Evaluator:	Ariane O. Conrad, PharmD, BCACP, CDE
DMEPA Team Leader:	Hina Mehta, PharmD

1 REASON FOR REVIEW

This review evaluates the proposed labels and labeling for Rybelsus (semaglutide), submitted under NDA 213051 on March 20, 2019, to determine if they are acceptable from a medication error perspective.

Novo Nordisk currently markets Ozempic (semaglutide) injection which is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes (NDA 209637). The Applicant proposes to introduce a tablet dosage form of semaglutide (under the proprietary name Rybelsus^a) for the treatment of type 2 diabetes (NDA 213051).

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	N/A
ISMP Newsletters*	N/A
FDA Adverse Event Reporting System (FAERS)*	N/A
Other	N/A
Labels and Labeling	C

N/A=not applicable for this review

*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance.

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Novo submitted a risk management analysis for semaglutide (under IND 114464) on April 17, 2018 for Agency concurrence that a human factors validation study was not necessary for the proposed semaglutide blister packs. Our review concluded that the Applicant adequately

^a Conrad A. Proprietary Name Review for Rybelsus (IND 114464, NDA 213051, NDA 213182). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US): 2019 May 8. RCM No.: 2018-27266112, 2019-30202491, 2019-30252981.

considered the risks associated with the proposed product packaging and we agreed that a human factors validation study was not indicated.^b

We performed a risk assessment of the proposed prescribing information (PI), medication guide, and blister pack carton labeling to identify areas of vulnerability that may lead to medication errors and other areas of improvement. We note Novo is proposing a professional sample for the 3 mg tablet strength only. We noted areas that could be clarified within the proposed labels and labeling, and we provide recommendations in Section 4.1 and Section 4.2.

4 CONCLUSION & RECOMMENDATIONS

The proposed labels and labeling for Rybelsus are not acceptable from a medication error perspective and we have provided recommendations to improve clarity below in Sections 4.1 and 4.2.

4.1 RECOMMENDATIONS FOR THE DIVISION

A. Prescribing Information

1. Highlights of Prescribing Information: Dosage and Administration

a. We recommend revising this section as follows for improved clarity:

- “Start at 3 mg once daily for 30 days then increase to 7 mg once daily. Dose may be increased to 14 mg once daily if additional glycemic control needed after 30 days on 7 mg.
- Administer with no more than 4 ounces of water on an empty stomach at least 30 minutes before first food, beverage, or other medications of the day.
- Swallow tablets whole. Do not cut, crush, or chew tablets.”

2. Full Prescribing Information: Section 2 Dosage and Administration

a. We recommend revising this section as follows for improved clarity:

- “Start RYBELSUS at a dose of 3 mg once daily for 30 days then increase to 7 mg once daily. Dose may be increased to 14 mg once daily if additional glycemic control is needed after 30 days on 7 mg.
- RYBELSUS must be administered on an empty stomach with no more than 4 ounces of water at least 30 minutes before first food, beverage, or other medications of the day.

^b Conrad A. Human Factors Use-Related Risk Analysis Review for semaglutide (IND 114464). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US): 2019 Jun 11. RCM No.: 2017-251-1.

- Waiting less than 30 minutes or drinking more than 4 ounces of water may impact the effect of RYBELSUS.
 - RYBELSUS should be swallowed whole. Do not split, crush, or chew tablets.
 - If a dose is missed, the missed dose should be skipped, and the next dose should be taken the following day."
3. Full Prescribing Information: Section 16 How Supplied/Storage and Handling Section

- a. We recommend revising the "How Supplied" information as follows for improved clarity:

"RYBELSUS is available as follows:

Tablet Strength	Description	Package Configuration	NDC No.
3 mg	White to light yellow, oval shaped debossed with "3" on one side and "novo" on the other side	Carton of 30 tablets (3 x 10 count blister packs)	0169-4303-13
7 mg	White to light yellow, oval shaped debossed with "7" on one side and "novo" on the other side	Carton of 30 tablets carton (3 x 10 count blister packs)	0169-4307-13
14 mg	White to light yellow, oval shaped debossed with "14" on one side and "novo" on the other side	Carton of 30 tablets (3 x 10 count blister packs)	0169-4314-13

- b. We recommend combining the "Storage" and "Handling" information as follows for improved clarity: "Store at 68° to 77°F (20 to 25°C); excursions permitted to 59° to 86°F (15° to 30°C) [see USP Controlled Room Temperature]. Store and dispense blister packs in the original carton to protect from moisture."

4.2 RECOMMENDATIONS FOR NOVO NORDISK INC. (NOVO)

We recommend the following be implemented prior to approval of this NDA:

A. General Comments (Inner and Outer Carton Labeling-Trade)

1. To ensure consistency with the Prescribing Information, revise the statement, “(b) (4)” to read “Recommended Dosage: See prescribing information.” per 21 CFR 201.55.
2. Decrease the prominence of the statement “Rx only” by removing the bold font so that it is less prominent than other important information on the label.
3. As currently presented, the format for the expiration date is not defined. To minimize confusion and reduce the risk for deteriorated drug medication errors, identify the format you intend to use. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or a space be used to separate the portions of the expiration date.

B. Inner Carton Labeling-Trade

1. We recommend revising the tablet strength to read “3 mg (7 mg or 14 mg as applicable) per tablet” in the colored box for improved clarity that the labeled strength is per unit. We also recommend removing the “3 mg (7 mg or 14 mg)” notation under the established name as it appears redundant.
2. We recommend removing the statements “once daily” as frequency of administration is not required on the Principal Display Panel (PDP).
3. We recommend removing the statement (b) (4) from the PDP for improved clarity of the label.
4. We recommend revising the directions provided on the inner flaps as noted below for improved clarity and for consistency with the prescribing information. In addition, we recommend that you consider removing the images noted for each statement as they do not clearly depict the warning.

“Keep tablet in the blister pack until you are ready to take it.

Push tablet out of blister. Do not cut from the packaging.

Swallow tablet whole. Do not cut, crush, or chew.”

“Take on an empty stomach when you first wake up.

Take with no more than 4 ounces of water.

Wait 30 minutes before eating, drinking, or taking other medications.”

C. Outer Carton Labeling-Trade

1. We recommend adding the statement “Dispense the Enclosed Medication Guide to Each Patient” to the principal display panel per 21 CFR 208.24(d).
2. In September 2018, FDA released draft guidance on product identifiers required under the Drug Supply Chain Security Act.¹ The Act requires manufacturers and repackagers, respectively, to affix or imprint a product identifier to each package and homogenous case of a product intended to be introduced in a transaction in(to) commerce beginning November 27, 2017 and November 27, 2018, respectively. We recommend that you review the draft guidance to determine if the product identifier requirements apply to your product’s labeling. The draft guidance is available from: <https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm621044.pdf>.
3. We recommend revising the “Directions for Use” as follows for consistency with the prescribing information and the inner carton labeling:

“Take on an empty stomach when you first wake up, with no more than 4 ounces of water. Wait 30 minutes before eating, drinking, or taking other medications.”

D. Inner Carton Labeling-Professional Sample

1. See comments B1 through B4.
2. We recommend increasing the size of the statement “Sample. Not for Resale” so that it is clearly identified as a product sample.
3. We recommend adding the following Usual Dose statement: “Usual dose: 1 tablet daily at least 30 minutes before first food, beverage, or other medications of the day.”

E. Outer Carton Labeling-Professional Sample

1. See comments C1 through and C4.
2. We recommend increasing the size of the statement “Sample. Not for Resale” so that it is clearly identified as a product sample.
3. Decrease the prominence of the statement “Rx only” by removing the bold font so that it is less prominent than other important information on the label.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Rybelsus received on March 20, 2019 from Novo Nordisk Inc. (Novo), and Ozempic.

Table 2. Relevant Product Information for Rybelsus and Ozempic		
Product Name	Rybelsus	Ozempic ^c (NDA 209637)
Initial Approval Date	N/A	December 5, 2017
Active Ingredient	semaglutide	
Indication	adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes	
Route of Administration	Oral	Subcutaneous
Dosage Form	tablet	injection
Strength	3 mg, 7 mg, and 14 mg	2 mg per 1.5 mL (1.34 mg/mL) and 4 mg per 3 mL (1.34 mg/mL)
Dose and Frequency	<ul style="list-style-type: none"> • 3 mg, 7 mg or 14 mg by mouth once daily at least 30 minutes before first food, beverage, or other medications • 3 mg once daily for 1 month, then increase to 7 mg daily. If additional benefit is needed after 1 month on the 7 mg dose, then can increase to 14 mg daily. • The maximum daily dose is 14 mg 	<ul style="list-style-type: none"> • Inject subcutaneously in the abdomen, thigh, or upper arm once weekly at any time of the day, with or without meals • 0.25 mg once weekly then increase to 0.5 mg once weekly after 4 weeks; if after 4 weeks on the 0.5 mg dose, increase to 1 mg once weekly
How Supplied	<ul style="list-style-type: none"> • Trade Packs: 30-day supply (3x10) of 3 mg, 7 mg, or 14 mg blister pack • Sample Pack:30-day supply (3x10) of 3 mg in blister pack 	Single use pens containing a total of 2 mg/1.5 mL and delivers <ul style="list-style-type: none"> • 0.25 mg or 0.5 mg per injection <u>OR</u> • 1 mg per injection

^c Ozempic [Prescribing Information]. Drugs@FDA. U.S. Food and Drug Administration. 2019 Apr. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/209637s001lbl.pdf.

		<p>Single use pen containing a total of 4 mg/3 mL and delivers</p> <ul style="list-style-type: none"> • 1 mg per injection
Storage	<p>Store at 68°-77°F (20-25°C); excursions permitted to 59°-86°F (15°-30°C) [see USP Controlled Room Temperature]</p>	<p><u>Prior to first use:</u> Refrigerated 36°F to 46°F (2°C to 8°C) until expiration date</p> <p><u>After first use:</u> Room Temperature 59°F to 86°F (15°C to 30°C) OR Refrigerated 36°F to 46°F (2°C to 8°C) for up to 56 days</p>
Container Closure	Blister packs	pre-filled, disposable, single-patient-use pens

APPENDIX B. PREVIOUS DMEPA REVIEWS

On July 9, 2019, we searched for previous DMEPA reviews relevant to this current review using the terms, “semaglutide and 114464” and “semaglutide and 213051”. Our search identified 1 previous review^d.

^d Conrad A. Human Factors Use Related Risk Analysis Review for semaglutide (IND 114464). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 June 11. RCM No.: 2017-251-1.

APPENDIX C. LABELS AND LABELING

C.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,^e along with postmarket medication error data, we reviewed the following Rybelsus labels and labeling submitted by Novo Nordisk Inc. (Novo).

- Carton labeling received on March 20, 2019
- Professional Sample Carton Labeling received on March 20, 2019
- Medication Guide received on March 20, 2019
 - NDA 213051: <\\cdsesub1\evsprod\nda213051\0001\m1\us\prop-med-guide.pdf>
- Prescribing Information received on March 20, 2019
 - NDA 213051: <\\cdsesub1\evsprod\nda213051\0001\m1\us\prop-pi.pdf>

C.2 Label and Labeling Images

^e Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

ARIANE O CONRAD
08/02/2019 12:27:23 PM

MISHALE P MISTRY on behalf of HINA S MEHTA
08/05/2019 07:57:28 AM

NDA: 213051

Subject: Immunogenicity review memo –Once daily, oral Semaglutide tablets indicated as an adjunct to diet and exercise to improve glycemic control in type 2 diabetes mellitus patients.

Review Date: 7/25/2019

PDUFA due Date: 09/20/2019

Primary Reviewer: Mohanraj Manangeeswaran, Ph.D

Secondary Reviewer: Daniela Verthelyi, M.D., Ph.D

Applicant: Novo Nordisk Inc

Associated IND: 114464

Proposed Proprietary Name: Rybelsus

Nonproprietary Name: Semaglutide

Dosage form: oral tablets

Indication: Treatment of patients with type 2 diabetes mellitus

Clinical Division: OND/ODEII/DMEP

RPM: Peter Franks

1. Recommendation:

New drug application for oral Semaglutide (Rybelsus) is recommended for approval from an immunogenicity standpoint. However, given deficiencies in the assay developed to assess neutralizing activity, PMRs are recommended to address the development of a suitable assay to assess neutralizing activity of anti-semaglutide antibodies and to assess the incidence of neutralizing antibodies in the treated population to semaglutide and to native GLP-1.

PMC 1 : The assay used to monitor neutralizing activity of anti-drug antibodies is not sensitive. Develop a sensitive assay to assess the neutralizing activity of anti-semaglutide antibodies and its cross-neutralizing effect on native GLP-1.

PMC 2: Assess the incidence of neutralizing antibodies to semaglutide and GLP-1 in subjects treated with Semaglutide. The samples can be derived from pre-existing clinical studies, but a plan to select the samples should be agreed upon with the Agency.

2. Executive summary:

The sponsor conducted studies to assess the immunogenicity of oral Semaglutide. The screening and confirmatory assays used in monitoring the ADA response were validated and found suitable for their intended purpose, however the assay used to assess neutralizing activity was found to lack sensitivity. The clinical studies included three phase I multiple dose trials (Trials 3692, 3991 and 4140), single phase 2 dose finding trial (Trial 3790) and 6 phase 3a trials (Trials PIONEER 1-5 and Pioneer 9) that collectively assessed the incidence of ADA in 2800 subjects who were treated with oral semaglutide. Fourteen subjects out of 2800 subjects (0.5%) tested positive for anti-semaglutide antibodies at any point post baseline. Approximately 52% (11 out of 21) of the samples testing positive for anti-semaglutide antibody showed cross-reactivity with endogenous GLP- 1. Titers of anti-semaglutide antibodies in confirmed positive subjects with ADA are generally low. Only one sample in PIONEER 1 trial had a % B/T value of 25 corresponding to approximately 700ng/mL of anti-semaglutide antibodies. No impact on PK, PD, safety or efficacy was evident in samples that contained anti-semaglutide antibodies. Regarding the neutralizing capacity of ADA, a single sample in PIONEER1 was identified as containing neutralizing antibodies, and it corresponded to the sample that had %B/T value of 25. Samples from the same subject at later time points had lower titers of binding antibodies and was negative for neutralizing antibodies suggesting that the assay cannot identify low titer NAB samples. The low sensitivity of the neutralizing assay was discussed with the sponsor. The sponsors have developed a new assay that is less sensitive to masking due to on-board drug. A PMC will be discussed with the Sponsor regarding assessment of neutralizing antibodies.

3. Review memorandum:

Summary of drug and use in proposed indication

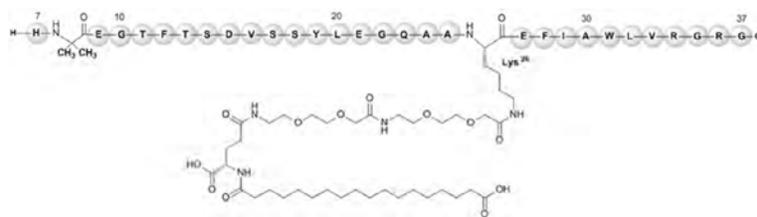
This is an original NDA submitted by Novo Nordisk Inc. on March 20, 2019, seeking a priority review for marketing approval of semaglutide tablets as an adjunct to diet and exercise to improve glycemic control in adult patients with Type 2 diabetes mellitus (T2DM). Semaglutide is proposed to be marketed under the tradename of Rybelsus.

Semaglutide is a GLP-1 receptor agonist that selectively binds to and activates the GLP-1 receptor, a target receptor for native GLP-1. The GLP-1 peptide hormone belongs to the superfamily of glucagon-related peptides. Physiologically, GLP-1 is secreted by the endocrine L-cells of the intestine in response to food intake and also by neurons of the hind brain. Secreted GLP-1 binds to GLP-1 receptor (GLP-1R) and induces glucose-dependent release of insulin as well as increased synthesis of insulin, glucokinase and glucose transporters. GLP-1 also induces glucose-dependent lowering of glucagon secretion, which in turn lowers the hepatic glucose output. Thus, GLP-1 stimulates insulin secretion and inhibits glucagon secretion in a glucose-dependent manner. Patients with T2DM have reduced response to GLP-1 but can respond to the blood glucose lowering effect of GLP-1 when administered at supraphysiological levels. In addition, GLP-1 can lower energy intake via inducing feelings of satiety and fullness and lowering feelings of hunger. GLP-1 receptors expressed in the hypothalamus and hind brain are implicated in reduced food intake. The decreased appetite, early satiety, and preference for low fat and low sugar diets may result in weight loss. GLP-1 receptor agonists are designed to mimic the effect of endogenous GLP-1. The half-life of native GLP-1 is 1.5 minutes after i.v administration and so are not suitable for therapeutic use.

Semaglutide is a long acting analogue of the endogenous GLP-1 molecule and so belongs to the GLP-1 receptor agonist class of drugs. When compared to human native GLP-1, the semaglutide molecule has 94% structural homology to native GLP-1 with three main modifications

1. Amino acid substitution at position 8 (alanine to alpha-amino isobutyric acid (Aib), a synthetic amino acid). This is expected to make semaglutide less susceptible to DPP-4 degradation.
2. Lysine to Arginine at position 34
3. Acylation of the peptide backbone with a spacer and C-18 fatty di-acid chain linked to the lysine at position 26. The fatty di-acid chain and the spacer are expected to mediate strong non-covalent binding to albumin, thereby reducing renal clearance and extending half-life of the product.

Structure of semaglutide:



The prolonged action profile of semaglutide is due to increased binding to albumin (decrease in renal clearance and protection from metabolic degradation), and an increased resistance to enzymatic degradation by dipeptidyl peptidase 4 (DPP-4) enzymes. Semaglutide is presented as white to yellow oval shaped tablets and available in three doses, 3, 7 and 14 mg tablets. Semaglutide is formulated with 300 mg Salcaprozate Sodium (SNAC) as absorption enhancer to facilitate oral absorption of the drug. Salcaprozate sodium is the sodium salt of salcaproic acid, a small fatty acid

derivative. SNAC is considered a novel excipient and toxicity studies were conducted to assess its safety.

Regulatory history:

Novo Nordisk submitted an original NDA 209637 for semaglutide once weekly (OW) subcutaneous (sc) injection indicated for glycemic control in subjects with type 2 diabetes mellitus (T2D). This NDA was approved in December 2017. The current application NDA 213051 is now seeking approval to use oral semaglutide, once daily tablet as an adjunct to diet and exercise to improve glycemic control in type 2 diabetes mellitus patients.

Past immunogenicity experience with the product class:

There are several GLP-1 receptor agonists that are commercially available. In the past, products that had low homology to human GLP-1 had high incidence of anti-drug antibodies (ADA) that associated with loss of efficacy particularly in subjects with high ADA titers, whereas those with high homology have shown low incidence of ADA that did not impact on safety and efficacy.

Products with high homology include: Liraglutide (Victoza and Saxenda), which has 97% homology to native GLP-1, have one amino acid substitution and are acylated in position 26. Dulaglutide (Trulicity) consists of dipeptidyl peptidase-IV-protected GLP-1 analogue that is covalently linked to a human IgG4-Fc heavy chain by a small peptide linker. Albiglutide (Eperzan /Tanzeum) is a GLP-1 dimer fused to human albumin. These GLP-1 RA that are human GLP-1 analogues reported low incidence of ADAs. In contrast, Exenatide (Byetta and Bydureon) and Lixisenatide which are GLP-1RA derived from peptide exendin-4 found in Gila monsters show higher immunogenicity. Lixisenatide is a GLP1-RA derived from the first 39 amino acids of exendin-4, without proline at position 38 and with six additional lysine residues. Exenatide and lixisenatide has been associated with high rates of treatment emergent ADA and also loss of efficacy in patients with high ADA titer.

The table below summarizes the past immunogenicity experience of various GLP-1RA.

Table 2–1 Marketed GLP-1 Receptor Agonists; Observed immunogenicity and impact on efficacy and safety

GLP-1 receptor agonist	Victoza ^{1,2}	Saxenda ^{3,4}	Trulicity ^{5,6}	Tanzeum ⁷ / Eperzan ⁸	Byetta ⁹	Bydureon ¹⁰	Adlyxin ¹¹ / Lyxumia ¹²
Level of ADA in Phase 3	8.6% (low titres)	2.8% (low titres)	1.6%	4%/5.5%	38% (low titres) 6% (high titres)	45% (low titres) 12 % (high titres)	70%
Level of Cross reactivity to GLP-1	5%	Few	0.9%	79% of ADA positive (~3.8%)	None	None	None
Level of in vitro neutralising ADA	1.5%	1.2%	0.9%	0%	-	-	-
Impact on efficacy	None	None	None	None	3% with highest titre had no glycaemic response	2.6% with highest titre had no glycaemic response	1.9-2.4% had an attenuated or no glycaemic response
Impact on safety		Mild injection site reactions		Mild injection site reactions	Injection site reactions	Greater incidence of Injection site reactions with higher titre	Mild injection site reactions

Reviewers comments:

Semaglutide has 94% homology to native human GLP-1. According to the past experience of ADA response in subcutaneous semaglutide (less than 2%), oral semaglutide is not expected to have high rates of ADA.

Non-Clinical studies:

Potential for oral semaglutide to elicit anti-drug antibodies was tested in four animal studies, two in rat (6 and 26 week toxicity study) and two in monkeys (6 and 17 week study). None of the animals tested positive for anti-semaglutide antibodies in these studies.

Salcaprozate sodium (SNAC)

For oral administration, oral semaglutide has been co-formulated in a tablet with an absorption enhancer Salcaprozate sodium (SNAC). It is the sodium salt of salcaproic acid, a small fatty acid derivative. The molecular weight of SNAC is 301.32 g/mol. SNAC is not a peptide and therefore does not hold immunogenic potential on its own. Immunogenicity of SNAC was not assessed in the clinical trials. Toxicity studies showed that SNAC at the doses used in semaglutide oral formulation is acceptable. SNAC was part of the formulation in different doses tested in the clinical trials. In addition, SNAC was also given alone along with placebo control in some arms. There were no serious adverse events reported in the SNAC alone treatment arm compared to placebo arm. Oral semaglutide tablets are available in three doses, 3 mg, 7 mg and 14 mg. All three tablet doses are formulated with 300 mg SNAC.

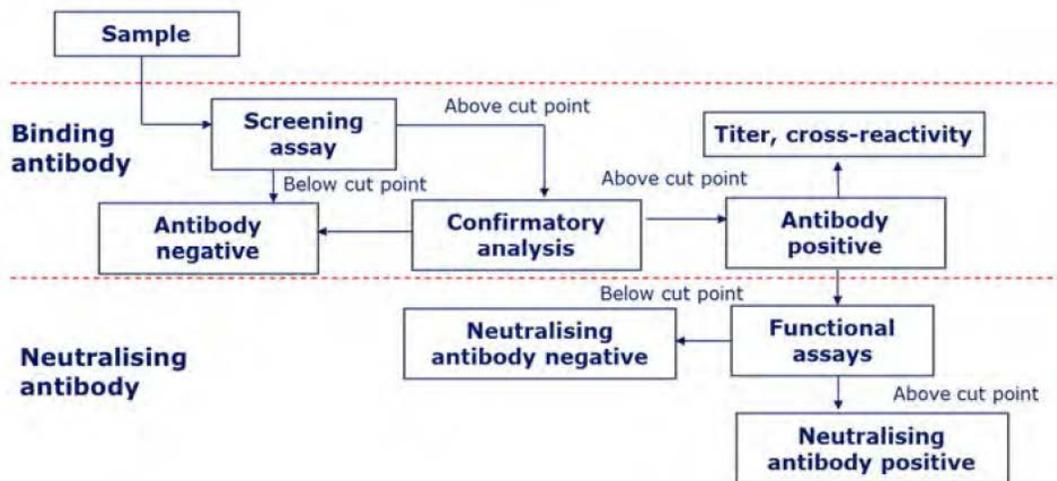
Reviewers comments: Eligen technologies, the company that is behind the use of SNAC as absorption enhancer has a B12 supplement formulated with SNAC that is commercially available.

Eligen B12 is an oral , medical food tablet indicated for the dietary management of patients who have diagnosed vitamin B12 deficiency. Each tablet contains 100 mg SNAC and need to be taken once daily on an empty stomach, at least 1 hour before a meal with about a quarter cup of water.

Although toxicity studies show that the levels of SNAC proposed are safe for human use, the mechanism of action of absorption enhancer to perturb the membrane barrier to get the drug across and the chronic use of oral semaglutide warrants more long-term studies in patient cohorts to understand the risk associated with chronic use.

ADA screening strategy:

Tiered antibody assay approach was used to monitor the development of ADA. The overview of the strategy is given below.



Assays to monitor Anti-drug antibodies:

Assays used to monitor anti-drug antibodies are the same assays previously reviewed for subcutaneous semaglutide (NDA 209637). Screening and confirmatory assays presented for NDA 209637 were found to be suitable and neutralization assay was not suitable as it lacked sensitivity. Two PMRs were issued for NDA 209637 to develop a more sensitive Neutralizing Antibody Assay and use it to assess neutralizing antibodies in the clinical samples. The PMRs are not yet fulfilled.

Given below is the list of ADA assays used during various phases of clinical trials for oral semaglutide.

Table 3-2 Antibody binding assays used during clinical development of oral semaglutide

Analysis	Method (validation study number)	Clinical Phase	Trials	Pre-treatment of samples	Validation
Anti-semaglutide antibody assay (Section 3.2.1.2)	RIA (Study 207194 [M 5.3.1.4])	Phase 1	3692 and 3991	No pre-treatment of samples	Validated by Novo Nordisk
Anti-semaglutide antibody assay (Section 3.2.1.3)	RIA (Study 212541 and 216098 [M 5.3.1.4])	Phase 1 and 2	4140 and 3790	Samples pre-treated with acid and PEG	Validated by (b) (4)
Anti-semaglutide antibody assay (Section 3.2.1.4)	RIA (Study 216142 [M 5.3.1.4])	Phase 3a	P1 4233, P2 4223, P3 4222, P4 4224, P5 4234, P9 4281	Samples pre-treated with acid and PEG	Re-validated by (b) (4)
Anti-semaglutide antibody assay (Section 3.2.1.5)	RIA (Study 214096 [M 5.3.1.4])	Phase 3a only for hypersensitivity samples	P6 4221	Samples pre-treated with acid and PEG	Validated by Novo Nordisk

PEG: polyethylene glycol; RIA: radioimmunoassay

RIA assay used to analyze phase I-II samples:

Screening Radio immuno assay (RIA):

In the screening assay, a known amount of radiolabelled semaglutide is added to the sample and the sample is precipitated with Polyethylene glycol (PEG 6000). Antibodies present in the sample bound to radiolabelled semaglutide. Radioactivity in the precipitate was measured using a gamma counter and served as a measure of the level of ADA present in the sample. Values were reported as percentage of radioactivity in the precipitate compared to total radioactivity added to the sample (%B/T). Sponsor reports that there is a linear relationship between the amount of antibody present in the sample and the %B/T measured. Linear relationship is shown in figure below: Dilution of anti-semaglutide control antibody GLIP-C-1F27 in normal human serum.

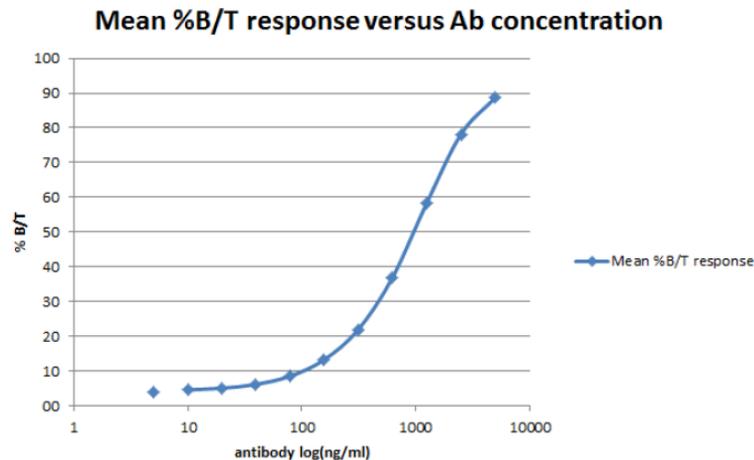


Figure 3-2 Two-fold dilution of an anti-semaglutide antibody (GLIP-C-1 F27) in the anti-semaglutide antibody RIA

Details of the antibody (isotype) were not provided, however any isotype would be suitable for a RIA assay.

Reviewers comments:

The level of ADA responses seen in the clinical development lies in the linear range of the curve. Although these assays are semi-quantitative, the %B/T values can be used as a surrogate to monitor the level of ADA

Confirmatory assay:

Samples that were positive in the screening assay were subjected to confirmatory assay. In this assay the samples were re-analyzed with or without surplus unlabelled semaglutide (5 µg/mL). Samples that had reduced radioactivity in the presence of unlabelled semaglutide were confirmed as positive for ADA.

Cross-reactivity assay:

Confirmed antibody positive samples were then tested for cross-reactivity to endogenous GLP-1. This was done by doing the RIA analysis in the presence (5 µg/mL) or absence of unlabelled GLP-1. Samples that showed reduced radioactivity in the presence of unlabelled GLP-1 were confirmed to cross react with endogenous GLP-1

Different assays were used for the monitoring of anti-semaglutide antibodies in the different clinical trials. Samples derived from the phase I and 2 studies were not acid dissociated and were therefore more likely to be inhibited by onboard GLP1, however the testing in phase I-II studies was conducted when levels of onboard drug would be minimal and only endogenous GLP1 would be expected to be present. One of the phase III studies involving 809 T2DM patients (in comparison with exenatide) was also conducted using samples that were not pre-treated.

RIA assay used to analyze phase I samples: Validation study no. 207194

An antibody radio immuno assay was developed and validated at Novo Nordisk A/S for the analysis of anti-semaglutide antibodies in phase I and phase II trials. This method had lower tolerance. During the development, sample volumes of 5,10,25 and 50 uL were tested to determine the minimum required dilution (MRD). The MRD was determined to be 6.7% (10 uL sample volume in a total of 150 uL buffer and radiolabelled drug). Increasing sample volume increased background in the assay leading to higher cut point and lower sensitivity.

The amount of unlabelled semaglutide needed for full inhibition of the binding of radiolabelled semaglutide to its antibodies even at a high levels of control antibody was 5 ug/mL. There was no further inhibition of binding when the unlabelled semaglutide was increased. This was the minimum amount of product needed to get maximum inhibition.

Positive control antibody:

Anti-semaglutide polyclonal antibodies raised in rabbit and three mAbs, raised against liraglutide (GLIP-C-1 F27), semaglutide (GLIP162-3F15) and GLP-1 (GLPb1 7F1) were tested. Polyclonal antibodies showed poor binding both in direct ELISA and in the RIA method. Of the three mAbs, GLIP-C1-F27 mAb had the best binding response and high %B/T values.

Reviewers comments:

Liraglutide has high homology (97%) with native GLP-1 and semaglutide. The use of anti-liraglutide antibody as the positive control is acceptable.

Suitability controls: Four levels of quality control (QC) samples, negative, low, medium and high positive controls were included. All QC samples were prepared in normal human serum with or without spiking of anti-semaglutide antibody. Positive QC samples were spiked with GLIP-C-1F27. This antibody was diluted in human serum to 100 ng/mL (QC low), 1000 ng/mL (QC medium) and 2500 ng/mL (QC high) to have different levels of QC.

Summary metrics of method validation from anti-semaglutide antibody assay used for phase I and phase II studies are given below.

7.2.1 Results of anti-semaglutide antibody RIA validation study no 207194

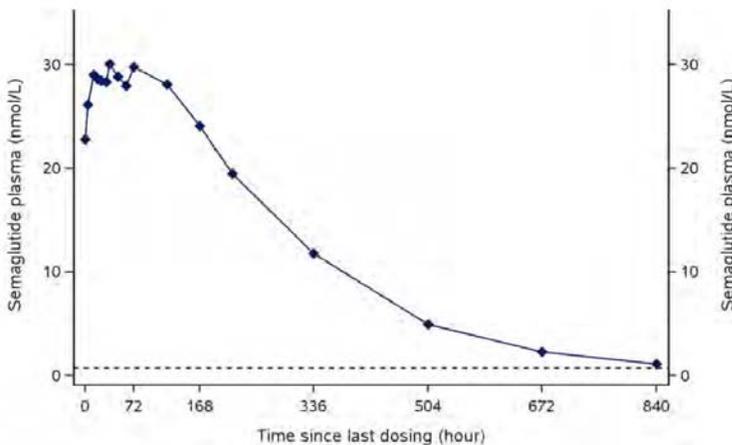
Validation Parameter	Description	Result
Minimum Required Dilution (MRD)	Volume of sample in assay	10 µl (6.7%) in a total of 150 µl, i.e. MRD = 15.
Screening cut point (SCP)	50 normal healthy sera mean %B/T + 1.645 x SD	4.6 %B/T
Normalisation factor (NF)	SCP – Mean QC neg	2.1
Assay specific cut point	Mean QC neg + NF	Mean QC neg + 2.1
Specificity cut point	Difference in %B/T of sample with (Series B) or without semaglutide (Series A)	$A - B > 1.96 * \sqrt{2} * SD$ SD = mean intra assay variation at medium and high control level
Cross reactivity cut point	Difference in %B/T of sample with (Series C) or without native GLP-1 (Series A)	$A - C > 1.96 * \sqrt{2} * SD$ SD = mean intra assay variation at medium and high control level
Sensitivity (linear interpolation)	Concentration of antibody producing a %B/T equal to the cut point GLIP-C1 F27 reference mAb	69 ng/ml
Recovery	10 individual sera spiked with 150 ng/ml GLIP-C1 F27 (reference mAb)	10 of 10 measured above cut point
Drug interference (linear interpolation)	Sensitivity at SCP in presence of 500 nM semaglutide 50 nM semaglutide 5 nM semaglutide	10000 ng/ml GLIP-C1 F27 1600 ng/ml GLIP-C1 F27 120 ng/ml
Drifting	At three levels, low medium and high positive level	No drifting at any of the tested levels, $p > 0.05$
Precision		
Intra assay variation	QC neg QC low QC medium QC high	7.6 %CV 7.5 %CV 7.8 %CV 5.4 %CV
Inter assay variation	QC neg QC low QC medium QC high	19.0 %CV 11.9 %CV 9.7 %CV 7.7 %CV
Validation Parameter	Description	Result
QC samples	QC neg	Normal healthy human serum without reference mAb
	QC low	Normal healthy human serum spiked with 100 ng/ml reference mAb
	QC medium	Normal healthy human serum spiked with 1000 ng/ml reference mAb
	QC high	Normal healthy human serum spiked with 2500 ng/ml reference mAb

Reviewers comments:

The sensitivity of the assay in the absence of excess drug was shown to be 69 ng/mL. In the presence of 5nmol/L drug , the sensitivity is 120ng/mL antibody. The sensitivity, specificity, and reproducibility are adequate to evaluate Phase I and II samples. However the tolerance to onboard drug was low.

The sensitivity of the assay in the presence of 50 nM semaglutide is 1600 ng/mL antibody. This is high, however the samples analyzed using this assay were taken 5 weeks (840 hours) post end of treatment with a visit window of one week. At this time, the level of semaglutide is expected to be less than 5 nmol/L drug. Therefore the level of sensitivity is acceptable for the samples analyzed using this assay.

Semaglutide concentration versus time profile following administration of 1.0 mg semaglutide at steady state in patients with T2D patients is given below (from trial 3635).



In patients with T2D, the mean steady state concentrations following SC administration of 0.5 mg and 1.0 mg semaglutide were approximately 16 nmol/L and 30 nmol/L respectively.

Validation of RIA assay used to analyze phase 1 and phase II samples: Validation study no. 212541 and 216098

A modified antibody RIA method was used to analyze phase 3A samples. This assay included pre-treatment of samples with Glycine-HCl and PEG 6000 precipitation. This step was included for the dissociation of antibodies and remaining systemic drug and purifying the antibodies by precipitation. This was aimed at improving the drug tolerance of the assay. The sponsor reported that it was important to keep the incubation time with acid to a minimum as the background of the assay increased with acid treatment. Treatment of samples with 150 nmol/L Glycin-HCl and 16% PEG for approximately 5 minutes was shown not to influence the background and allowed for the detection of 500 ng/mL antibody in the presence of 100 nmol/L semaglutide without loss of sensitivity.

The initial validation study (study # 212541) was performed with 25 normal human sera and 25 T2DM sera analyzed 6 times in the absence and presence of unlabelled semaglutide or GLP-1. The population of T2D sera in this validation had high background responses (%B/T) in the absence of unlabelled drug leading to a very high screening cut point and thereby reduced sensitivity. As a result, the drug tolerance of the assay could not be improved despite the addition of Glycine-HCl and PEG 6000 precipitation step. During the phase 3A development, it was noted that the high %B/T responses seen in the validation study was not observed in the trial specific T2D populations. Therefore a supplementary validation study (# 216098) was performed to reevaluate the sensitivity, drug tolerance and drug interference of this assay. These are the values considered for this review.

Sample cut point (SCP):

This validation utilized baseline results obtained from three phase 3a trials (450 baseline samples, 150 from each trial) for the determination of screening cut point and normalization factor. Three independent analytical runs performed at the beginning of each study to determine the study specific SCP and NF were used. The 9 analytical runs represent 9 independent data sets analysed in the presence of the QC0 lot. Due to the heterogeneity of the distribution of the 9 data sets where some showed non-normal distribution even after log transformation and outlier elimination, the sponsors used a non parametric approach to calculate SCP. Outliers in the original, untransformed datasets were identified and eliminated using the boxplot method. A SCP was then calculated for each dataset based on the 95th percentile dataset after outliers were taken out. The 95th percentile was selected to have 5% false positive rate for safety assessment. T2DM-specific sample cut point (SCP) was calculated as 7.7306 using non-parametric approach. The normalization factor (NF) was calculated as 1.9329 by subtraction.

Reviewers comments:

The determination of the cut point is appropriate.

This validation study showed that the sensitivity of the assay in the absence of the drug was 68 ng/mL reference mAb. Investigation of drug tolerance and drug interference showed that 500 ng/mL reference mAb could be detected as positive even in the presence of 40 nmol/L semaglutide. Summary values for the validation of anti-semaglutide antibody RIA assay used to test phase 3A and clin. Pharm trials (initial validation with commercial T2D patient samples that gave high background).

7.2.2 Results of anti-semaglutide antibody RIA validation study no 212541

Validation Parameter	Description	Result
Minimum Required Dilution (MRD)	Volume of sample in assay	10 µl (6.7%) in a total of 150 µl, i.e. MRD = 15.
Screening cut point (SCP)	25 normal healthy and 25 T2D ¹ subjects $\text{LogSCP} = \text{Median}[\log(\text{Binding}_{\text{meanA}})] + 1.645 \text{ MADn}[\log(\text{Binding}_{\text{meanA}})]$ $\text{SCP} = 10^{\frac{\text{Median}[\log(\text{Binding}_{\text{meanA}})] + 1.645 \text{ MADn}[\log(\text{Binding}_{\text{meanA}})]}{\text{MADn}[\log(\text{Binding}_{\text{meanA}})]}}$	15.2716 %B/T (T2D subjects)
Normalisation Factor (NF)	SCP/mean QC neg ²	1.6464
Normalised screening cut point	Assay specific cut point	NF * Mean QC neg
Specificity Cut point	99.9 % percentile of %inhibition A-B	21.0968%
Cross reactivity Cut point	99.9% percentile of %inhibition A-C	17.1769%
Sensitivity at cut point (linear interpolation)	Mean of 6 determinations	264.56 ng/ml
Sensitivity at 99% confidence level	$\text{Sensitivity}_{\log} = \text{mean}[\log(\text{conc at CP})] + t(0.02, \text{df}) \times \text{SD}[\log(\text{conc at CP})]$	342.52 ng/ml
Recovery	10 individual human sera QC low (300 ng/ml) QC low + 50% (450 ng/ml) QC high (2500 ng/ml)	% Recovery compared to buffer 105.24% - 121.80%, 10 of 10 > CP 78.57% - 111.75%, 8 of 10 > CP 94.07% - 105.82%, 10 of 10 > CP
Drug interference	Sensitivity at cut point in the presence of 123 ng/ml (30 nM) drug 82 ng/ml (20 nM) drug 6 ng/ml (1.5nM) drug	2500 ng/ml reference mAb (linear regression 1297 ~1300 ng/ml) 1250 ng/ml reference mAb (linear regression 1060 ng/ml) 625 ng/ml reference mAb (linear regression 291ng/ml)
Drug tolerance	300 ng/ml reference mAb 500 ng/ml reference mAb	3 ng/ml (0.07 nM) drug 12 ng/ml (3 nM) drug
Haemolysis interference	QC neg and QC low grade 1-4 haemolysis	No haemolytic interference from at any of the tested QC levels and grades of haemolysis
Drifting	4 QC levels: QC neg, QC low, QC med, QC high, Student's T test	QC neg: slight drifting (p=0.04) QC low, QC med, QC high: No drifting (p<0.05)
Precision	QC neg	10.6%CV
Total (inter assay variation)	QC low (300ng/ml)	6.9%CV
	QC med	10.2%CV

Validation Parameter	Description	Result
	QC high	8.8%CV
QC samples	QC neg	Normal healthy human serum without reference mAb
	QC low	Normal healthy human serum spiked with 300ng/ml reference mAb
	QC med	Normal healthy human serum spiked with 1000ng/ml reference mAb
	QC high	Normal healthy human serum spiked with 2500ng/ml reference mAb

1. T2D = Type 2 diabetes
2. QC neg = QC0 in the validation study

Supplementary validation of anti-semaglutide antibody RIA assay used to test phase 3A and clin. Pharm trials (validation with baseline samples T2D patient samples from the trial)

7.2.3 Results of anti-semaglutide antibody RIA supplementary validation study no 216098

Validation Parameter	Description	Result
Screening cut point (SCP)	T2D ¹ specific SCP based on non-parametric approach, 95% percentile	7.7 %B/T
Normalisation Factor	Calculated as SCP – mean QC neg ²	1.9
Normalised screening cut point	Assay specific cut point	Mean QC neg + NF
Sensitivity at cut point (linear interpolation)	Mean concentration of 6 determinations	67.96 ng/ml
Sensitivity at 99% confidence level	Sensitivity _{log} = mean[log(conc at CP)] + t(0.02, df x SD[log(conc at CP)]) Sensitivity(99% confidence level) = power(10, sensitivity _{log})	105.17 ng/ml
Titre	Final titre calculated	7.9 with a precision of 13.96%
Drug Tolerance	At 500 ng/ml antibody	40 nM semaglutide is tolerated
Drug interference	Sensitivity in presence of 1.25nM semaglutide Sensitivity in presence of 40nM semaglutide	85.44 ng/ml at 99% confidence level 135.90 ng/ml 678.04 ng/ml at 99% confidence level 1401.71 ng/ml

1. T2D baseline visit sera from study populations in trials 3623, 3624, 3626. At least 150 sera analysed over three set-ups for each trial
2. QC neg = QC0 in the supplementary validation study

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Reviewers comments:

The reason for high background in the T2DM sera in the initial validation study is not known, but it may be due to differences in how the commercial T2DM samples were obtained or stored..

The sensitivity and drug tolerance determined by using the samples of treatment naive subjects (the supplementary validation) is acceptable.

Cut point, normalization factor, sensitivity, recovery, drug tolerance and precision reported in the method validation are acceptable and the method is found suitable to monitor ADA in the clinical samples.

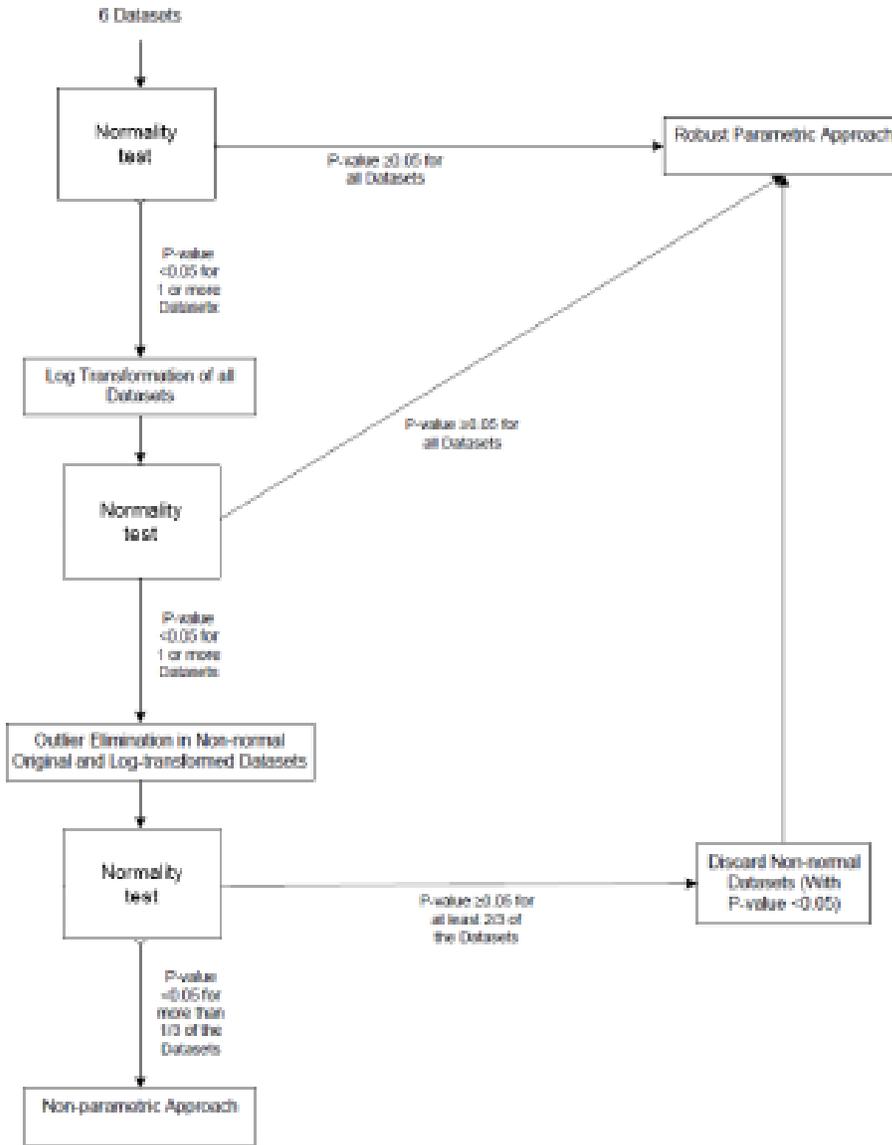
Validation of RIA assay used to analyze phase 3a samples: Validation study no. 216142

This is the assay used for assessing samples from phase 3a clinical trials. Assay in validation study no 207194 was re-validated after modifying the assay to limit the acid incubation time for an assay run to be maximum 7 minutes and with type 2 diabetes and obese clinical trial populations. This also validated optional use of Tecan Genesis liquid handling system. In this method, after initial acidic pre-treatment (between 5-7 minutes) and PEG precipitation to remove free semaglutide from samples, the precipitate containing the antibodies is dissolved in assay buffer in excess unlabelled semaglutide or in excess unlabelled GLP-1 and incubated with I125 labelled semaglutide (tracer) overnight at 5 C. The following day, antibodies are precipitated with any bound antigen and the precipitate is measured in a gamma counter for 5 minutes. The radioactive signal from the tracer is expressed in percent of the total amount of added radioactivity (% B/T)

50 human sera from type 2 diabetic patients (T2D) and 50 sera from obese patients were analysed for the validation. For each medical condition, the analysis of the 50 individuals was performed 6

times in series A, B and C for a total of 12 analytical runs. For each medical condition, the 6 analytical runs were at least performed by 2 different analysts and during a period of 2 weeks.

SCP calculation scheme [7]



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7.2.4 Results of anti-semaglutide antibody RIA validation study 216142

Parameter	Description	Result
MRD	Volume of sample in assay	10 μ l (6.7%) in a total of 150 μ l, i.e. MRD = 15.
Screening cut point (SCP)	50 T2D sera analysed 6x Calculated using robust-parametric approach with 5% false positive rate	8.8982 %B/T
Normalisation factor (NF)	SCP – Mean QC neg	1.4762
Normalised screening cut point	Mean QC neg + NF	Mean QC neg + 1.4762
Confirmatory cut point	%Inhibition of results with (Series B) or without unlabelled semaglutide (Series A) for T2D samples. Calculated to give a 1% false positive rate.	20.18%
Cross reactivity cut point	%Inhibition of results with (Series C) or without native GLP-1 (Series A) for T2D samples. Calculated to give a 1% false positive rate.	16.20%
Normalised titer cut point	Mean QC neg + 2xNF	Confirmed positive samples with results \geq normalised titer cut point subjected to titration. Confirmed positive samples with results $<$ normalised titer cut point assigned MRD adjusted titer = 15.
Control mAb for assay parameters and QC preparation	anti-semaglutide mAb	mAb GLIP-C1-F27
Sensitivity screening assay	anti-semaglutide mAb	67.21 ng/ml
Sensitivity confirmatory assay	anti-semaglutide mAb	39.06-78.13 ng/ml confirmed positive
Sensitivity cross reactivity assay	anti-semaglutide mAb	39.06-78.13 ng/ml confirmed cross reactive
Recovery	10 T2D sera spiked with anti-semaglutide mAb: 100 ng/ml mAb 150 ng/ml mAb 2500 ng/ml mAb	All had %Recovery compared to serum pool within +/- 20%, except one individual spiked with 150 ng/ml Ab ¹ . 9 of 10 individuals (95%) \geq SCP ¹ 9 of 10 individuals (95%) \geq SCP ¹ 10 of 10 individuals (95%) \geq SCP
Drug Interference	Sensitivity (1.25 nM semaglutide) Sensitivity (40 nM semaglutide) Sensitivity (100 nM semaglutide)	115 ng/ml 380 ng/ml 552 ng/ml

Parameter	Description	Result
Drug tolerance	100 ng/ml anti-semaglutide mAb	0.63 nM semaglutide
	500 ng/ml anti-semaglutide mAb	85 nM semaglutide.
Interference	Interference from haemolysis examined on QC samples	No interference at any level. All results < 20% difference to non-haemolysed sample.
	Interference from lipidemia examined on QC samples	No interference at any level. All results < 20% difference to non-lipaemic sample
Robustness	Effect of incubation time, analyst, drift and manual handling versus robot liquid handling system investigated	No effect, i.e. the assay is robust to variations in these parameters
Precision screening assay (intra assay / inter assay precision)	QC neg (0 ng/ml mAb)	2.0-7.9 %CV / 5.6 %CV
	QC lowT2D (80 ng/ml mAb)	1.3-6.5 %CV / 5.6 %CV
	QC low (100 ng/ml mAb)	0.5-6.0 %CV / 4.9%CV
	QC med (900 ng/ml mAb)	0.5-3.4 %CV / 5.0 %CV
	QC high (2500 ng/ml mAb)	0.7-4.7 %CV / 3.3 %CV
Precision confirmatory assay (intra assay / inter assay precision)	QC neg (0 ng/ml mAb)	12.5-42.3 %CV / 16.8 %CV
	QC lowT2D (80 ng/ml mAb)	3.5-25.8 %CV / 18.8 %CV
	QC low (100 ng/ml mAb)	4.0-16.3 %CV / 7.6 %CV
	QC med (900 ng/ml mAb)	0.5-11.1 %CV / 4.0 %CV
	QC high (2500 ng/ml mAb)	0.3-1.6 %CV / 1.0 %CV
Precision cross reactivity assay (intra assay / inter assay precision)	QC neg (0 ng/ml mAb)	16.2-43.5 %CV / 25.9 %CV
	QC lowT2D (80 ng/ml mAb)	4.1-15.0 %CV / 13.1 %CV
	QC low (100 ng/ml mAb)	4.7-17.6 %CV / 7.7 %CV
	QC med (900 ng/ml mAb)	0.7-2.2 %CV / 2.3 %CV
	QC high (2500 ng/ml mAb)	0.1-1.9 %CV / 1.0 %CV

1: The certificate for the subject with recovery < 80% at 150 ng/ml Ab level and testing < SCP at 100 and 150 ng/ml mAb showed that this subject received treatment with Victoza (liraglutide) 1.8 mg, explaining the reduced recovery and sensitivity for this subject.

Reviewers comments:

The parameteres validated are in-line in with previous validation study. Cut point, Sensitivity and drug tolerance reported are acceptable.

Revalidation of screening and confirmatory anti-semaglutide antibody RIA assay is acceptable.

Validation of RIA assay used to analyze PIONEER 6 samples: Validation study no. 214096

These samples were unscheduled and are not included in the immunogenicity samples. These samples were collected due to suspicion of hypersensitive reaction. These samples were assessed for the presence of anti-semaglutide antibodies using assay validation by study 214096. Serum

samples from 25 T2D patients and 25 obese individuals were used for the validation study. The 50 serum samples were analysed without semaglutide in 6 assay set-ups (three assay set-ups by two analysts). Outliers were inspected using the outlier box-plot approach. Since outliers were evenly distributed in both extremities, they were not excluded from the data set. Analysis of normality using Shapiro-Wilk W test provided evidence of normal distribution in 5 out of 6 assay set-ups. The assay set-ups were statistically different and the assay set-up variance were not statistically different and so a floating cut point was used. The screening cut point was set to detect 5% false positive samples (95% confidence level).

7.2.5 Results of anti-semaglutide antibody RIA validation study 214096

Parameter	Description	Result
Minimum Required Dilution (MRD)	Volume of sample in assay	10 µl (6.7%) in a total of 150 µl, i.e. MRD = 15.
Assay screening cut point	25 T2D sera and 25 obese sera	Mean QC neg (%B/T) + NF
	Normalisation factor (NF)	1.2
Specificity cut point	Signal inhibition: 100 x (A-B)/A (Drug)	>40%
	Signal inhibition: 100 x (A-C)/A (CrossR)	>24%
Sensitivity	GLIP-C1 F27 Control mAb	32 ng/ml
Recovery	60 ng/ml anti-semaglutide mAb	19 of 20 individuals (95%) ≥ screening cut point
Drug Interference	Sensitivity (40nM semaglutide)	500 ng/ml
	Sensitivity (4nM semaglutide)	250 ng/ml
	Sensitivity (0.4 nM semaglutide)	62.5 ng/ml
Drug tolerance	250 ng/ml anti-semaglutide mAb	25 nM semaglutide
	500 ng/ml anti-semaglutide mAb	100 nM semaglutide
Haemolysis	QC neg, QC low and high in grade 1-4 haemolysis	all samples between 92 - 121% of no haemolysis
Assay precision (inter-assay)	QC neg (%B/T)	16.3 %CV
	QC low (%B/T)	14.8 %CV
	QC high (%B/T)	6.4 %CV
Assay precision (intra-assay)	QC neg (%B/T)	10.6 %CV
	QC low (%B/T)	8.6 %CV
	QC high (%B/T)	5.2 %CV
Drifting	Drifting at 3 levels; QCneg, QClow and QChigh, Student's t test	No drifting at any of the three levels, neg, low and high (p>0.05)
QC samples	QC neg	Normal healthy human serum without reference mAb
	QC low	Normal healthy human serum with 60ng/ml GLIP-C-1F27
	QC high	Normal healthy human serum with 2500ng/ml GLIP-C-1 F27

Reviewers comments:

The screening cut point, sensitivity and drug tolerance are comparable to the previous validation studies for anti-semaglutide RIA assays. Validation of study 214096 is acceptable.

IgE assay for ADA to Semaglutide:

An ImmunoCAP method for the detection of drug specific IgE antibodies was previously developed, validated and used to assess clinical trial samples suspected to have hypersensitivity reaction during treatment of subcutaneous semaglutide for NDA 209637. In this assay, control antibody was produced by coupling semaglutide specific IgG to unsepcific human IgE by BS3 coupling. This assay did not have desired sensitivity. The control IgG GLIP C-1F27 antibody was isotype switched to have IgE backbonbe. This anti-semaglutie IgE mAb was used in a supplementary study (#307690) to reassess the validation parameters based on the control antibody. The sensitivity of the new control anti-semaglutide IgE mAb was investigated using the validated immno CAP assay.

7.2.7 Results of anti-semaglutide IgE immunoCAP supplementary study 307690

Parameter	Description	Result
Assay cut point	Lower Level of Quantification (LLOQ)	0.1 kUA/L
Control antibody used	mAb GLIP-C1 F27 with IgE backbone	Anti-semaglutide IgE
Sensitivity	Results from 3 set of experiments	0.5 - 1.0 ng/ml anti-semaglutide IgE
Interference from semaglutide	Anti-semaglutide IgE measured in presence of 0 – 100 nM semaglutide:	
	0.5 ng/ml anti-semaglutide IgE	Tolerates < 1 nM semaglutide
	1.0 ng/ml anti-semaglutide IgE	Tolerates 1 nM semaglutide
	5.0 ng/ml anti-semaglutide IgE	Tolerates 100 nM semaglutide
	50 ng/ml anti-semaglutide IgE	Tolerates 100 nM semaglutide
Recovery	Three concentrations of anti-semaglutide IgE spiked in 8 individual type 2 diabetes sera:	All subjects > LLOQ on all 3 ab levels. Mean results and %CV listed for each level:
	1 ng/ml anti-semaglutide IgE	0.29 kUA/l, 2.87 %CV
	5 ng/ml anti-semaglutide IgE	1.26 kUA/l, 16.1 %CV
	50 ng/ml anti-semaglutide IgE	13.4 kUA/L, 8.1 %CV

Reviewers comments:

The sensitivity was approximately 0.5-1 ng/mL. The previous assay had a sensitivity of 185ng/mL. The sensitivity and drug tolerance of the anti-semaglutide IgE assay are acceptable.

Neutralizing antibody assays:

In-vitro neutralizing effect was measured using a BHK cell-based neutralizing antibody assay. In this assay, the cells are transfected with the human GLP-1 receptor. Cellular stimulation is measured

as cAMP production upon GLP-1 receptor activation with semaglutide. The cAMP formed binds to the cAMP response element (CRE) in the luciferase promoter leading to luciferase production and a read out as Relative Luminescence Units (RLU). The assay is based on anti-semaglutide antibodies binding to semaglutide and blocking its interaction with the receptor. This reduced the production of cAMP and thereby production of luciferase. Thus reduction in luciferase directly correlates with the level of neutralizing anti-semaglutide antibodies. Controls included in the neutralising antibody assays include Non Specific Binding (NSB) which represents the background in the assay, MAX which represent the maximal response in the presence of the drug without antibody and QC samples at negative, low and high positive. The neutralizing effect was calculated as a percent neutralisation based on the RLU response in the test sample (X) in relation to the RLU response in the NSB and MAX samples by using the following formula:

$$\%N = (1 - (X - \text{NSB} / \text{MAX} - \text{NSB})) * 100$$

To test the level of cross-reactive neutralizing antibodies to native GLP-1, native GLP-1 is used instead of semaglutide in the assay.

The cutpoint for the in-vitro neutralizing antibody assay was calculated using sera from 60 individual human from T1D, T2D and obese individuals (20 each) and set to detect 0.1% false positive samples. Sponsor stated that the assay had low tolerance to on board drug. To reduce the on-board drug interference they pre- the serum samples treated with 18% PEG6000. Despite this, the sensitivity of the assay remained poor (34ug/ml). The sponsor tested several antibodies but only the GLIP-C-1 F27 was shown to neutralize semaglutide in the cell based assay, albeit with low affinity. Thus the sensitivity of the assay as determined using the mAb is low.

Table 3-3 Neutralising antibody assays used during clinical development of oral semaglutide

Analysis	Method (validation study number)	Clinical Phase	Trials	Pre-treatment of samples	Validation
Neutralising anti-semaglutide antibody assay (Section 3.2.2.1)	BHK cell based assay (Study 207300 [M 5.3.1.4]).	Phase 2	Trial 3790	No pre-treatment of samples	Validated by Novo Nordisk
Neutralising anti-semaglutide antibody assay (Section 3.2.2.2)	BHK cell based assay (Study 214429 [M 5.3.1.4]).	Phase 3a	P1 4233, P2 4223, P3 4222, P4 4224, P5 4234, P9 4281	Pre-treatment of samples with PEG to reduce matrix interference	Validated by Novo Nordisk
Neutralising anti-GLP-1 antibody assay (Section 3.2.2.3)	BHK cell based assay (Study 210031 [M 5.3.1.4]).	Phase 2	Trial 3790	No pre-treatment of samples	Validated by Novo Nordisk
Neutralising anti-GLP-1 antibody assay (Section 3.2.2.4)	BHK cell based assay (Study 214422 and 216154 [M 5.3.1.4]).	Phase 3a	P1 4233, P2 4223, P3 4222, P4 4224, P5 4234, P9 4281	Pre-treatment of samples with PEG to reduce matrix interference	Neutralising anti-GLP-1 antibody assay

BHK: baby hamster kidney; PEG: polyethylene glycol

Critical parameters of the NAB assay validation are shown in the sponsor's table below:

7.2.9 Results of *in vitro* neutralising anti-semaglutide antibody validation study 214429

Parameter	Description	Result
Minimum Required dilution	Volume of sample used in assay	30 %
Neutralising cut point	60 individual human sera (20 T1D, 20 T2D and 20 obese). Set with 99,9% confidence level	$\%N^1 = \text{Mean individuals} + t_{(0.001,df_0)} \times SD_{\text{total}}$
Normalisation Factor (NF)	Neutralising cut point – mean QCneg	30
Plate specific neutralising cut point	Floating cut point	Mean QCneg (%N) + NF
Sensitivity	Sensitivity reference mAb GLIP-C1 F27	3400ng/ml reference mAb
Recovery	4000ng/ml reference mAb spiked into 21 human sera (7 T1D, 7 T2D and 7 obese)	20 of 21 sera > neutralising cut point 1 T2D subject on Victoza treatment < neutralising cut point
Drug interference	Sensitivity in presence of 5 nM semaglutide	3130 – 6250ng/ml
Drug tolerance	3400 ng/ml anti-semaglutide mAb	2.5 nM drug can be tolerated
Assay precision (inter-assay variation)	QC low (%N)	24.7 %CV
	QC high (%N)	5.2 %CV
Assay precision (Intra-assay variation)	QC low (%N)	20.8 %CV
	QC high (%N)	2.1 %CV
Haemolysis	QC low and high in haemolysis grade 1-4	No interference from haemolysis
Drifting	Drifting at three levels; QC neg, QC low and QC high	Drifting at QC neg level ($p < 0.05$) ² No drifting at QC low ($p > 0.05$) Slight drifting at QC high ($P = 0.0352$)
QC samples	QC neg	Normal healthy human serum
	QC low	Normal healthy human serum spiked with 4000 ng/ml GLIP-C-1 F27
	QC high	Normal healthy human serum spiked with 10000 ng/ml GLIP-C-1 F27

1. %N = % Neutralisation

2. Drifting at QC neg level not significant as the differences in QC neg first and last in the assay are very small.

7.2.8 Results of *in vitro* neutralising anti-semaglutide antibody validation study 207300

Parameter	Description	Result
Minimum Required dilution	Volume of sample used in assay	5%
Neutralising cut point	10 individual normal healthy human sera. Set at 99% confidence level	Mean %N + $t_{(0.01,df=9)} \times SD = 14.8 \%N$
Assay specific cut point	Cut point based on individual baseline samples due to high inter individual variation	Mean baseline sample + 3xSD
Sensitivity	Last dilution above cut point	200 ng/ml GLIP-C-1 F27
Drug interference	500ng/ml GLIP-C-1 F27	Concentration of drug tolerated: 0.07nM semaglutide
Assay Precision (Intra assay)	QC low %N	8.7%CV
	QC high %N	2.4%CV
Assay Precision (inter assay)	QC low %N	7.1%CV
	QC high %N	1.7%CV
QC samples	QCB = QC neg	Normal healthy human serum
	QCD = QC low	Normal healthy human serum spiked with 400ng/ml GLIP-C-1 F27
	QCC = QC high	Normal healthy human serum spiked with 20000 ng/ml GLIP-C-1 F27

In-vitro neutralizing anti-GLP-1 antibody assay:

Anti-semaglutide antibody positive samples cross-reacting with endogenous GLP-1 were analyzed for in vitro neutralizing effect using the same cell based assay described above but stimulated cells with recombinant human GLP-1 rather than semaglutide. The concentration of GLP-1 used for the stimulation of cells was 1.5 ng/mL (EC80) recombinant human GLP-1. Sensitivity was determined using monoclonal reference anti-GLP-1 antibodies, mAb 26.1 and GLIP-C-1 F27. Using the individual mAbs, the sensitivity of the assay was determined to be 18.6 ug/mL (mAb 26.1) and 82.4 (GLIP-C-1F27). Using a pool of the two mAbs the sensitivity was shown to be 6.9 ug/mL.

7.2.11 Results of *in vitro* neutralising anti-GLP-1 antibody validation study 214422

Parameter	Description	Result
Minimum Required Dilution	Volume of sample in assay	30%
Neutralising cut point	60 individual human sera (20 T1D, 20 T2D and 20 obese). Set with 99,9% confidence level	$\%N^1 = \text{Mean individuals} + t_{(0.001,df)} \times SD_{total}$
Normalisation Factor (NF)	Neutralising cut point – mean QC neg	33
Plate specific neutralising cut point	Floating cut point	Mean QC neg (%N) + NF
Sensitivity (linear regression)	Reference mAb, Mab 26.1	18.6 µg/ml
	Reference mAb, GLIP C-1 F27	82.4 µg/ml
Drug interference	Sensitivity in presence of drug 1nM liraglutide	MAb26.1: 12.5 µg/ml GLIP C-1 F27: 100 µg/ml
	1nM semaglutide	GLIP C-1 F27: 100 µg/ml
Drug tolerance	Concentration of reference mAb detected in presence of 6.25nM liraglutide	33 µg/ml Mab26.1
	25nM semaglutide	133 µg/ml GLIP C-1 F27
Assay Precision (Intra assay variation)	QC low (%N)	5 %CV
	QC high (%N)	3 %CV
Assay Precision (Inter assay variation)	QC low (%N)	7 %CV
	QC high (%N)	9 %CV
Recovery	40 µg/ml Mab26.1 spiked into 21 individual human sera (7 T1D, 7 T2D and 7 obese)	21 of 21 spiked sera \geq plate specific cut point
Haemolysis	QC low and QC high in grade 1-4 haemolysis	no effect of haemolysis
%CV of triplicate RLU determinations	%N < 50	%CV \leq 25
	%N \geq 50	%CV \leq 35
Drifting	Drifting at three levels QC neg, QC low and QC high	No drifting at any level (p>0.05)
QC samples	QC neg	Normal healthy human serum
	QC low1	Normal healthy human serum spiked with 40µg/ml MAb26.1 ²
	QC low2	Normal healthy human serum spiked with 23µg/ml MAb26.1 ²
	QC high	Normal healthy human serum spiked with 50µg/ml MAb26.1

1. %N = % Neutralisation

2. QC low1 set based on last concentration of antibody above cut point in 6 individual cut points as opposed to QC low2 which is set based on the linear regression and the sensitivity at the cut point in 6 individual assays

7.1.10 Results of supplementary *in vitro* neutralising anti-GLP-1 antibody validation study 216154

Parameter	Description	Result
Sensitivity at cut point (Linear regression)	Pool of monoclonal antibodies: Mab26.1, GLPa-1 F5, GLIP-C-1 F27	6.9 µg/ml
Drug interference (linear regression)	Sensitivity in the presence of 1 nM semaglutide	8.8 µg/ml

7.2.10 Results of *in vitro* neutralising anti-GLP-1 antibody validation study 210031

Parameter	Description	Result
Minimum Required Dilution	Volume of sample in assay	25%
Neutralising cut point	Fixed cut point set with a 99% confidence level based on results from 30 individual human (20 T2D sera and 10 normal sera).	60 %N ¹ for T2D serum 40 %N for normal serum
Sensitivity (linear regression)	Reference mAb, Mab 26.1 Reference mAb; GLIP- C1-F27	0.8 µg/ml 6.3 µg/ml
Drug interference	Sensitivity in presence of drug: 0.3 nM liraglutide 3 nM liraglutide 0.4 nM semaglutide 4 nM semaglutide	mAb26.1: 1.2 µg/ml GLIP-C1-F27: 10.2 µg/ml mAb26.1: 1.6 µg/ml GLIP-C1-F27: 16.4 µg/ml mAb26.1: 1.6 µg/ml GLIP-C1-F27: 10.7 µg/ml mAb26.1: 23.5 µg/ml GLIP-C1-F27: 17.5 µg/ml
Assay Precision (Intra assay variation)	QC low (%N) QC high (%N)	11.0 %CV 2.2 %CV
Assay Precision (Inter assay variation)	QC low (%N) QC high (%N)	18.7 %CV 5.0 %CV
Haemolysis	QC low and QC high in grade 1-4 haemolysis	No effect of haemolysis
Drifting	Drifting at three levels QC neg, QC low and QC high	No drifting on QC low and QC high (p>0.05). Small drift on QC neg but with no impact on the analysis

1. %N = % Neutralisation

Reviewers comments: The NAB assay is inadequate. The sponsor has used the same assays presented for the subcutaneous semaglutide NDA 209637. The neutralizing antibody assays appears to have a very low sensitivity making it inadequate to determine whether any antibodies present have neutralizing activity. The sensitivity of the NAB assay, 3.4 ug/ml is insufficient to yield clinically relevant results. The apparent low sensitivity could be the result of the low affinity of the mab used to develop and validate the assay, however there is indication that the assay is valid. The Sponosrs will be asked to develop a new assay to assess neutralizing activity. Given the low incidence of ADA and the apparent abence of clinical impact this can be done as a post marketing commitment.

Overview of Clinical Trials

Development of Anti-Drug Antibodies (ADA) was investigated in three phase I multiple dose trials (Trials 3692, 3991 and 4140), single phase 2 dose finding trial (Trial 3790) and in 6 of the phase 3a trials (Trials PIONEER 1-5 and Pioneer 9).

Phase 3a trials – PIONEER 1-10

P1 4233 – monotherapy vs placebo	P6 4221 – CVOT vs placebo and standard-of-care
P2 4223 – vs empagliflozin	P7 4257 ^a – flexible dose vs sitagliptin
P3 4222 – long-term vs sitagliptin	P8 4280 – add-on to insulin vs placebo
P4 4224 – vs liraglutide and placebo	P9 4281 ^b – monotherapy vs liraglutide and placebo, Japan
P5 4234 – renal impairment vs placebo	P10 4282 – add-on to OADs vs dulaglutide, Japan

Phase 2 trial

3790 – dose finding

Phase 1/clinical pharmacology trials

Pharmacokinetics	Pharmacodynamics	4141 – omeprazole
3691 – single ascending dose (FHD)	NN9535-3685 – energy intake ^e	4394 – probenecid and cyclosporine
3692 – multiple ascending dose 1	NN9535-3635 – beta-cell function ^e	Special populations
3991 – multiple ascending dose 2	NN9535-3684 – hypoglycaemia ^e	4079 – renal impairment
4140 – Caucasian/Japanese	Drug-drug interaction	4082 – hepatic impairment
3794 – dosing conditions	4065 – lisinopril and warfarin	4267 – upper gastrointestinal disease
4154 – food effect	4145 – metformin and digoxin	Special studies
3957 – pharmacoscintigraphy	4249 – oral contraception	NN9535-3652 – QTc semaglutide ^e
NN9535-3789 – AME semaglutide ^c	4250 – furosemide and rosuvastatin	4247 – QTc SNAC
ERP23 – AME SNAC ^d	4279 – levothyroxine and placebo	

Blue mark indicates trial with immunogenicity assessments.

^a includes an extension, for which only blinded safety data will be included in the submission dossier; ^b combined phase 2/3 trial; ^c trials with s.c. semaglutide for T2D (Ozempic®); ^d Emisphere trials

AME: absorption, metabolism and excretion; CVOT: cardiovascular outcomes trial; FHD: first human dose; QTc: corrected QT interval

The sampling time points for all the clinical trials where a sample was drawn for the analysis of ADA are given below.

Table 3-1 Antibody sample collection time points – phase 1, 2 and 3a trials with antibody assessment

Antibody sample collection time point	Phase 1 (Trials 3692, 3991, 4140)	Phase 2 (Trial 3790)	Phase 3a (P1 4233, P5 4234)	Phase 3a (P2 4223, P4 4224, P9 4281)	Phase 3a (P3 4222)
Treatment duration	10-13 weeks	26 weeks	26 weeks	52 weeks	78 weeks
Week 0 (baseline)	x	x	x	x	x
Week 4			x	x	x
Week 8			x	x	x
Week 14			x	x	x
Week 16		x			
Week 26		x	x	x	x
Week 38				x	x
Week 52				x	x
Week 78					x
Follow-up	x ^a	x ^b	x ^c	x ^c	x ^c

^aFor trials 3692 and 3991 3-5 weeks post end of treatment, and for trial 4140 4-5 weeks post end of treatment.

^b5 weeks post end of treatment + a visit window of 5 days.

^c5 weeks post end of treatment + a visit window of 3 days.

Reviewers comments:

For all phase II and phase 3a clinical trials, the follow up antibody sample was taken after a drug wash out period of 5 weeks. This corresponds to 5 elimination half-lives with an additional 3-5 days to prevent interference in the assays from remaining residual semaglutide.

Levels of Semaglutide at follow-up visit

Appendix W Summary of PK samples at the follow-up visits

Table 8-23 PK samples at the follow-up visits

Trial	Number of Samples	Samples below LLOQ (%)	Highest PK value (nM)	95th Percentile (nM)	Number of samples >2.5 nM
PIONEER 1	457	90	6.08	1.174	6
PIONEER 3	491	96	7.53	0.3645	2
PIONEER 5	136	84	35.9	2.16	5
PIONEER 9	138	78	18.6	1.5405	3

Summary of clinical immunogenicity data from phase 3 trials:

Data from the following ten clinical trials are included in the overall assessment of Immunogenicity for oral semaglutide. Three phase 1 trials – Trials 3692, 3991 and 4140. One phase 2 trial - Trial 3790 and six phase 3a trials - PIONEER 1-5 and Pioneer 9.

Stratification of the Positive samples.

Total number of subjects positive for anti-semaglutide antibodies at any point in the study: 17
Total number of subjects positive at baseline: 5 (Three subjects were positive only at baseline and was negative at subsequent samplings, 2 samples showed positivity at subsequent samplings).
Of the 2800 subjects who were treated with oral semaglutide, 14 subjects (0.5%) tested positive for anti-semaglutide antibodies at any point post baseline.

Phase 3 A trials

In phase 3A trials (PIONEER 1-5 and 9), a total of 25 samples collected from 17 subjects tested positive for anti-semaglutide antibodies. Five of these subjects were positive at baseline and three of the five only showed positive results at baseline and were negative in subsequent samplings. Two other subjects showed anti-semaglutide antibody positive at baseline and also showed positivity at least at one time point post baseline. Overall, 14 subjects show ADA at any point post baseline.

Of the 12 subjects, that were negative at baseline and show ADA response at later time points, 10 of the subjects only showed ADA positive response at one time point. Two other subjects with treatment-induced ADA tested positive at 2 or 3 visits post baseline. One subject had anti-semaglutide antibodies at week 4 (2% B/T) and week 14 (3.42% B/T). The other subject had positive samples at weeks 4 (24.61% B/T), 8 (10.14% B/T) and week 14 (4.47% B/T). The week 4 sample also showed neutralizing activity. Both subjects had ADA cross-reacting to endogenous GLP-1. None of these subjects showed ADA positive response at the follow-up visit.

Two of the subjects with pre-existing antibodies tested positive at additional 1 or 2 visits. One subject had ADA (did not cross-react with endogenous GLP-1) at week 4 and another subject had ADA (cross-reacted with endogenous GLP-1) at weeks 4 and 8. In both of these subjects, the highest level of ADA was seen at baseline and declined after.

Reviewers comments:

Treatment with oral semaglutide did not boost pre-existing antibodies.

Phase 1 and 2 trials

No subjects developed anti-semaglutide antibodies in any of the phase I trials. In the phase 2 trial, 8 subjects treated with oral semaglutide tested positive at a single time point post baseline. One subject tested positive at baseline and at one additional visit. The level of ADA measured in these subjects were between 1.1 and 4.5. Four of the subjects had ADA that cross-reacted with endogenous GLP-1.

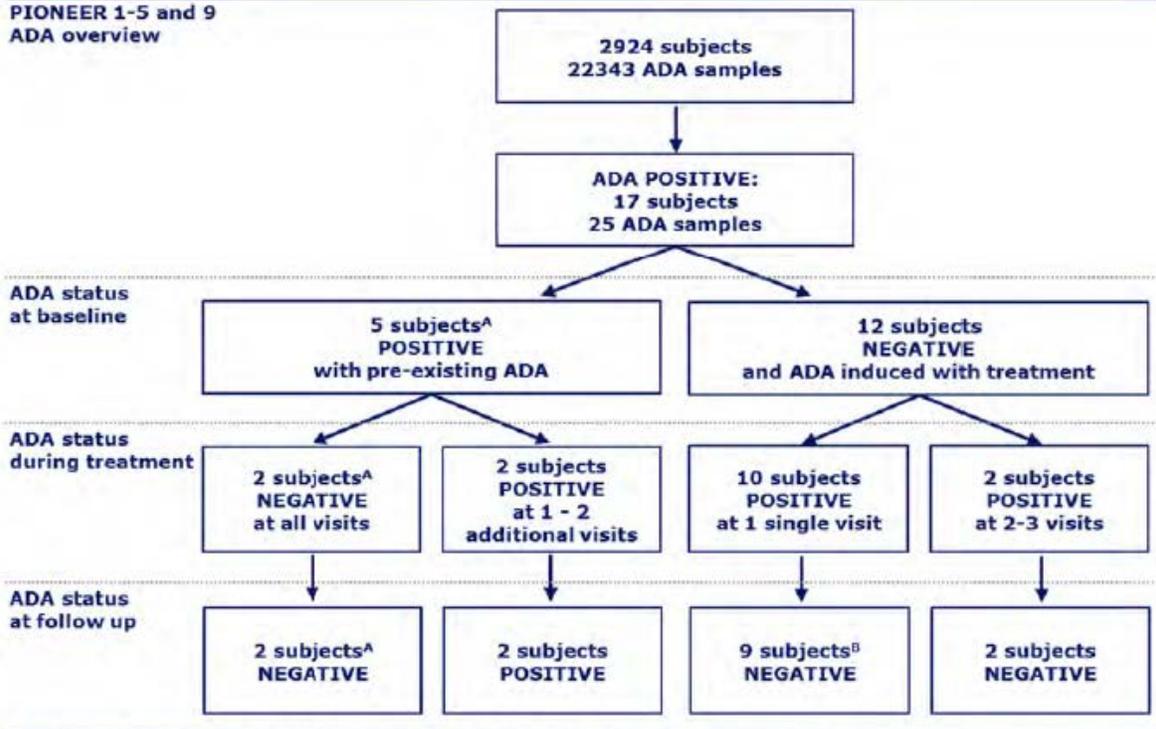
Table 4-1 Anti-semaglutide antibodies – PIONEER 1–5 and 9 – in-trial

	Oral sema 3 mg		Oral sema 7 mg		Oral sema 14 mg		Oral sema	
	N	(%)	N	(%)	N	(%)	N	(%)
Number of subjects	690		688		1546		2924	
Week 0								
N	688		685		1535		2908	
Negative	687 (99.9)		684 (99.9)		1532 (99.8)		2903 (99.8)	
Positive	1 (0.1)		1 (0.1)		3 (0.2)		5 (0.2)	
Week 4								
N	668		669		1515		2852	
Negative	666 (99.7)		668 (99.9)		1512 (99.8)		2846 (99.8)	
Positive	2 (0.3)		1 (0.1)		3 (0.2)		6 (0.2)	
Week 8								
N	669		662		1493		2824	
Negative	666 (99.6)		661 (99.8)		1492 (99.9)		2819 (99.8)	
Positive	3 (0.4)		1 (0.2)		1 (0.1)		5 (0.2)	
Week 14								
N	655		655		1459		2769	
Negative	654 (99.8)		653 (99.7)		1459 (100)		2766 (99.9)	
Positive	1 (0.2)		2 (0.3)		0		3 (0.1)	
Week 26								
N	639		641		1439		2719	
Negative	639 (100)		640 (99.8)		1438 (99.9)		2717 (99.9)	
Positive	0		1 (0.2)		1 (0.1)		2 (0.1)	
Week 38								
N	465		472		1100		2037	
Negative	465 (100)		472 (100)		1098 (99.8)		2035 (99.9)	
Positive	0		0		2 (0.2)		2 (0.1)	
Week 52								
N	464		475		1116		2055	
Negative	464 (100)		475 (100)		1116 (100)		2055 (100)	
Positive	0		0		0		0	
Week 78								
N	410		419		414		1243	
Negative	410 (100)		419 (100)		414 (100)		1243 (100)	
Positive	0		0		0		0	
Follow-up (week 31/57/83)								
N	583		593		1293		2469	
Negative	582 (99.8)		593 (100)		1292 (99.9)		2467 (99.9)	
Positive	1 (0.2)		0		1 (0.1)		2 (0.1)	
Anytime post-baseline								
N	681		680		1534		2895	
Negative	678 (99.6)		676 (99.4)		1527 (99.5)		2881 (99.5)	
Positive	3 (0.4)		4 (0.6)		7 (0.5)		14 (0.5)	

'Oral sema': data from all three oral semaglutide doses (3, 7 and 14 mg).
 PIONEER 1 and 5 have planned follow-up visit in week 31. PIONEER 2, 4 and 9 have planned follow-up visit in week 57. PIONEER 3 has planned follow-up visit in week 83.
 N: number of subjects with non-missing information.

Overview of Anti-drug antibody positive subjects in PIONEER 1-5 and 9.

**PIONEER 1-5 and 9
ADA overview**



A: 1 subject with pre-existing ADA were only sampled at baseline.

B: 1 subject positive with treatment induced ADA at a single visit during treatment, were not sampled at follow up.

Table 1

Overall summary of clinical immunogenicity data

Trial	Design	Dose/route	Number of subjects	Patient population	Duration	Antibody positive (%)	Cross-reacting	Neutralizing	%B/T (Titer)
NN9924-3692 Phase I	Randomized, DB, Placebo controlled (PC), with SNAC	Oral, 2, 5, 10 and 20 mg sema	96 Males	Healthy	10 wks	0/96 (1B+)	0	0	0
NN9924-3991 Phase I	Randomized DB, multiple dose, placebo controlled, SNAC alone control	Oral, 5, 10, 20 , 40 mg sema	107 Males	Healthy + T2D	10 wks	0/59	0	0	0
NN9924-4140 Phase I	Randomized, DB, PC, Multiple dose	Oral, 5, 10, 20 , 40 mg sema	48 Males	Healthy	91 days	0/36	0	0	0
NN9924-3790 Phase II	Randomized, partially blinded, PC, 9 arm, 7 OS, 1 SS, 1 placebo	Oral 2.5, 5, 10, 20 and 40 mg once daily, SS 1 mg once weekly, placebo daily.	630 (M395; F325)	T2D	26 wks wk31 (FU)	3.2% (9/279) 1B+	44%(4/9) 1B+	0	1.2, 1.1, 1.1, 2, 1.6, 2.2, 4.5, 2.2, 1.8, 2.1
NN9924-4233 PIONEER 1	Randomized, DB, PC.	Oral 3, 7 and 14 mg once daily, placebo	703 (M357;F346)	T2D	26 wks	0.58% (3/516)	100% (3/3)	1/3	10,6,25
NN9924-4223 PIONEER 2	Randomized, OL, active control-empagliflozin 25 mg	Oral 3, 7,14 mg Empagliflozin 10, 25 mg tablets	821 (M415; F406)	T2D	52 wks	0.5 (2/401) 1B+	0	0	2.17, 2.75 1B+ (5.15)
NN9924-4222 PIONEER 3	Randomized, DB, 4 arms (3 oral sem vs sitagliptin 100 mg	Oral sem 3, 7, 14 mg; Sitgliptin 100 mg tablets	1863 (M984; F879)	T2D	78 wks	0.4 (6/1395)	33% (2/6)	0	1.93 - 9.82 (2.84, 9.82, 1.93, 3.28, 2.39, 2.05, 2.24)

<p>NN9924-4224 PIONEER 4</p>	<p>Randomized, DB, active control SC 1.8 mg Liraglutide</p>	<p>Oral sema 3, 7, 14 mg; Liraglutide 1.8 mg, placebo</p>	<p>711 (M 370; F341)</p>	<p>T2D; inadequately controlled with SGLT-2 inhibitors or insulin</p>	<p>52 wks</p>	<p>0.4 (1/283)</p>	<p>0</p>	<p>0</p>	<p>2.29</p>
<p>NN9924-4234 PIONEER 5</p>	<p>Randomized, DB, PC, active control</p>	<p>Oral sema 3,7,14 mg; Placebo</p>	<p>324 (M156;F 168)</p>	<p>T2D moderate renal impairment, inadequately controlled on Met/insulin</p>	<p>26 wks</p>	<p>0.6 (1/160)</p>	<p>100 (1/1)</p>	<p>0</p>	<p>15</p>
<p>NN9924-4281 PIONEER 9</p>	<p>Randomized, DB, PC and OL; 5 arm (Oral sema 3, 7, 14, placebo, Liraglutide 0.9 mg SC).</p>	<p>Oral sema 3, 7, 14, placebo, Liraglutide 0.9 mg SC.</p>	<p>243 (M191;F 52)</p>	<p>T2D</p>	<p>52 wks</p>	<p>1.4% (2/146)</p>	<p>50% (1/2)</p>	<p>0</p>	<p>1.58. 2.4</p>

The titers need to be multiplied by 15 to get the dilution adjusted titer.

Abbreviation used in the table: T2D- type 2 diabetes patients; OW- Once weekly; OD-once a day; DB-double blind; placebo-placebo controlled trial; OL-open label; SD-standard deviation; CV- coefficient of variation; Sema-Semaglutide; Tx-treatment; SC-subcutaneous

Reviewers comments:

Semaglutide treatment groups had low rates of ADA positive subjects. The titer of anti-semaglutide antibodies in confirmed positive subjects with ADA are generally low (1-10). Note that the titers are expressed without the initial 1:15 dilution of the sample for the assay and thus the titers are 15-150, which are still considered low titers. Only one sample in PIONEER 1 trial had a titer of 25 (dilution adjusted titer of 375). None of the other patients developed high titer antibodies.

Approximately 52% (11 out of 21) of the samples testing positive for anti-semaglutide antibody showed cross-reactivity with endogenous GLP- 1. Among the subjects confirmed positive for anti-semaglutide antibodies, the rate of subjects showing cross-reactivity to endogenous GLP-1 is high. However, considering the high homology between semaglutide and native GLP-1, this is expected.

In three phase III studies daily administration of oral semaglutide for 26,52 and 78 weeks with sampling points at week 4, 8 and 14 after initiation of treatment and subsequent samples at frequent intervals captures the transient as well as persistent antibody responses after chronic exposure. The rate of subjects testing positive for anti-semaglutide antibodies did not exceed 4% in any of the clinical trials. At the follow-up time point the ADA rate was lower indicating most ADA are transient and the rate of ADA is low after repeated exposures.

One sample in PIONEER 1 trial that had a % B/T value of 25 showed positivity for Nab assay. The same subject at subsequent time points with further treatment had lower titers and was negative for the Nab assay. Once the subject develops nAbs, it tends to correlate to the titer of the ADAs in subsequent time points. The negative nAb assay result indicates that it could be due the low sensitivity of the assay.

Drug induced Hypersensitivity reactions:

No serious hypersensitivity responses were evident during the trials for Semaglutide.

According to the protocol, if suspicion of trial-induced severe acute hypersensitivity occurred during the clinical trials, antibody samples were to be collected from the patients as soon as possible to assess for IgE anti-semaglutide antibodies using Immuno CAP assay. Tryptase is elevated in cases of systemic anaphylaxis and these samples are also assessed for levels of tryptase. During the trials six subjects had serum samples collected due to suspicion of severe acute hypersensitivity. All samples collected tested negative for IgE anti-semaglutide antibodies. Levels of tryptase were found to be within range for the samples analyzed.

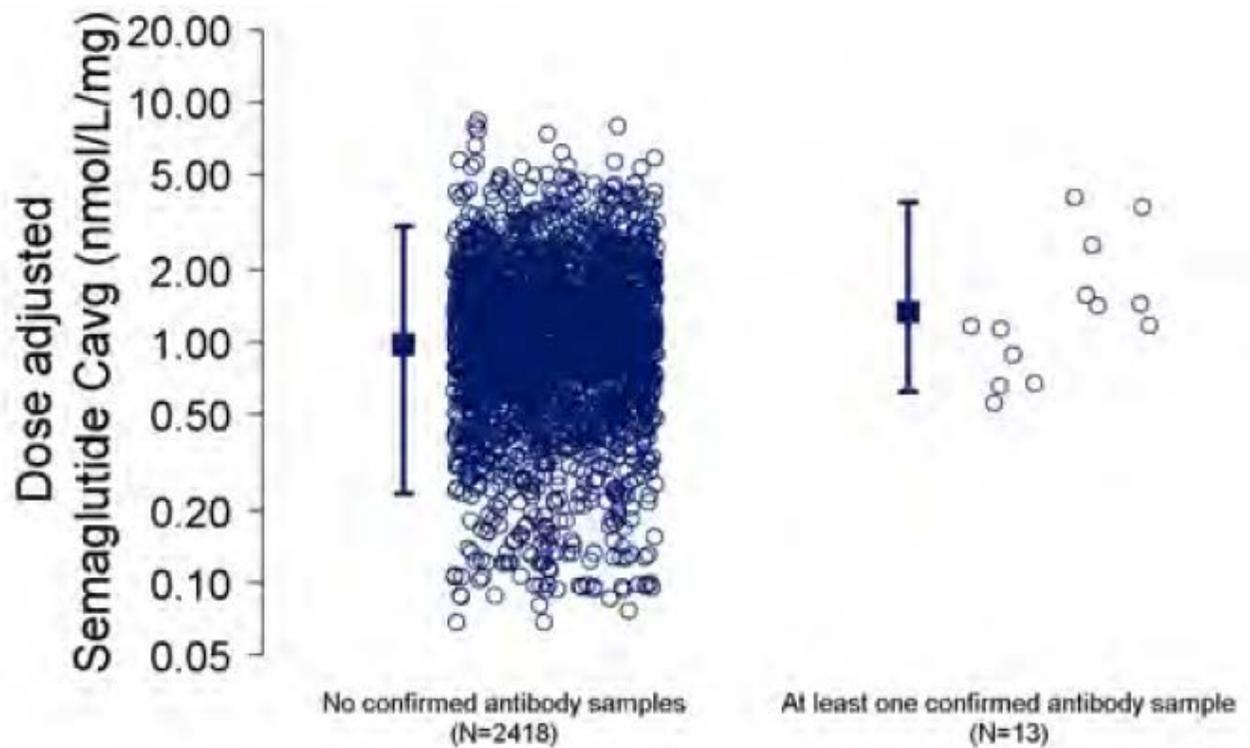
Reviewers comments:

Available data does not suggest that oral semaglutide can cause severe allergic reactions.

Effect of anti-semaglutide antibodies on semaglutide pharmacokinetics:

Only a few subjects developed anti-semaglutide antibodies during the trials. Of the subjects that were positive for anti-semaglutide antibodies, the exposure to the drug was similar to the subjects that were negative for anti-semaglutide antibodies.

Semaglutide exposure in subjects with and without anti-Semaglutide antibodies.



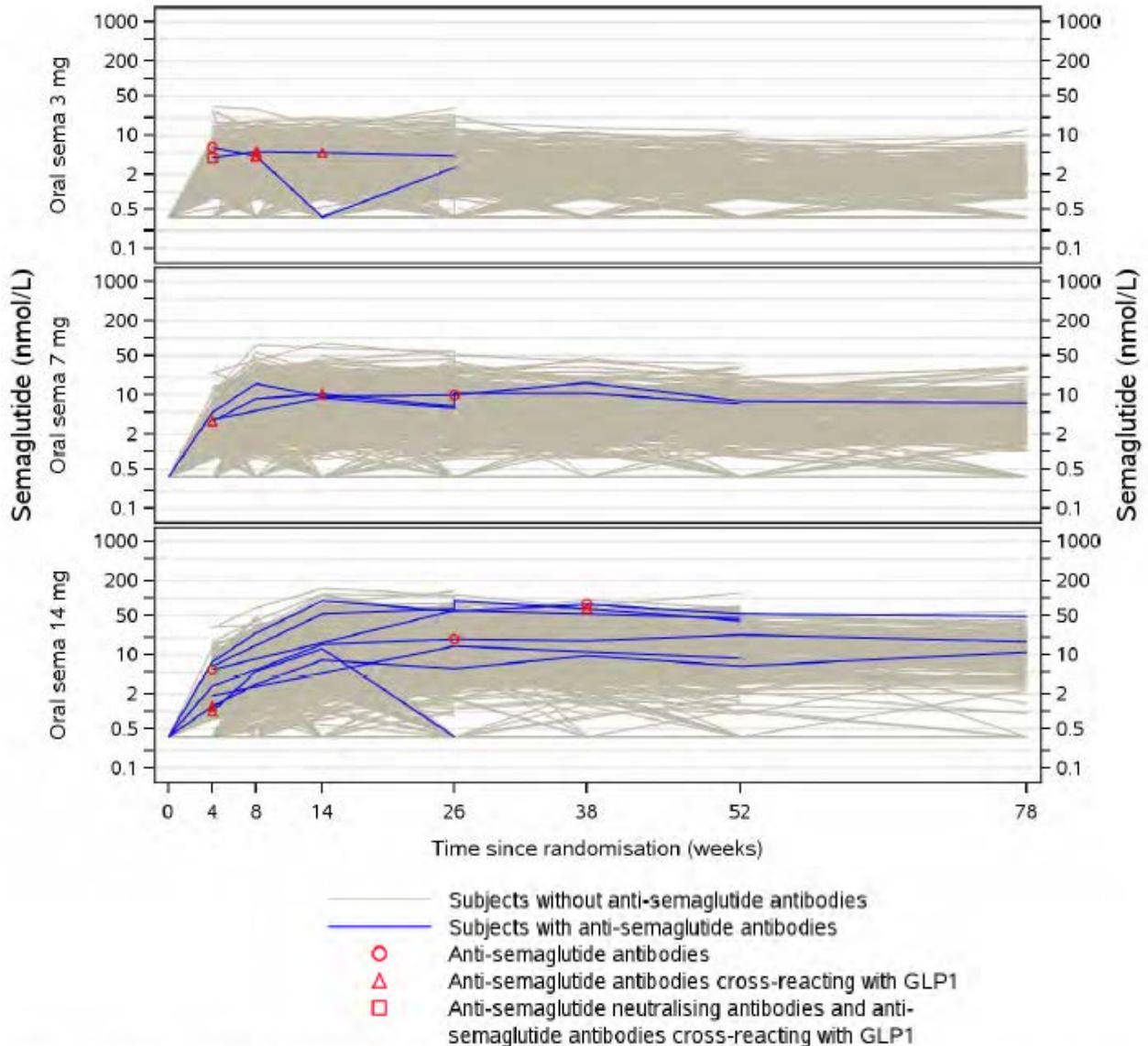
Data are individual (open circles) and geometric mean dose-normalised concentrations with 90% range (squares with error bars) for each group of subjects. Data from PIONEER 1, 2, 3, 5, 8 and 9.

N: number of PK observations

Reviewers comments:

The presence of antibodies does not seem to affect pharmacokinetics of semaglutide.

Semaglutide exposure in subjects with and without anti-Semaglutide antibodies.

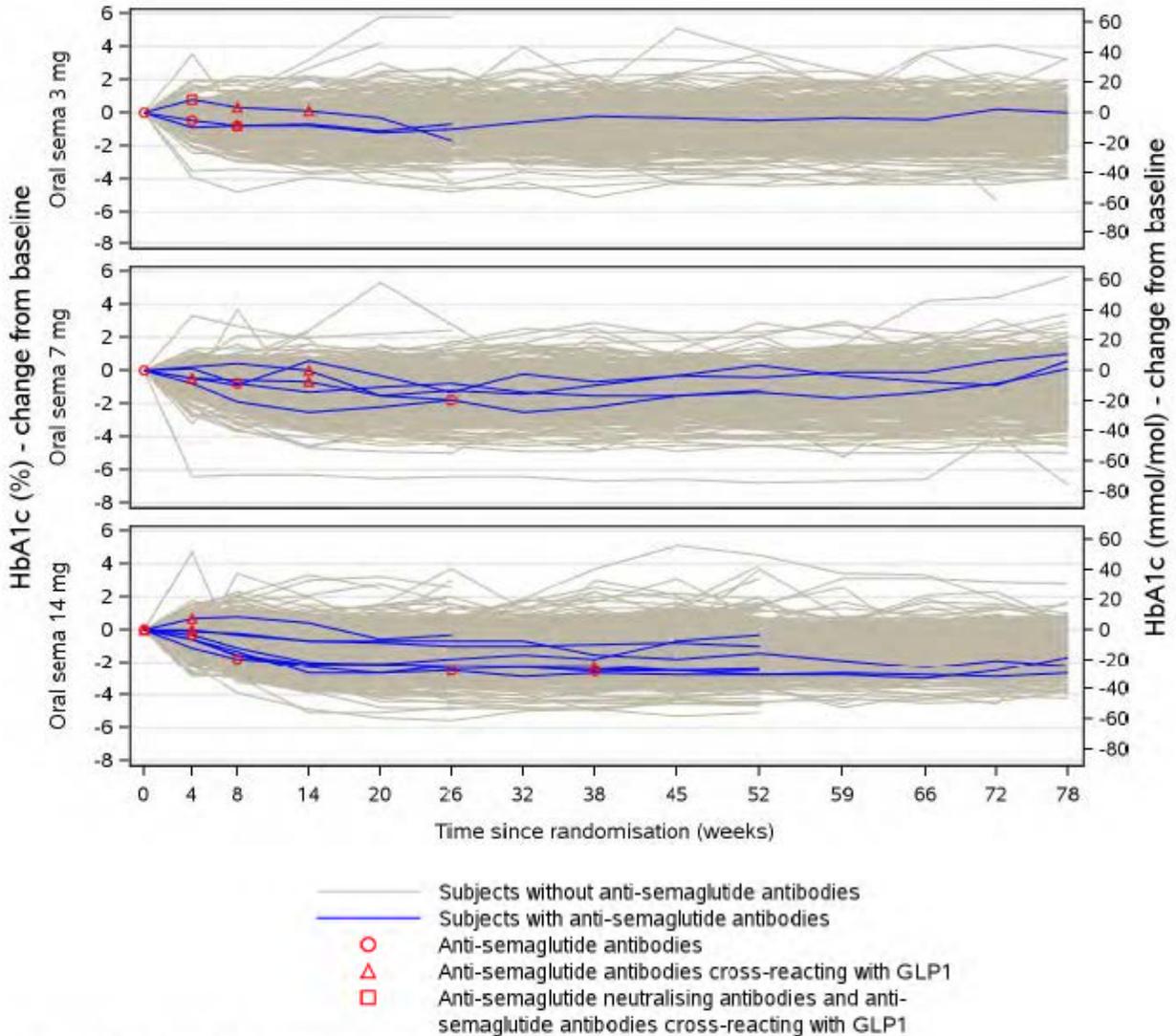


Observed data from the on-treatment observation period.

Solid lines (grey and blue) represent observed levels of semaglutide PK concentrations at each assessment over time 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.

There is no indication that ADA can impact on the product’s pharmacokinetics. Semaglutide plasma concentration was similar in subjects that tested positive for anti-semaglutide antibodies and in subjects without antibodies.

Impact of anti-semaglutide antibodies on efficacy as determined by the levels of HbA1c



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.

The investigation of the effect of ADA on efficacy was limited as the rate of ADA was low. The limited data available indicates that the occurrence of ADA did not modify the semaglutide-induced changes from baseline HbA1c for the individual subjects suggesting that the ADA did not impact on product efficacy.

Reviewers comments:

The presence of anti-semaglutide antibodies did not modify the PK or PD response

Presence of ADA did not influence the HbA1c lowering effect of semaglutide. Of note, doctors treat diabetes to normalize Hb1Ac, so this may not be the most reliable pharmacodynamic marker.

Impact of anti-semaglutide antibodies on safety

The sponsor provided a table assessing the association between adverse events and the development of anti-semaglutide antibodies in the phase 3a trials. In PIONEER 1-5 and 9, 14 subjects positive for anti-semaglutide antibodies post baseline reported 64 adverse events while on treatment. The Sponsor reported that the adverse events were non-serious and mild or moderate in severity. Most of these events were considered unlikely related to the treatment and most subjects recovered. There were two events, abdominal pain and vertigo, reported in one subject that led to premature discontinuation of treatment. The events reported in subjects positive for anti-semaglutide antibodies were distributed across without any specific clustering.

7.1.8 Adverse events by system organ class and preferred term reported for subjects positive for anti-semaglutide antibodies – oral semaglutide – phase 3a pool – on-treatment – safety analysis set

	Oral sema N	(%)	E	R
Number of subjects	17			
Exposure time (years)	19			
All events	14 (82.4)		64	333.0
Infections and infestations	9 (52.9)		15	78.1
Nasopharyngitis	4 (23.5)		6	31.2
Bronchitis	2 (11.8)		2	10.4
Gingivitis	2 (11.8)		2	10.4
Cystitis	1 (5.9)		1	5.2
Gastroenteritis	1 (5.9)		1	5.2
Gastroenteritis viral	1 (5.9)		1	5.2
Pharyngitis	1 (5.9)		1	5.2
Sinusitis	1 (5.9)		1	5.2
Gastrointestinal disorders	6 (35.3)		12	62.4
Dyspepsia	2 (11.8)		3	15.6
Nausea	2 (11.8)		4	20.8
Abdominal pain	1 (5.9)		1	5.2
Diarrhoea	1 (5.9)		1	5.2
Flatulence	1 (5.9)		1	5.2
Vomiting	1 (5.9)		2	10.4
Nervous system disorders	6 (35.3)		8	41.6
Headache	5 (29.4)		6	31.2
Sciatica	1 (5.9)		1	5.2
Sinus headache	1 (5.9)		1	5.2
Metabolism and nutrition disorders	4 (23.5)		4	20.8
Decreased appetite	2 (11.8)		2	10.4
Diabetic metabolic decompensation	1 (5.9)		1	5.2
Hypertriglyceridaemia	1 (5.9)		1	5.2
Respiratory, thoracic and mediastinal disorders	3 (17.6)		7	36.4
Asthma	1 (5.9)		1	5.2
Epistaxis	1 (5.9)		3	15.6
Oropharyngeal pain	1 (5.9)		1	5.2
Rhinorrhoea	1 (5.9)		1	5.2
Sinus congestion	1 (5.9)		1	5.2
Vascular disorders	3 (17.6)		3	15.6
Hypertension	3 (17.6)		3	15.6
Ear and labyrinth disorders	2 (11.8)		2	10.4
Vertigo	1 (5.9)		1	5.2
Vertigo positional	1 (5.9)		1	5.2
Musculoskeletal and connective tissue disorders	2 (11.8)		4	20.8
Back pain	2 (11.8)		3	15.6
Musculoskeletal pain	1 (5.9)		1	5.2
Blood and lymphatic system disorders	1 (5.9)		2	10.4
Iron deficiency anaemia	1 (5.9)		1	5.2
Leukocytosis	1 (5.9)		1	5.2

Phase 3a pool: PIONEER 1-5 and 7-10.

'Oral sema': data from all three oral semaglutide doses (3, 7 and 14 mg).

Sorted in descending order by system organ class and preferred term based on the proportion of subjects with at least one event in the oral semaglutide group.

N: number of subjects with at least one event; %: proportion of subjects with at least one event; E: number of events; R: events per 100 years of exposure.

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	Oral sema N	(%)	E	R
Eye disorders	1	(5.9)	1	5.2
Diabetic retinopathy	1	(5.9)	1	5.2
General disorders and administration site conditions	1	(5.9)	1	5.2
Swelling	1	(5.9)	1	5.2
Immune system disorders	1	(5.9)	1	5.2
Seasonal allergy	1	(5.9)	1	5.2
Injury, poisoning and procedural complications	1	(5.9)	1	5.2
Foot fracture	1	(5.9)	1	5.2
Investigations	1	(5.9)	1	5.2
Blood lactic acid increased	1	(5.9)	1	5.2
Psychiatric disorders	1	(5.9)	1	5.2
Nervousness	1	(5.9)	1	5.2
Skin and subcutaneous tissue disorders	1	(5.9)	1	5.2
Psoriasis	1	(5.9)	1	5.2

Reviewers comments:

No link was evident between adverse events and the presence of ADA. Therefore development of ADA does not appear to affect safety or efficacy of semaglutide.

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