CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209637Orig1s000

OTHER REVIEW(S)

PMR/PMC DEVELOPMENT TEMPLATE

For 506B Reportable[1] PMRs and PMCs only

This form describes and provides the rationale for postmarketing requirements/commitments (PMRs/PMCs) subject to reporting requirements under section 506B of the FDCA.

Complete this form using the *instructions* (see Appendix A) and by referring to ***MAPP 6010.9***, "Procedures and Responsibilities for Developing Postmarketing Commitments and Requirements."

Note: Do ***not*** use this template for CMC PMCs. Instead, use the CMC PMC Development Template.[1]

SECTION A: Administrative Information

NDA/BLA/Supplement #	NDA 209637
PMR/PMC Set (####-#)	3294-1
Product Name:	OZEMPIC (semaglutide) injection
Applicant Name:	Novo Nordisk, Inc.
ODE/Division:	ODE II / DMEP

SECTION B: PMR/PMC Information

1. PMR/PMC Description

Conduct a 26-week, randomized, double-blind, placebo-controlled parallel group study of the safety and efficacy of Ozempic (semaglutide) for the treatment of type 2 diabetes mellitus in pediatric patients ages 10 to 17 years (inclusive), followed by a 26-week open-label, controlled extension. Background therapy will consist of either metformin, insulin, or metformin plus insulin.

2. PMR/PMC Schedule Milestones[2, 3]

Draft Protocol Submission:	03/2018
Final Protocol Submission:	01/2019
Study Completion:	12/2026
Final Report Submission:	10/2027

[1] 506B "reportable" includes all studies/trials an applicant has agreed upon or is required to conduct related to clinical safety, clinical efficacy, clinical pharmacology, or nonclinical toxicology (21 CFR 314.81(b)(2)(vii) and 21 CFR 601.70(a)). All PMRs are considered 506 "reportable." A separate development template is used for 506 B non-reportable (e.g., chemistry, manufacturing, and controls (CMC)) PMCs, which is located in the CST.

[2] *Final protocol*, *study/trial completion*, and *final report* submissions are required milestones. *Draft protocol submissions* and *interim* milestones are optional. EXCEPTION: PMRs/PMCs for medical countermeasures may have only draft/final protocol submission dates and no other milestones, since the study/trial will only be initiated in the event of an emergency. Interim milestones may include interim report milestones for studies/trials that may be of long duration. May include interim subject accrual milestone (e.g., for accelerated approval PMRs). Other milestones should be justified in Section D, question 3.

[3] Dates should be numerical (e.g., 05/2016). PREA PMR date format may be MM/DD/YYYY if a day is specified.

SECTION C: PMR/PMC Rationale

1. Describe the particular review issue and the goal of the study[4] or clinical trial[5] in the text box below.

The goal of this PMR is to establish the safety and efficacy of Ozempic (semaglutide) in pediatric patients ages 10 to 17 (inclusive).

2. Explain why this issue can be evaluated post-approval and does not need to be addressed prior to approval. (Select one explanation below.)

- ☐ Subpart I or H (animal efficacy rule) PMR: Approved under Subpart I or H (animal efficacy rule) authorities; postmarketing study/trial required to verify and describe clinical benefit ***[Skip to Q.5]***
- ☐ Subpart H or E (accelerated approval) PMR: Approved under Subpart H or E (accelerated approval) authorities; postmarketing study/trial required to verify and describe clinical benefit ***[Skip to Q.5]***
- ☒ PREA PMR: Meets PREA postmarketing pediatric study *requirements* ***[Skip to Q.5]***
- ☐ FDAAA PMR (safety): Benefit/risk profile of the drug appears favorable; however, there are uncertainties about aspects of the drug's safety profile. Because the investigation will evaluate a serious risk, it meets FDAAA requirements for a postmarketing safety study or trial ***[Go to Q.3]***
- ☐ PMC (506B reportable): Benefit/risk profile of the drug appears favorable; however, there are uncertainties about aspects of the drug's efficacy profile or other issues. The purpose of the investigation does not meet requirements under Subpart I/H , H/E, PREA, or FDAAA to be a PMR, and therefore the investigation is a PMC. ***[Go to Q.3]***

3. For FDAAA PMRs and 506B PMCs only

The study or trial can be conducted post-approval because: ***[Select all that apply]***

- ☐ Longer-term data needed to further characterize the safety/efficacy of the drug
- ☐ Based on the purpose and/or design, it is only feasible to conduct the study/trial post-approval
- ☐ Prior clinical experience (e.g., with other drugs in the class) indicates adequate safety or efficacy data to support approval, but some uncertainties about safety or efficacy remain and should be further characterized
- ☐ Only a small subpopulation is affected (e.g., patients with severe renal impairment) and effects of the drug in the subpopulation can be further evaluated after approval
- ☐ Study/trial is to further explore a theoretical concern that does not impact the approval determination
- ☐ Other reason (describe in text box below)

[4] A "study" is an investigation that is not a clinical trial, such as an observational (epidemiologic) study, animal study, or laboratory experiment.

[5] A "clinical trial" is any prospective investigation in which the applicant or investigator determines the method of assigning the drug product(s) or other interventions to one or more human subjects. Note that under PREA, clinical trials involving pediatric patients are specifically referred to as "studies."

4. **<u>For FDAAA PMRs only</u>** ***[for PMCs skip to Q.5]. Complete this entire section***

a. The purpose of the study/clinical trial is to: ***[Select one, then go to Q.4.b]***

- ☐ Assess a <u>known serious risk</u> related to the use of the drug
- ☐ Assess a <u>signal of serious risk</u> related to the use of the drug
- ☐ Identify an <u>unexpected serious risk</u> when available data indicate the potential for a serious risk

Complete Q4.b if the necessary data can only be obtained through a particular type of nonclinical study or clinical pharmacology trial. Otherwise complete Q4.c and Q4.d.

b. FAERS[6] and Sentinel's postmarket ARIA[7] system are not sufficient for the purposes described in Q1. and Q4.a because the safety issue involves:

[Select all that apply then to skip to Q.5. If none apply, answer both Q4.c and Q4.d]

- ☐ A serious risk of genotoxicity, carcinogenicity, or reproductive toxicity, and these signals are initially best assessed through in vitro or animal studies.
- ☐ A potential drug interaction resulting in lower/higher drug exposure and resultant serious drug risks, and accurate assessment of an interaction is feasible only through in vitro mechanistic studies or clinical pharmacokinetic and pharmacodynamics trials.
- ☐ The potential for lower/higher drug exposure and resultant serious drug risks in patients with hepatic or renal impairment, or other metabolic abnormalities, and accurate assessment is feasible only through in vitro mechanistic studies or clinical pharmacokinetic and pharmacodynamics trials.
- ☐ An immunologic concern for which accurate assessment requires in vitro development or validation of specific assays.

[6] FDA Adverse Event Reporting System (FAERS)

[7] Active Risk Identification and Analysis (ARIA)

Complete Q4.c when FAERS cannot provide the necessary data and Q4.b does not apply

c. FAERS data cannot be used to fully characterize the serious risk of interest because:

[Select all that apply then go to Q.4.d]

- ☐ Assessment of the serious risk necessitates calculation of the rate of occurrence (e.g., incidence or odds ratio) of the adverse event(s), and FAERS data cannot be used for such a calculation.
- ☐ The serious risk of concern has a delayed time to onset, or delayed time to detection after exposure (e.g., cancer), and FAERS data are more useful for detecting events that are closely linked in time to initiation of drug therapy.
- ☐ The serious risk of concern occurs commonly in the population (e.g., myocardial infarction) and FAERS data are more useful in detecting rare serious adverse events for which the background rates are low.
- ☐ Other

Complete Q4.d when the ARIA system cannot provide the necessary data and Q4.b does not apply.

d. The currently available data within the ARIA system cannot be used to fully characterize the serious risk of interest because: *[Select all that apply then go to Q.4.e]*

- ☐ Cannot identify exposure to the drug(s) of interest in the database.
- ☐ Serious risk (adverse event) of concern cannot be identified in the database.
- ☐ The population(s) of interest cannot be identified in the database.
- ☐ Long-term follow-up information required to assess the serious risk are not available in the database.
- ☐ Important confounders or covariates are not available or well represented in the database.
- ☐ The database does not contain an adequate number of exposed patients to provide sufficient statistical power to analyze the association between the drug and the serious risk of concern.
- ☐ The purpose of the evaluation is to rule out a modest relative risk, and observational studies, such as an ARIA analysis, are not well suited for such use.
- ☐ Other

e. **If FAERS and the ARIA system are not sufficient for the purpose in Q1. and Q4.a, is a study sufficient?**
[Select either "Yes" or "No" and provide the appropriate responses.]

☐ **Yes**, a study is sufficient *[Explain your answer in the textbox and then go to Q.5]*

☐ **No**, a study is not sufficient *[Select all explanations that apply then go to Q.4.f]*

- ☐ Need to minimize bias and/or confounding via randomization
- ☐ Need for placebo control
- ☐ Need to capture detailed information about covariates or confounders that are either not routinely collected during the ususal course of medical practice, or are not collected at the frequency needed for assessment of the safety issue (e.g. hourly blood glucose measures, etc.).
- ☐ Need pre-specified and prospective active data collection of the outcome/endpoint of interest
- ☐ Other

f. ☐ **Because a study is not sufficient, a clinical trial is required.** *[Go to Q.5]*

5. **For all PMRs and PMCs: What type of study or clinical trial is needed to achieve the goal described in Q1 *or* Q4.a above?**
[Select ONE OPTION only under either "Type of Study" or "Type of clinical Trial"]

TYPE OF STUDY
☐ Drug interaction or bioavailability studies (nonclinical only)
☐ Epidemiologic (observational) study related to safe drug use
☐ Epidemiologic (observational) study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Immunogenicity study (nonclinical)
☐ Meta-analysis or pooled analysis of previous observational studies
☐ Nonclinical (animal) study (e.g., genotoxicity, carcinogenicity, reproductive toxicology)
☐ Nonclinical (in vitro) study (laboratory/microbiology resistance, receptor affinity)
☐ Pharmacogenetic or pharmacogenomic study
☐ Pharmacokinetic (PK) and/or pharmacodynamics (PD) study (nonclinical only)
☐ Quality CMC study (e.g., manufacturing, studies on impurities)
☐ Quality stability study
☐ Registry-based observational study

TYPE OF STUDY
☐ Other (describe) _____

TYPE OF CLINICAL TRIAL
☒ Combined PK/PD, safety and/or efficacy trial (*PREA* PMRs only*)
☐ Dose-response clinical trial
☐ Dosing trial (e.g., alternative dosing schedule)
☐ Drug interaction or bioavailability clinical trial (clinical only)
☐ Immunogenicity trial (clinical)
☐ Meta-analysis or pooled analysis of previous clinical trials
☐ Pharmacogenetic or pharmacogenomic clinical trial
☐ Pharmacokinetic (PK) and/or pharmacodynamic (PD) clinical trial
☐ Primary efficacy clinical trial (i.e, with a primary efficacy endpoint; to further define efficacy; may include secondary safety endpoints)
☐ Primary safety clinical trial (e.g., to evaluate the long-term safety of a drug; to evaluate drug toxicity in a subpopulation; may include secondary efficacy endpoints) – *excludes SOT*
☐ Safety outcomes trial (SOT)**
☐ Thorough Q-T clinical trial
☐ Other (describe) _____

* Note that under PREA, clinical trials involving pediatric patients are specifically referred to as "studies." However, for the purposes of this template, PREA investigations are categorized according to the established definitions of "studies" and "trials" (see Footnotes 3 and 4).

** A safety outcomes trial (SOT) is defined as a large, prospective, randomized, controlled trial that is specifically designed and adequately powered to test a safety hypothesis using a clinical outcome, generally irreversible morbidity or mortality, as the primary trial endpoint. A cardiovascular outcomes trial (CVOT) is an example of an SOT.

SECTION D: PMR/PMC Additional Information

1. This PMR/PMC applies to other drugs or applications (e.g. drugs in a therapeutic class; different formulations of the same drug).

☐ Yes

☒ No

2. **This study or clinical trial focuses on the following special population(s) or circumstance(s):** ***[Select all that apply]***

- ☐ *For non-PREA pediatric studies/trials only*: Pediatric population
- ☐ Geriatric population
- ☐ Lactating/nursing mothers
- ☐ Medical Countermeasures (e.g. anthrax exposure, bioterrorism)
- ☐ Orphan or rare disease population
- ☐ Pregnant women
- ☐ Racial/ethnic population
- ☒ Not applicable

3. **(Complete if applicable) Additional comments about the PMR/PMC** (e.g., points or concerns not previously described; explanation for inclusion of milestones other than the 3 "core" milestones or draft protocol submission)

SECTION E: PMR/PMC Development Coordinator Statements[8]

1. **The PMR/PMC is clear, feasible, and appropriate[9] because:** ***[Select all that apply]***

- ☒ The study/clinical trial meets criteria for a PMR or a PMC.
- ☒ The objectives of the study/clinical trial are clear from the description of the PMR/PMC.
- ☒ The applicant has adequately justified the choice of milestone dates.
- ☒ The applicant has had sufficient time to review the PMR/PMC, ask questions, determine feasibility, and contribute to the development process.

2. ☒ (***If the PMR/PMC is a randomized controlled clinical trial***) **The following ethical considerations were made with regard to:**

- There is a significant question about the public health risks of the drug.
- There is not enough existing information to assess the public health risks of the drug.
- Information about the public health risks cannot be gained through a different kind of investigation.
- The trial will be appropriately designed to answer question about a drug's efficacy or safety.

[8] This section is completed by the PMR/PMC Development Coordinator, who is usually the OND division's Deputy Director for Safety (DDS). See DEFINITIONS section of CDER MAPP 6010.9, *Procedures and Responsibilities for Developing Postmarketing Requirements and Commitments.*

[9] See POLICY section of CDER MAPP 6010.9.

- The trial will emphasize minimizing the risk minimization for participants as the protocol is developed.

3. ☒ This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

Refer to electronic DARRTS signature

PMR/PMC DEVELOPMENT TEMPLATE

For 506B Reportable[1] PMRs and PMCs only

This form describes and provides the rationale for postmarketing requirements/commitments (PMRs/PMCs) subject to reporting requirements under section 506B of the FDCA.

Complete this form using the *instructions* (see Appendix A) and by referring to ***MAPP 6010.9***, "Procedures and Responsibilities for Developing Postmarketing Commitments and Requirements."

Note: Do ***not*** use this template for CMC PMCs. Instead, use the CMC PMC Development Template.[1]

SECTION A: Administrative Information

NDA/BLA/Supplement #	NDA 209637
PMR/PMC Set (####-#)	3294-2
Product Name:	OZEMPIC (semaglutide) injection
Applicant Name:	Novo Nordisk, Inc.
ODE/Division:	ODE II / DMEP

SECTION B: PMR/PMC Information

1. PMR/PMC Description

Conduct a medullary thyroid carcinoma registry-based case series of at least 15 years duration to systematically monitor the annual incidence of medullary thyroid carcinoma in the United States and to identify any increase related to the introduction of Ozempic (semaglutide) into the marketplace. This study will also establish a registry of incident cases of medullary thyroid carcinoma and characterize their medical histories related to diabetes and use of Ozempic (semaglutide).

2. PMR/PMC Schedule Milestones[2, 3]

Draft Protocol Submission:	08/2018
Final Protocol Submission:	02/2019
Interim Report Submissions:	03/2020, 03/2021, 03/2022, 03/2023, 03/2024, 03/2025, 03/2026, 03/2027, 03/2028, 03/2029, 03/2030, 03/2031, 03/2032, 03/2033
Study Completion:	05/2034
Final Report Submission:	05/2035

[1] 506B "reportable" includes all studies/trials an applicant has agreed upon or is required to conduct related to clinical safety, clinical efficacy, clinical pharmacology, or nonclinical toxicology (21 CFR 314.81(b)(2)(vii) and 21 CFR 601.70(a)). All PMRs are considered 506 "reportable." A separate development template is used for 506 B non-reportable (e.g., chemistry, manufacturing, and controls (CMC)) PMCs, which is located in the CST.

[2] *Final protocol*, *study/trial completion*, and *final report* submissions are required milestones. *Draft protocol submissions* and *interim* milestones are optional. EXCEPTION: PMRs/PMCs for medical countermeasures may have only draft/final protocol submission dates and no other milestones, since the study/trial will only be initiated in the event of an emergency. Interim milestones may include interim report milestones for studies/trials that may be of long duration. May include interim subject accrual milestone (e.g., for accelerated approval PMRs). Other milestones should be justified in Section D, question 3.

[3] Dates should be numerical (e.g., 05/2016). PREA PMR date format may be MM/DD/YYYY if a day is specified.

SECTION C: PMR/PMC Rationale

1. Describe the particular review issue and the goal of the study[4] or clinical trial[5] in the text box below.

Based on nonclinical studies, glucagon-like peptide-1 (GLP-1) agonists have been associated with thyroid C-cell tumors. The goal of the registry is to detect the majority of cases of medullary thyroid carcinoma (MTC) which occur in the United States over the 15 year period after marketing approval of semaglutide, to evaluate all cases for risk factors for MTC and for exposure to diabetes medications, and to determine whether there is a relationship between semaglutide exposure and risk for MTC in humans.

2. Explain why this issue can be evaluated post-approval and does not need to be addressed prior to approval. (Select one explanation below.)

- ☐ Subpart I or H (animal efficacy rule) PMR: Approved under Subpart I or H (animal efficacy rule) authorities; postmarketing study/trial required to verify and describe clinical benefit ***[Skip to Q.5]***
- ☐ Subpart H or E (accelerated approval) PMR: Approved under Subpart H or E (accelerated approval) authorities; postmarketing study/trial required to verify and describe clinical benefit ***[Skip to Q.5]***
- ☐ PREA PMR: Meets PREA postmarketing pediatric study *requirements* ***[Skip to Q.5]***
- ☒ FDAAA PMR (safety): Benefit/risk profile of the drug appears favorable; however, there are uncertainties about aspects of the drug's safety profile. Because the investigation will evaluate a serious risk, it meets FDAAA requirements for a postmarketing safety study or trial ***[Go to Q.3]***
- ☐ PMC (506B reportable): Benefit/risk profile of the drug appears favorable; however, there are uncertainties about aspects of the drug's efficacy profile or other issues. The purpose of the investigation does not meet requirements under Subpart I/H , H/E, PREA, or FDAAA to be a PMR, and therefore the investigation is a PMC. ***[Go to Q.3]***

3. For FDAAA PMRs and 506B PMCs only

The study or trial can be conducted post-approval because: *[Select all that apply]*

- ☒ Longer-term data needed to further characterize the safety/efficacy of the drug
- ☒ Based on the purpose and/or design, it is only feasible to conduct the study/trial post-approval
- ☒ Prior clinical experience (e.g., with other drugs in the class) indicates adequate safety or efficacy data to support approval, but some uncertainties about safety or efficacy remain and should be further characterized
- ☐ Only a small subpopulation is affected (e.g., patients with severe renal impairment) and effects of the drug in the subpopulation can be further evaluated after approval
- ☐ Study/trial is to further explore a theoretical concern that does not impact the approval determination
- ☐ Other reason (describe in text box below)

[4] A "study" is an investigation that is not a clinical trial, such as an observational (epidemiologic) study, animal study, or laboratory experiment.

[5] A "clinical trial" is any prospective investigation in which the applicant or investigator determines the method of assigning the drug product(s) or other interventions to one or more human subjects. Note that under PREA, clinical trials involving pediatric patients are specifically referred to as "studies."

4. **<u>For FDAAA PMRs only</u>** ***[for PMCs skip to Q.5]. Complete this entire section***

a. The purpose of the study/clinical trial is to: ***[Select one, then go to Q.4.b]***

- ☐ Assess a <u>known serious risk</u> related to the use of the drug
- ☒ Assess a <u>signal of serious risk</u> related to the use of the drug
- ☐ Identify an <u>unexpected serious risk</u> when available data indicate the potential for a serious risk

Complete Q4.b if the necessary data can only be obtained through a particular type of nonclinical study or clinical pharmacology trial. Otherwise complete Q4.c and Q4.d.

b. FAERS[6] and Sentinel's postmarket ARIA[7] system are not sufficient for the purposes described in Q1. and Q4.a because the safety issue involves:

[Select all that apply then to skip to Q.5. If none apply, answer both Q4.c and Q4.d]

- ☐ A serious risk of genotoxicity, carcinogenicity, or reproductive toxicity, and these signals are initially best assessed through in vitro or animal studies.
- ☐ A potential drug interaction resulting in lower/higher drug exposure and resultant serious drug risks, and accurate assessment of an interaction is feasible only through in vitro mechanistic studies or clinical pharmacokinetic and pharmacodynamics trials.
- ☐ The potential for lower/higher drug exposure and resultant serious drug risks in patients with hepatic or renal impairment, or other metabolic abnormalities, and accurate assessment is feasible only through in vitro mechanistic studies or clinical pharmacokinetic and pharmacodynamics trials.
- ☐ An immunologic concern for which accurate assessment requires in vitro development or validation of specific assays.

[6] FDA Adverse Event Reporting System (FAERS)

[7] Active Risk Identification and Analysis (ARIA)

Complete Q4.c when FAERS cannot provide the necessary data and Q4.b does not apply

c. FAERS data cannot be used to fully characterize the serious risk of interest because:

[Select all that apply then go to Q.4.d]

- ☒ Assessment of the serious risk necessitates calculation of the rate of occurrence (e.g., incidence or odds ratio) of the adverse event(s), and FAERS data cannot be used for such a calculation.
- ☒ The serious risk of concern has a delayed time to onset, or delayed time to detection after exposure (e.g., cancer), and FAERS data are more useful for detecting events that are closely linked in time to initiation of drug therapy.
- ☐ The serious risk of concern occurs commonly in the population (e.g., myocardial infarction) and FAERS data are more useful in detecting rare serious adverse events for which the background rates are low.
- ☐ Other

Complete Q4.d when the ARIA system cannot provide the necessary data and Q4.b does not apply.

d. The currently available data within the ARIA system cannot be used to fully characterize the serious risk of interest because: *[Select all that apply then go to Q.4.e]*

- ☐ Cannot identify exposure to the drug(s) of interest in the database.
- ☐ Serious risk (adverse event) of concern cannot be identified in the database.
- ☐ The population(s) of interest cannot be identified in the database.
- ☒ Long-term follow-up information required to assess the serious risk are not available in the database.
- ☐ Important confounders or covariates are not available or well represented in the database.
- ☒ The database does not contain an adequate number of exposed patients to provide sufficient statistical power to analyze the association between the drug and the serious risk of concern.
- ☐ The purpose of the evaluation is to rule out a modest relative risk, and observational studies, such as an ARIA analysis, are not well suited for such use.
- ☐ Other

e. If FAERS and the ARIA system are not sufficient for the purpose in Q1. and Q4.a, is a study sufficient?
[Select either "Yes" or "No" and provide the appropriate responses.]

☒ **Yes**, a study is sufficient *[Explain your answer in the textbox and then go to Q.5]*

Upon FDA's approval of the first long-acting GLP-1 receptor agonists in 2010, the MTC case series registry was initiated to observe all new cases of MTC diagnosed in the United States for at least 15 years. This registry aims to monitor the annual incidence and change in incidence of MTC; and document demographic, medical and risk factors related to the MTC diagnosis among MTC cases in the MTC participating State Cancer Registries. All MTC cases were clinically confirmed and the MTC case series registry verifies GLP-1 receptor agonist treatment through treating physicians. Currently, the MTC case series registry covered (b)(4)% of the U.S. population from the (b)(4)participating states. As of January 2017, there were a total of (b) (4) MTC cases reported to the registry and (b) (4) finished participation. Given the challenges likely in obtaining a population with sufficient semaglutide exposure, duration of follow-up, and number of events given the rarity of MTC, the use of an MTC registry design is sufficient.

☐ **No**, a study is not sufficient *[Select all explanations that apply then go to Q.4.f]*

- ☐ Need to minimize bias and/or confounding via randomization
- ☐ Need for placebo control
- ☐ Need to capture detailed information about covariates or confounders that are either not routinely collected during the ususal course of medical practice, or are not collected at the frequency needed for assessment of the safety issue (e.g. hourly blood glucose measures, etc.).
- ☐ Need pre-specified and prospective active data collection of the outcome/endpoint of interest
- ☐ Other

f. ☐ **Because a study is not sufficient, a clinical trial is required.** *[Go to Q.5]*

5. <u>For all PMRs and PMCs</u>: What type of study or clinical trial is needed to achieve the goal described in Q1 *<u>or</u>* Q4.a above?
[Select ONE OPTION only under <u>either</u> "Type of Study" <u>or</u> "Type of clinical Trial"]

TYPE OF STUDY
☐ Drug interaction or bioavailability studies (nonclinical only)
☐ Epidemiologic (observational) study related to safe drug use
☐ Epidemiologic (observational) study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)

TYPE OF STUDY
☐ Immunogenicity study (nonclinical)
☐ Meta-analysis or pooled analysis of previous observational studies
☐ Nonclinical (animal) study (e.g., genotoxicity, carcinogenicity, reproductive toxicology)
☐ Nonclinical (in vitro) study (laboratory/microbiology resistance, receptor affinity)
☐ Pharmacogenetic or pharmacogenomic study
☐ Pharmacokinetic (PK) and/or pharmacodynamics (PD) study (nonclinical only)
☐ Quality CMC study (e.g., manufacturing, studies on impurities)
☐ Quality stability study
☒ Registry-based observational study
☐ Other (describe) _____

TYPE OF CLINICAL TRIAL
☐ Combined PK/PD, safety and/or efficacy trial (*PREA* PMRs only*)
☐ Dose-response clinical trial
☐ Dosing trial (e.g., alternative dosing schedule)
☐ Drug interaction or bioavailability clinical trial (clinical only)
☐ Immunogenicity trial (clinical)
☐ Meta-analysis or pooled analysis of previous clinical trials
☐ Pharmacogenetic or pharmacogenomic clinical trial
☐ Pharmacokinetic (PK) and/or pharmacodynamic (PD) clinical trial
☐ Primary efficacy clinical trial (i.e, with a primary efficacy endpoint; to further define efficacy; may include secondary safety endpoints)
☐ Primary safety clinical trial (e.g., to evaluate the long-term safety of a drug; to evaluate drug toxicity in a subpopulation; may include secondary efficacy endpoints) – *excludes SOT*
☐ Safety outcomes trial (SOT)**
☐ Thorough Q-T clinical trial
☐ Other (describe) _____

* Note that under PREA, clinical trials involving pediatric patients are specifically referred to as "studies." However, for the purposes of this template, PREA investigations are categorized according to the established definitions of "studies" and "trials" (see Footnotes 3 and 4).

** A safety outcomes trial (SOT) is defined as a large, prospective, randomized, controlled trial that is specifically designed and adequately powered to test a safety hypothesis using a clinical outcome, generally irreversible morbidity or mortality, as the primary trial endpoint. A cardiovascular outcomes trial (CVOT) is an example of an SOT.

SECTION D: PMR/PMC Additional Information

1. This PMR/PMC applies to other drugs or applications (e.g. drugs in a therapeutic class; different formulations of the same drug).

☒ Yes

☐ No

2. **This study or clinical trial focuses on the following special population(s) or circumstance(s):** ***[Select all that apply]***

- ☐ *For non-PREA pediatric studies/trials only*: Pediatric population
- ☐ Geriatric population
- ☐ Lactating/nursing mothers
- ☐ Medical Countermeasures (e.g. anthrax exposure, bioterrorism)
- ☐ Orphan or rare disease population
- ☐ Pregnant women
- ☐ Racial/ethnic population
- ☒ Not applicable

3. **(Complete if applicable) Additional comments about the PMR/PMC** (e.g., points or concerns not previously described; explanation for inclusion of milestones other than the 3 "core" milestones or draft protocol submission)

SECTION E: PMR/PMC Development Coordinator Statements[8]

1. **The PMR/PMC is clear, feasible, and appropriate[9] because:** ***[Select all that apply]***

- ☒ The study/clinical trial meets criteria for a PMR or a PMC.
- ☒ The objectives of the study/clinical trial are clear from the description of the PMR/PMC.
- ☒ The applicant has adequately justified the choice of milestone dates.
- ☒ The applicant has had sufficient time to review the PMR/PMC, ask questions, determine feasibility, and contribute to the development process.

2. ☐ (***If the PMR/PMC is a randomized controlled clinical trial***) **The following ethical considerations were made with regard to:**

- There is a significant question about the public health risks of the drug.
- There is not enough existing information to assess the public health risks of the drug.
- Information about the public health risks cannot be gained through a different kind of investigation.
- The trial will be appropriately designed to answer question about a drug's efficacy or safety.

[8] This section is completed by the PMR/PMC Development Coordinator, who is usually the OND division's Deputy Director for Safety (DDS). See DEFINITIONS section of CDER MAPP 6010.9, *Procedures and Responsibilities for Developing Postmarketing Requirements and Commitments.*

[9] See POLICY section of CDER MAPP 6010.9.

- The trial will emphasize minimizing the risk minimization for participants as the protocol is developed.

3. ☒ This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

Refer to electronic DARRTS signature

PMR/PMC DEVELOPMENT TEMPLATE

For 506B Reportable[1] PMRs and PMCs only

This form describes and provides the rationale for postmarketing requirements/commitments (PMRs/PMCs) subject to reporting requirements under section 506B of the FDCA.

Complete this form using the *instructions* (see Appendix A) and by referring to ***MAPP 6010.9***, "Procedures and Responsibilities for Developing Postmarketing Commitments and Requirements."

Note: Do ***not*** use this template for CMC PMCs. Instead, use the CMC PMC Development Template.[1]

SECTION A: Administrative Information

NDA/BLA/Supplement #	NDA 209637
PMR/PMC Set (####-#)	3294-3
Product Name:	OZEMPIC (semaglutide) injection
Applicant Name:	Novo Nordisk, Inc.
ODE/Division:	ODE II / DMEP

SECTION B: PMR/PMC Information

1. PMR/PMC Description

Develop and validate a sensitive assay to assess the neutralizing activity of anti-semaglutide antibodies and its cross-neutralizing effect on native GLP-1.

2. PMR/PMC Schedule Milestones[2, 3]

Final Report Submission: 11/2018

[1] 506B "reportable" includes all studies/trials an applicant has agreed upon or is required to conduct related to clinical safety, clinical efficacy, clinical pharmacology, or nonclinical toxicology (21 CFR 314.81(b)(2)(vii) and 21 CFR 601.70(a)). All PMRs are considered 506 "reportable." A separate development template is used for 506 B non-reportable (e.g., chemistry, manufacturing, and controls (CMC)) PMCs, which is located in the CST.

[2] *Final protocol*, *study/trial completion*, and *final report* submissions are required milestones. *Draft protocol submissions* and *interim* milestones are optional. EXCEPTION: PMRs/PMCs for medical countermeasures may have only draft/final protocol submission dates and no other milestones, since the study/trial will only be initiated in the event of an emergency. Interim milestones may include interim report milestones for studies/trials that may be of long duration. May include interim subject accrual milestone (e.g., for accelerated approval PMRs). Other milestones should be justified in Section D, question 3.

[3] Dates should be numerical (e.g., 05/2016). PREA PMR date format may be MM/DD/YYYY if a day is specified.

SECTION C: PMR/PMC Rationale

1. Describe the particular review issue and the goal of the study[4] or clinical trial[5] in the text box below.

The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. The sensitivity of the assays developed by the sponsor to assess neutralizing activity was inadequate to determine whether any neutralizing antibodies (Nabs) developed during the clinical trials. Development of an adequate Nab assay will allow for assessment of neutralizing antibodies to semaglutide and to endogenous GLP-1 and improve our assessment of the clinical impact of the product's immunogenicity.

2. Explain why this issue can be evaluated post-approval and does not need to be addressed prior to approval. (Select one explanation below.)

- ☐ Subpart I or H (animal efficacy rule) PMR: Approved under Subpart I or H (animal efficacy rule) authorities; postmarketing study/trial required to verify and describe clinical benefit ***[Skip to Q.5]***
- ☐ Subpart H or E (accelerated approval) PMR: Approved under Subpart H or E (accelerated approval) authorities; postmarketing study/trial required to verify and describe clinical benefit ***[Skip to Q.5]***
- ☐ PREA PMR: Meets PREA postmarketing pediatric study *requirements* ***[Skip to Q.5]***
- ☐ FDAAA PMR (safety): Benefit/risk profile of the drug appears favorable; however, there are uncertainties about aspects of the drug's safety profile. Because the investigation will evaluate a serious risk, it meets FDAAA requirements for a postmarketing safety study or trial ***[Go to Q.3]***
- ☒ PMC (506B reportable): Benefit/risk profile of the drug appears favorable; however, there are uncertainties about aspects of the drug's efficacy profile or other issues. The purpose of the investigation does not meet requirements under Subpart I/H , H/E, PREA, or FDAAA to be a PMR, and therefore the investigation is a PMC. ***[Go to Q.3]***

3. For FDAAA PMRs and 506B PMCs only

The study or trial can be conducted post-approval because: *[Select all that apply]*

- ☐ Longer-term data needed to further characterize the safety/efficacy of the drug
- ☐ Based on the purpose and/or design, it is only feasible to conduct the study/trial post-approval
- ☒ Prior clinical experience (e.g., with other drugs in the class) indicates adequate safety or efficacy data to support approval, but some uncertainties about safety or efficacy remain and should be further characterized
- ☐ Only a small subpopulation is affected (e.g., patients with severe renal impairment) and effects of the drug in the subpopulation can be further evaluated after approval
- ☐ Study/trial is to further explore a theoretical concern that does not impact the approval determination
- ☐ Other reason (describe in text box below)

[4] A "study" is an investigation that is not a clinical trial, such as an observational (epidemiologic) study, animal study, or laboratory experiment.

[5] A "clinical trial" is any prospective investigation in which the applicant or investigator determines the method of assigning the drug product(s) or other interventions to one or more human subjects. Note that under PREA, clinical trials involving pediatric patients are specifically referred to as "studies."

4. **For FDAAA PMRs only** ***[for PMCs skip to Q.5]. Complete this entire section***

a. The purpose of the study/clinical trial is to: ***[Select one, then go to Q.4.b]***

- ☐ Assess a known serious risk related to the use of the drug
- ☐ Assess a signal of serious risk related to the use of the drug
- ☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk

Complete Q4.b if the necessary data can only be obtained through a particular type of nonclinical study or clinical pharmacology trial. Otherwise complete Q4.c and Q4.d.

b. FAERS[6] and Sentinel's postmarket ARIA[7] system are not sufficient for the purposes described in Q1. and Q4.a because the safety issue involves:

[Select all that apply then to skip to Q.5. If none apply, answer both Q4.c and Q4.d]

- ☐ A serious risk of genotoxicity, carcinogenicity, or reproductive toxicity, and these signals are initially best assessed through in vitro or animal studies.
- ☐ A potential drug interaction resulting in lower/higher drug exposure and resultant serious drug risks, and accurate assessment of an interaction is feasible only through in vitro mechanistic studies or clinical pharmacokinetic and pharmacodynamics trials.
- ☐ The potential for lower/higher drug exposure and resultant serious drug risks in patients with hepatic or renal impairment, or other metabolic abnormalities, and accurate assessment is feasible only through in vitro mechanistic studies or clinical pharmacokinetic and pharmacodynamics trials.
- ☐ An immunologic concern for which accurate assessment requires in vitro development or validation of specific assays.

[6] FDA Adverse Event Reporting System (FAERS)

[7] Active Risk Identification and Analysis (ARIA)

Complete Q4.c when FAERS cannot provide the necessary data and Q4.b does not apply

c. FAERS data cannot be used to fully characterize the serious risk of interest because:

[Select all that apply then go to Q.4.d]

- ☐ Assessment of the serious risk necessitates calculation of the rate of occurrence (e.g., incidence or odds ratio) of the adverse event(s), and FAERS data cannot be used for such a calculation.
- ☐ The serious risk of concern has a delayed time to onset, or delayed time to detection after exposure (e.g., cancer), and FAERS data are more useful for detecting events that are closely linked in time to initiation of drug therapy.
- ☐ The serious risk of concern occurs commonly in the population (e.g., myocardial infarction) and FAERS data are more useful in detecting rare serious adverse events for which the background rates are low.
- ☐ Other

Complete Q4.d when the ARIA system cannot provide the necessary data and Q4.b does not apply.

d. The currently available data within the ARIA system cannot be used to fully characterize the serious risk of interest because: *[Select all that apply then go to Q.4.e]*

- ☐ Cannot identify exposure to the drug(s) of interest in the database.
- ☐ Serious risk (adverse event) of concern cannot be identified in the database.
- ☐ The population(s) of interest cannot be identified in the database.
- ☐ Long-term follow-up information required to assess the serious risk are not available in the database.
- ☐ Important confounders or covariates are not available or well represented in the database.
- ☐ The database does not contain an adequate number of exposed patients to provide sufficient statistical power to analyze the association between the drug and the serious risk of concern.
- ☐ The purpose of the evaluation is to rule out a modest relative risk, and observational studies, such as an ARIA analysis, are not well suited for such use.
- ☐ Other

e. **If FAERS and the ARIA system are not sufficient for the purpose in Q1. and Q4.a, is a study sufficient?**
[Select either "Yes" or "No" and provide the appropriate responses.]

☐ **Yes**, a study is sufficient *[Explain your answer in the textbox and then go to Q.5]*

☐ **No**, a study is not sufficient *[Select all explanations that apply then go to Q.4.f]*

- ☐ Need to minimize bias and/or confounding via randomization
- ☐ Need for placebo control
- ☐ Need to capture detailed information about covariates or confounders that are either not routinely collected during the ususal course of medical practice, or are not collected at the frequency needed for assessment of the safety issue (e.g. hourly blood glucose measures, etc.).
- ☐ Need pre-specified and prospective active data collection of the outcome/endpoint of interest
- ☐ Other

f. ☐ **Because a study is not sufficient, a clinical trial is required.** *[Go to Q.5]*

5. **For all PMRs and PMCs: What type of study or clinical trial is needed to achieve the goal described in Q1 *or* Q4.a above?**
[Select ONE OPTION only under either "Type of Study" or "Type of clinical Trial"]

TYPE OF STUDY
☐ Drug interaction or bioavailability studies (nonclinical only)
☐ Epidemiologic (observational) study related to safe drug use
☐ Epidemiologic (observational) study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Immunogenicity study (nonclinical)
☐ Meta-analysis or pooled analysis of previous observational studies
☐ Nonclinical (animal) study (e.g., genotoxicity, carcinogenicity, reproductive toxicology)
☒ Nonclinical (in vitro) study (e.g. laboratory/microbiology resistance, receptor affinity)
☐ Pharmacogenetic or pharmacogenomic study
☐ Pharmacokinetic (PK) and/or pharmacodynamics (PD) study (nonclinical only)
☐ Quality CMC study (e.g., manufacturing, studies on impurities)
☐ Quality stability study
☐ Registry-based observational study

TYPE OF STUDY
☐ Other (describe)

TYPE OF CLINICAL TRIAL
☐ Combined PK/PD, safety and/or efficacy trial (*PREA* PMRs only*)
☐ Dose-response clinical trial
☐ Dosing trial (e.g., alternative dosing schedule)
☐ Drug interaction or bioavailability clinical trial (clinical only)
☐ Immunogenicity trial (clinical)
☐ Meta-analysis or pooled analysis of previous clinical trials
☐ Pharmacogenetic or pharmacogenomic clinical trial
☐ Pharmacokinetic (PK) and/or pharmacodynamic (PD) clinical trial
☐ Primary efficacy clinical trial (i.e, with a primary efficacy endpoint; to further define efficacy; may include secondary safety endpoints)
☐ Primary safety clinical trial (e.g., to evaluate the long-term safety of a drug; to evaluate drug toxicity in a subpopulation; may include secondary efficacy endpoints) – *excludes SOT*
☐ Safety outcomes trial (SOT)**
☐ Thorough Q-T clinical trial
☐ Other (describe) _____

* Note that under PREA, clinical trials involving pediatric patients are specifically referred to as "studies." However, for the purposes of this template, PREA investigations are categorized according to the established definitions of "studies" and "trials" (see Footnotes 3 and 4).

** A safety outcomes trial (SOT) is defined as a large, prospective, randomized, controlled trial that is specifically designed and adequately powered to test a safety hypothesis using a clinical outcome, generally irreversible morbidity or mortality, as the primary trial endpoint. A cardiovascular outcomes trial (CVOT) is an example of an SOT.

SECTION D: PMR/PMC Additional Information

1. This PMR/PMC applies to other drugs or applications (e.g. drugs in a therapeutic class; different formulations of the same drug).

☐ Yes

☒ No

2. **This study or clinical trial focuses on the following special population(s) or circumstance(s):** ***[Select all that apply]***

- ☐ *For non-PREA pediatric studies/trials only*: Pediatric population
- ☐ Geriatric population
- ☐ Lactating/nursing mothers
- ☐ Medical Countermeasures (e.g. anthrax exposure, bioterrorism)
- ☐ Orphan or rare disease population
- ☐ Pregnant women
- ☐ Racial/ethnic population
- ☒ Not applicable

3. **(Complete if applicable) Additional comments about the PMR/PMC** (e.g., points or concerns not previously described; explanation for inclusion of milestones other than the 3 "core" milestones or draft protocol submission)

SECTION E: PMR/PMC Development Coordinator Statements[8]

1. **The PMR/PMC is clear, feasible, and appropriate[9] because:** ***[Select all that apply]***

- ☒ The study/clinical trial meets criteria for a PMR or a PMC.
- ☒ The objectives of the study/clinical trial are clear from the description of the PMR/PMC.
- ☒ The applicant has adequately justified the choice of milestone dates.
- ☒ The applicant has had sufficient time to review the PMR/PMC, ask questions, determine feasibility, and contribute to the development process.

2. ☐ (***If the PMR/PMC is a randomized controlled clinical trial***) **The following ethical considerations were made with regard to:**

- There is a significant question about the public health risks of the drug.
- There is not enough existing information to assess the public health risks of the drug.
- Information about the public health risks cannot be gained through a different kind of investigation.
- The trial will be appropriately designed to answer question about a drug's efficacy or safety.

[8] This section is completed by the PMR/PMC Development Coordinator, who is usually the OND division's Deputy Director for Safety (DDS). See DEFINITIONS section of CDER MAPP 6010.9, *Procedures and Responsibilities for Developing Postmarketing Requirements and Commitments*.

[9] See POLICY section of CDER MAPP 6010.9.

- The trial will emphasize minimizing the risk minimization for participants as the protocol is developed.

3. ☒ This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

Refer to electronic DARRTS signature

PMR/PMC DEVELOPMENT TEMPLATE

For 506B Reportable[1] PMRs and PMCs only

This form describes and provides the rationale for postmarketing requirements/commitments (PMRs/PMCs) subject to reporting requirements under section 506B of the FDCA.

Complete this form using the *instructions* (see Appendix A) and by referring to ***MAPP 6010.9***, "Procedures and Responsibilities for Developing Postmarketing Commitments and Requirements."

Note: Do ***not*** use this template for CMC PMCs. Instead, use the CMC PMC Development Template.[1]

SECTION A: Administrative Information

NDA/BLA/Supplement #	NDA 209637
PMR/PMC Set (####-#)	3294-4
Product Name:	OZEMPIC (semaglutide) injection
Applicant Name:	Novo Nordisk, Inc.
ODE/Division:	ODE II / DMEP

SECTION B: PMR/PMC Information

1. PMR/PMC Description

Conduct a study to assess the incidence of neutralizing antibodies to semaglutide and GLP-1 in subjects treated with semaglutide using the assays developed under PMC 3294-3. The samples may be derived from pre-existing clinical studies. Sample selection criteria will be submitted to and reviewed by the Agency prior to initiation of sample analysis.

2. PMR/PMC Schedule Milestones[2, 3]

Final Protocol Submission:	11/2018
Final Report Submission:	05/2019

[1] 506B "reportable" includes all studies/trials an applicant has agreed upon or is required to conduct related to clinical safety, clinical efficacy, clinical pharmacology, or nonclinical toxicology (21 CFR 314.81(b)(2)(vii) and 21 CFR 601.70(a)). All PMRs are considered 506 "reportable." A separate development template is used for 506 B non-reportable (e.g., chemistry, manufacturing, and controls (CMC)) PMCs, which is located in the CST.

[2] *Final protocol*, *study/trial completion*, and *final report* submissions are required milestones. *Draft protocol submissions* and *interim* milestones are optional. EXCEPTION: PMRs/PMCs for medical countermeasures may have only draft/final protocol submission dates and no other milestones, since the study/trial will only be initiated in the event of an emergency. Interim milestones may include interim report milestones for studies/trials that may be of long duration. May include interim subject accrual milestone (e.g., for accelerated approval PMRs). Other milestones should be justified in Section D, question 3.

[3] Dates should be numerical (e.g., 05/2016). PREA PMR date format may be MM/DD/YYYY if a day is specified.

SECTION C: PMR/PMC Rationale

1. Describe the particular review issue and the goal of the study[4] or clinical trial[5] in the text box below.

Neutralizing antibodies to semaglutide may result in reduced product efficacy or can lead to neutralization of endogenous GLP-1. Once the sponsor develops a sensitive assay for neutralizing antibodies, they will reassess the clinical samples from their trials and determine whether there are clinical signals that are associated with the presence of these antibodies.

2. Explain why this issue can be evaluated post-approval and does not need to be addressed prior to approval. (Select one explanation below.)

- ☐ Subpart I or H (animal efficacy rule) PMR: Approved under Subpart I or H (animal efficacy rule) authorities; postmarketing study/trial required to verify and describe clinical benefit ***[Skip to Q.5]***
- ☐ Subpart H or E (accelerated approval) PMR: Approved under Subpart H or E (accelerated approval) authorities; postmarketing study/trial required to verify and describe clinical benefit ***[Skip to Q.5]***
- ☐ PREA PMR: Meets PREA postmarketing pediatric study *requirements* ***[Skip to Q.5]***
- ☐ FDAAA PMR (safety): Benefit/risk profile of the drug appears favorable; however, there are uncertainties about aspects of the drug's safety profile. Because the investigation will evaluate a serious risk, it meets FDAAA requirements for a postmarketing safety study or trial ***[Go to Q.3]***
- ☒ PMC (506B reportable): Benefit/risk profile of the drug appears favorable; however, there are uncertainties about aspects of the drug's efficacy profile or other issues. The purpose of the investigation does not meet requirements under Subpart I/H , H/E, PREA, or FDAAA to be a PMR, and therefore the investigation is a PMC. ***[Go to Q.3]***

3. For FDAAA PMRs and 506B PMCs only

The study or trial can be conducted post-approval because: ***[Select all that apply]***

- ☐ Longer-term data needed to further characterize the safety/efficacy of the drug
- ☐ Based on the purpose and/or design, it is only feasible to conduct the study/trial post-approval
- ☒ Prior clinical experience (e.g., with other drugs in the class) indicates adequate safety or efficacy data to support approval, but some uncertainties about safety or efficacy remain and should be further characterized
- ☐ Only a small subpopulation is affected (e.g., patients with severe renal impairment) and effects of the drug in the subpopulation can be further evaluated after approval
- ☐ Study/trial is to further explore a theoretical concern that does not impact the approval determination
- ☐ Other reason (describe in text box below)

[4] A "study" is an investigation that is not a clinical trial, such as an observational (epidemiologic) study, animal study, or laboratory experiment.

[5] A "clinical trial" is any prospective investigation in which the applicant or investigator determines the method of assigning the drug product(s) or other interventions to one or more human subjects. Note that under PREA, clinical trials involving pediatric patients are specifically referred to as "studies."

4. **<u>For FDAAA PMRs only</u>** ***[for PMCs skip to Q.5]. Complete this entire section***

a. The purpose of the study/clinical trial is to: ***[Select one, then go to Q.4.b]***

- ☐ Assess a <u>known serious risk</u> related to the use of the drug
- ☐ Assess a <u>signal of serious risk</u> related to the use of the drug
- ☐ Identify an <u>unexpected serious risk</u> when available data indicate the potential for a serious risk

Complete Q4.b if the necessary data can only be obtained through a particular type of nonclinical study or clinical pharmacology trial. Otherwise complete Q4.c and Q4.d.

b. FAERS[6] and Sentinel's postmarket ARIA[7] system are not sufficient for the purposes described in Q1. and Q4.a because the safety issue involves:

[Select all that apply then to skip to Q.5. If none apply, answer both Q4.c and Q4.d]

- ☐ A serious risk of genotoxicity, carcinogenicity, or reproductive toxicity, and these signals are initially best assessed through in vitro or animal studies.
- ☐ A potential drug interaction resulting in lower/higher drug exposure and resultant serious drug risks, and accurate assessment of an interaction is feasible only through in vitro mechanistic studies or clinical pharmacokinetic and pharmacodynamics trials.
- ☐ The potential for lower/higher drug exposure and resultant serious drug risks in patients with hepatic or renal impairment, or other metabolic abnormalities, and accurate assessment is feasible only through in vitro mechanistic studies or clinical pharmacokinetic and pharmacodynamics trials.
- ☐ An immunologic concern for which accurate assessment requires in vitro development or validation of specific assays.

[6] FDA Adverse Event Reporting System (FAERS)

[7] Active Risk Identification and Analysis (ARIA)

Complete Q4.c when FAERS cannot provide the necessary data and Q4.b does not apply

c. FAERS data cannot be used to fully characterize the serious risk of interest because:

[Select all that apply then go to Q.4.d]

- ☐ Assessment of the serious risk necessitates calculation of the rate of occurrence (e.g., incidence or odds ratio) of the adverse event(s), and FAERS data cannot be used for such a calculation.
- ☐ The serious risk of concern has a delayed time to onset, or delayed time to detection after exposure (e.g., cancer), and FAERS data are more useful for detecting events that are closely linked in time to initiation of drug therapy.
- ☐ The serious risk of concern occurs commonly in the population (e.g., myocardial infarction) and FAERS data are more useful in detecting rare serious adverse events for which the background rates are low.
- ☐ Other

Complete Q4.d when the ARIA system cannot provide the necessary data and Q4.b does not apply.

d. The currently available data within the ARIA system cannot be used to fully characterize the serious risk of interest because: *[Select all that apply then go to Q.4.e]*

- ☐ Cannot identify exposure to the drug(s) of interest in the database.
- ☐ Serious risk (adverse event) of concern cannot be identified in the database.
- ☐ The population(s) of interest cannot be identified in the database.
- ☐ Long-term follow-up information required to assess the serious risk are not available in the database.
- ☐ Important confounders or covariates are not available or well represented in the database.
- ☐ The database does not contain an adequate number of exposed patients to provide sufficient statistical power to analyze the association between the drug and the serious risk of concern.
- ☐ The purpose of the evaluation is to rule out a modest relative risk, and observational studies, such as an ARIA analysis, are not well suited for such use.
- ☐ Other

e. **If FAERS and the ARIA system are not sufficient for the purpose in Q1. and Q4.a, is a study sufficient?**
[Select either "Yes" or "No" and provide the appropriate responses.]

☐ **Yes**, a study is sufficient *[Explain your answer in the textbox and then go to Q.5]*

☐ **No**, a study is not sufficient *[Select all explanations that apply then go to Q.4.f]*

- ☐ Need to minimize bias and/or confounding via randomization
- ☐ Need for placebo control
- ☐ Need to capture detailed information about covariates or confounders that are either not routinely collected during the ususal course of medical practice, or are not collected at the frequency needed for assessment of the safety issue (e.g. hourly blood glucose measures, etc.).
- ☐ Need pre-specified and prospective active data collection of the outcome/endpoint of interest
- ☐ Other

f. ☐ **Because a study is not sufficient, a clinical trial is required.** *[Go to Q.5]*

5. **For all PMRs and PMCs: What type of study or clinical trial is needed to achieve the goal described in Q1 *or* Q4.a above?**
[Select ONE OPTION only under either "Type of Study" or "Type of clinical Trial"]

TYPE OF STUDY
☐ Drug interaction or bioavailability studies (nonclinical only)
☐ Epidemiologic (observational) study related to safe drug use
☐ Epidemiologic (observational) study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Immunogenicity study (nonclinical)
☐ Meta-analysis or pooled analysis of previous observational studies
☐ Nonclinical (animal) study (e.g., genotoxicity, carcinogenicity, reproductive toxicology)
☐ Nonclinical (in vitro) study (laboratory/microbiology resistance, receptor affinity)
☐ Pharmacogenetic or pharmacogenomic study
☐ Pharmacokinetic (PK) and/or pharmacodynamics (PD) study (nonclinical only)
☐ Quality CMC study (e.g., manufacturing, studies on impurities)
☐ Quality stability study
☐ Registry-based observational study

TYPE OF STUDY
☒ Other (describe) Assesing neutralizing anti-semaglutide and neutralizing anti-GLP-1 antibody rates and titers in semaglutide treated population.

TYPE OF CLINICAL TRIAL
☐ Combined PK/PD, safety and/or efficacy trial (*PREA* PMRs only*)
☐ Dose-response clinical trial
☐ Dosing trial (e.g., alternative dosing schedule)
☐ Drug interaction or bioavailability clinical trial (clinical only)
☐ Immunogenicity trial (clinical)
☐ Meta-analysis or pooled analysis of previous clinical trials
☐ Pharmacogenetic or pharmacogenomic clinical trial
☐ Pharmacokinetic (PK) and/or pharmacodynamic (PD) clinical trial
☐ Primary efficacy clinical trial (i.e, with a primary efficacy endpoint; to further define efficacy; may include secondary safety endpoints)
☐ Primary safety clinical trial (e.g., to evaluate the long-term safety of a drug; to evaluate drug toxicity in a subpopulation; may include secondary efficacy endpoints) – *excludes SOT*
☐ Safety outcomes trial (SOT)**
☐ Thorough Q-T clinical trial
☐ Other (describe) _____

* Note that under PREA, clinical trials involving pediatric patients are specifically referred to as "studies." However, for the purposes of this template, PREA investigations are categorized according to the established definitions of "studies" and "trials" (see Footnotes 3 and 4).

** A safety outcomes trial (SOT) is defined as a large, prospective, randomized, controlled trial that is specifically designed and adequately powered to test a safety hypothesis using a clinical outcome, generally irreversible morbidity or mortality, as the primary trial endpoint. A cardiovascular outcomes trial (CVOT) is an example of an SOT.

SECTION D: PMR/PMC Additional Information

1. This PMR/PMC applies to other drugs or applications (e.g. drugs in a therapeutic class; different formulations of the same drug).

☐ Yes

☒ No

2. **This study or clinical trial focuses on the following special population(s) or circumstance(s):** ***[Select all that apply]***

- ☐ *For non-PREA pediatric studies/trials only*: Pediatric population
- ☐ Geriatric population
- ☐ Lactating/nursing mothers
- ☐ Medical Countermeasures (e.g. anthrax exposure, bioterrorism)
- ☐ Orphan or rare disease population
- ☐ Pregnant women
- ☐ Racial/ethnic population
- ☒ Not applicable

3. **(Complete if applicable) Additional comments about the PMR/PMC** (e.g., points or concerns not previously described; explanation for inclusion of milestones other than the 3 "core" milestones or draft protocol submission)

SECTION E: PMR/PMC Development Coordinator Statements[8]

1. **The PMR/PMC is clear, feasible, and appropriate[9] because:** ***[Select all that apply]***

- ☒ The study/clinical trial meets criteria for a PMR or a PMC.
- ☒ The objectives of the study/clinical trial are clear from the description of the PMR/PMC.
- ☒ The applicant has adequately justified the choice of milestone dates.
- ☒ The applicant has had sufficient time to review the PMR/PMC, ask questions, determine feasibility, and contribute to the development process.

2. ☐ (***If the PMR/PMC is a randomized controlled clinical trial***) **The following ethical considerations were made with regard to:**

- There is a significant question about the public health risks of the drug.
- There is not enough existing information to assess the public health risks of the drug.
- Information about the public health risks cannot be gained through a different kind of investigation.
- The trial will be appropriately designed to answer question about a drug's efficacy or safety.

[8] This section is completed by the PMR/PMC Development Coordinator, who is usually the OND division's Deputy Director for Safety (DDS). See DEFINITIONS section of CDER MAPP 6010.9, *Procedures and Responsibilities for Developing Postmarketing Requirements and Commitments.*

[9] See POLICY section of CDER MAPP 6010.9.

- The trial will emphasize minimizing the risk minimization for participants as the protocol is developed.

3. ☒ This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JAMES P SMITH
12/04/2017

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:	December 4, 2017
Requesting Office or Division:	Division of Metabolism and Endocrinology Products (DMEP)
Application Type and Number:	NDA 209637
Product Name and Strength:	Ozempic (semaglutide) injection, 2 mg/1.5 mL (1.34 mg/mL)
Applicant/Sponsor Name:	Novo Nordisk
Submission Date:	December 1, 2017
OSE RCM #:	2016-2765-2
DMEPA Safety Evaluator:	Susan Rimmel, PharmD
DMEPA Team Leader:	Hina Mehta, PharmD

1 PURPOSE OF MEMO

The Division of Metabolism and Endocrinology Products (DMEP) requested that we review the revised container labels, carton labeling, Rx Sticker (on sample carton), Medication Guide, Instructions for Use (IFU), and electronic health record (EHR) systems and pharmacy systems screenshots for Ozempic (semaglutide) injection (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during previous label and labeling reviews.[a] [b]

2 CONCLUSION

The revised container labels, carton labeling, Rx Sticker, Medication Guide, IFUs, and EHR systems and pharmacy systems screenshots for Ozempic is acceptable from a medication error perspective. We have no further recommendations at this time.

[a] Rimmel, S. Label, Labeling, and Human Factors Results Review for Ozempic (NDA 209637). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 NOV 22. RCM No.: 2016-2765 and 2017-139.

[b] Rimmel, S. Label and Labeling Review Memo for Ozempic (NDA 209637). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 NOV 22. RCM No.: 2016-2765-1.

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/s/

SUSAN RIMMEL
12/04/2017

HINA S MEHTA
12/04/2017

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:	November 30, 2017
Requesting Office or Division:	Division of Metabolism and Endocrinology Products (DMEP)
Application Type and Number:	NDA 209637
Product Name and Strength:	Ozempic (semaglutide) injection, 2 mg/1.5 mL (1.34 mg/mL)
Applicant/Sponsor Name:	Novo Nordisk
Submission Date:	November 30, 2017
OSE RCM #:	2016-2765-1
DMEPA Safety Evaluator:	Susan Rimmel, PharmD
DMEPA Team Leader:	Hina Mehta, PharmD

1 PURPOSE OF MEMO

The Division of Metabolism and Endocrinology Products (DMEP) requested that we review the revised electronic health record (EHR) systems and pharmacy systems screenshots for Ozempic (semaglutide) injection (Appendix A) to determine if it is 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 EHR systems and pharmacy systems display of how the naming convention may appear in an EHR can still be improved for better readability and to mitigate potential confusion regarding the dose the pen-injector delivers.

[a]Rimmel, S. Label, Labeling, and Human Factors Results Review for Ozempic (NDA 209637). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 NOV 22. RCM No.: 2016-2765 and 2017-139.

3 RECOMMENDATIONS FOR NOVO NORDISK

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

1. Figure 1 Example Screenshots of How Requested Naming Convention May Appear in an EHR – For added clarity and to mitigate any confusion, revise the following statements:
    a. Screenshot Example 1
        i. The dose unit is missing for the 0.5 mg dose display. Revise "Ozempic 0.25 mg or 0.5 doses, …" to "Ozempic 0.25 mg or 0.5 mg doses, …"
    b. Screenshot Example 3
        i. Remove the trailing zero from the *Dose* field (i.e., change "1.0" to "1").

APPENDIX A. LABEL AND LABELING SUBMITTED NOVEMBER 30, 2017

Figure 1 Example Screenshots of How Requested Naming Convention May Appear in an EHR (submitted in IR reply on November 30, 2017)

Application 209637 - Sequence 0044 - Response to Nov 24th IR (Question 5)
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(b) (4)

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/s/

SUSAN RIMMEL
12/01/2017

HINA S MEHTA
12/01/2017

LABEL, LABELING, AND HUMAN FACTORS RESULTS 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:	November 22, 2017
Requesting Office or Division:	Division of Metabolism and Endocrinology Products (DMEP)
Application Type and Number:	NDA 209637
Product Name and Strength:	Ozempic (semaglutide) injection, 2 mg/1.5 mL (1.34 mg/mL)
Product Type:	Combination Product (single ingredient drug + device)
Rx or OTC:	Rx
Applicant/Sponsor Name:	Novo Nordisk
Submission Date:	December 5, 2016, March 1, 2017, and June 19, 2017
OSE RCM #:	2016-2765 and 2017-139
DMEPA Safety Evaluator:	Susan Rimmel, PharmD
DMEPA Team Leader:	Hina Mehta, PharmD
DMEPA Associate Director for Human Factors:	QuynhNhu Nguyen, MS
DMEPA Associate Director (Acting):	Mishale Mistry, PharmD, MPH

1 REASON FOR REVIEW

The Division of Metabolism and Endocrinology Products (DMEP) consulted DMEPA to evaluate the labels, labeling, and human factors (HF) study results for Ozempic (semaglutide) injection 2 mg/1.5 mL (1.34 mg/mL), under NDA 209637, submitted by Novo Nordisk on December 5, 2016.

1.1 BACKGROUND

The HF validation study protocol submitted on September 15, 2015, was reviewed as part of a Type C Meeting Written Responses Only on November 13, 2015. We recommended that the Applicant conduct a use-related risk analysis (URRA) for the proposed product, which utilizes the same pen-injector platform and is intended for the same user population as several currently approved products (e.g., Saxenda, Victoza, Novolog FlexTouch, Levemir FlexTouch, and Norditropin FlexPro). In addition, we requested the Applicant perform differentiation testing because we expect users may have multiple, similar pen-injectors currently in use.

We reviewed the URRA and Validation of Device Use HF Engineering and Usability Evaluation Report submitted by the Applicant on December 5, 2016, and agreed with the Applicant's determination that only a differentiation study is needed for the proposed product. Finally, we confirmed all other comments (e.g., choosing a consistent training decay period, revisions to the use scenarios, including comparator products, and revisions to the Instructions for Use) were addressed or implemented in the December 5, 2016, submission.

The original HF validation study protocol that we reviewed proposed one strength variant for Ozempic (a pen-injector that doses 0.25 mg, 0.5 mg, or 1 mg). However, the original NDA submission on December 5, 2016, proposed two strength variations of Ozempic (a pen-injector that doses 1 mg only and a pen-injector that doses 0.25 mg, 0.5 mg, or 1 mg). Therefore, on April 7, 2017, we submitted an information request (IR) to Novo Nordisk for their rationale in marketing the additional strength variant. Novo Nordisk replied on April 13, 2017, (see Appendix F) indicating that the pen-injector delivering doses of 0.25 mg, 0.5 mg, or 1 mg is intended primarily for dose escalation and treatment at the 0.5 mg maintenance dose. The pen-injector delivering only doses of 1 mg is intended solely for the maintenance dose of 1 mg, thereby facilitating ease of use for the patient, simplifying dose selection, and decreasing the risk of underdosing. Furthermore, Novo Nordisk expects the majority of patients will be on the 1 mg maintenance dose.

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 – N/A
Human Factors Study	C
ISMP Newsletters	D – N/A
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Novo Nordisk Reply to DMEPA IR's	F
Labels and Labeling	G

N/A=not applicable for this review
*We do not typically search FAERS 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

The sections below provide a summary of the differentiation study design, errors observed with critical tasks, and our analysis of the differentiation study results.

We consulted the Center for Devices and Radiological Health (CDRH) to review the URRA, Validation of Device Use HF Engineering and Usability Evaluation Report, and differentiation study design and results. CDRH determined that the results were adequate to demonstrate that the user interface of the combination product supports safe and effective use.

3.1 SUMMARY OF DIFFERENTIATION STUDY DESIGN

The Applicant conducted a differentiation study for the two strength variations. The differentiation study was conducted with 105 untrained participants (15 adult pen naïve patients, 15 adult pen experienced patients, 15 elderly pen naïve patients, 15 elderly pen experienced patients, 15 pharmacists, 15 healthcare professionals excluding pharmacists, and 15 in-patient nurses with no specific diabetes knowledge). Half of the participants needed to select the 3-dose variant (0.25 mg/0.5 mg/1 mg) pen and/or carton during all tasks. The other half needed to select the 1-dose variant (1 mg) pen and/or carton for all tasks. In terms of task order, the participants needed to select the correct Ozempic product (3-dose variant or 1-dose variant) from the other Ozempic variant and then from among other comparator products.

Overall, we disagree with some of the methodology used during the study. We note that the Applicant used leading language regarding the moderator script by specifying to "select the box containing one pen-injector that can deliver doses of 0.25 mg, 0.5 mg, or 1 mg" or "select the box containing two pen-injectors that can each deliver two doses of 1 mg." This may have introduced bias, as participants may have identified the correct product by the *number* of pen-injectors in the box, rather than by the strength or dose the pen-injector can deliver.

Regardless, it does not change our determination that users were not reliably able to differentiate between the two originally proposed strength variations.

3.2 RESULTS AND ANALYSIS

The study results showed that several healthcare professionals and patients (three, one of which committed two selection errors) were not reliably able to differentiate between the two strength variations. Specifically, there were seven selection errors and two close calls, as described in Table 2 below:

Table 2. Description of Selection Errors Between Ozempic Variants

	Intended Product	Selected Product	Participant and Applicant Root Cause Summary	DMEPA Analysis and Recommendations
Selection errors (n = 7)				
2 participants (1 pen-naive adult patient that made two selection errors and 1 pharmacist)	0.25 mg, 0.5 mg, or 1 mg carton or pen-injector	1 mg carton or pen-injector	1. The participant (pen-naive adult patient) noticed the "1 mg" label sooner on the 1 mg box because it is the only dosage featured on the box and it is somewhat larger than the dosage labels on the 0.25 mg/0.5 mg/1 mg box. This participant also selected the incorrect pen-injector during the subsequent task (see 2 below). 2. The participant (pen-naive adult patient) incorrectly selected the 1 mg pen-injector instead of the 0.25 mg/0.5 mg/1 mg pen-injector when selecting between the two pen-injector variants. The participant explained she did not recall all of the different dosages printed on the 0.25 mg/0.5 mg/1 mg box from the test material presentation period and only recalled seeing "1 mg" on the box. Therefore, she mistakenly assumed she	Per the Applicant's Amendment submitted on June 7, 2017, the pen-injector will now provide doses of 0.25 mg or 0.5 mg, thereby removing the 1 mg dose, which is reflected in the product labels and labeling. The removal of the 1 mg dose from the flexible-dose pen-injector may be sufficient to mitigate confusion between the two pen-injector variants and potential for harm.

			should retrieve the 1 mg pen-injector. The participant did not open the 0.25 mg/0.5 mg/1 mg box to see the pen-injector during the test material presentation period. This participant also selected the incorrect box during the previous task (see 1 above). 3. Pharmacist focused on the "1.34 mg/mL" prescription order text only, rather than on the "0.25 mg/week for 4 weeks" text and assumed he should look for the box with "1.34 mg/mL" concentration. The participant immediately noticed the 1.34 mg/mL concentration stated on the 1 mg box and assumed the 1 mg box matched the product described on the prescription order.	Despite the Amendment to remove the 1 mg dose from the flexible-dose pen-injector, we believe the labeling can be improved to provide clarity and mitigate confusion between the two pen-injector variants. Therefore, we provide additional container label and carton labeling revisions (see Recommendations in Section 4.2).
2 participants (diabetes education nurse and pen-naive elderly patient)	1 mg carton or pen-injector	0.25 mg, 0.5 mg, or 1 mg carton or pen-injector	1. Diabetes education nurse incorrectly selected two 0.25 mg/0.5 mg/1 mg boxes instead of one 1 mg box when selecting between the two Ozempic box variants. The participant explained that she misinterpreted the text "Package delivers 4 doses of 1 mg only" on the 1 mg box to mean that each pen-injector in the box could deliver four 1 mg doses and thought the 1 mg box was the incorrect product. Furthermore, because the 0.25 mg/0.5 mg/1 mg box did not state the number of 1 mg doses it could deliver,	This type of selection error will not result in patient harm, as the 1 mg dose can still be administered. Per the Applicant's Amendment submitted on June 7, 2017, the pen-injector will now provide doses of 0.25 mg or 0.5 mg, thereby removing the 1 mg dose, which is reflected in the product labels and labeling. The removal of the 1 mg dose from the flexible-dose pen-injector may be sufficient to mitigate confusion between the two pen-injector variants and potential for harm.

			the participant assumed the box contained the correct product. As a result, she selected two 0.25 mg/0.5 mg/1 mg boxes from the refrigerator to ensure she retrieved two pen-injectors as instructed. 2. The participant (pen-naive elderly patient) incorrectly selected the 0.25 mg/0.5 mg/1 mg pen-injector instead of the 1 mg pen-injector when selecting the between the two pen variants. This participant explained that the 0.25 mg/0.5 mg/1 mg pen-injector's red label drew his attention more than the 1 mg pen-injector's teal label because the red color stood out more to him and decided to read the red label more closely and thoroughly than the teal label. As a result, he only noticed the 1 mg dosage printed on the 0.25 mg/0.5 mg/1 mg pen-injector and assumed he should retrieve that pen-injector from the tray.	
2 participants (nurse and pen-naive adult patient)	1 mg carton or pen-injector	1 mg carton or pen-injector AND 0.25 mg, 0.5 mg, or 1 mg carton or pen-injector	1. Nurse incorrectly selected both box variants instead of only the 1 mg box when selecting between the two box variants. The participant explained that she misinterpreted the task instruction "select the Ozempic box containing two pen-injectors that can each deliver two doses of 1 mg" to mean that she could	Participants thought they could choose either product because both products displayed the 1 mg dose. Per the Applicant's Amendment submitted on June 7, 2017, the pen-injector will now provide doses of 0.25 mg or 0.5 mg, thereby removing the 1 mg dose. The removal of the 1 mg dose from the flexible-dose pen-injector may be sufficient to mitigate confusion

			select any pen-injector that could deliver a 1 mg dose and assumed the 0.25 mg/0.5 mg/1 mg box matched the task instruction. Furthermore, she explained that she incorrectly recalled the task instruction while performing the task, and thought the task instruction stated "two boxes" rather than "two pen-injectors." As a result, she retrieved both the 0.25 mg/0.5 mg/1 mg box and 1 mg box. 2. The participant (pen-naive adult patient) incorrectly selected both pen-injector variants instead of only the 1 mg pen-injector when selecting between the two pen-injector variants. The participant assumed both pen-injector variants were the same because they both featured the same name, Ozempic, and he did not notice the dosages printed on the box. Furthermore, he was unsure based on the task instructions whether he should retrieve one or two pen-injectors. As a result, he retrieved both pen-injector variants from the tray.	between the two pen-injector variants and potential for harm.
Close calls (n = 2)				
1 participant (nurse)	0.25 mg, 0.5 mg, or 1 mg carton	1 mg carton AND 0.25 mg, 0.5 mg, or 1 mg	1. The participant initially selected both box variants instead of only the 0.25 mg/0.5 mg/1 mg box when selecting between the two box variants. The participant explained that she saw the 1	For these two close calls, participants thought they could choose either product because both products displayed the 1 mg dose. Per the Applicant's Amendment submitted on June 7, 2017, the pen-injector will

		carton	mg dosage label on both boxes and initially assumed that both boxes matched the product described on the task card. The test administrator asked the participant whether she felt confident that she completed the task, and the participant reread the task card. The participant then realized she was supposed to retrieve the box containing a pen-injector that could deliver three different dosages, and she subsequently returned the 1 mg box to the refrigerator and correctly handed the 0.25 mg/0.5 mg/1 mg box to the test administrator.	now provide doses of 0.25 mg or 0.5 mg, thereby removing the 1 mg dose. The removal of the 1 mg dose from the flexible-dose pen-injector may be sufficient to mitigate confusion between the two pen-injector variants and potential for harm. .
1 participant (endocrinologist)	1 mg carton	1 mg carton AND 0.25 mg, 0.5 mg, or 1 mg carton	1. The participant initially selected both box variants instead of only the 1 mg box when selecting between the two box variants. This participant explained that he initially focused on identifying the product featuring the Ozempic name and the 1 mg dosage. Because both box variants featured the same name and were able to deliver a 1 mg dose, the participant brought both box variants back to the table. The test administrator asked the participant whether he felt confident that he selected the product stated on the task card, and the participant reread the task card. He realized he was	

			supposed to retrieve the box containing two pen-injectors, and he subsequently returned the 0.25 mg/0.5 mg/1 mg box to the refrigerator and correctly handed the 1 mg box to the test administrator.	

In addition to the above errors, one pen-injector experienced participant incorrectly chose a comparator pen-injector product (Ryzodeg FlexTouch), rather than the intended Ozempic pen-injector that doses 1 mg only. The participant explained that she looked for the blue pen-injector she was introduced to but could not remember the specific shade of blue and selected the Ryzodeg pen-injector because it seemed most familiar to her. While this selection error can result in significant glycemic variation, the Applicant determined that several mitigation barriers must be ignored for this use error to occur. Specifically, the following mitigations that are part of the design must be ignored for selection errors to occur:

- pen-injector design (color branding on cartridge holder, container label, and dose button)
- different tactile coding
- different graphic label design
- different product name
- IFU addresses the need to check pen-injector label before each use

However, these mitigation barriers were not effective in preventing this user from experiencing this selection error. We note the variables regarding this participant played a role in the ability to perform the necessary tasks, particularly the vague mental image of the pen-injector because the box was never opened. Notably, the participant correctly selected the 1 mg Ozempic product in the three previous tasks (task 1 carton retrieval between Ozempic variants, task 2 pen-injector retrieval between Ozempic variants, and task 3 carton retrieval among comparator products). Therefore, we believe there is adequate differentiation between the pen-injectors to mitigate confusion and selection errors.

Participants that chose both carton or pen-injector variants thought they could choose either variant because both variants displayed the 1 mg dose. The majority of use errors and close calls were deemed by the Applicant to have no potential for harm or impact on the prescribed therapy, thereby resulting in no clinical consequence. We disagree that no harm or clinical consequence would result with regard to the three use errors where participants selected the pen-injector that doses 1 mg only, rather than the intended pen-injector that doses 0.25 mg, 0.5 mg, or 1 mg, as due to the risk of wrong dose errors if patients take a higher than prescribed dose.

The Applicant submitted an Amendment (see Appendix C) on June 7, 2017, to remove the 1 mg dose from the pen-injector that doses 0.25 mg, 0.5 mg, or 1 mg. Therefore, the Applicant now proposes two pen-injectors, one that delivers doses of 0.25 mg and 0.5 mg, and one that

delivers doses of 1 mg. We believe the proposed change in the doses delivered by the flexible-dose pen-injector will help to mitigate the confusion between the two pen-injectors that was observed in the differentiation study results. We consider this change to be self-evident, as removing the 1 mg dose from the flexible-dose pen-injector and all labels and labeling has eliminated the risk of confusion due to the 1 mg overlap in both pen-injectors because the 1 mg dose will not be achievable in the flexible-dose pen-injector. However, we believe the labeling can be further optimized to provide additional clarity on the doses delivered by the two pen-injectors. Therefore, we provide additional container label and carton labeling revisions in Section 4.2.

We noted the Applicant determined from the formative studies that a Quick Guide, which is aligned with the Instructions for Use (IFU), should be included on the carton labeling. Therefore, on June 22, 2017, we submitted an IR to the Applicant asking for a summary of all formative testing results, highlighting where it was determined a Quick Guide is necessary and the rationale for why it is believed the Quick Guide will address the results of the formative testing. The Applicant responded on June 28, 2017, (see Appendix F) that the Quick Guide was evaluated in a formative differentiation and handling test, and concluded that the test did not reveal any new use errors caused by the design or content of the Quick Guide. We agree with the Applicant's determination that the Quick Guide is fully aligned with the IFU.

3.3 LABELS AND LABELING

We reviewed the IFU and noted the Applicant's reference (b) (4) On June 22, 2017, we submitted an information request to the Applicant asking for the rationale and data to support the use of the (b) (4) . The Applicant responded on June 28, 2017, (see Appendix F) that the intent of the (b) (4) Therefore, the Applicant will (b) (4) provided in the IFU. We provide additional changes to the IFU to improve readability, highlight important critical tasks and safety risks, and to mitigate potential use errors with the pen-injector in Section 4.2.

We sent preliminary comments in regards to the pen-injector and an information request regarding the "Rx Sticker" to the Applicant on September 1, 2017. We recommended the Applicant remove the line markings between doses in the pen-injectors to mitigate confusion and prevent users from using the line markings to dial other than intended doses, as there are no design features preventing users from dialing and injecting between doses. In addition, we recommended the Applicant remove the trailing zero displayed in the dosing window of the 1 mg pen-injector to mitigate any confusion of a 10-fold dosing error. Furthermore, we asked the Applicant to clarify the purpose of the "Rx Sticker," where it is intended to be placed, and who will place the sticker. The Applicant responded to the IR on September 6, 2017:

1. Trailing zero: The Applicant agreed to remove the trailing zero displayed in the dosing window of the 1 mg pen-injector.

2. Line markings between the doses: The Applicant clarified that the line markings are a design feature intended to support the user when setting a prescribed dose. Specifically, the line markings move from right to left on the dose counter as the user turns the dose selector forward towards the prescribed dose. Therefore, the Applicant proposed to maintain the line markings between doses and update the IFU explaining the function of the line markings and what the user will observe when operating the pen-injectors. Given the length required to dial each dose (19 "clicks" or 12 line markings to reach 0.25 mg, 37 "clicks" or 11 line markings—23 line markings total from 0—to reach 0.5 mg, and 74 "clicks" or 47.5 line markings to reach 1 mg) before the user sees their prescribed dose in the "dose counter" window, we find the Applicant's proposal reasonable to maintain the line markings in the pen-injectors and revising the IFU to explain the function of the line markings and what the user will observe when operating the pen-injectors. We provide additional recommendations in Section 4.2.

3. Rx sticker: The Applicant indicated that the "Rx Sticker" is placed on the sample carton at the production line and is intended to provide a service to the prescriber. For example, the "Rx Sticker" can be removed by the healthcare professional (HCP) prior to giving the patient the sample carton. The HCP can then place the "Rx Sticker" on a prescription pad and give the patient the prescription to take to the pharmacy.

We note that both proposed pen-injector variants have the same strength (2 mg/1.5 mL) and concentration (1.34 mg/mL), which may lead to confusion regarding orders or prescriptions, and product selection. Therefore, we submitted an IR on October 26, 2017, requesting the Applicant provide their strategies to overcome these use-related risks. The Applicant responded on October 30, 2017, (see Appendix F) that they are working with the compendia to ensure electronic health record (EHR) systems and pharmacy systems display the two pen-injectors in a differentiated manner, which allows the healthcare provider to prescribe the correct dose. Consequently, the pharmacist will know which of the two trade cartons to dispense to the patient. In addition, clear differentiation in labeling is implemented. We agree with the Applicant's strategy to partner with compendia to ensure electronic health systems and pharmacy systems are adequately differentiated, and believe this strategy will help to mitigate confusion between the two pen-injector variants in the marketplace. However, the proposed format displayed in these electronic systems can be improved to increase the readability and prominence of important information, and promote the safe use of the product and mitigate any confusion. We provide recommendations in Section 4.2.

We reviewed the proposed container labels, carton labeling, and Prescribing Information and determined they can be improved to increase the readability and prominence of important information, and promote the safe use of the product and mitigate any confusion. We provide recommendations in Section 4.1 and Section 4.2.

4 CONCLUSION & RECOMMENDATIONS

The results of the differentiation study indicated some use errors and close calls. Based on these results, the Applicant decided to remove the 1 mg dose from the pen-injector that doses 0.25 mg, 0.5 mg, or 1 mg. In addition, the Applicant has made changes to the product labels

and labeling to reflect this change. We consider this change to be self-evident, and do not require additional data to support the change. However, we conclude that the proposed labels and labeling can be improved to increase the readability and prominence of important information, and promote the safe use of the product and mitigate any confusion. We recommend that the Applicant implement these improvements prior to product approval.

4.1 RECOMMENDATIONS FOR THE DIVISION

1. Highlights of Prescribing Information
    a. Dosage and Administration
        i. To provide clarity, revise the first bullet, "Administer once weekly at any time of day (2.1)." to read, "Administer once weekly at any time of day, with or without meals (2.1)."
        ii. For better readability and to mitigate any confusion, revise the third bullet, (b) (4) " to read, "Start at 0.25 mg once weekly. After 4 weeks, increase the dose to 0.5 mg once weekly. If after at least 4 weeks additional glycemic control is needed, increase to 1 mg once weekly (2.1)."
    b. Dosage Forms and Strengths – To align this section with the Applicant's Amendment submitted on June 7, 2017, revise this section as follows:

CHANGE

(b) (4)

TO

Injection: 2 mg/1.5 mL (1.34 mg/mL) available in:

Single-patient-use pen that delivers 0.25 mg or 0.5 mg per injection (3).

Single-patient-use pen that delivers 1 mg per injection (3).

2. Full Prescribing Information
    a. Section 2 Dosage and Administration – For better readability and to mitigate any confusion, revise the first paragraph, (b) (4)

2.1 Recommended Dosage

- Start OZEMPIC with a 0.25 mg subcutaneous injection once weekly for 4 weeks. The 0.25 mg dose is intended for treatment initiation and is not effective for glycemic control.
- After 4 weeks on the 0.25 mg dose, increase the dose to 0.5 mg once weekly.
- If after at least 4 weeks on the 0.5 mg dose additional glycemic control is needed, the dose may be increased to 1 mg once weekly after at least 4 weeks. The maximum recommended dose is 1 mg once weekly.

b. Section 3 Dosage Forms and Strengths – To align this section with the Applicant's Amendment submitted on June 7, 2017, revise this section as follows:

CHANGE

(b) (4)

TO

Injection: 2 mg/1.5 mL (1.34 mg/mL) of semaglutide as a clear, colorless solution available in:

- Pre-filled, disposable, single-patient-use pen that delivers 0.25 mg (for treatment initiation) or 0.5 mg (for maintenance treatment) per injection, and a
- Prefilled, disposable, single-patient-use pen that delivers 1 mg (for maintenance treatment) per injection

c. Section 16.1 How Supplied – To mitigate any confusion, we recommend revising this section as follows:
   i. Change (b) (4) to "Pen delivers doses of 0.25 mg or 0.5 mg per injection"
   ii. For the "Carton of 1 Pen…," change (b) (4) to "6 NovoFine Plus needles"
   iii. Change (b) (4) to "Intended for treatment initiation at the 0.25 mg dose and maintenance treatment at the 0.5 mg dose"
   iv. Change "(b) (4) to "Pen delivers doses of 1 mg per injection"
   v. Change (b) (4) to "Intended for maintenance treatment at the 1 mg dose only"

d. Section 16.2 Recommended Storage – To align labeling with currently approved products, revise the statement, (b) (4) to

"After (b) (4) use of the OZEMPIC pen, the pen can be stored for 56 days at controlled room temperature….," including Table 8 accordingly.

4.2 RECOMMENDATIONS FOR NOVO NORDISK

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

1. Container Labels – Pen-injector that doses 0.25 mg and 0.5 mg
    a. In accordance with USP Chapter <1> Injections, revise the total product strength expression as follows: "2 mg/1.5 mL (1.34 mg/mL)"
    b. Move the location of the net quantity statement, "1.5 mL prefilled pen" away from the strength expression, as currently presented it may cause confusion with other prominent information.
    c. To align labeling with currently approved products, add the following important statement if space permits: "Discard pen 56 days after first use."
    d. For added clarity and to mitigate any confusion, change "(b) (4) to "Pen delivers doses of 0.25 mg or 0.5 mg"
2. Container Labels - Pen-injector that doses 1 mg only
    a. See 1.a., 1.b., and 1.c.
    b. For added clarity and to mitigate any confusion, change (b) (4) to "Pen delivers doses of 1 mg"
3. Carton Labeling – Pen-injector that doses 0.25 mg and 0.5 mg
    a. See 1.a. and 1.b.
    b. To align labeling with currently approved products, revise the statement, (b) (4) to "Discard pen 56 days after first use."
    c. For added clarity and to mitigate any confusion, change the following:
        i. "(b) (4) to "Pen delivers doses of 0.25 mg or 0.5 mg."
        ii. (b) (4) to "Each prefilled pen contains 2 mg semaglutide in 1.5 mL and will deliver 8 doses of 0.25 mg or 4 doses of 0.5 mg."
        iii. "(b) (4) to "Contains: 1 Ozempic pen, ..."
    d. Inner flap marked "Lift here"
        i. For added clarity and to mitigate any confusion, change the following:
            1. (b) (4) to "**Use Ozempic 1 time a week**"
            2. (b) (4)" to "Write the day of the week you choose to inject," (b) (4)
        ii. To allow users to accurately record injection dates and align the labeling with the intended dosing escalation schedule for users initiating therapy (4 doses of 0.25 mg and 2 doses of 0.5 mg) and maintaining therapy (4 doses of 0.5 mg), we recommend revising the inner carton flap as follows:

            I injected my **weekly 0.25 mg dose** on the (b) (4) dates

I injected my **weekly 0.5 mg dose** on the [redacted] dates

e. Quick Guide on inner carton flap
    i. Modify the first sentence as follows: "This is a Quick Guide. **Read the Instructions for Use** leaflet for important safety information **before using the pen**."
    ii. Add arrows between each task to show the order of each step. In addition, include a downward arrow after task 3 with the following statement: "Go to **Give your injection** (see opposite flap on box)"
    iii. Modify task 4 to read as follows: "...until the dose counter shows the dose you need to inject (0.25 mg or 0.5 mg)."

f. Professional Sample Rx Sticker – For added clarity and to mitigate any confusion, change the following:

[redacted]	Rx: (semaglutide) injection Inject 0.5 mg under skin once weekly Quantity: 1 pen (NDC 0169-4137-03 with 6 NovoFine Plus needles)
TO	

4. Carton Labeling - Pen-injector that doses 1 mg only
    a. See 1.a., 1.b., 3.d.i.1., 3.d.i.2., 3.e.i., and 3.e.ii.
    b. To align labeling with currently approved products, revise the statement, [redacted] to "Discard each pen 56 days after first use."
    c. For added clarity and to mitigate any confusion, change the following:
        i. [redacted]" to "Each pen delivers doses of 1 mg only"
        ii. [redacted] to "Each prefilled pen contains 2 mg semaglutide in 1.5 mL and will deliver 2 doses of 1 mg."
    d. Inner flap marked "Lift here"
        i. For added clarity and to mitigate any confusion, change [redacted] to "I injected my **weekly 1 mg dose** on the [redacted] dates"

5. For added clarity and to mitigate any confusion, we provide the following recommendations for the proposed strategy to ensure electronic health systems and pharmacy systems are adequately differentiated:
    a. Ensure that this strategy is applied across all electronic health systems and pharmacy systems in order to adequately differentiate the products.
    b. Figure 1 Example of Product Search in the EHR System
        i. Change [redacted] (b) (4) to "Ozempic 0.25 mg or 0.5 mg doses, 2 mg/1.5 mL (Subcutaneous Solution, 1 Pen)"
        ii. Change [redacted] (b) (4) to "Ozempic 1 mg doses, 2 mg/1.5 mL (Subcutaneous Solution, 2 Pens)"
    c. Figure 2 Example of Prescription Entry in the EHR System
        i. Change [redacted] (b) (4) to "Ozempic 0.25 mg or 0.5 mg doses, 2 mg/1.5 mL (Subcutaneous Solution, 1 Pen)"
        ii. Change [redacted] (b) (4) to "Ozempic 0.25 mg or 0.5 mg doses, 2 mg/1.5 mL"
        iii. Change [redacted] (b) (4) to "2 mg/1.5 mL (Subcutaneous Solution)"
        iv. Change [redacted] (b) (4) to "Ozempic 1 mg doses, 2 mg/1.5 mL (Subcutaneous Solution, 2 Pens)"
        v. Change [redacted] (b) (4)" to "Ozempic 1 mg doses, 2 mg/1.5 mL"
6. We provide the following recommendations for the IFU:

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

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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SUSAN RIMMEL
11/22/2017

QUYNHNHU T NGUYEN on behalf of HINA S MEHTA
11/22/2017

QUYNHNHU T NGUYEN
11/22/2017

QUYNHNHU T NGUYEN on behalf of MISHALE P MISTRY
11/24/2017

Final Clinical Inspection Summary

Date	Final: 11/13/2017 Original: 8/1/2017
From	Cynthia F. Kleppinger, M.D., Senior Medical Officer Janice Pohlman, M.D., M.P.H., 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 William Chong, M.D., Team Leader Peter Franks, Regulatory Project Manager Division of Metabolism and Endocrinology Products (DMEP)
NDA/BLA #	NDA 209637
Applicant	Novo Nordisk, Inc.
Drug	Semaglutide
NME (Yes/No)	Yes
Therapeutic Classification	Antidiabetic
Proposed Indication(s)	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (b) (4) [redacted]
Consultation Request Date	1/25/2017
Summary Goal Date	8/2/2017
Action Goal Date	12/5/2017
PDUFA Date	12/5/2017

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The inspection for this NDA consisted of five domestic clinical sites, five foreign clinical sites, the sponsor and the added inspection of the contract research organization (CRO). The addition of the CRO inspection was based on information reported by the sponsor during the review of the application (see discussion below). At the time of the initial Clinical Inspection Summary, the inspection of the CRO was pending. It has now completed. The inspection of two clinical investigators listed below revealed regulatory violations. The inspection of the CRO revealed regulatory violations. The inspection of the sponsor and the remaining clinical investigators revealed no regulatory violations.

In general, based on the inspections of the 10 clinical sites, the sponsor, and the CRO, the

inspectional findings support validity of data as reported by the sponsor under this NDA.

The classification for Drs. Armas and Frechtel is Voluntary Action Indicated (VAI). Although regulatory violations were noted (as described below), they are unlikely to significantly impact primary safety and efficacy analyses. Reliability of data from these sites is acceptable for use in support of the indication for this application. The full Establishment Inspection Reports (EIRs) were submitted for review.

The classification for [redacted] (b) (4) is Voluntary Action Indicated (VAI). Although regulatory violations were noted (as described below), they are unlikely to significantly impact primary safety and efficacy analyses. Reliability of data from this CRO is acceptable for use in support of the indication for this application. The full Establishment Inspection Report (EIR) was submitted for review.

The classification for Drs. Busch, Cannon, Cheung, Deshpande, Duckor, Kiyosue, Maffei, Matsuoka and the sponsor is No Action Indicated (NAI). Data from these sites and the sponsor are considered reliable based on the available information. The full Establishment Inspection Reports (EIR) were submitted for review.

II. BACKGROUND

Novo Nordisk is seeking approval of a New Drug Application (NDA) for Ozempic® (semaglutide) injection indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus [redacted] (b) (4)

Inspections were requested for the following four studies:

- **NN9535-3623** SUSTAIN 1: Efficacy and safety of semaglutide once-weekly versus placebo in drug-naïve subjects with type 2 diabetes

The trial began February 3, 2014 and completed May 8, 2015. Database lock was June 22, 2015. There were 72 sites in 8 countries that randomized subjects. There were 652 subjects screened and 388 subjects randomized. The primary endpoint was change from baseline to week 30 in HbA1c.

- **NN9535-3625** SUSTAIN 4: Efficacy and safety of semaglutide once weekly versus insulin glargine once daily as add on to metformin with or without sulphonylurea in insulin-naïve subjects with type 2 diabetes

The study began August 4, 2014 and completed September 3, 2015. Database lock was October 23, 2015. There were 196 sites in 14 countries that randomized subjects. There were 1610 subjects screened and 1089 subjects were randomized. The primary endpoint was change from baseline in HbA1c at week 30.

- **NN9535-3627** Efficacy and safety of semaglutide once-weekly versus placebo as add-on to basal insulin alone or basal insulin in combination with metformin in subjects with type 2 diabetes (T2D)

The study began December 1, 2014 and completed November 21, 2015. Database lock was January 21, 2016. There were 90 sites in five countries that randomized subjects. There were 534 subjects screened and 397 subjects randomized. The primary endpoint was change from baseline in HbA1c at week 30.

- **NN9535-3744** SUSTAIN 6 – Long-term Outcomes A long-term, randomized, double-blind, placebo-controlled, multinational, multi-center trial to evaluate cardiovascular and other long-term outcomes with semaglutide in subjects with type 2 diabetes.

The study began February 21, 2013 and completed March 15, 2016. There were 229 sites in 20 countries that randomized subjects. The primary endpoint was time from randomization to first occurrence of a major adverse cardiovascular event (MACE), defined as cardiovascular (CV) death, non-fatal myocardial infarction (MI), or non-fatal stroke.

Novo Nordisk informed FDA July 5, 2017 during the review of application NDA 209637 that a deviation had been identified from the predefined adjudication process for the four open-label trials in the semaglutide phase 3a program (SUSTAIN). The affected open-label trials are Study 3624, Study 3625 and two local Japanese trials (Studies 4091 and 4092).

According to the Event Adjudication Committee (EAC) charter, the adjudicators were to be blinded to treatment in all trials in the SUSTAIN program, regardless of whether the trials were double-blind or open-label, and even though treatment allocation was known by investigators and site personnel in the open-label trials. To maintain blinding, all information that could potentially unblind the EAC members was to be redacted before sending the packages to the EAC members. The adjudication process was handled by the external, independent contract research organization, (b) (4) who managed the collection and verification of relevant information from the clinical trial sites for events sent for adjudication, and ensured that the information was blinded with respect to treatment assignment and anonymized before forwarding it to the EAC members.

In addition to source data from the clinical sites, all events sent for adjudication had information from the electronic case report form (eCRF) provided from Novo Nordisk. The eCRF in the open label trials contains information on trial product, dose and/or route of administration, which is not the case in the double-blinded trials. Novo Nordisk discovered on June 1, 2017 that the eCRF information was not consistently redacted by (b) (4) and was inadvertently included in the packages sent to the EAC members. In the four affected trials, the redaction of treatment assignment, dose or administration route was not consistently implemented in the supporting eCRF. The eCRFs were provided to the independent EAC members in addition to source data from investigators in the open-label trials, thereby leading to potential unblinding of EAC members.

A total of 2,994 events were sent for adjudication in all trials in the SUSTAIN phase 3a program. After an investigation by the sponsor, it was determined that 275 packages (from 185 patients) included unredacted information in the eCRF where the EAC members could have been unblinded to treatment information. Novo Nordisk formed a new EAC to reassess the 275 cases in a blinded manner. As the

trials have been completed, (b) (4) needed to re-open the event adjudication system. The blinded adjudication was to be performed using the same process and definitions as the original adjudication; additional source data could not be requested and new events could not be identified.

III. RESULTS (by Site):

Name of CI/ Address Site#	**Protocol # and # of Subjects Randomized**	**Inspection Date**	**Classification**
Mayura Deshpande MeDiNova North London Clinical Studies Centre Mount Vernon Hospital Rickmansworth Road Northwood, NA HA6 2RN Great Britain Site 111 and Site 528	P3625 Site 111 15 subjects P3744 Site 528 12 subjects	04/28 – 05/05/2017	No Action Indicated (NAI)
Gustavo Frechtel Fernandez de Enciso 4620 CABA, NA C1419AHN Argentina Site 122	P3744 30 subjects	05/29 – 06/02/2017	Voluntary Action Indicated (VAI)
Laura Maffei Consultorios Asociados de Endocrinologia Cerviño 3365/75, Piso 1, Office 2 Buenos Aires, NA C1425AGC Argentina Site 804	P3625 16 subjects	06/05 – 06/08/2017	No Action Indicated (NAI)
Arihiro Kiyosue 3-3-14, Nihombashi Chuo-ku, Tokyo, NA 103 0027 Japan Site 901 and Site 152	P3623 Site 901 15 subjects P3627 Site 152 11 subjects	05/29 – 06/02/2017	No Action Indicated (NAI)
Osamu Matsuoka 6-26-8, Shinjuku Shinjuku-ku, Tokyo, NA 160-0022 Japan Site 903	P3623 14 subjects	06/05 – 06/08/2017	No Action Indicated (NAI)
Eddie Armas 7000 SW 62nd Ave Suite 100 Miami, FL 33143-4717 Site 412	P3623 11 subjects	04/26 – 05/02/2017	Voluntary Action Indicated (VAI)
Robert Busch 1365 Washington Avenue Suite 300 Albany, NY 12206 Site 604	P3744 33 subjects	06/26 – 06/29/2017	No Action Indicated (NAI)
Kevin Cannon PMG Research of Wilmington 1907 Tradd Court	P3625 Site 692 6 subjects	05/08 – 05/11/2017	No Action Indicated (NAI)

Wilmington, NC 28401 Site 692 and 683	P3744 Site 683 30 subjects		
Deanna Cheung 3745 Long Beach Blvd. Suite 100 Long Beach, CA 90807 Site 728	P3625 7 subjects	07/13 – 07/20/2017	No Action Indicated (NAI)
Steven Duckor 1085 N. Harbor Blvd Anaheim, CA 92801 Site 734 and Site 309 and Site 610	P3625 Site 734 8 subjects P3627 Site 309 8 subjects P3744 Site 610 16 subjects	07/24 – 07/28/2017	No Action Indicated (NAI)
Novo Nordisk A/S Vandtaarnsvej 114 DK 2860 Soeborg Denmark	P3623 P3625 P3627 P3744	06/12 – 06/15/2017	No Action Indicated (NAI)
(b) (4)	P3623 P3624 P3625 P3627 P3744 P4091 P4092	(b) (4)	Voluntary Action Indicated (VAI)*

Key to Compliance Classifications
NAI = No deviation from regulations
VAI = Deviation(s) from regulations
OAI = Significant deviations from regulations; data unreliable.
*Pending = Preliminary classification based on information in 483 (if applicable) and preliminary communication with the field; final classification is pending letter to site.

NOTE: Site inspections focused on 100% 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.

The non-U.S. sites were not conducted under IND.

1. Mayura Deshpande/ Site 111 P3625 / Site 528 P3744

The MeDiNova North London Clinical Studies Centre is a dedicated clinical research center since 1997 physically located on the Mount Vernon Hospital campus in Northwood (North London), U.K. Dr. Mayura Deshpande, M.D. was the Principal Investigator (PI) responsible for both clinical trials at the time of completion. Dr. Deshpande is no longer employed at the site. She accepted a position at another institution in April 2016. Dr. Ronnie Beboso, M.D. was assigned as the PI of record for record/document access and inspection purposes. He was not involved in either clinical trial inspected. Three different PIs were involved in the conduct of P3625 at the inspected site. There were two different PIs involved in the conduct of P3744 at the inspected site.

For Study P3625, there were 20 subjects screened and 15 subjects enrolled into the study; 11 subjects completed the study (two subjects were enrolled and randomized but withdrew consent at the time of randomization and two subjects were discontinued from participation due to adverse events as required by the protocol). There were 20 subject records reviewed.

The central Research Ethics Committee (REC) of record is (b) (4)

For Study P3744, there were 21 subjects screened and 12 subjects enrolled into the study; six subjects completed the study (one subject died, four subjects withdrew due to serious adverse events and one additional subject was withdrawn due to protocol non-compliance). There were 21 subject records reviewed.

The central Research Ethics Committee (REC) of record is (b) (4)

For both studies, study records were orderly and available for inspection. There were dedicated Site Files or Trial Master File binders that included general and regulatory type records. The files for both trials were similar and included much of the same sections and information pertaining to the respective trial. Source records verified all inclusion/ exclusion criteria. Clinical trial activities and conduct was well documented. There was no under-reporting of adverse events. The primary efficacy endpoints were verifiable as well as the secondary efficacy endpoints reviewed. Data was verifiable by comparing the source documents to the eCRFs and/or the sponsor data listings/tables.

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. Gustavo Frechtel/ Site 122 P3744

There were 34 subjects screened and 30 subjects enrolled into the study; 30 subjects completed the study. There were 11 subject records reviewed.

The study was conducted at an office affiliated with the hospital about three blocks away. Dr. Frechtel has a private practice adjacent to the hospital and devotes about 50 percent of his time to clinical studies. The subjects recruited for these studies were already patients of the hospital, his private practice and/or from referring physicians who are subinvestigators.

There were two Ethics Committees (ECs) for the study as there were new regulations that were passed for ECs in Argentina. The original EC that approved the study was (b) (4) (b) (4) The subsequent EC was

There was a sponsor audit performed at the site on 6/30/2015 which identified a high number of protocol deviations and laboratory reports with evaluations documented out of timelines. Corrective actions were instituted and the sponsor retrained the staff.

The study files were well organized and available. There was no under-reporting of adverse events. The primary endpoint was verifiable. All protocol deviations were captured and reported. The source records confirmed the data in the sponsor data line listings except for the inspectional observations noted of missing concomitant medications.

At the conclusion of the inspection, a Form FDA-483, Inspectional Observations, was issued for the following deficiencies:

1. Failure to ensure that an investigation was conducted in accordance with the general investigational plan and protocols as specified in the IND. Specifically, the following concomitant medications found in the source records were not listed in the eCRF/data submitted to the sponsor:

Subject #	Date taking medication and/or listed on source	Concomitant Medications listed on source document
122-019	04/08/2014	Brimonidina, Timolol 0.50%, Travoprost, Terazosina 5mg, and Alprazolam
122-028	09/26/2013	Aspirina 100 mg

In addition, while reviewing the medical notes for subject 122-001, there is a date entry 5/7/2014 for a flu vaccine that was also not listed as a concomitant medication.

Dr. Frechtel responded to the observations on 6/15/2017 with appropriate corrective and preventive actions.

3. Laura Maffei/ Site 804 P3625

There were 26 subjects screened and 16 subjects enrolled into the study; 16 subjects completed the study. There were 16 subject records reviewed.

Dr. Maffei devotes about 65 % of her time to clinical studies and 35 % to her private practice. The subjects were recruited from the site's database and also had patients that were referred to the site.

The IRB for this study was (b) (4)

Documents were orally translated during the inspection. The study files were available and organized. Source records were compared to the sponsor data line listings and there were no discrepancies. There was no under-reporting of adverse events. The primary efficacy endpoint was verifiable.

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. Arihiro Kiyosue/ Site 901 P3623/ Site 152 P3627

For Study P3623, there were 16 subjects screened and 15 subjects enrolled into the study; 15 subjects completed the study. There were 16 subject records reviewed.

Records were adequate and very well organized. There was no evidence of under-reporting of AEs. The primary endpoints were verifiable. There were no discrepancies with source data and sponsor's data line listings.

For Study P3627, there were 13 subjects screened and 11 subjects enrolled into the study; 10 subjects completed the study. There were 13 subject records reviewed.

Records were adequate and very well organized. There was no evidence of under-reporting of AEs. The primary endpoints were verifiable. There were no discrepancies with source data and sponsor's data line listings.

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. Osamu Matsuoka/ Site 903 P3623

There were 16 subjects screened and 14 subjects enrolled into the study; 13 subjects completed the study. There were 16 subject records reviewed. Of note, only one woman was entered into the trial. The clinical investigator indicated that women are reluctant to enter into clinical studies in Japan.

Records were adequate and very well organized. There was no evidence of under-reporting of AEs. The primary endpoints were verifiable. There were no discrepancies with source data and sponsor's data line listings.

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. Eddie Armas/ Site 412 P3623

There were 16 subjects screened and 11 subjects enrolled into the study; 10 subjects completed the study. There were 11 subject records reviewed.

The clinical trial took place at Well Pharma Medical Research, which is a site management organization partly owned by Dr. Armas and also serves as Dr. Armas' private practice. The subjects enrolled were recruited mostly through his private practice, but some were also referred to him by physician assistants that he works with.

The IRB used for the clinical trial was (b) (4)

A review of the source documents showed no major deviations from the protocol and all instances were documented and communicated to the sponsor. There were no major discrepancies noted between the source documents and data listings. There was no under-reporting of adverse events. The primary efficacy endpoint was verifiable. The subject records were found to be organized and complete except for the documentation of patient compliance with taking the investigational product.

At the conclusion of the inspection, a Form FDA-483, Inspectional Observations, was issued for the following deficiencies:

1. Failure to prepare or maintain adequate and accurate case histories with respect to observations and data pertinent to the investigation. The site created its own source documentation templates based on the protocol requirements. According to the source documents, the site verifies subject compliance with taking their weekly injection by reviewing the subject diary where subjects record the date they took each injection. However, the subject diary does not have a space for every dose that is required to be taken, therefore this method is ineffective in verifying subject compliance.

The study coordinator for the study stated that the source documents were incorrect in that the subject compliance was not based solely on the entries in the subject diary. She stated she used the subject diaries as well as subject interviews to ensure that the subjects were compliant. It was difficult to document compliance because the injector pens did not have a counter which would countdown the amount of product left in the pen, so the only way they could document compliance is through the subject diary and subject interviews.

OSI Reviewer Comment: The root cause of the problem was that the diary was improperly designed and did not capture all doses. Dr. Armas responded to the observations May 10, 2017 with corrective and preventive actions deemed to be acceptable.

7. Robert Busch/ Site 604/ P3744

There were 38 subjects screened and 33 subjects enrolled into the study; 33 subjects completed the study (25 subjects who completed the study on study medication and eight subjects who completed off study medication). There were 24 subject records reviewed.

Dr. Busch is the Director of Clinical Research of the Endocrine Group which is comprised of multiple endocrinologists and ancillary staff and is part of the Albany Medical Faculty Physicians. Potential subjects were identified within the electronic data base of patients at his endocrinology practice.

The IRB of record is the centralized (b) (4)

The study files were well organized and available. There was no under-reporting of adverse events. The primary endpoint was verifiable. All protocol deviations were captured and reported. The source records confirmed the data in the sponsor data line listings.

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. Kevin Cannon/ Site 692 P3625/Site 683 P3744

For Study P3625, there were eight subjects screened and six subjects enrolled into the study; six subjects completed the study. There were eight subject records reviewed.

For Study P3744, there were 48 subjects screened and 30 subjects enrolled into the study; 28 subjects completed the study (two withdrew consent). There were 12 subject records reviewed.

The IRB used for the studies is (b) (4).

For both studies, the inspection found no significant deficiencies. All subjects appeared to have met eligibility criteria. Data listings were compared to and found consistent with source documents. Primary efficacy endpoint data were verifiable. There was no evidence of under-reporting of AEs.

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. Deanna Cheung/ Site 728 P3625

There were 13 subjects screened and seven subjects enrolled into the study; four subjects completed the study. There were 13 subject records reviewed.

Study records were available, organized and legible. The inspection found no significant deficiencies. All subjects appeared to have met eligibility criteria. Data listings were compared to and found consistent with source documents. Primary efficacy endpoint data were verifiable. There was no evidence of under-reporting of AEs.

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. Steven Duckor/ Site 734 P3625/ Site 309 P3627/ Site 610 P3744

For Study P3625, there were 11 subjects screened and eight subjects enrolled into the study; seven subjects completed the study. There were 11 subject records reviewed.

For Study P3627, there were 12 subjects screened and eight subjects enrolled into the study; eight subjects completed the study. There were 12 subject records reviewed.

For Study P3744, there were 19 subjects screened and 16 subjects enrolled into the study; 15 subjects completed the study. There were 19 subject records reviewed.

For all three studies, all subject records were organized, legible, and available. There were no discrepancies noted in comparing the source documents to the data listings. There was no under-reporting of adverse events. The primary efficacy endpoints for the three studies were verifiable. No issues were noted regarding the eligibility criteria, test article accountability or randomization procedures.

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.

11. Novo Nordisk A/S/ Sponsor

The inspection consisted of reviewing the organizational structure and responsibilities, transfer of obligations, contractual agreements, selection of sites, training, investigational product accountability, the evaluation of the adequacy of monitoring and corrective actions taken by the sponsor/monitor/CRO, deviations related to key safety and efficacy endpoints, quality assurance and audits, adverse events evaluation and reporting, 1572s and investigator agreements, the interactive voice/web response system, financial disclosures, standard operating procedures (SOPs), trial master file review, record retention, selection criteria for all committee members, oversight of committees, data management, escalation

of issues, and clinical trial oversight.

Several trial-level issues were also assessed, including the following:

1. Source documents for Medical Events of Special Interest (MESIs) requiring event adjudication were to be loaded within four weeks of event identification by the sites into (b) (4) (b) (4) Event Adjudication System (EAS). Requesting access to the (b) (4) EAS database and the timeline for upload of source documents within four weeks of event identification had not been possible in the period of January 23, 2014 to March 17, 2014 due to technical issues. As the Site IDs (Site numbers) in the SUSTAIN program are not unique, (b) (4) had to correct the Site list by adding the Trial ID to all the Site numbers created in the (b) (4) EAS database. The database was not available for uploading during the time of the corrections. Data transfer from the FTP server used for the transfer of events from Novo Nordisk to (b) (4) EAS had not been possible. It was confirmed that this had no impact on MESIs/SAEs reporting as there was monitoring of the adverse events reported by the investigator in the eCRF (Inform).
2. For the time period of June 17, 2014 until September 30, 2014, SUSAR reports in Mexico were delivered late (105 days delayed) mainly owing to missing oversight from the responsible clinical trial administrator and the loss of airway bills from the SUSAR packages by the courier. This issue was captured in a country level protocol deviation. The sponsor assessed the deviation when it was discovered. No safety issues warranting actions were identified based on review of safety information reported. No actions were recommended by the DMC based on safety data reported. The SUSAR reports in question did not change the overall safety profile of semaglutide from the IB versions 9 and 10 effective before and after the late SUSAR reporting to investigators; no updates were made based on the SUSARs in question.
3. A total of 25 subjects had been treated with investigational medicinal product (IMP) stored at an incorrect temperature. There were 18 deviations between April 23, 2014 and June 11, 2014 related to US Site 415. An investigation was done by the sponsor. The site used a back-up thermometer only during this period that only recorded actual temperatures. The site misunderstood how to properly monitor and document temperature recordings with the back-up device. This was not picked up by the site monitor. Therefore, trial product was stored at an unknown temperature, and quality was not supported by stability data. This was discovered during a site audit on April 1, 2015. Out of the 18 subject level protocol deviations the trial product was deemed acceptable for use for 10 subjects after review of available documentation by the clinical supply temperature deviation team. The remaining eight deviations cover six subjects that had trial product dispensed which was deemed unacceptable for use. Some were returned and some were lost by the subject. There have been no AEs. The site staff was retrained to ensure correct use and reading of temperature devices.
4. Dr. Uzoaga was an investigator for US Site 697 that was activated on August 13, 2013. Nine patients were enrolled at this site. Dr. Uzoaga was found guilty of health care fraud and conspiracy to commit health care fraud in November 2015 and sentenced to 42 months prison in March 2016. The sponsor learned of the indictment of Dr. Uzoaga on October 22, 2014. The FDA inspector reviewed all of the Uzoaga monitoring visit reports and confirmed that there were no issues identified during those visits. It was asked why it was not possible to transfer the subjects or get a new investigator. It was explained that there was only one site

within reasonable travel distance from Dr. Uzoaga's site. It was determined that this other site was not a viable option as the site already had 21 ongoing patients and not adequate resources for a transfer of more subjects. Also, the trial was near to completion at the Dr. Uzoaga site with only off-study drug follow-up visits remaining. Based on the internal evaluation of the charges against Dr. Uzoaga along with the outcome of the Quality Assessment visit (Dec-2014), Novo Nordisk determined that it was not necessary to either transfer the subjects or change investigators. It was confirmed that there were four remaining subjects at the time the sponsor learned of the conviction. All patients were off trial product and the four patients were scheduled for the final visit.

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.

12. (b) (4) Contract Research Organization

(b) (4) was contracted by Novo Nordisk to manage the clinical event adjudication processes for the studies. Records reviewed during the inspection included standard operating procedures (SOPs), contracts, ECG processing, data files, training files, curriculum vitaes (CVs) of study personnel, and corrective action records. The clinical event adjudication process was fully evaluated.

The Clinical Event Validation and Adjudication (CEVA) department at (b) (4) managed the event adjudication process and served as the Event Adjudication Data Coordinating Center, supporting the sites and the Event Adjudication Committee (EAC).

The qualifications, CVs, and financial disclosure forms of the EAC members for both committees were reviewed. An EAC member could not be a member of the steering committee or advisory board or a Clinical Investigator. There were no inspectional observations regarding members' qualifications.

There appeared to be adequate oversight by Novo Nordisk. In fact, it was Novo Nordisk who found that study treatment information on the Safety Information Form (SIF) in a different study (not a SUSTAIN study) was not redacted. The same issue was identified in the open-label studies for the SUSTAIN program.

The root cause/contributing factor for the lack of redaction was failure of the CEVA Coordinators who were to do the redaction to fully understand the requirements for redaction of study treatment assignment. This was attributed to failure of the Endpoint Management Plan (EMP) Versions 2, 3, and 4 to include specific and detailed information regarding study treatment identification. The CEVA Coordinators are based in the (b) (4) office. There is no requirement for any medical/clinical background. The job required only a high school diploma and one year of relevant work experience. The initial training for the CEVA Coordinators was not adequate. There were also no slides or training materials that the staff could reference while performing the redaction.

(b) (4) subcontracted (b) (4) to develop and maintain the Endpoint Adjudication System (EAS). The (b) (4) EAS was independent from the clinical database. Periodically, according to a schedule specified by Novo Nordisk, (b) (4) Data Management Programming extracted the adjudication results from the EAS, converted them into Oracle Clinical (OC) loadable files, and loaded these data into the live Oracle Clinical database maintained by Novo Nordisk.

Novo Nordisk had an Event Adjudication Group (NN-EAG) that approved the EAC Charter, the EAC Chairperson, and EAC members. NN-EAG captured all adjudicable events into its Tracking Tool (TT) and automatically notified (b) (4) for upload into the EAS. CEVA would then query the study sites for any additional information and prepare the dossiers for the EAC.

In November 2015, Novo Nordisk decided that all SUSTAIN trials (closed and ongoing) had to be reconciled due to a (b) (4) audit finding of issues that occurred when results were being pulled from (b) (4) EAS and made ready to be loaded to OC. (b) (4) data management performed manual reconciliation via validated reports from OC (RDLs) and similar validated reports from (b) (4) EAS. Novo Nordisk continued to work with (b) (4) to make sure that all adjudicable events in its Tracking Tool (TT) were recorded in the EAS.

(b) (4) was also responsible for providing CDs (or other appropriate media like a hard drive) with database content, including all source documents and evaluation results in a searchable format, for archiving at the end of the studies.

It was discovered during the inspection that the database never had to be unlocked for re-adjudication as it had never been officially locked. On 4/20/2016, (b) (4) put the database into Maintenance mode. This meant that no one had read/write access to the EAS (i.e., neither Novo Nordisk or (b) (4) staff). Only (b) (4) personnel had read-only access to the database in order to be able to generate the closeout materials (i.e., all completed subject PDFs, source documents and dossiers, and SAS datasets containing all data collected during the trial and the complete audit trail). This was confirmed during the inspection by staff interviews, record review, and review of the EAS audit trails.

(b) (4) initially tried repeatedly to transfer the files but they were too large for their system. On 7/11/2016, (b) (4) generated the closeout materials and sent them directly to Novo Nordisk via courier. Novo Nordisk never confirmed that the closeout materials were acceptable so that (b) (4) could close and archive the EAS. It remained in Maintenance status until 7/6/2017 when the EAS was re-opened in Live mode for the re-adjudication. Re-adjudication was completed 8/4/2017. The EAS will be closed for a second time at a date to be determined according to the (b) (4) process for closing and archiving an EAS, and the EAS will be archived at a date to be determined according to the (b) (4) process for closing and archiving an EAS.

The event dossiers were difficult to review during the inspection because their contents were spread among several different systems and repositories. The FDA inspectors had to refer to audit trails, queries in other systems, emails, or spreadsheets to determine how an event was processed. In addition, when it was determined that all events would be re-adjudicated, using the (b) (4) EAS required that all previous documents related to the first adjudication be removed by CEVA from the system. Each document that was requested from the first adjudication had to be retrieved through the audit system.

The second adjudication was to be performed using the same process and definitions as the original adjudication. Additional source data could not be requested and new events could not be identified. However, it was observed during the inspection that this was not the case. Several dossiers submitted to the new EAC were 'cleaned' prior to submission to the new EAC (e.g., documentation that became available after the event had been reviewed by the original EAC was included). There were 20 (of the 275) events in which there were differences between the dossiers submitted to the original EAC and the dossiers submitted to the new EAC.

The list below details the events where the orginal dossiers submitted was updated and corrected:

Trial ID	Subject ID	Event Type	Unique TT identifier	AE Number	Adjudication Number
NN9535-3625	104004-3625	Fatal	5039	4	1
NN9535-4091	116003-4091	Neoplasm	7338	5	1
NN9535-4091	117003-4091	Heart Failure	4482	1	1
NN9535-4091	117006-4091	Neoplasm	3886	5	1
NN9535-4091	117015-4091	Neoplasm	6135	1	1
NN9535-4091	117022-4091	Neoplasm	4483	1	1
NN9535-4091	128016-4091	Neoplasm	4854	7	1
NN9535-4091	129007-4091	Neoplasm	4080	1	1
NN9535-4091	142019-4091	Neoplasm	5733	3	1
NN9535-3624	153001-3624	Neoplasm	4133	6	1
NN9535 3625	206009-3625	Cerebrovascular	5738	3	1
NN9535-4092	218007-4092	Neoplasm	5706	5	3
NN9535-3624	304003-3624	Cerebrovascular	2685	5	1
NN9535-3624	352003-3624	Pancreatitis	3759	3	1
NN9535-3624	705002-3624	Thyroid	1666	4	1
NN9535-3624	709002-3624	Neoplasm	3987	9	1
NN9535-3624	728006-3624	Pancreatitis	2549	2	1
NN9535-3624	741002-3624	Thyroid	1471	1	1
NN9535-3624	742013-3624	Pancreatitis	1417	6	1
NN9535-3624	759001-3624	Neoplasm	1395	1	1

Four event dossiers had negligible changes. An additional 12 event dossiers had extra source documents included in their dossiers when submitted to the new EAC. However, according to the EAC Chair, none of these dossiers warranted re-adjudication due to these extra source documents. Four of the events listed were listed by mistake. All previously translated and non-translated

documents not previously provided to the EAC were included in the re-adjudicated dossiers. All duplicate pages not previously removed from the original dossier were excluded in the re-adjudicated dossiers. All source documentation previously included in a dossier for the incorrect subject was excluded from the re-adjudication dossiers. For these events, there were no differences between the dossiers submitted to the original EAC and the dossiers submitted to the new EAC.

The definition of pancreatic was expanded from EAC Charter Version 1.0 to Version 4.0, which required re-review of events to classify according to degree of severity. A list of all the pancreatitis cases with the adjudication and re-adjudication results was reviewed. There were two event changes. One was later determined to be a duplicate case, Subject # 3744-524006-AE20. One was later determined not to be pancreatitis, Subject 3624-742013-AE6. The dossier packages for both adjudications for both AEs were identical except the second ones have redaction of identifiable information.

The nephropathy definition was amended at Version 4.0 because the wrong laboratory unit was used. This led to 19 events being re-reviewed. In evaluating where the error occurred, the unit of measurement was found to be correct in the study protocol but was not correct in the Requirements Specification document provided by Novo Nordisk as part of the project's Work Order. The CEVA manager used the definitions from the Work Order rather than the study protocol. A list of all nephropathy cases with the adjudication and re-adjudication results was reviewed. There were no changes.

The definition of Neoplasm was amended with EAC Charter Version 3.0. A total of 53 events confirmed by the EAC as neoplasms at the original adjudication were not confirmed by the second adjudication. Specifically, 48 events were not confirmed, two events were evaluated as duplicate events, and three events were evaluated as unable to adjudicate due to insufficient information. The files for Subject 3625-205002-AE5, both before and after re-adjudication and -AE6, both before and after re-adjudication were reviewed. The dossier packages for both adjudications for both AEs are identical except the second ones have redaction of identifiable information. The files for Subject 3624-105009-AE9, both before and after re-adjudication were reviewed. The dossier packages for both adjudications are identical except the second has redaction of identifiable information.

Several cases that had a different adjudication result between the two EACs were reviewed. There appear to be no consistent pattern. For example:

- One event (Subject # 3624-356009-AE9, Semaglutide 1 mg) was reviewed that was not confirmed by the EAC at the original adjudication, but was confirmed by the EAC as an acute MI at the second adjudication. The discharge summary "Conclusions" (page 16) notes, "Recent ECG and ultrasound diagnosis of lateral AMI (silent course)." Review of the translated documents appears to confirm an MI (as decided by the second EAC).
- One event (Subject # 3624-781004-AE2, Exenatide ER) reviewed was confirmed by the EAC as a TIA at the original adjudication but was not confirmed by the EAC at the second adjudication. The Emergency Room Report and the Final Report (pages 3 & 20) note,

"Patient's Chief Complaint reports uncontrolled movement of right hand, unable to grip with right hand and period of 'difficulty understanding' x3 episodes today that last under 15 seconds each***The patient presents with right, upper extremity weakness, altered speech and altered coordination. Time onset was 2 weeks ago. The course/duration of symptoms is resolved and episodic with multiple episodes lasting 3 seconds. ***Impression and Plan TIA***Assessment Diagnosis Problem # L hemispheric TIA". Review of the documents appears to confirm a TIA (as decided by the first EAC).

At the conclusion of the inspection, a Form FDA-483, Inspectional Observations, was issued for the following deficiencies:

1. At least 275 out of 2999 (~9.2%) source document dossiers for the four open-label studies did not have the study treatment information adequately redacted. This resulted in the potential unblinding of the EAC to the treatments received by the subjects who experienced these adverse events. During the inspection, 33 medical events were randomly selected from the list of 275 events with potential unblinding issues, and the electronic data files were reviewed. The files included the original dossiers that were sent to the EAC with the audit trails, and the corrected dossiers that were sent for re-adjudication to the EAC with the audit trails. It was verified that the original dossiers contained unredacted treatment information.

   When (b) (4) reviewed the affected dossiers to redact the treatment information prior to submission to a second EAC, the packages were not to be submitted to the EAC until approved by Novo Nordisk. Novo Nordisk found at least 11 of the 275 records (~4%) still contained information that could lead to potential unblinding of the EAC to study treatment.

   OSI Reviewer Comment: In reviewing the records, it did not appear that the members of the original EAC were aware that unredacted information was present in the dossiers. All dossiers were eventually properly redacted before submission to the second EAC for re-adjudication.

   Furthermore, randomly selected medical events from the blinded studies (Protocols NN9535-3623, NN9535-3626, NN9535-3627, and NN9535-3744) were reviewed during the inspection and all required information was fully redacted.

2. (b) (4) failed to ensure that sufficient documentation critical for adjudication (such as progress notes, hospital discharge summaries, history and physicals, laboratory tests, imaging studies, pathology reports, etc.) were submitted to the EAC or that a letter of explanation from the site was submitted if these were not available. Several events were adjudicated as "unable to adjudicate" due to insufficient documentation. At least 82 events were annotated as "unable to adjudicate" due to insufficient documentation.

   OSI Reviewer Comment: It was ultimately the site's responsibility to try to retrieve all necessary source information and upload that into (b) (4) EAS.

However, the EMP, Version 4.0, 12/8/2015, states, "the packet (dossier) will not be forwarded to the EAC until the packet is complete". CEVA did not follow its own procedures.

3. The EAC Charter states that "the EAC chair will QC in detail the first 100 events that achieve an agreement at first consensus, and all events with a 'Duplicate event' outcome that have achieved an agreement at first consensus within 7 calendar days. The EAC chair will sign off on all agreements prior to the event being considered final. The EAC chair will distinguish the events that have completed a thorough QC and clinical assessment by indicating 'QC' in the comments section of the final sign off form." However, there is no documentation that this process occurred. A memo from the EAC Chair to the (b) (4) CEVA Manager, dated 15 June 2017, states, "Unfortunately, I did not record QC in the comments field when I reviewed the first 100 cases even though I did perform the review."

   OSI Reviewer Comment: Since these reviews are not documented, it is not possible to confirm that they were performed as required. It is possible that the unredacted documents may have been discovered during the initial adjudication if these procedures had been followed.

4. The EAC Charter states that the Chair will ensure "that each event is not positively adjudicated more than once as part of a multiple events assessment by QC of events through a final sign off form". However, there were several events that were positively adjudicated more than once. For example, Subject 3644-604025:
   - AE1 - papillary thyroid cancer with event date 10 July 2013 was positively adjudicated.
   - AE2 - papillary thyroid cancer with event date 10 July 2013 positively adjudicated.
   - AE5 - papillary thyroid cancer with event date 3 April 2014 positively adjudicated.

   On October 30, 2015, the sponsor representative brought it to CEVA's attention that there were three confirmed thyroid events for the same subject with the same onset date. It was later confirmed that AE2 and AE5 were duplicates.

   OSI Reviewer Comment: These duplicates occurred during the first adjudication process.

5. The EAC Charter states that, if two EAC reviewers were unable to agree on an event, it was referred for a "full committee review" or "second consensus" under the direction of the EAC Chair. However, there was insufficient documentation present to determine whether the EAC Chair discussed some of these cases with other CEC members as part of the Second consensus process.

OSI Reviewer Comment: On Version 4 of the SUSTAIN EAC Charter, a consensus process was introduced which allowed for resolution by e-mail. The CEVA lead was not always copied on e-mail communications between EAC members resulting in inadequate documentation of the conversations that occurred at the second consensus. A letter from the EAC Chair, dated 9/4/2017, states that he did discuss these cases with the other committee members and he submitted the documentation to [redacted] (b) (4) *has adjusted their procedures and no longer allows any consensus processes by email. There must now be a meeting with full meeting minutes.*

Although regulatory violations were noted as described above, they are unlikely to significantly impact primary safety and efficacy analyses. As communicated by the sponsor to FDA in the correspondence of August 24, 2017, the second adjudication resulted in some differences in adjudication outcome compared with the original adjudication. A total of 83 of 275 events (30.2%) that occurred in the open-label studies had different outcome at the second adjudication as compared with the original adjudication. The majority of the events (53 of the 83 events, 64% with different outcomes were neoplasm events as described above). There was no evidence to show that the original EAC members were aware of the unblinded information. The small number of updated dossiers (20) may have had some influence on the decisions of the second EAC, but this would be very minimal. The second EAC did have the advantage of having the full dossier at the initial assessment, while updated information was given to the original EAC as the information became available. The adjudication process itself underwent a very intense, focused approach with the second EAC over a shorter timeline. All these subtle changes could have influenced the different outcomes noted. There were also some duplicate events that were adjudicated as two separate events during the first adjudication process. These were discovered and corrected for the second EAC. There was no evidence of significant GCP non-compliance that could have negatively affected the adjudication process.

The review division was advised of these findings and has already considered the significance of any impact the readjudicated outcomes have on important safety outcomes.

{See appended electronic signature page}

Cynthia F. Kleppinger, M.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

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CC:

Central Doc. Rm./ NDA 209637
DMEP/Division Director/ Jean-Marc Guettier
DMEP /Deputy Director/Jim P. Smith
DMEP/Team Lead/William Chong
DMEP/Clinical Reviewer/ Andreea (Ondina) Lungu
DMEP /Regulatory Project Manager/Peter Franks
OSI/DCCE/Division Director/Ni Aye Khin
OSI/DCCE/GCPAB/Branch Chief/Kassa Ayalew
OSI/DCCE/GCPAB/Team Leader/Janice Pohlman
OSI/DCCE/GCPAB Reviewer/Cynthia Kleppinger
OSI/DCCE/GCPAB/Program Analyst/Joseph Peacock/Yolanda Patague
OSI/DCCE/Database Project Manager/Dana Walters

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/s/

CYNTHIA F KLEPPINGER
11/13/2017

JANICE K POHLMAN
11/13/2017

KASSA AYALEW
11/13/2017

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

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

Memorandum

Date: November 13, 2017

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

Monika Houstoun, Associate Director for Labeling, (DMEP)

From: Domenic D'Alessandro, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Twyla Thompson, Acting Team Leader, OPDP

Subject: OPDP Labeling Comments for Ozempic (semaglutide) injection, for subcutaneous use

NDA: 209637

In response to DMEP consult request dated December 13, 2016, OPDP has reviewed the proposed product labeling (PI), Medication Guide/Instructions for Use (IFU), and carton and container labeling for the original NDA submission for Ozempic.

PI and Medication Guide/IFU: OPDP's comments on the proposed labeling are based on the draft PI received by electronic mail from DMEP, accessed via Sharepoint on November 8, 2017, and are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed, and comments on the proposed Medication Guide/IFU were sent under separate cover on November 9, 2017.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling received from DMPP on November 8, 2017, and we do not have any comments.

Thank you for your consult. If you have any questions, please contact Domenic D'Alessandro, reviewer at (301) 796-3316 or domenic.dalessandro@fda.hhs.gov.

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/s/

DOMENIC G DALESSANDRO
11/13/2017

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:	November 09, 2017
To:	Jean-Marc Guettier, M.D., Director 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:	Sharon W. Williams, MSN, BSN, RN Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Domenic D'Alessandro, PharmD, MBA, CDE Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Medication Guide (MG), Instructions for Use (IFU), and Quick Reference Guide (QRG)
Drug Name (established name):	OZEMPIC (semaglutide)
Dosage Form and Route:	injection, for subcutaneous use
Application Type/Number:	NDA 209637
Applicant:	Novo Nordisk Inc.

1 INTRODUCTION

On December 5, 2016, Novo Nordisk Inc. submitted for the Agency's review a New Drug Application (NDA) for OZEMPIC (semaglutide) injection, for subcutaneous use. OZEMPIC (semaglutide) injection, for subcutaneous use is indicated as an adjunct to diet and exercise to improve ghycemic 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 December 13, 2016 for DMPP and OPDP to review the Applicant's proposed MG, IFUs, and QRGs for OZEMPIC (semaglutide) injection, for subcutaneous use.

DMPP conferred with the Division of Medication Error, Prevention, and Analysis (DMEPA) and a separate DMEPA review of the IFUs and QRGs will be forthcoming.

2 MATERIAL REVIEWED

- Draft OZEMPIC (semaglutide) injection, for subcutaneous use MG, IFUs, and QRGs received on December 5, 2016 and received by DMPP on December 21, 2016 and September 15, 2017.
- Draft OZEMPIC (semaglutide) injection, for subcutaneous use MG, IFUs, and QRGs received on June 19, 2017 and received by OPDP on November 8, 2017.
- Draft OZEMPIC (semaglutide) injection, for subcutaneous use Prescribing Information (PI) received on December 5, 2016, revised by the Review Division throughout the review cycle, and received by DMPP on November 3, 2017.
- Draft OZEMPIC (semaglutide) injection, for subcutaneous use Prescribing Information (PI) received on December 5, 2016, revised by the Review Division throughout the review cycle, and received by OPDP on November 8, 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%. A reading ease score of 60% corresponds to an 8th grade reading level.

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, IFUs, and QRGs we:

- simplified wording and clarified concepts where possible
- ensured that the MG, IFUs, and QRGs are consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG, IFUs, and QRGs are 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, IFUs, and QRGs meet the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

- The MG is acceptable with our recommended changes.
- The IFUs and QRGs are acceptable as submitted.

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 PPI.

Please let us know if you have any questions.

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/s/

SHARON W WILLIAMS
11/09/2017

DOMENIC G DALESSANDRO
11/09/2017

MARCIA B WILLIAMS
11/09/2017

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research| Office of Surveillance and Epidemiology (OSE)

Epidemiology: ARIA[a] Sufficiency Memorandum

Date:	October 27, 2017
Reviewer(s):	Yandong Qiang, MD, PhD, MPH, MHS, Epidemiologist, Division of Epidemiology I (DEPI-I), Office of Pharmacovigilance and Epidemiology (OPE), Office of Surveillance and Epidemiology (OSE)
Team Leader:	Patricia L. Bright, MSPH, PhD, Epidemiology Team Lead, DEPI-I, OPE, OSE
Division Director:	Simone P Pinheiro, ScD, MSc, ALM, Director DEPI-I, OPE, OSE
Subject:	ARIA Sufficiency Memo— An assessment of the Sentinel Active Risk Identification and Analysis (ARIA) system to evaluate the association between Semaglutide and Medullary Thyroid Carcinoma (MTC) during the postmarketing safety surveillance of Ozempic® (Semaglutide) injection.
Drug Name(s):	Ozempic® (Semaglutide Injection)
Application Type/Number:	NDA 209637/IND 079754
Applicant/sponsor:	Novo Nordisk
OSE RCM #:	2017-971

[a]Active Risk Identification and Analysis

EXECUTIVE SUMMARY *(place "X" in appropriate boxes)*

Memo type	
-Initial	X
-Interim	
-Final	
Source of safety concern	
-Peri-approval	X
-Post-approval	
Is ARIA sufficient to help characterize the safety concern?	
-Yes	
-No	X
If "No", please identify the area(s) of concern.	
-Surveillance or Study Population	X
-Exposure	
-Outcome(s) of Interest	X
-Covariate(s) of Interest	
-Surveillance Design/Analytic Tools	

1. BACKGROUND INFORMATION

1.1. Medical Product

Ozempic® (Semaglutide) injection, a Nova Nordisk product, is a long-acting glucagon-like peptide-1 (GLP-1) receptor agonist. It is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. The sponsor in pursuing approval of Semaglutide through the 505(b)(1) pathway[b,1]. In addition, the Food and Drug Administration (FDA) will review this New Drug Application (NDA) under the Prescription Drug User Fee Act (PDUFA) V Program.

FDA received the original NDA on December 5, 2016. The targeted action date for this NDA application is December 5, 2017.

1.2. Describe the Safety Concern

Medullary Thyroid Carcinoma (MTC), accounting for approximately 5-8% of all thyroid carcinoma[2], is a malignant thyroid impairment caused by production of calcitonin by the proliferation of the parafollicular C cells[2,3].

Nonclinical toxicology data indicated that all evaluable[c] long-acting GLP-1 receptor agonists caused dose-related and treatment-duration-dependent thyroid C-cell tumors (adenomas or carcinomas) in rodents[4-9]. A hypothetical mechanism is that the long-term exposure to long-acting GLP-1 receptor agonists may stimulate the GLP-1 receptors on the thyroid C cells of rodents which is sufficient to increase cyclic adenosine monophosphate (cAMP) and initiate the release of calcitonin[3,10]. However, the GLP-1 receptors in humans are expressed less frequently and do not induce cAMP elevation and calcitonin secretion[3] and there appeared no reports of MTC following GLP-1 receptor agonists in clinical studies among humans[10,11]. The causal link between GLP-1 receptor agonists and thyroid C-cell tumors, including MTC, in humans remains unknown because of limited duration of follow up and interspecies difference[11].

FDA first approved long-acting GLP-1 receptor agonist, Victoza®, on January 25, 2010. Table 1 summarized the currently FDA approved long-acting GLP-1 receptor agonists.

[b] "A 505(b)(1) application is an application that contains full reports of investigations of safety and effectiveness. The investigations the applicant relied on for approval were conducted by, or for the applicant, or the applicant has obtained a right of reference or use for the investigations."[1]

[c] All long-acting GLP-1R agonists that could be tested cause C-cell tumors. However, Albiglutide could not be tested due to a rapid, neutralizing antidrug antibody [ADA] response.

Table 1. List of current FDA approved long-acting GLP-1 receptor agonists, June 30, 2017

Brand Name	Active Ingredient	Sponsor/Application Tracking Number	FDA Approval Date	Boxed Warning with Thyroid C-Cell tumor*
Victoza	Liraglutide recombinant	Novo Nordisk /NDA022341	January 25, 2010	Yes
Bydureon	Exenatide synthetic	Astrazeneca /NDA022200	January 27, 2012	Yes
Tanzeum	Albiglutide	GSK /BLA125431	April 15, 2014	Yes
Saxenda	Liraglutide recombinant	Novo Nordisk /NDA206321	December 23, 2014	Yes
Trulicity	Dulaglutide	Eli Lilly /BLA125469	September 19, 2014	Yes
Xultophy	Insulin degludec and liraglutide	Novo Nordisk /NDA208583	November 21, 2016	Yes

*Including medullary thyroid carcinoma (MTC).

Although "FDA concluded increases in the incidence of carcinomas among rodents translated into a low risk for humans, because statistically significant increases occurred only at drug-exposure levels many times those anticipated in humans, and the increase in cancers did not affect overall survival rates"[12], the product labeling of Victoza[4], Bydureon[5], Tanzeum[6], Saxenda[7], Trulicity[8], and Xultophy[9] (with Xultophy® labeling[9] for Thyroid C-cell tumor listed verbatim below) includes thyroid C-cell tumor in the Boxed Warning because of increased risk of MTC among rodents.

WARNING: RISK OF THYROID C-CELL TUMORS

See full prescribing information for complete boxed warning.

- Liraglutide, one of the components of XULTOPHY 100/3.6, causes thyroid C-cell tumors at clinically relevant exposures in both genders of rats and mice. It is unknown whether XULTOPHY 100/3.6 causes thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans, as the human relevance of liraglutide-induced rodent thyroid C-cell tumors has not been determined (5.1, 13.1).
- XULTOPHY 100/3.6 is contraindicated in patients with a personal or family history of MTC or in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2). Counsel patients regarding the potential risk of MTC and the symptoms of thyroid tumors (4, 5.1).

Under Sections 505(o)(3), 505(k)(1), and 505(k)(3) of the Federal Food, Drug, and Cosmetic Act (FDCA), FDA issued a postmarketing requirement (PMR) for the sponsors of long-acting GLP-1 receptor agonists to join in a MTC case series registry to investigate the relationship between long-acting GLP-1 receptor agonist treatment and the development of MTC in humans. The sponsors then formed a MTC Registry Consortium to address this PMR after FDA approved more than one GLP-1 receptor agonists. Within the MTC Registry Consortium, the sponsors monitor the annual incidence and change in incidence of MTC through the North American Association of Central Center Registries (NAACCR); and document

demographic, medical and risk factors related to the MTC diagnosis among MTC cases in the MTC participating State Cancer Registries (SCRs). The MTC case series registry verifies GLP-1 receptor agonist treatment through treating physicians.

Because of the potential association between long-acting GLP-1 receptor agonists and risk of MTC, and in order to ensure the benefit of long-acting GLP-1 receptor agonists outweigh the potential risk of MTC, FDA also requires a class wide Risk Evaluation and Mitigation Strategy (REMS) for approved long-acting GLP-1 receptor agonists as these drugs are indicated for a large patient population with wide range of potential prescribers for prescription and dispensing.

1.3. FDAAA Purpose (per Section 505(o)(3)(B))

Purpose (place an "X" in the appropriate boxes; more than one may be chosen)	
Assess a known serious risk	
Assess signals of serious risk	X
Identify unexpected serious risk when available data indicate potential for serious risk	

1.4. Statement of Purpose

Since the FDA approval of the first long-acting GLP-1 receptor agonist, Victoza (Liraglutide), FDA requires all the subsequent approved GLP-1 receptor agonists to join a MTC case series registry for a class-wide postmarketing surveillance to systemically monitor the annual incidence of MTC in the United States for at least 15 years and characterize the MTC cases regarding their medical history and possible risk factors including history of GLP-1 receptor agonist treatment[13,14]. The sponsors[d] and the American Thyroid Association (ATA) initiated the MTC case series registry in 2010.

Per the request of Division of Metabolism and Endocrinology Products (DMEP) in the Office of New Drugs (OND), the Division of Epidemiology-I (DEPI-I) conducted an assessment of the Sentinel Active Risk Identification and Analysis (ARIA) system to determine, instead of join in the class-wide MTC case series registry, if Sentinel ARIA is sufficient to assess the MTC safety signal in human, under Section 505(o)(3)(B) Food and Drug Administration Amendments Act (FDAAA), during the postmarketing safety surveillance of Ozempic® (Semaglutide) injection.

1.5. Effect Size of Interest or Estimated Sample Size Desired

Skipped, given responses in Sections 2, 3 and 4.

2. SURVEILLANCE OR DESIRED STUDY POPULATION

2.1 Population

MTC is a rare disease. It occurs in people at all ages and the incidence varies with age, sex, and racial/ethnic group[15,16]. According to the Surveillance, Epidemiology, and End Results (SEER) program of

[d] Currently, the MTC case registry covers exenatide extended release (Bydureon) of AstraZeneca, albiglutide (Tanzeum) of GlaxoSmithKline, dulaglutide (Trulicity) of Eli Lily, liraglutide for diabetes treatment (Victoza), and liraglutide for weight loss management (Saxenda) of Novo Nordisk

the National Cancer Institute during the period between 1992 and 2006, the incidence of MTC in the United States ranged from 0.10 per 100,000 person-years in black males to 0.22 per 100,000 person-years in white females[15]. Each year, there are approximately 600 incident cases of MTC in the United States[12].

2.2 Is ARIA sufficient to assess the intended population?

The Sentinel ARIA system currently has approximately 200 million patients[17] of all ages from 17 data partners[18]. Although Sentinel allows for the evaluation of data on a large number of patients:

- The number of patients exposed to long-acting GLP-1 receptor agonists products would be a fraction of the total Sentinel patients;
- Semaglutide is the sixth[e] product in class of long-acting GLP-1 receptor agonists (Section 3), decreasing the likely market share across long-acting GLP-1 receptor agonists products;
- "The clinical course of MTC varies from an extremely indolent tumor that can go unchanged for years to an aggressive variant that is associated with a high mortality rate."[19] Therefore, to study a possible increased risk of MTC would require long-term follow-up (Section 4);
- Approximately 50% of patients with MTC have metastases at the time of diagnosis[2,19-21], suggesting that the disease had been ongoing and making it difficult epidemiologically to identify disease onset with respect to an exposure;
- Sentinel includes a small proportion of patients with long-term exposure and follow-up.

The number of patients in Sentinel with long-term follow-up and with Semaglutide exposure would likely be insufficient to support an ARIA evaluation given that MTC is a rare event. DEPI-I concludes that the Sentinel ARIA system is unlikely to provide a sufficient size of the intended population during a reasonable period to assess the relationship between Semaglutide and the risk of MTC among humans.

3 EXPOSURES

3.1 Treatment Exposure(s)

Upon approval, Semaglutide, would be the sixth product in the class of long-acting GLP-1 receptor agonists. Therefore, product uptake would likely be diminished by the availability of other products in the class already on the market according to the 2017 Novo Nordisk diabetic care market share summary[22] (appendix I).

3.2 Comparator Exposure(s)

Skipped. Insufficiency in population and study outcome precluded further discussion.

3.3 Is ARIA sufficient to identify the exposure of interest?

[e] Victoza and Saxenda are both a liraglutide recombinant, but administered in different doses and for different indications.

No. Given that Semaglutide is the sixth product in the class of long-acting GLP-1 receptor agonists, it would be unlikely that market uptake would be sufficient to allow for identifying this rare outcome among those with the exposure of interest.

4 OUTCOME(S)

4.1 Outcomes of Interest

There are 4 types of thyroid cancer: papillary, follicular, medullary and anaplastic. MTC is a rare disease and accounts for 1-2% of all thyroid cancers. Most (75%) medullary thyroid cancers are sporadic, while 25% are familial occurring in association with multiple endocrine neoplasia type 2 syndrome. Each year, there are approximately 600 incident cases of MTC in the United States[12]. MTC can be cured only by complete resection of the thyroid tumor and metastases. Furthermore, MTC takes over decades to develop symptoms/signs inducting medical visit and studies of limited duration are insufficient to characterize an increase in MTC risk[2,19-21].

There is only one ICD-10 code for thyroid cancer and it is nonspecific: C73 "malignant neoplasm of thyroid gland." There are several surgical removal codes, shown below, but they are also nonspecific to MTC and surgery is the primary treatment modality for thyroid cancer in general. Although laboratory measurements for calcitonin and carcinoembryonic antigen (CEA) are also performed as part of the evaluation, their results would not be available in Sentinel. CEA is a tumor marker that is also routinely used in colon cancer screening and is elevated in other malignancies such as breast, pancreas and lung cancers. There are no known validation studies using ICD10 code and CEA procedure code (92378) to identify MTC. Also, genetic screening results using the RET germline mutation would not be available in Sentinel and would only identify a proportion of the patients with genetically based MTC.

SURGEON CPT CODE[1]	PROCEDURE
60210	Partial thyroid lobectomy, unilateral; with or without isthmusectomy
60212	Partial thyroid lobectomy, unilateral; with contralateral subtotal lobectomy, including isthmusectomy
60220	Total thyroid lobectomy, unilateral; with or without isthmusectomy
60225	Total thyroid lobectomy, unilateral; with contralateral subtotal lobectomy, including isthmusectomy
60240	Thyroidectomy, total or complete
60252	Thyroidectomy, total or subtotal for malignancy; with limited neck dissection
60254	Thyroidectomy, total or subtotal for malignancy; with radical neck dissection
60260	Thyroidectomy, removal of all remaining thyroid tissue following previous removal of a portion of thyroid
60270	Thyroidectomy, including substernal thyroid; sternal split or transthoracic approach
60271	Thyroidectomy, including substernal thyroid; cervical approach
60500	Parathyroidectomy or exploration of parathyroid

4.2 Is ARIA sufficient to assess the outcome of interest?

No. MTC is a rare event typically requiring a long duration to develop[2,20,21]. The Sentinel ARIA system would likely have an insufficient number of patients with the exposure, the outcome, and with a duration of follow-up sufficient to evaluate any increased risk in the development of MTC. Moreover, administrative codes used to identify thyroid cancers are not specific.

5 COVARIATES

5.1 Covariates of Interest

Skipped. Insufficiency in population and study outcome precluded further discussion.

5.2 Is ARIA sufficient to assess the covariates of interest?

Not assessed.

6 SURVEILLANCE DESIGN / ANALYTIC TOOLS

6.1 Surveillance or Study Design

Skipped. Insufficiency in population and study outcome precluded further discussion.

6.2 Is ARIA sufficient with respect to the design/analytic tools available to assess the question of interest?

No.

The MTC case series registry status report dated March 14, 2017 indicated that the registry currently covered (b) (4)% of the U.S. population from the (b) (4) participating states. As of January 24, 2017, a total of (b) (4) MTC cases were reported to the registry and (b) (4) finished participation. Though the duration of exposure and follow-up were relatively short to evaluate for MTC malignancy, these data did not suggest a safety signal for MTC following long-acting GLP-1 receptor agonist exposure[13]. Table 1 and Table 2 in DEPI-I's review by Dr. Patricia Bright provided status details of the MTC registry before and after long-acting GLP-1 receptor agonists introduced to the Unite State[13].

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Not assessed.

7 NEXT STEPS

In order to fulfill the postmarketing requirement of the FDA approval of the first long-acting GLP-1 receptor agonist, Victoza (Liraglutide), the sponsor and the American Thyroid Association (ATA) initiated a MTC case series registry in 2010 to observe all new cases of MTC diagnosed in the United States for at least 15 years. FDA then obligated the subsequently approved long-acting GLP-1 receptor agonists to join the MTC case series registry for a class-wide postmarketing surveillance to systemically monitor the annual incidence of MTC in the United States and characterize the MTC cases regarding their medical history and possible risk factors including history of GLP-1 receptor agonist treatment[13,14].

In alignment with other long-acting GLP-1 receptor agonists in the class, DEPI-I recommends the FDA issue a postmarketing requirement (PMR) for Semaglutide s.c. to assess the MTC safety signal, under Section 505(o)(3)(B) Food and Drug Administration Amendments Act (FDAAA). Given the challenges likely in obtaining a population with sufficient Semaglutide exposure, duration of follow-up, and number of events given the rarity of MTC, DEPI-I concurs with the use of an MTC registry design.

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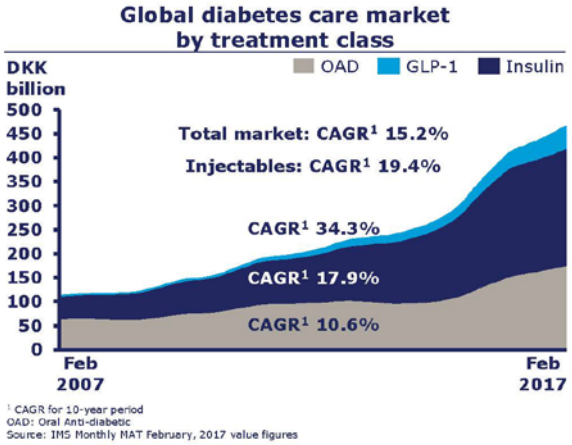
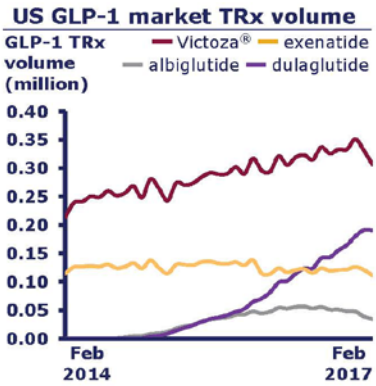
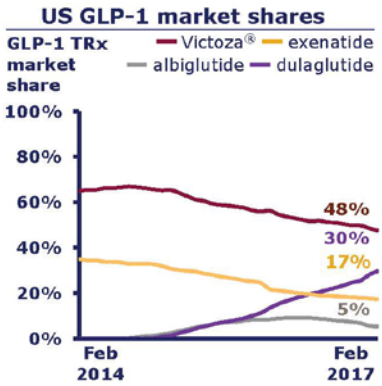
Appendix I: Market Share of GLP-1 drugs, Novo Nordisk 2017[22]







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YANDONG QIANG
10/27/2017

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10/27/2017

JUDITH W ZANDER
10/27/2017

MICHAEL D NGUYEN
10/31/2017

ROBERT BALL
11/02/2017

NDA:	209637
Subject:	Immunogenicity review memo – Semaglutide, once a week injection as an adjunct to diet and excercise to improve glycemic control in type 2 diabetes mellitus pateints.
Review Date:	9/26/2017
PDUFA due Date:	12/5/2017
Primary Reviewer:	Mohanraj Manangeeswaran, Ph.D
Secondary Reviewer:	Daniela Verthelyi, M.D., Ph.D
Applicant:	Novo Nordisk Inc
Associated IND:	079754
Proposed Proprietary Name:	**Ozempic**
Nonproprietary Name:	**Semaglutide**
Dosage form:	Injection, solution
Indication:	Treatment of patients with type 2 diabetes mellitus
Clinical Division:	OND/ODEII/DMEP
RPM:	Peter Franks

1. Recommendation:

New drug application for Semaglutide is recommeded for approval from an immunogenicity standpoint. However, given deficiencies in the assay developed to assess neutralizing activity, PMCs 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 :Novo Nordisk is required to develop a sensitive assay to assess the neutralizing activity of anti-Semaglutide antibodies and its cross-neutralizing effect on native GLP-1.

PMC 2: Novo Nordisk is required to utilize the sensitive assay to assess the neutralizing activity of anti-Semaglutide antibodies developed for PMC1 to assess the incidence of neutralizing antibodies to semaglutide and GLP-1in 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 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 9 phase III trials that collectively assessed the incidence of ADA in 8124 adult patients with Type 2 diabetes mellitus (T2DM) (5228 treated with Semaglutide). The overall incidence of ADA for the different trials was 1.4% (73/5228). Among those subjects that seroconverted, 61% were found to crossreact with endogenous GLP1 but ADA titers were low (<100). The neutralizing activity of the antibodies is unknown at this time. No impact on PK, PD, safety or efficacy was evident. Of note, assessment of immunogenicity took place starting at 4 months of treatment so early transient ADA may have been missed. 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 December 5th, 2016, seeking marketing approval for semaglutide 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 Ozempic.

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 brian. 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 admininstered 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 apetite, early satiety, and preference for low fat and low sugar diets may results 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.

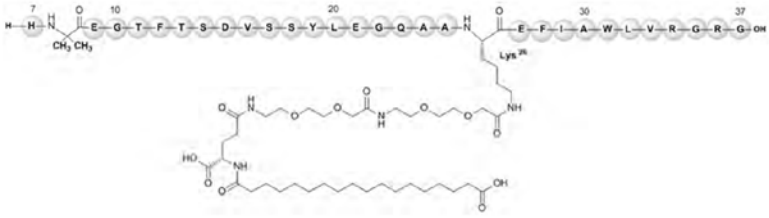
Semaglutide is a long acting analogue of the endogenous GLP-1 molecule and so belongs to the GLP-1 receptor agonist class of drugs. When compared to human native GLP-1, the semaglutide molecule has 94% structural homology to native GLP-1 with three main modifications

1. Amino acid substitution at position 8 (alanine to alfa-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:



Semaglutide formulation is a clear and colorless 1.34 mg/mL solution for injection available in a pre-filled disposable pen injector.The route of administration for semaglutide is once-weekly (OW) subcutaneous injection. It is intended to improve glycemic control in patients with T2D as an adjunct to diet and excercise.

Following subcutaneous (SC) administration, semaglutide has a relatively long terminal half-life ($t_{1/2}$) which allows for once weekly dosing. The Applicant claimed that the prolonged action profile of semaglutide is due to the following mechanisms: delayed absorption from the subcutaneous tissue, 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.

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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). (b) (4) Therefeore, this review memo only discusses the glycemic control indication.

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-1had 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-1Receptor Agonists; Observed immunogenicity and impact on efficacy and safety

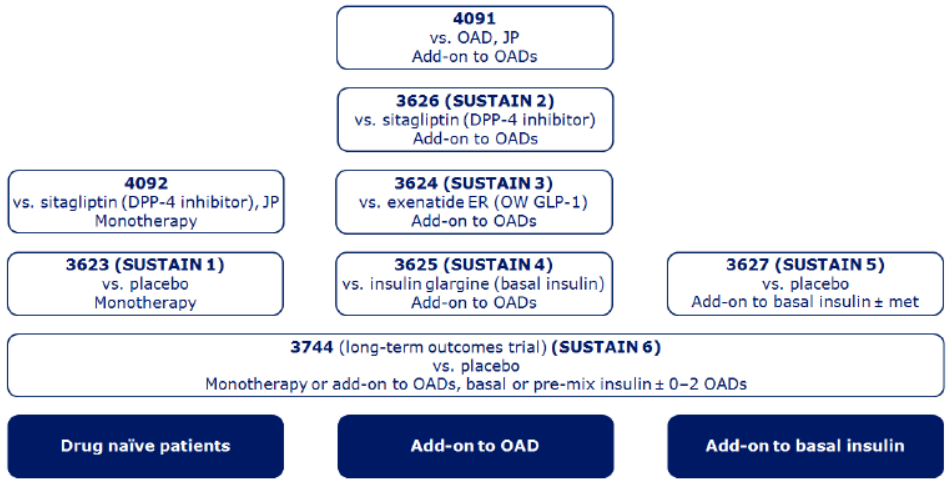
GLP-1 receptor agonist	Victoza[1,2]	Saxenda[3,4]	Trulicity[5,6]	Tanzeum[7]/ Eperzan[8]	Byetta[9]	Bydureon[10]	Adlyxin[11]/ Lyxumia[12]
Level of ADA in Phase 3	8.6% (low titres)	2.8% (low titres)	1.6%	4%/5.5%	38% (low titres) 6% (high titres)	45% (low titres) 12 % (high titres)	70%
Level of Cross reactivity 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 its product class, semaglutide was not expected to have high rates of ADA.

Overview of clinical trials:

Development of ADA was investigated in the first human dose single SC dose trial (trial 1820) conducted in healthy subjects and in the multi-dose phase 2 dose finding trial conducted in T2DM pts - (trial 1821). In these trials, blood samples were taken before treatment (baseline) and at the follow-up visit after conclusion of treatment (Week 17). The phase III program that evaluated the safety and efficacy of semaglutide included seven parallel arm trials (see Table 1below). These are Trials 3623, 3624, 3625, 3626, 3627, 4091 and 4092. These trials had a treatment duration of 30 to 56 weeks and evaluated monotherapies as well as combination therapy with other anti-diabetic therapies and compared safety and efficacy to competitor product available in the market. In these pivotal trials, samples were taken at baseline, weeks 16, 30, 40, 56 and at follow-up at 5 weeks after last dose. In addition there was phase III long-term cardiovascular outcomes trial (CVOT, # 3744) where samples were collected to look at ADA rates. (b) (4) immunogenicity data from this study is also included in the package and was reviewed as supportive data. Overall phase III studies included 8124 patients (4593 receiving the drug and the remainder receiving placebo or alternative product). The following are the phase III clinical trials that contributed to the immunogencity data set.



Abbreviations: GLP-1: glucagon-like peptide-1; JP: Japan; met: metformin; OAD: oral antidiabetic drug; OW: once-weekly; PBO: placebo.

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 (excluding CVOT)

Clinical phase	Week 0 (baseline)	Week 16	Week 30	Week 40	Week 56	Follow-up[a]
Phase 1 (trials 1820, 3633, 3634, 3635, 3651, 3652, 3684, 3685, 3817, 3818, 3819)	x					x
Phase 2 (trial 1821)	x					x
Phase 3a (trials 3623, 3625, 3627, 4092)	x	x	x			x
Phase 3a (trials 3624, 3626, 4091)	x	x	x	x	x	x

Note: [a]5 weeks post end of treatment + a visit window of 1 week.

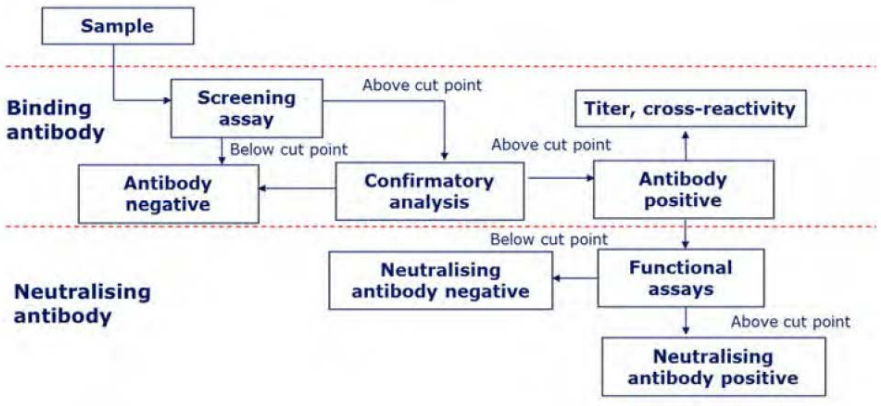
Table 3–2 Antibody sample collection time points – CVOT

Clinical phase	Week 0	Week 30	Week 44	Week 56	Week 80	Week 104	Follow-up[a]
Phase 3a (trial 3744)	x	x	x	x	x	x	x

Note: [a]5 weeks post end of treatment + a visit window of 1 week.

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:

<u>RIA assay used to analyze phase I-II samples:</u>

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 meaured 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 betweent 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.

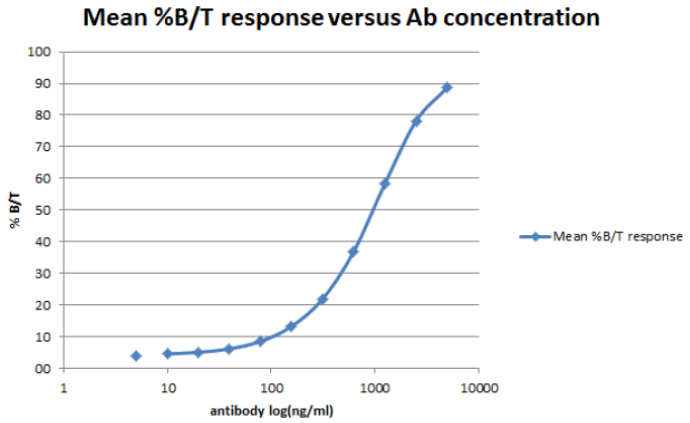


Figure 3–2 Two-fold dilution of an anti-semaglutide antibody (GLIP-C-1 F27) in the anti-semaglutide antibody RIA

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 expelcted 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.

Table 3–3 Antibody binding assays used during clinical development of 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)	Phase 1 and 2	1820, 1821, 3633, 3819	No pre-treatment of samples	Validated by Novo Nordisk
Anti-semaglutide antibody assay (Section 3.2.1.3)	RIA (study 212541 and 216098)	Phase 3a and Clin.Pharm. trials	3623, 3624, 3625, 3626, 3627, 3744, 4091, 4092[a]	Samples pre-treated with acid and PEG	Validated by (b) (4)
Anti-semaglutide antibody assay (Section 3.2.1.3)	RIA (study 214096)	Phase 3a for hypersensitivity samples	3627, 3744	Samples pre-treated with acid and PEG	Validated by Novo Nordisk
Anti-exenatide antibody assay (Section 3.2.1.4)	RIA (study 208105)	Phase 3a	3624	No pre-treatment of samples	Validated by (b) (4)

Note: [a]Including remaining clinical pharmacology trials; 3634, 3635, 3651, 3652, 3684, 3685, 3817, 3818

Abbreviations: Clin.Pharm.: clinical pharmacology; PEG: poly ethylene glycol; RIA: radioimmunoassay

RIA assay used to analyze phase I and phase II 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 tolerence. 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.

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

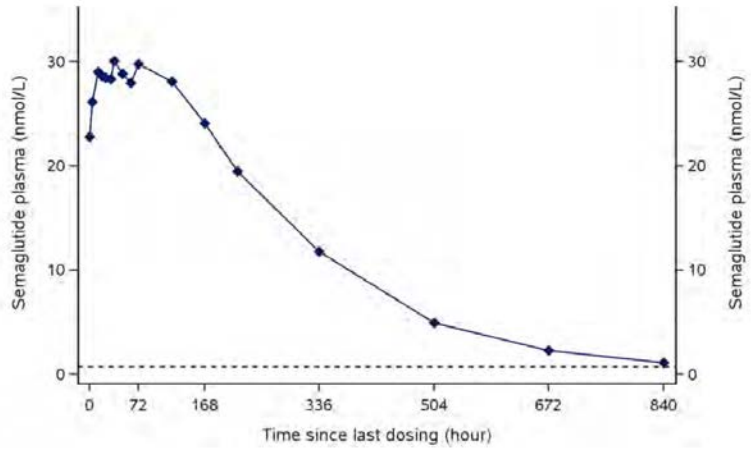
Validation Parameter	Description	Result
Minimum Required Dilution (MRD)	Volume of sample in assay	10 µl (6.7%)
Screening cut point (SCP)	50 normal healthy sera mean %B/T + 1.645 x SD	4.6 %B/T
Normalisation factor (NF)	SCP – Mean QC neg	2.1
Assay specific cut point	Mean QC neg + NF	Mean QC neg + 2.1
Specificity cut point	Difference in %B/T of sample with (Series B) or without semaglutide (Series A)	A – B > 1.96 * √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 * √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

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 referecne 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 adequateto 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 3A 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 tolerence 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 tolerence 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 substraction.

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 tolerence 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).

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7.1.2 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%)
Screening cut point (SCP)	25 normal healthy and 25 T2D[1] subjects $LogSCP = Median[log(Binding_{meanA})] + 1.645\ MADn[log(Binding_{meanA})]$ $SCP = 10^{Median[log(BindingmeanA)] + 1.645\ MADn[log(BindingmeanA)]}$	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) Sensitivity at 99% confidence level	Mean of 6 determinations Sensitivitylog = mean[log(conc at CP)]+t(0.02,df xSD[log(conc at CP)]	264.56 ng/ml 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 ($p \geq 0.05$)
Precision Total (inter assay variation)	QC neg QC low (300ng/ml) QC med QC high	10.6%CV 6.9%CV 10.2%CV 8.8%CV
QC samples	QC neg QC low QC med QC high	Normal healthy human serum without reference mAb Normal healthy human serum spiked with 300ng/ml reference mAb Normal healthy human serum spiked with 1000ng/ml reference mAb 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)

7.1.3 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) Sensitivity at 99% confidence level	Mean concentration of 6 determinations Sensitivitylog = mean[log(conc at CP)]+t(0.02,df xSD[log(conc at CP)] Sensitivity(99%confidence level) = power(10,sensitivitylog)	67.96 ng/ml 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 tolerence determined by using the samples of treatment naive subjects (the supplementary validation) is acceptable.

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

Anti-exenatide binding antibody RIA method:

In trial 3624, exenatide was used in the comparator arm. Anti-exenatide antibodies were monitored using an RIA assay (208105). Calculation of the cut point and normalization factor were based on 50 normal human sera. A protein-A purified rabbit anti-Exendin-4 polyclonal antibody sourced from Bachem was used as reference antibody. The critical parameters of this assay are given below.

7.1.5 Results of anti-exenatide antibody RIA validation study 208105

Parameter	Description	Result
MRD	Volume of sample required	10 µl
Screening cut point	50 normal healthy human sera analysed in series A Median + 1.645 x Madn	2.25% B/T
Specificity cut point	50 normal healthy human sera analysed in series A and B	A-B > 0.60 %B/T
Precision (Total or Inter assay variation) Evaluated on specific binding (A-B)	QC low QC medium QC high Mean of QC neg (A-B) Mean at cut point (A-B)	6.3%CV 6.6% CV 8.3%CV 0.25% B/T 1.11% B/T
Precision (intra assay variation) Evaluated on specific binding (A-B)	QC low QC medium QC high Mean QC neg (A-B) Mean at cut point (A-B)	8.3% CV 7.7% CV 9.1% CV 0.04% B/T 1.15% B/T.
Sensitivity	LLOQ	66.7 ng/ml
Interference	Two levels, QC low and QC medium 10pg/ml, 100 pg/ml and 1000 pg/ml drug	No interference from 10 pg/ml and 100 pg/ml drug at QC low and QC medium level. Interference from 1000 pg/ml approximately 60% at QC low and QC medium level.
QC samples	QC neg QC low QC medium QC high QC at cut point level	Normal healthy human serum without anti-exenatide antibody Normal healthy human serum spiked with 125 ng/ml anti-exendin 4 pAb Normal healthy human serum spiked with 500 ng/ml anti-exendin 4 pAb Normal healthy human serum spiked with 1670 ng/ml anti-exendin 4 pAb Normal healthy human serum spiked with 20 ng/ml anti-exendin 4 pAb

Reviewers comments:
Cut point, Sensitivity, precision and drug tolerence reported in this method validation are acceptable.
Validation studies for the confirmatory, cross-reacting and neutralization assays were also found to be suitable for their intended purpose.

IgE assay for ADA to Semaglutide:

7.1.6 Results of anti-semaglutide IgE immunoCAP validation study 213540

Parameter	Description	Result
Assay cut point	Lower Level of Quantification (LLOQ)	0.1 kUA/L
Sensitivity	Mean conc above LLOQ + t(0.05,df)xSD	185 ng/ml
Interference from semaglutide	Anti-semaglutide IgE measured in presence of 0 – 100 nM semaglutide	
	0.18 µg/ml anti-semaglutide IgE	No interference up to 11nM semaglutide
	20 µg/ml anti-semaglutide IgE	No interference up to 100nM semaglutide
Interference from anti-semaglutide IgG	Anti-semaglutide IgE measured in presence of different GLIP-C1 F27 concentrations	
	0.18 µg/ml anti-semaglutide IgE	No interference up to 50 µg/ml GLIP-C1 F27
	20 µg/ml anti-semaglutide IgE	No interference up to 50 µg/ml GLIP-C1 F27
Recovery	Two concentrations of anti-semaglutide IgE spiked in 6 sera	
	0.18 µg/ml anti-semaglutide IgE	5 of 6 subejcts > LLOQ
	20 µg/ml anti-semaglutide IgE	6 of 6 Subjects > LLOQ
Drifting	Three levels, negative low and high positive	No drifting observed at any level (p>0.05)
Assay precision (intra-assay)	QC neg (human serum pool)	6.8 %CV
	QC low (GLIP-C-1 F27-IgE)	6.1 %CV
	QC high (GLIP-C-1 F27-IgE)	10.4 %CV
Assay precision (inter-assay)	QC neg (human serum pool)	11.8 %CV
	QC low (GLIP-C-1 F27-IgE)	8.6 %CV
	QC high (GLIP-C-1 F27-IgE)	12.9 %CV
QC samples	QC neg (Human serum pool)	Normal healthy human serum without reference mAb
	QC low	Normal healthy human serum spiked with 300ng/ml GLIP-C-1 F27-IgE
	QC high	Normal healthy human serum spiked with 20000 ng/ml GLIP-C-1 F27-IgE

Reviewers comments:
The cut point, precision and drug tolerence of the hypersensitivity assay is acceptable, however the sensitivity of the assay is low for an IgE assay and thus the data yielded by the assay is not very informative. Given that there was no drug-related hypersensitivity, there is no need to re-develop the assay at this time.

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 promotor 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 corelates 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 calucated 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-NSB/MAX-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 treatedwith 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.
Critical parameters of the NAB assay validation are shown in the sponsor's table below:

7.1.8 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]= Mean individuals + $t_{(0.001,df\infty)}$ x SD_{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) QC high (%N)	24.7 %CV 5.2 %CV
Assay precision (Intra-assay variation)	QC low (%N) QC high (%N)	20.8 %CV 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 QC low QC high	Normal healthy human serum Normal healthy human serum spiked with 4000 ng/ml GLIP-C-1 F27 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.

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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.

7.1.9 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]= Mean individuals + $t_{(0.001,df\infty)}$ x 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 Reference mAb; GLIP C-1 F27	18.6 µg/ml 82.4 µg/ml
Drug interference	Sensitivity in presence of drug 1nM liraglutide 1nM semaglutide	 MAb26.1: 12.5 µg/ml GLIP C-1 F27: 100 µg/ml GLIP C-1 F27: 100 µg/ml
Drug tolerance	Concentration of reference mAb detected in presence of 6.25nM liraglutide 25nM semaglutide	 33 µg/ml Mab26.1 133 µg/ml GLIP C-1 F27
Assay Precision (Intra assay variation)	QC low (%N) QC high (%N)	5 %CV 3 %CV
Assay Precision (Inter assay variation)	QC low (%N) QC high (%N)	7 %CV 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 ≥ 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 %N ≥ 50	%CV ≤ 25 %CV ≤ 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 QC low1 QC low2 QC high	Normal healthy human serum Normal healthy human serum spiked with 40µg/ml MAb26.1[2] Normal healthy human serum spiked with 23µg/ml MAb26.1[2] 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

Reviewers comments: The NAB assay is inadequate

The neutralizing antibody assays appears to have a very low sensitivity making it inadequate to determine whether any antibodies present have neutralizing activity. 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.

The following issues raise questions regarding the adequacy of the NAB assay:

- *The cell line can respond to several growth factors. This was not controlled for in the assay.*
- *The sensitivity of the NAB assay, 3.4 ug/ml is insufficient to yield clinically relevant results.*
- *The cut point was calculated using a 0.1% false positive rate. This is inadequate as it increases the chances of positive samples going undetected.*
- *Assay precision is low as inter and intraassay variations exceed 20%*

Summary of clinical immunogenicity data from phase 3 trials:

The summary consists of data from 25 trials that had been completed. This includes 16 phase I clinical pharmacology trials, 1 phase 2 dose finding trial and 8 phase 3A therapeutic confirmatory trials. In addition one phase 3b trial is ongoing. Semaglutide s.c OW was used as comparator in other development programs and data from those studies are included in the summary as supportive data.

No subjects developed antibodies in any of the 16 phase I trials. One subject developed anti-semaglutide antibodies in the phase 2 trials.
In phase 3, seven trials (3623, 3624, 3625, 3626, 3627, 4091 and 4092) with treatment durations of 30 to 56 weeks were evaluated for mono and combination therapy with other antidiabetic therapies and compared semaglutide with the most important competitor products available at the time of initiation of the phase 3a program. A total of 8,124 subjects with T2D were randomized in completed phase 3a trials. This forms the basis of anti-drug antibody levels and immunogenicity response to semaglutide s.c OW treatment. Immunogenicity data from One Cardio Vascular Outcome Trial (CVOT), trial 3744 was also considered.

Table 1

Overall summary of clinical immunogenicity data

Trial	Design	Dose/route	Number of subjects	Patient population	Duration	Antibody positive (%)	Cross-reacting	Neutralizing	Titer
NN9535-3623	Randomized DB, Parallel arm, placebo 4 arm	Semaglutide 0.5 and 1 mg or placebo controlled, OW, SC	387 (M210;F177) Sema 0.5-128; Sema 1mg-130 Placebo-129	Drug naïve T2D	30 wks	N=258 T0-1/385 (0.3%) ES: 3/234 (1.3%)	2/3 (66%) T0-(1/1)	0	Mean 4.98 (SD 3.17)
NN9535-3627	Randomized DB, Parallel arm placebo 4 arm	Semaglutide 0.5 and 1 mg or placebo controlled, OW, SC	396 (M122;F174) Sema 0.5-132; sema1-131; Placebo-133 (65+65)	T2D (on treatment with basal insulin or without metmorphin	30 wks	N=263 Sema- 0.5 mg:0/263 Sema-1 mg : 0/263	0	0	
NN9535-3626	Randomized, DB, double dummy, parallel group, 4 arm	Semaglutide 0.5 and 1 mg OW, s.c, sitagliptin 100 mg, OD oral	1225 (M620;F605)	T2D (on treatment with OADs)	56 wks	0.5 and 1 mg sema (N=818) T0=0.1% 1/805 ES= 3 / 777 (0.4 %)	3/3 (100%)	0	
NN9535-3624	Randomized OL, parallel group 2arm	Semaglutide 1 mg OW, SC. Exenatide ER 2mg, OW, SC	809 (M447; F362) Semaglutide 404; Exenatide 405	T2D (in treatment with 1-2 OADs)	56 wks	Sema (N=404) T0-0.5%; Max 1.5% (week 56) ES-1.1% Exenatide (N=405) T0 5.5%; ES -68.9%	Sema - 2 out of 4 (50%) Exe-1/239 (0.4%)	Sema-0 Exe-39/214 (15.4 %)	Sema-Mean titer 3.00 (SD 2.31) Exe-Mean titer 766 (SD 3082.4)
NN9535- 3625	Randomized OL, parallel group, 3 arm	Semaglutide 0.5 and 1 mg, OW, SC Insulin glargine SC	1082 (M574;F508) 362+360+360	T2D (insulin naïve, on Tx with metmorphin)	30 wks	N=722 (T0-2/322) ES: Sema 0.5 mg-2/362; Sema 1mg 0/360	2/2 (100%)	0	%B/T 6.74 (mean)
NN9535-4091	Randomized, OL, parallel group, active control	Semaglutide 0.5 and 1 mg OW, SC One OAD	600 (M429;F171)	T2D (on Tx with one OAD)	30 wks	N=480 T0=0 ES 1/472 (0.2)	0	0	3.02
NN9535-3744 (CVOT-trial)	Randomized, DB, Parallel group, placebo, 4 arm	Semaglutide 0.1 and 1 mg or placebo, OW, SC	3297 (M2002;F1295)	T2D (on Tx with 1-2 OADs or with insulin	104 wks	N=1648 T0-2/1552 (0.1%) ES-4/1334 (0.3%)	1/4	0	Geo mean 6.78 (CV-70)
Phase 3 A pool	Anytime post baseline					ES: 32/3099(1%)	19/33	0	5.99 (4.84)
Trials with Placebo group	Any time post baseline					ES: 11/511 (2.2%)	8/11	0	4.98 (3.17)

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; OAD-oral antidiabetic drug, OL-open label; T0-Baseline; ES-end of study(at follow up); SD-standard deviation; CV- coefficient of variation; Sema-Semaglutide; Tx-treatment; SC-subcutaneous

In the CVOT, anti semaglutide antibody formation was low. A total of 30 subjects (1.9%) tested positive at any point post baseline. The peak incidence of positive subjects was recorded around week 44. Generally, the rate was higher during the first year of treatment, compared to the second year. At the follow up visit, 4 subjects (0.3%) tested positive for anti-semaglutide antibodies indicating the few subjects had sustained ADA.

Table 4–1 Anti-semaglutide antibodies – in-trial – CVOT

	Sema 0.5 mg N (%)	Sema 1.0 mg N (%)	All sema N (%)
Number of subjects	826	822	1648
Baseline (week 0)			
Positive	1 (0.1)	1 (0.1)	2 (0.1)
Negative	775 (99.9)	775 (99.9)	1550 (99.9)
Week 30			
Positive	4 (0.5)	5 (0.7)	9 (0.6)
Negative	757 (99.5)	756 (99.3)	1513 (99.4)
Week 44			
Positive	5 (0.7)	9 (1.2)	14 (1.0)
Negative	729 (99.3)	717 (98.8)	1446 (99.0)
Week 56			
Positive	3 (0.4)	5 (0.7)	8 (0.6)
Negative	724 (99.6)	713 (99.3)	1437 (99.4)
Week 80			
Positive	2 (0.3)	2 (0.3)	4 (0.3)
Negative	706 (99.7)	698 (99.7)	1404 (99.7)
Week 104			
Positive	2 (0.3)	4 (0.6)	6 (0.4)
Negative	699 (99.7)	685 (99.4)	1384 (99.6)
Follow-up (week 109)			
Positive	2 (0.3)	2 (0.3)	4 (0.3)
Negative	670 (99.7)	660 (99.7)	1330 (99.7)
Anytime post-baseline			
Positive	11 (1.4)	19 (2.3)	30 (1.9)
Negative	798 (98.6)	790 (97.7)	1588 (98.1)

Abbreviations: N: number of subjects in full analysis set; %: percentage of subjects.

Anti-semaglutide antibody levels:

	Sema 0.5 mg	Sema 1.0 mg	Total
Number of subjects	826	822	1648
Anti-semaglutide antibody level - Observed 'in-trial' data			
Visit 2 (week 0)			
N	1	1	2
Geom. mean (CV)	2.73 (.)	4.19 (.)	3.38 (31.00)
Median	2.73	4.19	3.46
P5 ; P95	2.73 ; 2.73	4.19 ; 4.19	2.73 ; 4.19
Min ; Max	2.73 ; 2.73	4.19 ; 4.19	2.73 ; 4.19
N<LLOQ ; N>ULOQ	0 ; 0	0 ; 0	0 ; 0
Visit 7 (week 30)			
N	5	6	11
Geom. mean (CV)	4.02 (66.53)	3.98 (72.15)	4.00 (65.41)
Median	4.27	4.28	4.27
P5 ; P95	2.01 ; 9.93	1.77 ; 9.24	1.77 ; 9.93
Min ; Max	2.01 ; 9.93	1.77 ; 9.24	1.77 ; 9.93
N<LLOQ ; N>ULOQ	0 ; 0	0 ; 0	0 ; 0
Visit 9 (week 44)			
N	5	9	14
Geom. mean (CV)	3.05 (18.63)	4.44 (54.54)	3.88 (47.74)
Median	3.20	5.05	3.62
P5 ; P95	2.47 ; 3.79	2.41 ; 9.90	2.41 ; 9.90
Min ; Max	2.47 ; 3.79	2.41 ; 9.90	2.41 ; 9.90
N<LLOQ ; N>ULOQ	0 ; 0	0 ; 0	0 ; 0
Visit 11 (week 56)			
N	3	5	8
Geom. mean (CV)	2.90 (21.01)	7.23 (88.70)	5.13 (87.41)
Median	2.64	12.40	3.44
P5 ; P95	2.51 ; 3.68	3.09 ; 12.97	2.51 ; 12.97
Min ; Max	2.51 ; 3.68	3.09 ; 12.97	2.51 ; 12.97

	Sema 0.5 mg	Sema 1.0 mg	Total
N<LLOQ ; N>ULOQ	0 ; 0	0 ; 0	0 ; 0
Visit 15 (week 80)			
N	2	2	4
Geom. mean (CV)	5.15 (15.16)	5.58 (84.98)	5.36 (45.86)
Median	5.18	6.35	5.18
P5 ; P95	4.63 ; 5.73	3.31 ; 9.39	3.31 ; 9.39
Min ; Max	4.63 ; 5.73	3.31 ; 9.39	3.31 ; 9.39
N<LLOQ ; N>ULOQ	0 ; 0	0 ; 0	0 ; 0
Visit 25 (week 104)			
N	2	4	6
Geom. mean (CV)	3.94 (18.96)	4.34 (48.50)	4.20 (38.22)
Median	3.98	4.09	4.09
P5 ; P95	3.45 ; 4.50	2.65 ; 8.04	2.65 ; 8.04
Min ; Max	3.45 ; 4.50	2.65 ; 8.04	2.65 ; 8.04
N<LLOQ ; N>ULOQ	0 ; 0	0 ; 0	0 ; 0
Visit 26 (week 109)			
N	2	2	4
Geom. mean (CV)	5.97 (100.06)	7.70 (74.30)	6.78 (70.09)
Median	7.03	8.57	7.79
P5 ; P95	3.31 ; 10.75	4.82 ; 12.31	3.31 ; 12.31
Min ; Max	3.31 ; 10.75	4.82 ; 12.31	3.31 ; 12.31
N<LLOQ ; N>ULOQ	0 ; 0	0 ; 0	0 ; 0

Reviewers comments:
The phase III studies involved weekly administration for 2 years with sampling points at 30, 44, 56, 80 and 104 weeks after treatment. The rate of subjects that testing positive for anti-semaglutide antibodies at any given point did not exceed 1%. At the follow-up time point the

ADA rate was 0.3% indicating most ADA are transient and the rate of ADA is low after repeated exposures. Indeed the highest rate was at week 44 and decreased after that.
The studies were not set up to inform us about transient antibody responses that arise within weeks after initial dosing. The study only looks at long term antibody response. Of the 3099 patient treated with Semaglutide, 30 had ADA for a total of 47 samples indicating that a few subjects were positive for ADA more than once. None of the patients developed high titer antibodies.

Phase 3 a trials excluding CVOT:
In the pool of phase 3 studies, a total of 3099 patients were treated with semaglutide. Of these, 32 subjects (1%) were confirmed positive for anti-semaglutide antibodies at any time post-baseline as compared to 0-0.2% that were positive at baseline. No trend towards increasing rate of ADA positive patients were evident as the trial progressed suggesting that a late surge in ADA with chronic treatment is unlikely. Some subjects had anti-semaglutide antibodies at different timepoints accounting for 56 positive samples from 32 subjects. Anti-semaglutide antibody titer was calculated as the highest dilution of a sample which gives a %B/T value above the normalized screening cut point. None of the patients developed high titer antibodies.

7.3.1 Occurrence of anti-semaglutide antibodies by treatment week - categorical summary - Ph 3a pool

	Sema 0.5 mg N (%)	Sema 1.0 mg N (%)	All sema N (%)
Number of subjects	1373	1777	3150
Anti-sema antibodies - observed data			
Week 0			
N	1324 (100.0)	1731 (100.0)	3055 (100.0)
Positive	3 (0.2)	3 (0.2)	6 (0.2)
Negative	1321 (99.8)	1728 (99.8)	3049 (99.8)
Week 16			
N	1319 (100.0)	1711 (100.0)	3030 (100.0)
Positive	7 (0.5)	4 (0.2)	11 (0.4)
Negative	1312 (99.5)	1707 (99.8)	3019 (99.6)
Week 30			
N	1274 (100.0)	1611 (100.0)	2885 (100.0)
Positive	0	7 (0.4)	7 (0.2)
Negative	1274 (100.0)	1604 (99.6)	2878 (99.8)
Week 35			
N	646 (100.0)	632 (100.0)	1278 (100.0)
Positive	2 (0.3)	1 (0.2)	3 (0.2)
Negative	644 (99.7)	631 (99.8)	1275 (99.8)
Week 40			
N	618 (100.0)	974 (100.0)	1592 (100.0)
Positive	0	4 (0.4)	4 (0.3)
Negative	618 (100.0)	970 (99.6)	1588 (99.7)
Week 56			
N	608 (100.0)	965 (100.0)	1573 (100.0)
Positive	0	8 (0.8)	8 (0.5)
Negative	608 (100.0)	957 (99.2)	1565 (99.5)
Week 61			
N	600 (100.0)	944 (100.0)	1544 (100.0)
Positive	2 (0.3)	5 (0.5)	7 (0.5)
Negative	598 (99.7)	939 (99.5)	1537 (99.5)
Follow-up			
N	1246 (100.0)	1576 (100.0)	2822 (100.0)
Positive	4 (0.3)	6 (0.4)	10 (0.4)
Negative	1242 (99.7)	1570 (99.6)	2812 (99.6)
Anytime post-baseline			
N	1353 (100.0)	1746 (100.0)	3099 (100.0)
Positive	12 (0.9)	20 (1.1)	32 (1.0)
Negative	1341 (99.1)	1726 (98.9)	3067 (99.0)

Anti-sema antibodies cross-reacting with endogenous GLP-1 - observed data

Week 0			
N	4 (100.0)	4 (100.0)	8 (100.0)
Positive	2 (50.0)	2 (50.0)	4 (50.0)
Negative	2 (50.0)	2 (50.0)	4 (50.0)
Week 16			
N	8 (100.0)	4 (100.0)	12 (100.0)
Positive	4 (50.0)	2 (50.0)	6 (50.0)
Negative	4 (50.0)	2 (50.0)	6 (50.0)
Week 30			
N		7 (100.0)	7 (100.0)
Positive		4 (57.1)	4 (57.1)
Negative		3 (42.9)	3 (42.9)
Week 35			
N	2 (100.0)	1 (100.0)	3 (100.0)
Positive	1 (50.0)	1 (100.0)	2 (66.7)
Negative	1 (50.0)	0	1 (33.3)
Week 40			
N		4 (100.0)	4 (100.0)
Positive		2 (50.0)	2 (50.0)
Negative		2 (50.0)	2 (50.0)
Week 56			
N		8 (100.0)	8 (100.0)
Positive		6 (75.0)	6 (75.0)
Negative		2 (25.0)	2 (25.0)
Week 61			
N	2 (100.0)	5 (100.0)	7 (100.0)
Positive	2 (100.0)	3 (60.0)	5 (71.4)
Negative	0	2 (40.0)	2 (28.6)
Follow-up			
N	4 (100.0)	6 (100.0)	10 (100.0)
Positive	3 (75.0)	4 (66.7)	7 (70.0)
Negative	1 (25.0)	2 (33.3)	3 (30.0)
Anytime post-baseline			
N	13 (100.0)	20 (100.0)	33 (100.0)
Positive	7 (53.8)	12 (60.0)	19 (57.6)
Negative	6 (46.2)	8 (40.0)	14 (42.4)

Antibody titer

Anti-semaglutide antibody levels by treatment week - descriptive statistics - Ph 3a pool

	Sema 0.5 mg	Sema 1.0 mg	All sema
Anti-semaglutide binding antibodies titre - observed data			
Week 0			
N		2	2
Mean (SD)		1.00 (0.00)	1.00 (0.00)
Median		1.00	1.00
P5 ; P95		1.00 ; 1.00	1.00 ; 1.00
Min ; Max		1.00 ; 1.00	1.00 ; 1.00
N<LLOQ ; N>ULOQ		0 ; 0	0 ; 0

Week 16		
N	1	1
Mean (SD)	1.00 (.)	1.00 (.)
Median	1.00	1.00
P5 ; P95	1.00 ; 1.00	1.00 ; 1.00
Min ; Max	1.00 ; 1.00	1.00 ; 1.00
N<LLOQ ; N>ULOQ	0 ; 0	0 ; 0
Week 30		
N	2	2
Mean (SD)	1.00 (0.00)	1.00 (0.00)
Median	1.00	1.00
P5 ; P95	1.00 ; 1.00	1.00 ; 1.00
Min ; Max	1.00 ; 1.00	1.00 ; 1.00
N<LLOQ ; N>ULOQ	0 ; 0	0 ; 0
Week 40		
N	3	3
Mean (SD)	2.33 (2.31)	2.33 (2.31)
Median	1.00	1.00
P5 ; P95	1.00 ; 5.00	1.00 ; 5.00
Min ; Max	1.00 ; 5.00	1.00 ; 5.00
N<LLOQ ; N>ULOQ	0 ; 0	0 ; 0
Week 56		
N	6	6
Mean (SD)	5.67 (9.61)	5.67 (9.61)
Median	1.00	1.00
P5 ; P95	1.00 ; 25.00	1.00 ; 25.00
Min ; Max	1.00 ; 25.00	1.00 ; 25.00
N<LLOQ ; N>ULOQ	0 ; 0	0 ; 0
Week 61		
N	4	4
Mean (SD)	3.00 (2.31)	3.00 (2.31)
Median	3.00	3.00
P5 ; P95	1.00 ; 5.00	1.00 ; 5.00
Min ; Max	1.00 ; 5.00	1.00 ; 5.00
N<LLOQ ; N>ULOQ	0 ; 0	0 ; 0
Follow-up		
N	4	4
Mean (SD)	3.00 (2.31)	3.00 (2.31)
Median	3.00	3.00
P5 ; P95	1.00 ; 5.00	1.00 ; 5.00
Min ; Max	1.00 ; 5.00	1.00 ; 5.00
N<LLOQ ; N>ULOQ	0 ; 0	0 ; 0

Reviewers comments:
Both 0.5 mg and 1.0 mg 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 (1-6). Note that the titers are expressed without the initial 1:15 dilution of the sample for the assay and thus the titers are 15-90, which are still considered low titers.

Approximately 60% (19 out of 33) of the samples testing positive for anti-semaglutide antibody showed cross-reactity 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.*

Placebo controlled trials pool:

The sponsor performed an additional analysis of the phase III data that is based on the studies that were placebo controlled as opposed to the analysis above where the analysis included those studies where the incidence of ADA was obtained from all phase III studies (including those that compared the incidence with that of other products). In this analysis, a total of 11 subjects (2.2%) were tested positive for anti-semaglutide antibodies at any point post-baseline. The proportion of subjects that tested positive for ADA was highest (1.2%) at treatment week 16. At the follow-up visit, 3 subjects (0.6%) tested positive for anti-semaglutide antibodies. The level of ADA in

subjects that tested positive was low (up to 8.62% B/T). At the end of the study 2/3 subjects with ADA showed cross-reactivity with endogenous GLP-1.

7.3.2 Occurrence of anti-semaglutide antibodies by treatment week - categorical summary - Placebo pool

	Sema 0.5 mg N (%)	Sema 1.0 mg N (%)	All sema N (%)
Number of subjects	260	261	521
Anti-sema antibodies - observed data			
Week 0			
N	258 (100.0)	259 (100.0)	517 (100.0)
Positive	1 (0.4)	0	1 (0.2)
Negative	257 (99.6)	259 (100.0)	516 (99.8)
Week 16			
N	252 (100.0)	250 (100.0)	502 (100.0)
Positive	4 (1.6)	2 (0.8)	6 (1.2)
Negative	248 (98.4)	248 (99.2)	496 (98.8)
Week 30			
N	240 (100.0)	242 (100.0)	482 (100.0)
Positive	0	3 (1.2)	3 (0.6)
Negative	240 (100.0)	239 (98.8)	479 (99.4)
Week 35			
N	230 (100.0)	236 (100.0)	466 (100.0)
Positive	2 (0.9)	1 (0.4)	3 (0.6)
Negative	228 (99.1)	235 (99.6)	463 (99.4)
Follow-up			
N	230 (100.0)	236 (100.0)	466 (100.0)
Positive	2 (0.9)	1 (0.4)	3 (0.6)
Negative	228 (99.1)	235 (99.6)	463 (99.4)
Anytime post-baseline			
N	255 (100.0)	256 (100.0)	511 (100.0)
Positive	6 (2.4)	5 (2.0)	11 (2.2)
Negative	249 (97.6)	251 (98.0)	500 (97.8)

N: Number of subjects in the safety analysis set in the summary statistics, %: Percentage of subjects

Occurrence of anti-semaglutide antibodies by treatment week - categorical summary - Placebo pool

	Sema 0.5 mg N (%)	Sema 1.0 mg N (%)	All sema N (%)
Anti-sema antibodies cross-reacting with endogenous GLP-1 - observed data			
Week 0			
N	1 (100.0)		1 (100.0)
Positive	0		0
Negative	1 (100.0)		1 (100.0)
Week 16			
N	4 (100.0)	2 (100.0)	6 (100.0)
Positive	3 (75.0)	1 (50.0)	4 (66.7)
Negative	1 (25.0)	1 (50.0)	2 (33.3)
Week 30			
N		3 (100.0)	3 (100.0)
Positive		3 (100.0)	3 (100.0)
Negative		0	0
Week 35			
N	2 (100.0)	1 (100.0)	3 (100.0)
Positive	1 (50.0)	1 (100.0)	2 (66.7)
Negative	1 (50.0)	0	1 (33.3)
Follow-up			
N	2 (100.0)	1 (100.0)	3 (100.0)
Positive	1 (50.0)	1 (100.0)	2 (66.7)
Negative	1 (50.0)	0	1 (33.3)
Anytime post-baseline			
N	6 (100.0)	5 (100.0)	11 (100.0)
Positive	4 (66.7)	4 (80.0)	8 (72.7)
Negative	2 (33.3)	1 (20.0)	3 (27.3)

7.3.4 Anti-semaglutide antibody levels by treatment week - descriptive statistics - Placebo pool

	Sema 0.5 mg	Sema 1.0 mg	All sema
Number of subjects	260	261	521
Anti-sema antibody level (% B/T) - observed data			
Week 0			
N	1		1
Mean (SD)	3.55 (.)		3.55 (.)
Median	3.55		3.55
P5 ; P95	3.55 ; 3.55		3.55 ; 3.55
Min ; Max	3.55 ; 3.55		3.55 ; 3.55
N<LLOQ ; N>ULOQ	0 ; 0		0 ; 0
Week 16			
N	4	2	6
Mean (SD)	3.44 (0.84)	3.18 (1.20)	3.35 (0.86)
Median	3.47	3.18	3.47
P5 ; P95	2.41 ; 4.42	2.33 ; 4.03	2.33 ; 4.42
Min ; Max	2.41 ; 4.42	2.33 ; 4.03	2.33 ; 4.42
N<LLOQ ; N>ULOQ	0 ; 0	0 ; 0	0 ; 0
Week 30			
N		3	3
Mean (SD)		4.63 (1.41)	4.63 (1.41)
Median		4.02	4.02
P5 ; P95		3.63 ; 6.25	3.63 ; 6.25
Min ; Max		3.63 ; 6.25	3.63 ; 6.25
N<LLOQ ; N>ULOQ		0 ; 0	0 ; 0
Week 35			
N	2	1	3
Mean (SD)	3.16 (0.45)	8.62 (.)	4.98 (3.17)
Median	3.16	8.62	3.48
P5 ; P95	2.84 ; 3.48	8.62 ; 8.62	2.84 ; 8.62
Min ; Max	2.84 ; 3.48	8.62 ; 8.62	2.84 ; 8.62
N<LLOQ ; N>ULOQ	0 ; 0	0 ; 0	0 ; 0
Follow-up			
N	2	1	3
Mean (SD)	3.16 (0.45)	8.62 (.)	4.98 (3.17)
Median	3.16	8.62	3.48
P5 ; P95	2.84 ; 3.48	8.62 ; 8.62	2.84 ; 8.62
Min ; Max	2.84 ; 3.48	8.62 ; 8.62	2.84 ; 8.62
N<LLOQ ; N>ULOQ	0 ; 0	0 ; 0	0 ; 0

Anti-Exenatide antibodies in Exenatide treated subjects:

2307 samples were screened; confirmatory results were run for1698 samples; titer and cross-reactivity was determined for 1420 samples.

Results show that a large fraction of Exenatide treated patients developed ADA.

ADA at baseline was 5.5%. The rate increased to 83.7% at week 16 and 68.9% at week 61. 15.4% of samples were NAB positive at week 61, but only 1 subject developed ADA that cross-reacted with endogenous GLP-1 and none neutralized endogenous GLP-1 at week 61. These rates are higher compared to the rates reported in the label for Exenatide (Byetta)

14.3.5.192 Occurrence of anti-exenatide antibodies by treatment week - categorical summary - safety analysis set

	Sema 1.0 mg N	Sema 1.0 mg (%)	Exenatide ER N	Exenatide ER (%)
Number of subjects	404		405	
Anti-exenatide binding antibodies - Observed 'in-trial' data				
Visit 2 (week 0)				
Positive			22	(5.5)
Negative			381	(94.5)
Visit 7 (week 16)				
Positive			323	(83.7)
Negative			63	(16.3)
Visit 9 (week 30)				
Positive			278	(76.2)
Negative			87	(23.8)
Visit 11 (week 40)				
Positive			260	(72.2)
Negative			100	(27.8)
Visit 13 (week 56)				
Positive			240	(67.6)
Negative			115	(32.4)
Visit 14 (week 61)				
Positive			252	(68.9)
Negative			114	(31.1)
Anti-exenatide antibodies cross-reacting with endogenous GLP-1 - Observed 'in-trial' data				
Visit 2 (week 0)				
Positive			7	(31.8)
Negative			15	(68.2)
Visit 7 (week 16)				
Positive			1	(0.3)
Negative			322	(99.7)
Visit 9 (week 30)				
Positive				
Negative			279	(100.0)
Visit 11 (week 40)				
Positive			1	(0.4)
Negative			258	(99.6)
Visit 13 (week 56)				
Positive			1	(0.4)
Negative			239	(99.6)
Visit 14 (week 61)				
Positive			1	(0.4)
Negative			251	(99.6)
Anti-exenatide neutralising antibodies - Observed 'in-trial' data				
Visit 14 (week 61)				
Positive			39	(15.4)
Negative			214	(84.6)

N: Number of subjects in the summary statistic, %: Percentage of subjects.

	Sema 1.0 mg N	Sema 1.0 mg (%)	Exenatide ER N	Exenatide ER (%)
Anti-exenatide antibodies with endogenous GLP-1 neutralising effect - Observed 'in-trial' data				
Visit 14 (week 61)				
Positive				
Negative			1	(100.0)

Reviewers comments:
The level of screening and confirmatory antibodies to Semaglutide is lower than exenatide (1.1% vs 69%) throughout the testing period. This is to be expected given that Semaglutide is based on the human sequence whereas Exenetide is based on the hila monster sequence.

Drug induced Hypersensitivity reactions:

No serious hypersensitivity responses were evident during the trials for Semaglutide.
During the phase III clinical studies, one event of anaphylactic shock was reported in a patient randomized to semaglutide. This event was reported after more than one year of repeated exposures to semaglutide 0.5 mg and as an adverse reaction to following the administration of cefazolin.
Injection site reactions were reported in approximately 1% of the patients and were not recurrent in those individuals. Most injection site reactions were of mild or moderate severity and did not lead to premature treatment discontinuation. Rate of these reactions are similar to the levels seen in placebo.
During the trials 3 subjects had additional serum samples collected due to suspicion of severe acute hypersensitivity. All samples collected tested negative for IgE antibodies however the sensitivity of the IgE assay was poor so no conclusions should be drwan from the results provided.. No tryptase samples were collected or analyzed at any time during the phase 3a development program.
Reviewers comments:
Although the sensitivity of the IgE assay was poor, the clinical reviewer pointed out that there was no dose response for semaglutide as it pertains to allergic reactions and that the available data does not suggest that semaglutide can cause severe allergic reactions.

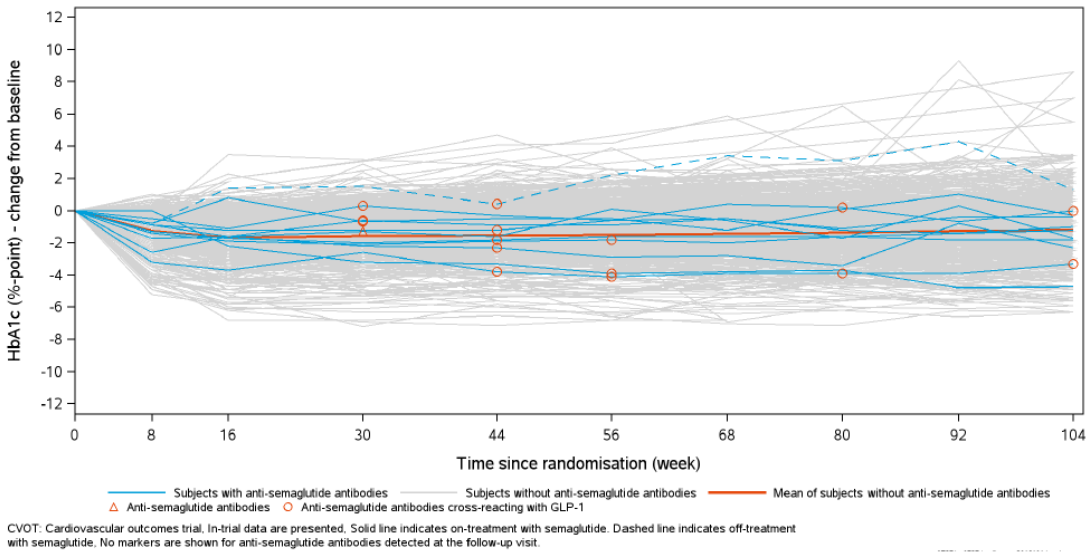
Effect of anti-semaglutide antibodies on semaglutide pharmacokinetics:

There is no indication that ADA impact on the product's pharmacokinetics or pharmacodynamics.

- 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:

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.



HbA_{1c} (%-point) change from baseline for subjects with and without anti-semaglutide antibodies – spaghetti plot – semaglutide 0.5 mg – CVOT

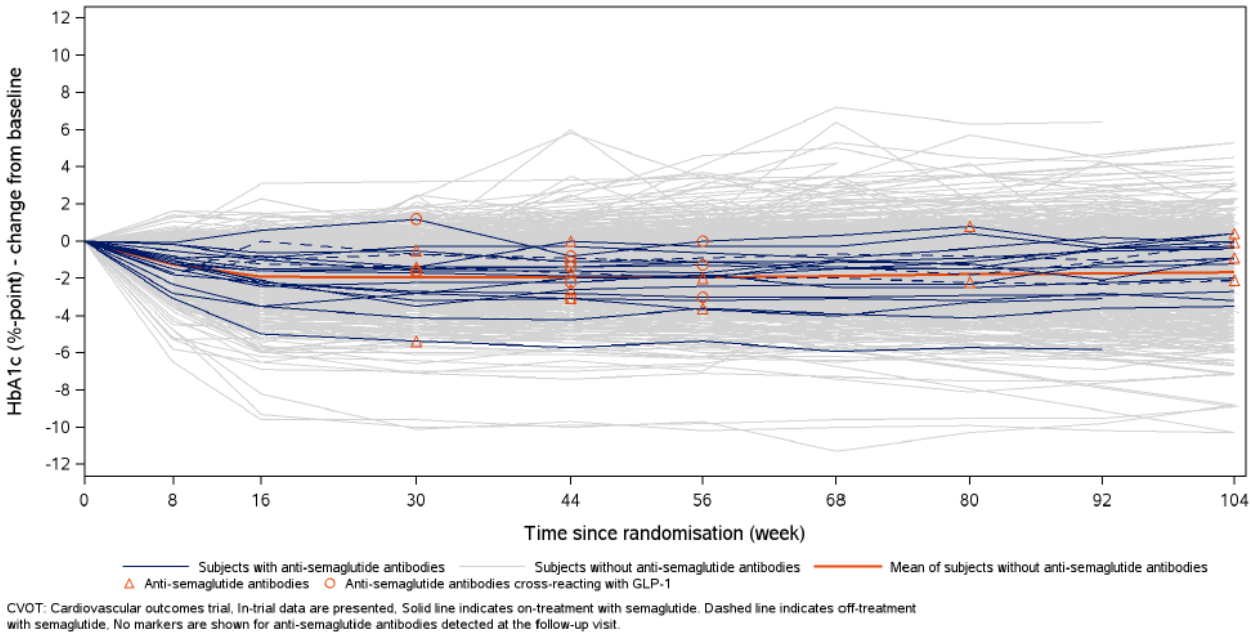


Figure 4–2 HbA_{1c} (%-point) change from baseline for subjects with and without anti-semaglutide antibodies – spaghetti plot – semaglutide 1.0 mg – CVOT

Reviewers comments:

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

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 including the CVOT. The proportion of subjects with events and rate of events by severity, outcome and action taken

including SAE leading to premature treatment discontinuation were also similar in subjects with and without anti-semaglutide antibodies.

Table 4–7 Adverse events in anti-semaglutide positive and anti-semaglutide negative subjects – on-treatment – CVOT

	Subjects with antibodies N	(%)	E	R	Subjects without antibodies N	(%)	E	R
Number of subjects	30				1612			
PYE (year)	55				2877			
All Events	27	(90.0)	171	308.7	1427	(88.5)	9866	343.0
Serious								
Yes	6	(20.0)	9	16.2	498	(30.9)	1071	37.2
No	27	(90.0)	162	292.4	1398	(86.7)	8795	305.7
Severity								
Severe	6	(20.0)	10	18.1	364	(22.6)	681	23.7
Moderate	20	(66.7)	60	108.3	932	(57.8)	3119	108.4
Mild	21	(70.0)	101	182.3	1258	(78.0)	6065	210.8
Unknown					1	(<0.1)	1	<0.1
Outcome								
Fatal	1	(3.3)	2	3.6	46	(2.9)	70	2.4
Not recovered	15	(50.0)	30	54.2	792	(49.1)	1972	68.5
Recovered with sequelae	0				50	(3.1)	55	1.9
Recovering	2	(6.7)	2	3.6	168	(10.4)	328	11.4
Recovered	24	(80.0)	137	247.3	1330	(82.5)	7423	258.0
Unknown	0				10	(0.6)	18	0.6
Leading to premature treatment discontinuation								
Yes	3	(10.0)	6	10.8	211	(13.1)	341	11.9
No	27	(90.0)	165	297.8	1395	(86.5)	9525	331.1
Action taken								
Dose Not Changed	25	(83.3)	146	263.5	1364	(84.6)	8647	300.6
Dose Reduced	0				6	(0.4)	11	0.4
Drug Interrupted	1	(3.3)	1	1.8	93	(5.8)	178	6.2
Drug Withdrawn	3	(10.0)	6	10.8	211	(13.1)	341	11.9
Not Applicable	10	(33.3)	18	32.5	319	(19.8)	681	23.7
Unknown	0				6	(0.4)	8	0.3

Notes: Subjects with antibodies: at least one positive post-baseline anti-semaglutide antibody sample. Subjects without antibodies: all post-baseline anti-semaglutide antibody samples were negative. Table only includes subjects treated with semaglutide. On-treatment is defined as the observation period from the date of first dose to either the end-of-treatment follow-up visit, the date of last dose plus 42 days, the end-of-trial follow-up visit, or the date of withdrawal from trial, whichever comes first. PYE is calculated as the duration of the on-treatment period. The events are considered treatment-emergent. MedDRA version 18.0

Abbreviations: E: number of events; N: number of subjects in the safety analysis set with at least one event; PYE: patient years of exposure; R: event rate per 100 PYE; %: percentage of subjects with at least one event.

Table 4–8 Adverse events in anti-semaglutide positive and anti-semaglutide negative subjects – on-treatment – phase 3a pool

	Subjects with antibodies N (Adj.%)	E	Adj.R	Subjects without antibodies N (Adj.%)	E	Adj.R
Number of subjects	32			3118		
PYE (year)	29			2683		
All Events	20 (62.8)	71	239.7	2296 (70.3)	9945	440.7
Serious						
Yes	1 (3.1)	1	3.4	209 (6.1)	289	13.1
No	20 (62.8)	70	236.3	2258 (69.3)	9656	427.6
Severity						
Severe	1 (3.1)	1	3.4	182 (6.4)	274	16.6
Moderate	6 (18.7)	18	60.4	822 (29.6)	1882	93.7
Mild	17 (53.5)	52	175.8	2049 (61.0)	7789	330.4
Outcome						
Fatal	0			10 (0.4)	10	0.6
Not recovered	7 (21.8)	9	30.5	874 (24.5)	1545	63.1
Recovered with sequelae	0			16 (0.6)	20	1.0
Recovering	1 (3.1)	1	3.3	188 (4.2)	239	8.6
Recovered	17 (53.3)	61	205.8	2127 (64.9)	8125	367.4
Unknown	0			6 (<0.1)	6	<0.1
Leading to premature treatment discontinuation						
Yes	2 (6.3)	3	10.2	238 (6.3)	369	15.3
No	19 (59.7)	68	229.4	2242 (69.1)	9576	425.5
Action taken						
Dose Not Changed	19 (59.7)	66	222.5	2145 (66.1)	8696	385.2
Dose Reduced	0			12 (0.3)	16	0.7
Drug Interrupted	0			87 (2.8)	133	6.7
Drug Withdrawn	2 (6.3)	3	10.2	238 (6.3)	368	15.2
Not Applicable	2 (6.4)	2	6.9	504 (14.5)	711	32.7
Unknown	0			2 (0.1)	2	0.2

Notes: % and R are the Cochran-Mantel-Haenszel adjusted percentage and event rate. Subjects with antibodies: at least one positive post-baseline anti-semaglutide antibody sample. Subjects without antibodies: all post-baseline anti-semaglutide antibody samples were negative. Table only includes subjects treated with semaglutide. On-treatment is defined as the observation period from the date of first dose to either the end-of-treatment follow-up visit, the date of last dose plus 42 days, the end-of-trial follow-up visit, or the date of withdrawal from trial, whichever comes first. PYE is calculated as the duration of the on-treatment period. The events are considered treatment-emergent. MedDRA version 18.0. Trials included: 3623, 3624, 3625, 3626, 3627, 4091 and 4092.

Abbreviations: Adj.: adjusted; E: number of events; N: number of subjects in the safety analysis set with at least one event; PYE: patient years of exposure; R: event rate per 100 PYE; %: percentage of subjects with at least one event.

Reviewers comments:
Presence of ADA did not influence the HbAlc lowering effect of semaglutide. Of note, doctors treat diabetes to normalize Hb1Ac, so this may not be the most reliable pharmacodynamic marker. No link was evident between adverse events and the presence of ADA. Therefore development of ADA does not appear to the affect safety or efficacy of semaglutide.

Appendix 1

An information request was sent to the sponsor on May 26, 2017 regarding the raw data for ADA testing for clinical samples.

1.1 Question 1

The clinical study report for your pivotal trials shows no values for ADA testing for several clinical samples. The list states that several samples were "not collected", however the samples for the same subjects and same time points have results for the confirmatory assay. Please explain this discrepancy and correct any errors as needed. If samples were not collected please specify the cause

May 30th Clarification from FDA: As an example in your study reports 5.3.5.1 –NN9535-3626/data listing data/BIMO MM9535-3626 Data listings by site Part I, "clinical laboratory test results-Antibodies- site 101" (page 212 of 9896) , several subject IDs have "Not collected" in the comment section and the value filed is blank for Anti-semaglutide antibody. However, for the same subject IDs you have "negative" in the value field for Antisemaglutide antibody confirmation. This same issue is seen in other sites and in other parts as well.

Response from the sponsor:

1.1.1 Response to Question 1

Novo Nordisk has confirmed that all antibody positive sample results have been reported correctly in the BIMO lists; however, inconsistencies in the way antibody negative sample results were reported in the BIMO lists were identified.

Novo Nordisk would therefore like to provide clarification on the antibody sample analysis flow and how antibody negative sample results were reported in the BIMO lists for the pivotal (phase 3a) trials.

Evaluation of anti-semaglutide antibodies was performed using a tiered approach with screening analysis in tier 1, confirmation analysis in tier 2 and characterization, i.e. cross-reactivity to endogenous GLP-1 and *in vitro* neutralizing antibody analysis in tier 3 (Figure 1).

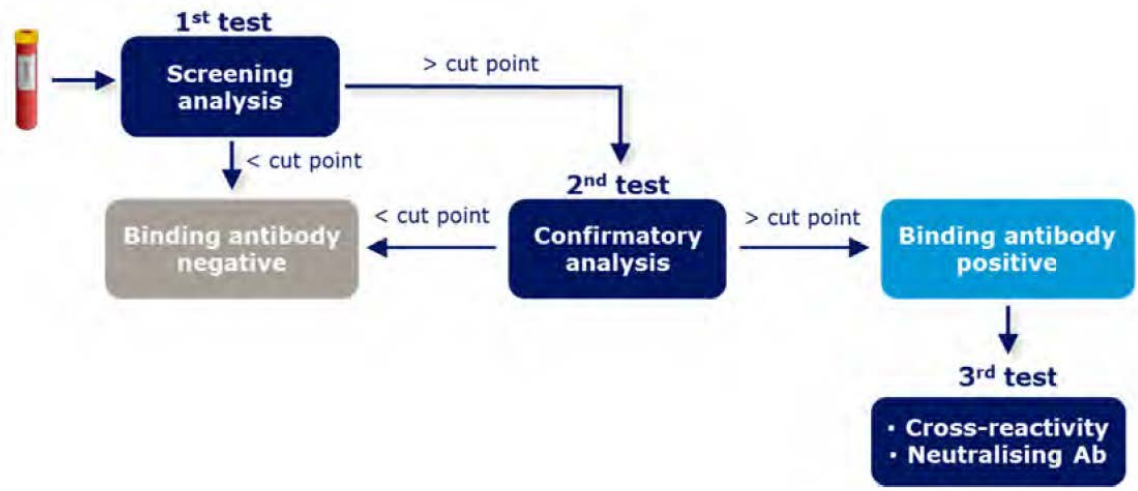


Figure 1 Tiered antibody assay approach

Samples that were below the screening cut point (at 5% false positive rate) in the screening analysis (1st test) and samples that were confirmed negative in the confirmatory analysis (2nd test) were reported as negative.

The antibody negative results (grey box in Figure 1) appear in the BIMO listings as follows, see subject NN9535-3623/101006 in Table 1 as an example:

- In the 'Anti-Semaglutide Antibody Confirmation' field in the 'parameter' column, the antibody negative results were reported as 'negative' in the 'value' column
- In the 'Anti-Semaglutide Antibody' field in the 'parameter' column, the antibody negative results were reported as either 'NAP' (not applicable) or as 'blank' in the 'value' column
- In the 'Anti-Semaglutide Antibody' field in the 'comment' column, the statement 'not collected' should be interpreted as if the antibody sample value was 'NAP' (not applicable).

Novo Nordisk confirms that data presented in the antibody analytical reports are correct.

Reviewers comment:

The sponsor's statement that the statement "not collected" should be interpreted as if the antibody sample value was "not applicable" in the reports was ambigous. However, the sponsor confirmed that the data presented in the antibody analytical reports are correct. Moreover, based on the inspections of the 10 clinical sites and the sponsor, the clinical inspection team reported that the inspectional findings supported the validity of data as reported by the sponsor under this NDA (refer inspection memo filed as part of the NDA review). Thus we understand that the statement "not collected" refers to not tested because the screening assay was negative.

Appendix 2

A second information request was sent to the sponsor on August, 29, 2017 requesting further clarification regarding ADAs. The response from the sponsor was submitted on September 8, 2017.

1.1 FDA Request 1

Confirm that the sensitivity of the NAB assay is 32ug/ml

1.1.1 Response to Question 1

The sensitivity of the anti-semaglutide neutralising antibody (NAB) assay used in the clinical phase 3 programme was determined to be 3.4 µg/ml. This is described in the validation report, 214429 (M 5.3.1.4), Section 5.3 and was discussed in the Integrated Summary of Immunogenicity (M 5.3.5.3), Section 3.2.2.2.

Reviewers comments:

The sponsor confirmed that the sensitivity of the assay was 3.4 ug/mL. The sensitivity of the assay is low. This will not be enough to identify the level of neutralizing antibodies in the clinical samples. The sponsor will be asked to develop a sensitive NAb assay.

1.2 FDA Request 2

Describe each dilution step during ADA testing and titer determination

1.2.1 Response to Question 2

The screening and confirmatory anti-semaglutide antibody assay includes pre-treatment of samples with Glycin-HCl and PEG 6000 precipitation prior to the analysis of samples.
Initially 10 µl sample is precipitated in the pre-treatment step. The precipitate is then dissolved in

100 µl buffer in the absence or presence of unlabelled drug followed by addition of 50 µl labelled drug (tracer) to a total volume of 150 µl. Thus, the assay dilution factor/minimum required dilution (MRD) is 15.
When determining titre, the 10 µl sample is serially diluted in human serum prior to the pretreatment, with at least one dilution below the normalized screening cut point. The reported titre is determined as the highest dilution of this 10 µl sample which gives a %B/T value above the normalized screening cut point in the analysis, corresponding to an MRD adjusted titre of 15x the reported titre.
Reviewers comments:
The response fromt the sponsor clarified that the MRD was 15 and the reported titer of 1-6 is 15-90 with the dilution factor.

1.3 FDA Request 3
A description of the outlier determination in the calculation of the cut point for the screening and confirmatory ADA assays
1.3.1 Response to Question 3
Outlier determination was performed as described by Shankar et al 20081 by using a box-plot method that removes outliers based on quartile calculations of original non-transformed datasets. The plot identifies all the points ("high outliers") that are above the 75th percentile (Q3) plus 1.5 times the interquartile range (Q3–Q1) and all the points ("low outliers") that are below the 25th percentile (Q1) minus 1.5 times inter-quartile range. Thus, high outliers >Q3 + 1.5 x (Q3-Q1) and low outliers <Q1 – 1.5 x (Q3-Q1) were removed from the datasets. The outlier determination was only performed if neither non-transformed nor log-transformed datasets were normal distributed. Normal distribution was investigated for both non-transformed and log-transformed datasets using the Shapiro Wilks W test.
The box-plot method for identification of outliers was used for the determination of cut points for the screening -, confirmatory - and cross-reactivity assays.
Reviewers comments:
This is acceptable.

1.4 FDA Request 4
A sortable table (preferably in excel) that identifies:
☐ *Individual patient that screened positive for ADA*
☐ *Individual patient that had confirmed ADA positive samples*
☐ *The titer of each samples that was confirmed positive for ADA. Titers should be calculated considering every dilution step including the acid dissociation steps.*
☐ *The crossreactivity with endogenous GLP-1*
1.4.1 Response to Question 4
Please find attached the requested table in Q4 Excel table. Data in the Excel-sheet are based on raw data from the analytical laboratory (b) (4)
In the Excel table, the following requested information is presented for the semaglutide phase 3a trials:

- Individual patients that screened positive for ADA
- Individual patients that had confirmed ADA positive samples
- The reported titre of each sample that was confirmed positive for ADA

- The titres calculated considering all dilution steps in the analysis (MRD adjusted titre).
- The results of the cross reactivity with endogenous GLP-1

In addition to the requested information, the Excel table also contains the antibody results reported as background adjusted %B/T (bound over total added radioactivity). The results in %B/T were used instead of the titre in all but one trial (NN9535-3624); see details on titre determination below.
As shown in the Integrated Summary of Immunogenicity (M 5.3.5.3), Figure 3-2, there is a dose response relationship between the amount of antibody present in a sample and the level of %B/T measured. In the clinical development programme for semaglutide only low levels of ADA responses were observed. At these low levels, %B/T corresponds to a titre determination.
Titre determination was included in trial NN9535-3624 in order to compare the anti-semaglutide antibody response with that of the comparator (exenatide ER) which was expected to yield ADA signals above the dynamic range of the anti-exenatide antibody assay. Due to the high response for anti-exenatide antibodies a five-fold dilution was chosen for both types of ADA (anti-semaglutide antibodies and anti-exenatide antibodies) to be able to compare the titres. Samples which were confirmed positive for ADAs but negative in the first 5-fold dilution were reported with a titre of '1'. In the Excel table provided, both the 'Reported titre' corresponding to the pre-treatment dilution with serum as well as the 'MRD adjusted titre' (dilution factor multiplied with the MRD = 15) have been included.

Reviewers comments:
Sponsor provided the data in an excel sheet. This is acceptable.

1.5 FDA Request 5
A summary table for each of the phase III studies with the:
number of samples tested for ADA at each time point,
number of samples that screened positive at each time point,
number of samples that were confirmed positive at each time point,
mean titer at each time point.
Number of confirmed ADA samples that crossreact with GLP1

1.5.1 Response to Question 5
The requested summary tables for each of the phase 3a trials are included in Appendix A, Tables 1 to 16. These summary tables are based on the Excel sheet provided in the response to Question 4, Q4 Excel table. As described in the response to Question 4, the results in %B/T are reported for all trials and in addition the 'MRD adjusted titre' is reported for one trial (NN9535-3624).

Reviewers comments:
Sponsor provided the data in an excel sheet. This is acceptable

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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MOHANRAJ MANANGEESWARAN
09/29/2017

DANIELA I VERTHELYI
09/29/2017

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Pediatric and Maternal Health
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-2200
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Division of Pediatric and Maternal Health Memorandum

Date: September 6, 2017 **Date consulted:** December 13, 2016

From: Jane Liedtka, M.D. Medical Officer, Maternal Health
Division of Pediatric and Maternal Health (DPMH)

Through: Miriam Dinatale, DO, Team Leader, Maternal Health
Division of Pediatric and Maternal Health

Lynne P. Yao, MD, OND, Director
Division of Pediatric and Maternal Health

To: Martin White, M.S., Regulatory Health Project Manager (RPM)
Division of Metabolic and Endocrine Products (DMEP)

Drug/NDA: Ozempic (semaglutide) injection NDA 209637

Applicant: Novo Nordisk Inc.

Subject: Pregnancy and Lactation Labeling

Indications:

- an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2DM)

(b) (4)

Materials Reviewed:

- Applicant's submitted background package for NDAs 209637.
- DPMH consult request dated December 13, 2016, DARRTS Reference ID 4026961.
- DPMH review of XULTOPHY (Insulin degludec and liraglutide) NDA 208583. Carol Kasten, MD, Medical Officer. September 28, 2016. DARRTS Reference ID 3989125.

- DPMH review of Ryzodeg 70/30 (insulin degludec and insulin aspart injection), NDA 203313. Jane Liedtka, MD, Medical Officer. November 14, 2016. DARRTS Reference ID 4012685.

Consult Question:

Please confirm PLLR format is acceptable.

INTRODUCTION

DMEP consulted DPMH on December 13, 2016, to provide input for appropriate labeling of the pregnancy and lactation subsections of NDA 209637 to comply with the Pregnancy and Lactation Labeling Rule (PLLR) format.

REGULATORY HISTORY

- On December 5, 2016, Novo Nordisk, Inc. submitted a new drug application (NDA) for a new molecular entity (NME) OZEMPIC (semaglutide) injection indicated as an adjunct to diet and exercise to improve glycemic control in adults with T2DM (b) (4)
- The Applicant proposes dosing as a subcutaneous once-weekly injection.
- The original submission included a review of the literature and a summary of the pharmacoviglance database regarding pregnancy, lactaion and effects on fertility.

BACKGROUND

Diabetes Mellitus and Pregnancy

See DPMH review of Ryzodeg 70/30[1] for details on this topic.

Semaglutide and Drug Characteristics[2]

- A glucagon-like peptide (GLP)-1 analogue with 94% sequence homology to human GLP-1 that selectively binds to and activates the GLP-1 receptor.
- GLP-1 is a physiological hormone that has multiple actions in regulating glucose (b) (4), mediated by the GLP-1 receptors.
- Semaglutide reduces blood glucose through a mechanism where it stimulates insulin secretion, lowers glucagon secretion (both in a glucose-dependent manner), reduces insulin resistance and delays gastric emptying.
- Semaglutide is structurally similar to liraglutide (Victoza and Saxenda) but modified to have a longer half-life suitable for once per week dosing.

[1] DPMH review of Ryzodeg 70/30 (insulin degludec and insulin aspart injection), NDA 203313. Jane Liedtka, MD, Medical Officer. November 14, 2016. DARRTS Reference ID 4012685.
[2] OZEMPIC proposed product labeling

- The principal mechanism of action resulting in the long half-life is albumin binding, which results in decreased renal clearance and protection from metabolic degradation.
- Molecular weight of ≈ 4 kilodaltons.
- Half-life of ≈ one week. Semaglutide will be present in the circulation for about 5 weeks after the last dose.
- Absolute bioavailability of 89%.
- Protein binding ≈ 99%.
- Most common adverse reactions, reported in ≥5% of patients are: nausea, vomiting, diarrhea, abdominal pain and constipation.

REVIEW

PREGNANCY

Nonclinical Experience

Semaglutide caused embryotoxicity in rats, comprising embryofetal mortality, structural abnormalities and alterations to growth at maternal exposures ≥ 0.4-fold the maximum recommended human dose (MRHD) of 1 mg/week, based on AUC. The effects were mediated by a GLP-1 receptor dependent mechanism which is considered unlikely to be relevant to humans. 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 ≥5-fold the MRHD (monkey). These findings coincided with a marked maternal body weight loss in both animal species.

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

Applicant's Review of Literature

The applicant conducted a "broad, multiple database literature search for published literature regarding semaglutide use in pregnant women". One published article on a nonclinical toxicology study was captured but is of "no relevance for semaglutide use in pregnant and lactating women or human fertility".

DPMH's Review of Literature

DPMH also conducted a review of PubMed, Embase, ReproTox[3], Shepard's and TERIS[4] for published literature regarding semaglutide and use in pregnancy. DPMH findings were similar to those of the applicant with no relevant publications identified. No relevant publications discussing class effects of glucagon-like peptide (GLP)-1 analogues were identified.

[3] Reprotox® Website: www.Reprotox.org. REPROTOX® system was developed as an adjunct information source for clinicians, scientists, and government agencies. Accessed June 22, 2017.
[4] TERIS database, Truven Health Analytics, Micromedex Solutions, Accessed June 22, 2016.

Summary of the Applicant's Pharmacovigilance Database

The Novo Nordisk safety database contains information up to the cut-off date April 18, 2016. Eight pregnancies were reported across the trials included in this summary (4 in subjects exposed to semaglutide, 4 in subjects exposed to comparator). Two additional pregnancies were reported in trials investigating semaglutide in other development programs where treatment is still blinded. The information available on those pregnancies is summarized in Table 1 below. No congenital abnormalities were reported in the babies born of women who had been exposed to semaglutide.

Table 1: Pregnancies Reported in the Semaglutide Development Programme and the Supportive NN9924-3790 Trial

Treatment	Subject ID	Age/Gender/ Country/BMI	Exposure to fetus (approximate weeks + day)[a]	Pregnancy outcome
Semaglutide				
Semaglutide 0.5 mg	NN9535-3627/327002	28/ F/ US/ 45.1	8+6	Healthy child
Semaglutide 1.0 mg	NN9535-3625/694001	29/ F/ US/ 43.1	5+0	Healthy child
Semaglutide 1.0 mg	NN9535-4091/139010	34/ F/ JP/ 28.8	6+6	Healthy child
Oral semaglutide 40 mg S	NN9924-3790/774006	29/ F/ US/ 35.1	7+2	Healthy child
Comparators				
Placebo	NN9535-3623/803009	33/ F/ ZA/ 40.4	9+0	Healthy child
Exenatide ER	NN9535-3624/450005	37/ F/ RS/ 44.7	5+1	Elective abortion
Insulin Glargine	NN9535-3625/705003	35/ F/ US/ 42.2	3+4	Healthy child
Placebo/moxifloxacin	NN9535-3652/104047	37/ F/ DE/ 22.7	No information	Elective abortion

Note: [a]Due to the long half-life of semaglutide, 5 weeks were added to the gestational exposure time for subjects treated with semaglutide.
Abbreviations: BMI: body mass index; F: female.

Cross-reference: ISS (M 5.3.5.3), Appendix 7.24

Source: Applicant's ISS pg. 263.

Summary

The limited available data with semaglutide in pregnant women are not sufficient to inform a drug-associated risk for adverse developmental outcomes. There are risks to the mother and the fetus associated with poorly controlled diabetes in pregnancy. Based on findings in animal studies, the following language [which has been included in labeling for other GLP-1 analogues such as Trulicity (dulaglutide), Victoza (liraglutide), Byetta (Exenatide), and Adlyxin (lixisenatide)] will be included in labeling for this product:

> …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.

The following background risk statement, derived from the currently available literature and composed by DPMH, has also been added to recent labels for products to treat DM:

> The estimated background risk of major birth defects is 6-10% in women with pre-gestational diabetes with a HbA1c >7 and has been reported to be as high as 20-25% in women with a HbA1c >10. (b) (4) 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.

In addition, the following Clinical Consideration has been included in section 8.1 of labeling for products used to treat DM:

> 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, stillbirth and delivery complications. Poorly controlled diabetes increases the fetal risk for major birth defects, stillbirth, and macrosomia related morbidity.

LACTATION

Nonclinical

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

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

Literature Review

The applicant did not identify any articles on semaglutide and lactation or breastfeeding in their literature search. DPMH also conducted a review of PubMed, Embase, ReproTox[7], MicroMedex[5], Shepard's and TERIS[8] and LactMed[6] for published literature regarding semaglutide and use in lactation. Semaglutide was not referenced in Hale[7], Briggs[8] or LactMed.[9]

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[5] Truven Health Analytics information, http://www micromedexsolutions.com/. Accessed 6/22/17.
[6] http://toxnet.nlm nih.gov/cgi-bin/sis/htmlgen?LACT. The LactMed database is a National Library of Medicine (NLM) database with information on drugs and lactation geared toward healthcare practitioners and nursing women. The LactMed database provides information when available on maternal levels in breast milk, infant blood levels, any potential effects in the breastfed infants if known, alternative drugs that can be

Summary

There are no studies on semaglutide and its presence in human milk, its effects on the breastfed child or its effects on milk production/excretion. Semaglutide was present in the milk of lactating rats; however, due to species-specific differences in lactation physiology, the clinical relevance of these data is not clear. Pharmacokinetic characteristics, such as high molecular weight (semaglutide = 4 kilodaltons) and high protein binding (99% protein bound), would predict that the transfer of the drug into milk is probably limited. Therefore, the following risk/benefit statement will be added to section 8.2:

> 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.

FEMALES AND MALES OF REPRODUCTIVE POTENTIAL

Nonclinical

In a 2-year carcinogenicity study in CD-1 mice, subcutaneous doses of 0.3, 1 and 3 mg/kg/day (5-, 17-, and 59-fold the maximum recommended human dose (MRHD) of 1 mg/week, based on AUC) was administered to the males, and 0.1, 0.3 and 1 mg/kg/day (2-, 5-, and 17-fold MRHD) was administered to the females. A statistically significant increase in thyroid C-cell adenomas and a numerical increase in C-cell carcinomas were observed in males and females at all dose levels.

In a 2-year carcinogenicity study in Sprague Dawley rats, subcutaneous doses of 0.0025, 0.01, 0.025 and 0.1 mg/kg/day were administered (below quantification, 0.4-, 1-, and 6-fold the exposure at the MRHD). A statistically significant increase in thyroid C-cell adenomas was observed in males and females at all dose levels, and a statistically significant increase in thyroid C-cell carcinomas was observed in males at ≥0.01 mg/kg/day (b) (4)

Human relevance of thyroid C-cell tumors in rats is unknown and could not be determined by clinical studies or nonclinical studies.

Semaglutide was not mutagenic or clastogenic in a standard battery of genotoxicity tests (bacterial mutagenicity (Ames), human lymphocyte chromosome aberration, rat bone marrow micronucleus).

In a combined fertility and embryo-fetal 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 male and

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considered and the American Academy of Pediatrics category indicating the level of compatibility of the drugwith breastfeeding. Accessed June 22, 2017.

[7] Hale, Thomas (2012) Medications and Mothers' Milk. Amarillo, Texas Hale Publishing.

[8] Briggs, GG. Freeman, RK. & Yaffe, SJ. (2015). Drugs in pregnancy and lactation: a reference guide to fetal and neonatal risk. Philadelphia, Pa, Lippincott Williams & Wilkins.

female rats. Males were dosed for 4 weeks prior to mating, and females were dosed for 2 weeks prior to mating and throughout organogenesis until Gestation Day 17. No effects were observed on male fertility. In females, an increase in estrus cycle length was observed at all dose levels, together with a small reduction in numbers of corpora lutea at ≥0.03 mg/kg/day. These effects were likely an adaptive response secondary to the pharmacological effect of semaglutide on food consumption and body weight.

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

Review of Literature

In addition to the applicant's search of published literature for information regarding insulin aspart and fertility, DPMH also conducted a review of published literature in PubMed and Embase to evaluate the use of semaglutide and its effects on fertility. No relevant publications were found in either search.

The Applicant has proposed a recommendation for contraception to be included in Highlights and Section 8.3 as follows:

·····USE IN SPECIFIC POPULATIONS·····

- Females and Males of Reproductive Potential: (b) (4) discontinue OZEMPIC at least 2 months before a planned pregnancy due to the long washout period for semaglutide (8.3).

8.3 Females and Males of Reproductive Potential

(b) (4) discontinue OZEMPIC at least 2 months before a planned pregnancy due to the long washout period for semaglutide.

Reviewer's Comment:

Recent PLLR conversions for other GLP-1 analogues (lixisenatide and dulaglutide) do not include a recommendation for contraception despite similar nonclinical findings. These labels do include a reminder to prescribers that the drug should be discontinued two months before a planned pregnancy. DMPH recommends aligning the label for semaglutide with the other recently approved GLP-1 analogues. This would include the following statement in Highlights and Section 8 " Women should discontinue OZEMPIC at least 2 months before a planned pregnancy due to the long washout period for semaglutide".

Summary

No significant safety information was identified concerning fertility disorders in male and female subjects of reproductive potential associated with semaglutide use in the semaglutide development program. The following statement will be included in Section 8.3:

Women should discontinue OZEMPIC at least 2 months before a planned pregnancy due to the long washout period for semaglutide.

CONCLUSIONS

The OZEMPIC label has been updated to comply with the PLLR. DPMH has the following recommendations for labeling:

- **Pregnancy, Section 8.1**
  - The "Pregnancy" subsection of was formatted in the PLLR format to include: "Risk Summary," "Clinical Considerations," and "Data" sections[9].
- **Lactation, Section 8.2**
  - The "Lactation" subsection of labeling was formatted in the PLLR format to include: the "Risk Summary" section.[10]
- **Females and Males of Reproductive Potential, Section 8.3**
  - The "Females and Males of Reproductive Potential" subsection of labeling was formatted in the PLLR format to include the statement "Women should discontinue OZEMPIC at least 2 months before a planned pregnancy due to the long washout period for semaglutide". [11]
- **Patient Counseling Information, Section 17**
  - The "Patient Counseling Information" section of labeling was updated to correspond with changes made to sections 8.1 and 8.3 of labeling.

RECOMMENDATIONS

DPMH revised the HPI and sections 8.1, 8.2, and 8.3 of labeling for compliance with the PLLR (see below). DPMH refers to the final NDA action for final labeling.

[9] Guidance for Industry: Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products-Content and Format. December 2014. Part IV Specific Subsection A-8.1 Pregnancy, 2-Risk Summary.
[10] Guidance for Industry: Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products-Content and Format. December 2014. Part IV Specific Subsection, B- 8.2 Lactation, 1-Risk Summary.
[11] Guidance for Industry: Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products-Content and Format. December 2014. Part IV Specific Subsection, C-8.3 Females and Males of Reproductive Potential.

DPMH Proposed OZEMPIC (semaglutide) Pregnancy and Lactation Labeling

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

(b) (4)

FULL PRESCRIBING INFORMATION

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are limited data with semaglutide 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 (b) (4) the maximum recommended human dose (MRHD) based on AUC. (b) (4) In rabbits and cynomolgus monkeys, early pregnancy losses and structural abnormalities, (b) (4) 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 (b) (4) is 6 to 10%. (b) (4) 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 ana (b) (4) *fetal risk*

Poorly controlled diabetes in pregnancy increases the maternal risk for diabetic ketoacidosis, pre-eclampsia, spontaneous abortions, preterm delivery, stillbirth 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 (0.1-, 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 and skeletal abnormalities were observed (b) (4)

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 from Gestation Day 6 (b) (4) 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 and skeletal fetal abnormalities were observed at ≥0.0025 mg/kg/day.

In (b) (4) embryofetal development study in 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 at ≥0.075 mg/kg twice weekly.

In a pre- and postnatal development study in 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.

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

(b) (4) discontinue OZEMPIC at least 2 months before a planned pregnancy due to the long washout period for semaglutide.

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)]*.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JANE E LIEDTKA
09/06/2017

MIRIAM C DINATALE
09/06/2017

LYNNE P YAO
09/12/2017

OFFICE OF DEVICE EVALUATION

DIVISION OF ANESTHESIOLOGY, GENERAL HOSPITAL,
RESPIRATORY, INFECTION CONTROL, AND DENTAL DEVICES

GENERAL HOSPITAL DEVICES BRANCH

INTERCENTER CONSULT MEMORANDUM

Date	August 28, 2017
To	Peter Franks, Regulatory Project Manager OMPT/CDER/OND/ODEII/DMEP
Requesting Division	DMEP
From	Sarah Mollo CDRH/ODE/DAGRRID/GHDB
Through (Team Lead)	Carolyn Cochenour, ICC Team Lead CDRH/ODE/DAGRRID/GHDB
Through (Branch Chief)	CDR Alan Stevens CDRH/ODE/DAGRID/GHDB
Subject	Consult for Submission: NDA 209637; ICC1600857
Recommendation	The device is approvable based on the design and performance review of the device constituent of the combination product

Digital Signature Concurrence Table		
Reviewer	Sarah B. Mollo -S	Digitally signed by Sarah B. Mollo -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Sarah B. Mollo -S, 0.9.2342.19200300.100.1.1=2001712033 Date: 2017.08.29 10:48:26 -04'00'
Team Lead	Carolyn C. Dorgan -S	Digitally signed by Carolyn C. Dorgan -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2001800814, cn=Carolyn C. Dorgan -S Date: 2017.08.29 10:48:26 -04'00'
Branch Chief	Alan M. Stevens -S	Digitally signed by Alan M. Stevens -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300189211, cn=Alan M. Stevens -S Date: 2017.08.29 12:55:52 -04'00'

1. Submission Overview

Table 1. Submission Information	
ICCR # (Lead)	ICC1600857
ICCR SharePoint Link	
ICC tracking # (Lead)	
Submission Number	NDA 209637
Sponsor	Novo Nordisk Inc.
Drug/Biologic	Semaglutide
Indications for Use	• an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (b) (4) [redacted]
Device Constituent	PDS290 pen-injector
Related Files	n/a

Table 2. Review Team				
CDER/CBER Lead Review Division	DMEP			
Submission RPM	Peter Franks			
Lead Device Reviewer	Sarah Mollo			
The CDRH review is being managed under ICC #: ICC1600857				
Below is a list of the Discipline Specific ICCR#, ICC# and CON#. The CON# are under ICC1600857 in CTS.				
Discipline Specific Consults	**Reviewer Name (Center/Office/Division/Branch)**	**ICCR #**	**ICC #**	**CON #**
n/a				

Table 3. Important Dates		
Final Lead Device Review Memo Due	September 5, 2017	
Interim Due Dates	**Meeting Date**	**Due Date**
Filing		
74-Day Letter		
Mid-Cycle	May 10, 2017	
Primary Review	September 5, 2017	
Internal Meeting		
Safety Meeting		
Sponsor Meeting		
Late Cycle Communication Meeting	September 19, 2017	

Advisory Committee Meeting	October, 18, 2017	
Other		

TABLE OF CONTENTS

2. PURPOSE/BACKGROUND

2.1. Scope

The sharepoint consult requested the following:

The drug product is a sterile solution for SC injection, packaged in pen injectors. A consult is requested for an evaluation of the device.

The combination product being reviewed is a pre-filled pen-injector for Semaglutide (OZEMPIC).

The recommended starting dose of OZEMPIC is 0.25 mg once weekly. OZEMPIC 0.25 mg is not a therapeutic dose. After 4 weeks, the dose should be increased to 0.5 mg once weekly. After 4 weeks, the dose may be increased to 1 mg once weekly to further improve glycemic control. The maximum recommended dose is 1 mg once weekly.

This review covered the following review content for the pen-injector constituent of the combination product:

- Inspection of sponsor's design input activities
- Inspection of sponsor's design verification activities
- Confirmation of standards conformance, where relied upon
- Inspection of test methods and results of bench top testing completed
- Inspection of stability testing completed on the device constituent part

This review **did not** cover the following content:

- Review of drug product
- Review of primary container closure-drug product interaction, sterility, or toxicology
- Manufacturing of the drug product
- Manufacturing of the device constituent part of the combination product
- Design input, verification testing, or biocompatibility of the pumps that were used for the clinical trial

2.2. Indications for Use

Product	Indications for Use
semaglutide	• an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus

2.3. Device Constituent

Device Name	Proposed Indications for Use
PDS290 pen-injector	See above for the Indications for Use for the combination product. The PDS290 pen-injector for semaglutide 1.34 mg/ml is intended to be used for a once weekly ubcutaneous injection of the glucagon-like-peptide-1 (GLP-1) analogue semaglutide. Semaglutide is intended for the treatment of Type 2 Diabetes Mellitus (T2DM) in adults (b) (4) .

3. ADMINISTRATIVE

3.1. Documents Reviewed

Document Title	Document Number	Date - Version	Location
Reviewer's Guide for 3.2.P.7-container Closure and Device Documenation		09 September 2016 Version: 1.0	Seq.0001; 3.2.P.7
Essential Device Performance and Safety Requirements (0.25 mg/0.5 mg/1.0 mg) and (1.0 mg)	novoDOCS ID 002981942	24 October 2016 Version: 1.0	Seq.0001; 3.2.P.7
PDS290 Pen-injector for Semaglutide 1.34 mg_ml - Technical Description	novoDOCS ID 002562348	05 April 2016	Seq.0001; 3.2.P.7
PDS290 Pen-injector for Semaglutide 1.34 mg_ml - Materials	novoDOCS ID 002561712	14 December 2015	Seq.0001; 3.2.P.7
PDS290 Pen-injector for Semaglutide 1.34 mg_ml - Comparison to other PDS290 Pen-injectors	novoDOCS ID 002562150	01 September 2016	Seq.0001; 3.2.P.7
Proposed Instructions for Use 0.25-0.5-1 mg Pen	Draft under seq 0000	Draft under seq 0000	Seq. 0001, 1.14 labeling;
Extract of Verification Reports for PDS290 Pen-injector for Semaglutide 1.34 mg/ml (0.25 mg/0.5 mg/1.0 mg)	novoDOCS ID 002972619	02 September 2016	Seq.0001; 3.2.P.7
Validation of Device Use – Human Factors Engineering/Usability Evaluation Report (UT179)	novoDOCS ID: 002976117	17 October 2016	Seq.0001; 3.2.P.7
Semaglutide Stability Summary and Conclusion	novoDOCS ID 002918401	08 September 2016	Seq.0001; 3.2.P.8.1
Primary Stability Data for Semaglutide 1.34	novoDOCS ID 002752960		

mg/ml Solution for Injection Up to 36 Months at 5°C, 6 Months at 25°C (Interim Report)			
PDS290 Pen-injector for Semaglutide 1.34 mg/ml(0.25 mg/0.5 mg) Summary of Comparison to the PDS290 Pen-injector for Semaglutide 1.34 mg/ml (0.25 mg/0.5 mg/1.0 mg)	novoDOCS ID 003664075	09 August 2017	Seq.0035; 1.11.1
PDS290 Pen-injector for Semaglutide 1.34 mg/ml (0.25 mg/0.5 mg) Dose Accuracy Data	novoDOCS ID 003691177	03 August 2017	Seq.0035; 3.2.P.7
PDS290 Pen-injector for Semaglutide 1.34 mg/ml (0.25 mg/0.5 mg) Test Report According to ISO 11608-1 - Needle Based Injection Systems for Medical Use	novoDOCS ID 003711642	11 August 2017	Seq.0035; 3.2.P.7
PDS290 Pen-injector for semaglutide 1.34 mg/ml (0.25 mg/0.5 mg) PDS290 Pen-injector for semaglutide 1.34 mg/ml (1.0 mg) Specification(s)	novoDOCS ID 002936134	10 August 2017	Seq.0035; 3.2.P.5.1
Semaglutide Justification of Specification	novoDOCS ID 003499580	30 June 2017	Seq.0035; 3.2.P.5.6

3.2. CDRH Review Team

Team Member	Role	Deficiencies
Sarah Mollo CDRH/ODE/DAGRID/GHDB	Lead Reviewer	
Xin Feng	Consultant – Human Factors	**Human factors recommendation:** Human Factors data is adequate to

		demonstrate that the user interface of the subject combination product supports safe and effective use. **No deficiencies were identified.**

DMEPA consulted CDRH/Human Factors to review the human factors validation study under a separate ICC (ICC1700100). Xin Feng was consulted and provided a review. His review memo was sent separately to DMEMPA as they requested his consult.

4. DEVICE DESCRIPTION AND PERFORMANCE REQUIREMENTS

The PDS290 pen-injector for semaglutide 1.34 mg/ml is intended to be used for a once weekly subcutaneous injection of the glucagon-like-peptide-1 (GLP-1) analogue semaglutide. Semaglutide is intended for the treatment of Type 2 Diabetes Mellitus (T2DM) in adults (b) (4)

The PDS290 pen-injector for semaglutide 1.34 mg/ml has two variants, both containing semaglutide 1.34 mg/ml solution for injection filled in a 1.5 ml cartridge. There is no direct contact between the PDS290 pen-injector and the product. The two variants of the PDS290 pen-injector for semaglutide 1.34 mg/ml are as follows:

- PDS290 pen-injector for semaglutide 1.34 mg/ml (0.25 mg/0.5 mg), which can deliver doses of 0.25 mg or 0.5 mg
- PDS290 pen-injector for semaglutide 1.34 mg/ml (1.0 mg), which can only deliver doses of 1.0 mg

The difference between the two variants of the PDS290 pen-injector for semaglutide 1.34 mg/ml is limited to the imprint on the scale drum.

When the term PDS290 pen-injector for semaglutide 1.34 mg/ml is used in the module 2.3 and 3 documentation, both of the variants above are covered.

The following images were located in section 1 of the pen-injector, technical description document under 3.2.P.7:

Figure 1 PDS290 pen-injector for semaglutide 1.34 mg/ml

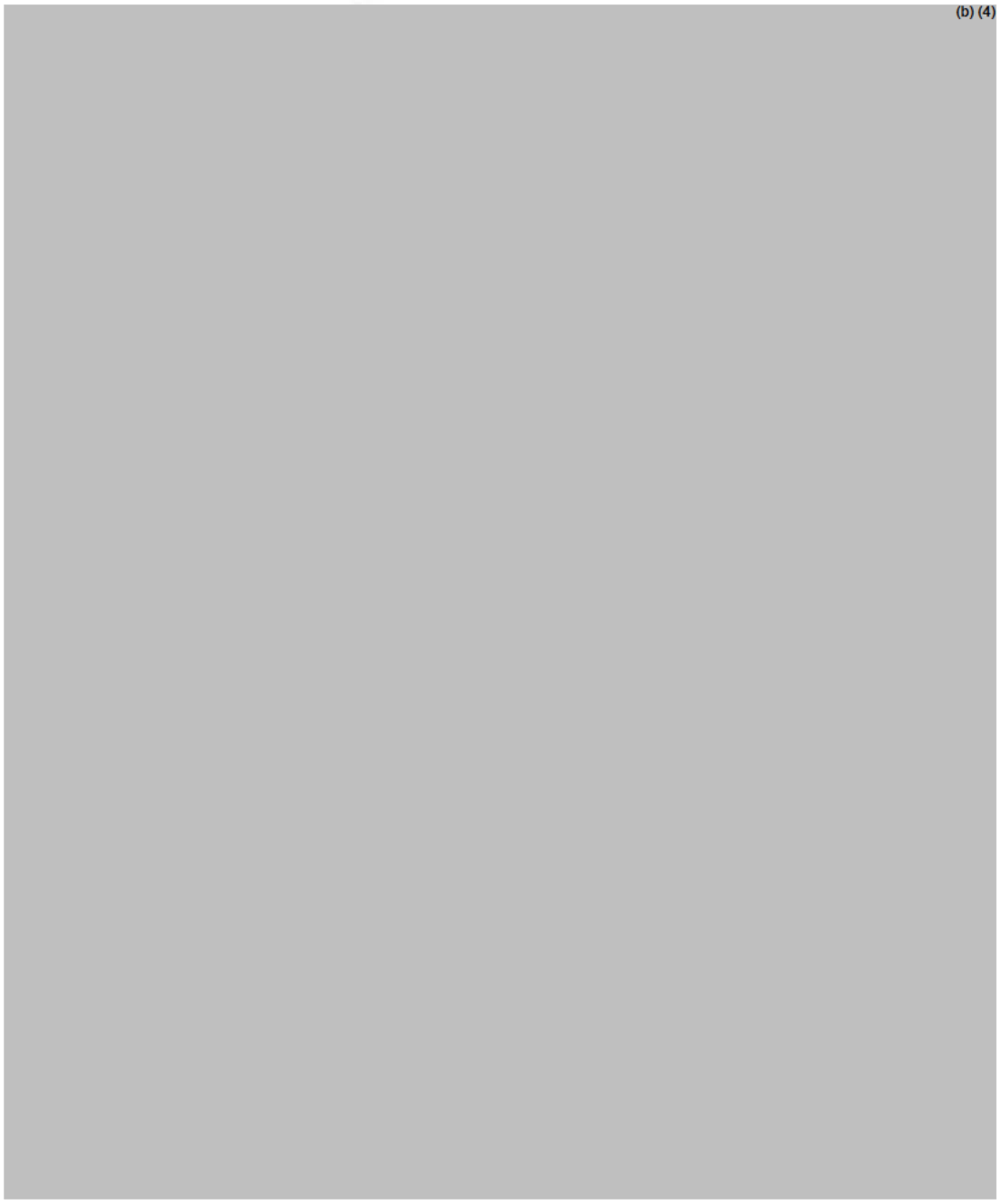


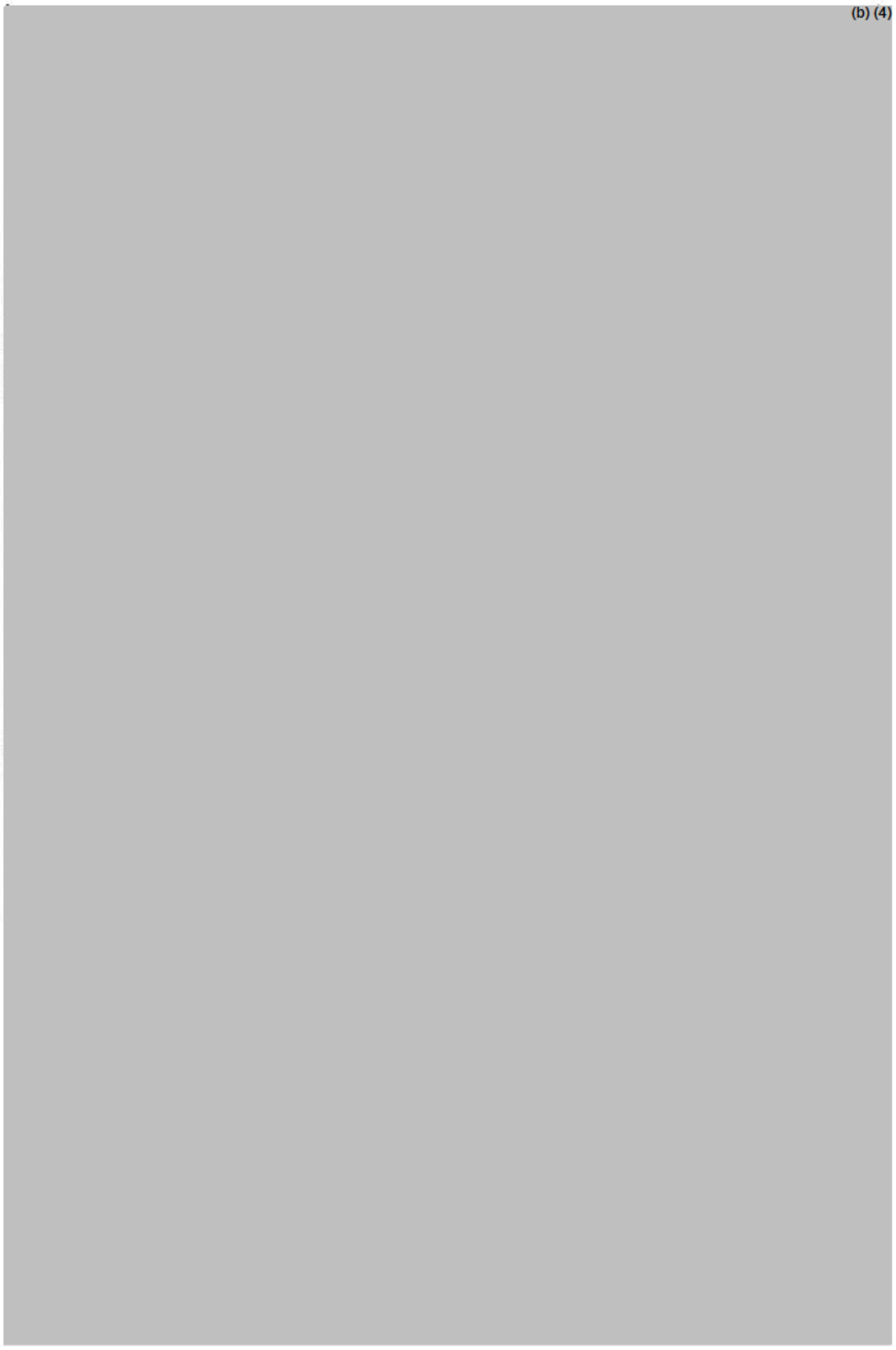
Figure 2 Exploded view of the PDS290 pen-injector for semaglutide 1.34 mg/ml not shown in true colours (the injection needle (19) is not part of the pen-injector but is needed in order to make an injection).

The following information is located in the Annotated Draft Labeling Text Under 1.14.1.2 in Seq. 0001:

ANNOTATED DRAFT PACKAGE INSERT

(b) (4)

(b) (4)



Reviewer Comment

On August 14, 2017, the sponsor provided information to support the chang from a 0.25 mg/0.5 mg/1.0 mg pen to a 0.25 mg/0.5 mg pen. Therefore, the two marketed pens will be 0.25 mg/0.5 mg and 1.0 mg.

For more information on this change and the supporting information, please refer to **section 12** of this memo.

Summary of Steps for Use of Combination Product (for full instructions, see labeling section):

1. Prepare your pen with a new needle
    a. check that drug is clear and colorless or almost colorless
b. pull off outer and inner pen caps
2. Check the flow with each new pen (priming step).
    a. turn does selector to flow check symbol
    b. hold the pen with the needle pointing up.
    c. press and hold the dose button until the dose counter shows 0.
    d. look for a drop of drug at tip
    e. repeat above steps up to 6 times if no drop occurs.
    f. if no drop, do not use pen

3. select dose
    a. turn dose selector until it shows dose (0.25 mg, 0.5 mg, or 1 mg)
    b. You will hear a click every time you turn the dose selector. **Do not set the dose by counting the number of clicks you hear**
    c. You can select up to 1 mg for each dose. When your pen contains less than 1 mg, the dose counter stops before 1 mg is shown

4. inject dose
    a. Choose your injection site and wipe the skin with an alcohol swab. Let site dry
    b. insert needle into skin
    c. press and hold down button until dose counter says 0
    d. keep needle in skin after dose counter has reached 0 and count slowly to 6
    e. remove needle

5. after injection
    a. remove needle from pen
    b. dispose of needle in sharps container
    c. put the outer cap only on to needle

Device Characteristic	Description / Specification
Injector Name	PDS290 pen-injector
Injector Platform Name	PDS290 pen-injector
Priming Dose / Volume	The instructions for use direct the user to turn dose selector to the flow check symbol (⋯) In comparison to other PDS290 document-priming steps states, *"2 increments (to Flow check symbol)"*

Dose accuracy	Dose accuracy after the test at Cool conditions, Normal conditions with Flow Check, Normal conditions without Flow Check, Warm conditions: 0.25 mg: (b) (4) 0.5 mg: (b) (4) 1.0 mg: (b) (4) There is a specification for maximum dose (b) (4) The essential performance and safety requirements document states the following: *The Design Verification test of the PDS290 semaglutide pen-injector (0.25 mg/0.5 mg/1.0 mg) complies with the Dose accuracy acceptance criteria according to ISO 11608-1.Furthermore, the PDS290 semaglutide pen-injector (0.25 mg/0.5 mg/1.0 mg) meets the specifications for total content of the pen-injector, Dose accuracy of last dose, Dose accuracy after free fall and vibration pre-conditioning and visual inspection according to ISO 11608-1.*
Injection Time	(b) (4)
Injection Site	subcutaneous tissue of the abdominal wall, thigh, or upper arm
Injection tissue and depth of injection	-Subcutaneous -depth is based on needle, labeling indicates that 4 NovoFine Plus needles are included with (b) (4) Carton of 2 Pens (1 mg) -sponsor provided document- Validation of Depth

	and Route of Injection with the following conclusion: *Based upon the literature data presented above, and the substantial clinical effect achieved in the semaglutide clinical programme, which utilised the PDS290 pen-injector for semaglutide 1.34 mg/ml and needles with a length of up to 8 mm, it is concluded that semaglutide is deposited into the intended subcutaneous tissue at a sufficient injection depth, when the injection recommendations are followed. Therefore, the injection depth and route of injection are considered validated.* There is a functional requirement in the essential device performance requirements that lists: *Compatibility with (b) (4) and NovoFine® (b) (4) x 8mm or shorter)* **Reviewer Comment** Looking at the cleared 510(k)s of NovoFine and (b) (4), the needles appear to come only in lengths of 4mm – 8 mm
Audible / visual feedback	Acceptance Criteria of device requirement: • During the dose setting and resetting sequence, the clicks should be audible • During the injection phase, the clicks should be audible • At the end of the injection phase, a distinct click should be audible There is an end of dose click. When click occurs and dose is set to "0", the user is directed to count to 6 seconds to ensure the entire dose is delivered. The sponsor states (in the technical document) that, "*This feature compensates for the lack of a moving dose button during injection such as in the currently approved FlexPen® and other manual injection devices.*" In the instructions for use the user is told that the pen clicks every time the dose selector is turned, but not to count the clicks. The user is instructed to use the dose counter and pointer to select the dose and to determine that the dose has been completely administered. • *Press and hold down the dose button until the dose counter shows 0.* • *The 0 must line up with the dose pointer.*

	You may then hear or feel a click. • *Keep the needle in your skin after the dose counter has returned to 0 and count slowly to 6.* • *If the needle is removed earlier, you may see a stream of Ozempic coming from the needle tip. If this happens, the full dose will not be delivered.*
Force to pull off cap and to put on cap during use	Removal cap: (b) (4) N Put on cap: Max (b) (4) N
Dose button activation	Pen-injector- n/a; however, essential performance requirements include: Activation force: Min: (b) (4) Max N Activation travel: Min: (b) (4) mm Max: mm
Visibility of medication container	The cartridge is made from glass, rubber, and aluminum. The cartridge holder has a visability window through which the glass cartridge is visible. In the instructions for use the user is instructed to: *Check that Ozempic in your pen is clear, colorless or almost colorless.*
Last Dose Specifications and Safety Features	The dose counter is designed to only allow the user to select a dose if sufficient volume is left. Therefore, if the pen has less than the desired next dose, there dose counter will not reach that dose. The following information on the last dose is in the instructions for use: *You can select (b) (4) 1 mg for each dose. When your pen contains less than 1 mg, the dose counter stops before 1 mg is shown.* ***To see how much Ozempic is left in your pen,*** *use the dose counter:* *Turn the dose selector until the* ***dose counter***

	stops. *If it shows 1, **at least 1 mg** is left in your pen. If the **dose counter stops before 1 mg,** there is not enough Ozempic left for a full dose of 1 mg.* *If there is not enough Ozempic left in your pen for a full dose, do not use it. Use a new Ozempic pen.*
Needle Specifications • Length(s) • Gauge(s) • Connection type o ISO 11608-2:2012 o Prestaked	• Length(s)- 8 mm • Gauge(s)- (b) (4) • Connection type- o ISO 11608-2:2012 o **Reviewer Comment**: The NDA does not state that the needles have been tested according to ISO 11608-2. However, the labeling calls out NovoFine Plus needles, which have been tested according to ***EN ISO 11608-2:2012 Needle-based injection systems for medical use - Requirements and test methods -- Part 2: Needles.*** Additionally, the sponsor has included a Functional Requirement in essential performance requirements document: *NovoFine® (b) (4) mounting and unmounting requirements*
Type of Use (e.g. single use, disposable, reusable, other)	disposable
Intended user (e.g., self-administration, professional use, user characteristics and / or disease state that impact device use)	self-injection by the patients
Injection mechanism (e.g., manual piston, spring, gas, etc.)	Manual (b) (4)
Method of actuation	*To deliver a set dose, the dose button is pushed by the user. (b) (4) Now the dial mechanism returns to "zero" (b) (4) leading to a dosage.*

	It is possible to stop/start a dose at any time by releasing/pushing the dose button during injection.
Automated Functions	none
Residual Medication	In response to an IR request for residual volume on April 21, 2017, the sponsor stated the following: *To ensure that the specified numbers of doses are always available in a new pen-injector, tolerance calculations have required that a minor additional volume is available in the pen-injector. On the basis of these calculations, the additional volume will, in the worst case and without medical consequences, be* [redacted] (b) (4) *, but typically only* [redacted] (b) (4) *This additional volume of up to* [redacted] (b) (4) *is, as described, included to accommodate tolerance variations within the components of the pen-injector and is not part of the intended use. Based on this, Novo Nordisk considers that a specification for residual volume is not required.* The sponsor has adequate mitigations in place to ensure that the patient can administer the specified amount of doses. A residual volume requirement is not necessary for the device constituent.
Delivered Volume (for single dose or selectable volume range for multidose pens)	<u>Dosing</u> [redacted] (b) (4) [redacted] (b) (4) 1 mg <u>Specification for extractable volume</u> Min of [redacted] (b) (4) ml can be extracted from the cartridge Total content: min. [redacted] (b) (4) increments (after flow check has been performed) The user should be able to get 2 (1 mg) doses, 4 (.5 mg) doses, or 8 (.25 mg) doses. **Please note**:

	The 0.25 mg dose is not considered to be therapeutic. It is the starting dose.
Drug Container Type	The cartridge 1.5 ml consists of the following components: 1. A cartridge 1.5 ml made of type I glass, colourless. 2. A rubber plunger made of (b) (4) rubber (rubber plunger grey). 3. A laminate rubber disc (primary packaging) inserted in an aluminium cap (secondary packaging). The rubber disc is made of (b) (4) (b) (4) rubber. The (b) (4) rubber is in direct contact with the drug product.
Dose Units of Measure (e.g., mL, Units, mg, increments, etc.)	mg The user is instructed to choose 0.25 mg, 0.5 mg, or 1.0 mg. The increments in between these doses are labeled as (-)/

Environments of use	The device can be used in a non-sterile environment.
	
	The human factors validation report contained the following information on the intended users and use environments:
	The intended users of the pen-injector are described below:
	• *Patients (with T2DM)*
	  ○ *Adults (age 18-64) who are able to perform their own injections*
	  ○ *Elderly adults (age 65 and above) who are able to perform their own injections and who may have various impairments, e.g. limited vision, hearing, dexterity, but are still able to perform their own injections, e.g. when using their own individually corrected hearing- and vision-impairment accessories*
	• *Caregivers (e.g. spouses, adult offspring) who are not clinicians, but provide care for someone who is ill or disabled*
	• *HCPs, who treat patients with diabetes, teach others how to perform injections, and/or dispense drug:*
	  ○ *Pharmacists who dispense drug products*
	  ○ *Physicians (e.g. Primary Care Practitioners (PCPs), endocrinologists, diabetes*

	specialists) and physician office staff (e.g. physician assistants and nurse practitioners), who treat patients with diabetes, and/or teach others how to perform injections o *Nurses (e.g. In-patients nurses, Registered Nurses (RN), Diabetes nurses)* o *Certified Diabetes Educators (CDEs) who help patients manage their diabetes, and are likely to train patients in the use of pen-injectors, either in an office or at a home visit* *Where to use* • *Primary use - for self-treatment, in a home environment* • *Secondary use - for healthcare facility*
Storage conditions and expiry	Shelf-life: 36 months (based on drug) The following directions regarding storage are in the instructions for use: • Store your **new, unused** Ozempic pens in the refrigerator at 36°F to 46°F (2°C to 8°C). • **Store your pen in use** for (b) (4) below 86°F (30°C) or in a refrigerator at 36°F to 46°F (2°C to 8°C).
Graduation marks / fill lines	Cartridge has a scale printed onto it, which is intended to aid the user in determining the number of units remaining within the device • 0.25, .5, and 1.0 are printed on the scale drum • Increments in between are marked by "-"
Preparation and administration (describe all that are applicable) • Warm to room temp prior to injection • Assembling components • Prime steps • Setting dose • Skin preparation	See instruction section above and labeling section below.

steps (e.g., pinch skin, inject through clothing, etc.) • Changing / disposing needles • Etc.	
Safety Features • Needle safety	a pen cap is incorporated as part of the pen system
Electronics / Data transmission • Display • Control functions • Data transmission technology • Data being transferred	n/a
Material composition of injector	The plastic components (1, 3, 4, 5, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16 and 17) in the PDS290 peninjector for semaglutide 1.34 mg/ml are made from the following materials: (b) (4) [redacted] The 1.5 ml cartridge (18) is made from glass, rubber and aluminium.

5. CLINICAL DEVELOPMENT

5.1. Current Study Summary

5.1.1. Specific Study Issues

The Dose accuracy of the peninjector at end of shelf life was conducted on the PDS290 peninjector for semaglutide used in the phase 3a clinical trial program which is considered representative for the PDS290 pen-injector for semaglutide 1.34 mg/ml (0.25 mg/0.5 mg/1.0 mg)

The sponsor has provided a comparison to other PDS290 Pen-injectors document which includes a comparison of the to-be marketed pen for semaglutide and the pen-injector used for semaglutide in the phase 3a clinical trial program.

Feature	PDS290 pen-injector for semaglutide 1.34 mg/ml	PDS290 pen-injector for semaglutide used in the phase 3a clinical trial program
Length with cap (approximately)	138 mm	156 mm
Diameter (approximately)	19 mm	19 mm
Weight excluding cartridge (approximately)	27 g	29 g[1]
Dose accuracy specification	ISO 11608-1	ISO 11608-1
Activation force	(b) (4)	N
Dose button extension at maximum dose size	0 mm	0 mm
Dose increment	(b) (4)	
Maximum dose		
Priming steps		

Feature	PDS290 pen-injector for semaglutide 1.34 mg/ml	PDS290 pen-injector for semaglutide used in the phase 3a clinical trial program
Number of components (needle and cartridge excluded)	(b) (4)	
Basic pen colour		
Cartridge holder colour		
Dose button colour		
Materials (needle and cartridge excluded)		
Click during dose setting	Yes	Yes
Click during dosing	Yes	Yes
Click at end of dose	Yes	Yes
Dials back to zero during injection	Yes	Yes
Dose accuracy	ISO 11608-1	ISO 11608-1
Intended use	Intended for once weekly subcutaneous injection of semaglutide	Intended for once weekly subcutaneous injection of semaglutide

Feature	PDS290 pen-injector for semaglutide 1.34 mg/ml	PDS290 pen-injector for semaglutide used in the phase 3a clinical trial program
Indications for use	Incorporates a design containing a 1.5 ml cartridge to assist in the subcutaneous injection of semaglutide drug product for the treatment of adults with type 2 diabetes mellitus	Incorporates a design containing a 1.5 ml cartridge to assist in the subcutaneous injection of semaglutide drug product for the treatment of adults with type 2 diabetes mellitus
Product type	Pre-filled, multiple-dose, disposable pen containing a 1.5 ml cartridge with semaglutide	Pre-filled, multiple-dose, disposable pen containing a 1.5 ml cartridge with semaglutide
Target population/age group	Adult	Adult
Biocompatibility	ISO 10993-1 Only contact with intact skin during handling	ISO 10993-1 Only contact with intact skin during handling
Anatomical sites for injection	As recommended in the Physician Insert	As recommended in the Physician Insert
Where used	Home or in hospital	Home or in hospital
Energy used and/or delivered	Manual	Manual
Human factors	Needle attachment needed before injection	Needle attachment needed before injection

Feature	PDS290 pen-injector for semaglutide 1.34 mg/ml	PDS290 pen-injector for semaglutide used in the phase 3a clinical trial program
Performance test	Dose accuracy test Function test Physical stress test	Dose accuracy test Function test Physical stress test
Standards met	ISO 11608-1	ISO 11608-1
Sterility	N/A	N/A
Mechanical safety	N/A	N/A

The PDS290 pen-injector for semaglutide is a prefilled pen integrated with a 1.5 mL cartridge containing semaglutide 1.34 mg/mL and is designed to be used with NovoFine®, NovoFine®Plus and (b) (4) *disposable needles. For the present trial, the PDS290 pen-injector was supplie with NovoFine® needles.*

6. DESIGN CONTROL REVIEW

6.1. Design Review Summary

6.1.1. Design Control Documentation Check

Design Control Requirement*	Signed/Dated Document Present		Submission Location
	Yes	No	

Design Requirements Specifications included in the NDA / BLA by the Combination Product Developer	X		
Design Verification Data included in the NDA / BLA or adequately cross-referenced to a master file.	X		
Risk Analysis supplied in the NDA / BLA by the Combination Product Developer	X		
Validation Data • Human factors • Clinical data	X X		
Traceability Documentation	X		

6.1.2. Design Control Review

7. DESIGN VERIFICATION AND VALIDATION REVIEW

7.1. Summary of Design V&V Attributes

Design Verification / Validation Attributes	Yes	No	N/A
Validation of essential requirements covered by clinical and human factors testing	X		
To-be-marketed device was used in the pivotal clinical trial	X (see section 5.1)		
Verification methods relevant to specific use conditions as described in design documents and labeling	X		
Device reliability is acceptable to support the indications for use (i.e. emergency use combination product may require separate reliability study)			
Traceability demonstrated for specifications to performance data	X		

Discipline -Specific Design Verification / Validation adequately addressed*						
	Consult needed			Consultant	Attributes Acceptable	
	Yes	No	N/A		Yes	No
Engineering (Materials, Mechanical, General)		X			X	
Biocompatibility		X			X	
Sterility			X		n/a	
Software / Cybersecurity			X		n/a	
Electrical Safety / EMC			X		n/a	
Human Factors	X			Xin Feng	X	

7.2. Design Validation Review

Design Validation Attributes	Yes	No	N/A
Phase I/II/III Study utilized the to-be-marketed device	X (see section 5.1)		

7.2.1. Prior Clinical Studies

PDS290 pen-injector for semaglutide used in the phase 3a clinical trial programme

The PDS290 pen-injector for semaglutide has been used in 8 clinical pharmacology trials and 8 phase 3a trials (listed in Table 1-1). For trial design, see Module 5.2 Tabular Listing of All Clinical Studies.

In Trial 3626, 1 adverse event (AE) in 1 subject with semaglutide 0.5 mg was reported as being related to a technical complaint (injection site pain). The AE was non-serious, of mild severity and was considered a medical event of special interest (MESI). Upon inspection, the pen-injector was found to be normal functioning (Table 1-1 and Trial 3626 [M 5.3.5.1], Sections 12.3.2.4 and 12.6.8.4).

Table 1–1 Clinical trials using the PDS290 pen-injector for semaglutide

Trial ID	Number of subjects randomized	Number of subjects exposed to the PDS290 pen-injector		Number of AEs related to a PDS290 pen-injector technical complaint	
		Semaglutide	Placebo[a]	Semaglutide	Placebo
Clinical pharmacology trials					
3634	44	32	12	0	0
3635	75	37	38	0	0
3651	44[b]	44	0	0	0
3652	168	83	83	0	0
3684	38	38	38	0	0
3685	30	30	30	0	0
3817	24[b]	24	0	0	0
3818	31[b]	31	0	0	0
Phase 3a trials					
3623	388	258	129	0	0
3624	813	404	0	0	0
3625	1089	722	0	0	0
3626	1231	818	407	1	0
3627	397	263	133	0	0
3744	3297	1642	1644	0	0
4091	601	480	0	0	0
4092	308	205	0	0	0

Notes: [a]Subjects exposed to a test pen are not included; [b]Non-randomized trial and number refers to number of subjects exposed to trial products.
Abbreviation: AE: adverse event.

<u>Usability</u>

Xin Feng, at the request of DMEPA performed a review of the Human Factors study on differentiation. Xin Feng found that "*the data is adequate to demonstrate that the user interface of the subject combination product supports safe and effective use*". However, during my review of the essential performance requirements, I had questions/concerns regarding usability and after speaking with Xin and the DMEPA reviewer, Ariane Conrad. I sent the following IRs on April 21, 2017:

1. The Semaglutide 1.34 mg/ml (0.25 mg/0.5 mg/1.0 mg) Pen-injector is labeled for administration of three doses, 0.25 mg/0.5 mg/1.0 mg. However, the dose dial includes unlabeled increments in between the labeled doses. The user/patient is able to select and administer any of the unlabeled dose increments on the dose dial. Please provide a risk analysis of incorrect dosing based on the user/patient setting the dose at one of the unlabeled increments (therefore, over or under dosing). Please include in the risk analysis how the risk(s) to the patient if an unlabeled dose is selected, have been mitigated. For example, a human factors validation study including a critical task for users to select and administer the correct dose in which the user/patient has to select from multiple doses with increments in between doses unlabeled.

The following was included in the sponsor's response:

> *The PDS290 pen-injector for semaglutide 1.34 mg/ml shares use scenarios, potential hazards and user steps with the approved PDS290 pen-injector for liraglutide (0.6 mg/1.2 mg/1.8 mg/2.4 mg/ 3.0 mg), which is intended to be used for once-daily subcutaneous administration of liraglutide used in weight management (reference is made to Saxenda® (NDA 206321) approved on December 23, 2014).*
>
> *In the final human factors validation testing of the Saxenda® pen-injector (PDS290 pen-injector for liraglutide. Validation of device use. Summative Usability Testing Report, submitted on December 20, 2013 in NDA 206321), the participants were asked to complete simulated injections of different dose sizes, which required that the participant was able to select the correct dose size on the dose selector.*
>
> *In the referenced human factors validation test, a total of eight use errors were recorded among 145 participants, seven of these involved setting a dose just one increment above or below the intended dose. Setting a dose one increment above or below the intended dose with the PDS290 pen-injector for semaglutide 1.34 mg/ml would not have any medical consequences (S2) since one increment would be much below the therapeutic dose.*
>
> *Based on the human factors validation results from the final validation of the Saxenda® pen-injector, several mitigations have been implemented in the IFU in relation to setting the dose*

correctly. These mitigations were implemented during the development of the IFU for the PDS290 pen-injector for semaglutide 1.34 mg/ml.

IFU section 3: "Select your dose" describes in figures and text how to set the dose correctly

- *"Turn the dose selector until the dose counter shows your dose (0.25 mg, 0.5 mg, (b) (4)*
- *"Make sure you know the dose of Ozempic® you should use"*
- *"If you select the wrong dose, you can turn the dose selector forward or backwards to the correct dose"*
- *Example figure showing how to set a correct dose*

Warning symbol and bold text in IFU section 3:

- *"Always use the dose counter and the dose pointer to see how many mg you select. You will hear a click every time you turn the dose selector. Do not set the dose by counting the number of clicks you hear."*
- *"Only doses of 0.25 mg, 0.5 mg, or 1 mg must be selected with the dose selector. The selected dose must line up precisely with the dose pointer to ensure that you get a correct dose."*

With the implementation of the additional guidance in the IFU, Novo Nordisk has assessed that the risk is reduced to 'as low as reasonably practicable' (ALARP) and meets the criteria of risk acceptability.

Reviewer Comment
The sponsor has provided adequate discussion on the validation testing performed assessing the dose selection when there are unlabeled dose increments.

2. The injection time specification for the pen-injector is: (b) (4) seconds. The performance testing results for this specification ranged from (b) (4) seconds, depending on the gauge and length of needle; however, if the maximum injection time specification is (b) (4) seconds, that injection time should be validated for the user population . Please provide validation data that the patient is able to understand that the injection is completed based on audible and visual feedback cues. Additionally, please provide validation that that the patient population is capable of holding the pen injector for (b) (4) seconds, if necessary . Alternatively, please tighten the injection time specification to be closer to the actual verification testing results.

The generic PDS290 pen-injector specification limit of (b) (4) µl/s, which corresponds to the theoretically maximum injection time of (b) (4) seconds, is implemented to accommodate other drug products with higher viscosities.

As the PDS290 pen-injector for semaglutide 1.34 mg/ml is part of a PDS290 pen-injector portfolio containing several approved pen-injector variants with different viscosities, Novo Nordisk proposes to have the same specifications for all PDS290 pen-injector variants.

In the final human factors validation testing of the Saxenda® pen-injector (PDS290 pen-injector for liraglutide. Validation of device use. Summative Usability Testing Report), the participants were asked to complete simulated injections of different dose sizes, which required that the participant was able to understand when the injection was completed, based on the visual and/or audible feedback from the pen-injector.

The Use Error Risk Analysis for the PDS290 pen-injector for semaglutide 1.34 mg/ml has concluded that for the potential use error "The user does not hold down the dose button until the dose counter returns to "0" " (i.e. the user fails to understand the visual and/or audible feedback), it could lead to a single underdose. In the referenced human factors validation testing of the Saxenda® pen-injector, two out of 145 participants committed a total of two use errors by not holding down the dose button until the dose counter returned to "0" when making the injection. The clinical evaluation for this type of use error has concluded that it would not have any medical consequences (S2) for PDS290 pen-injector for semaglutide 1.34 mg/ml.

Based on the validation results from the final human factors validation of the Saxenda® pen-injector, several mitigations have been implemented for the IFU in relation to holding down the dose button until the dose counter returns to "0". These mitigations were transferred to the development of the IFU for the PDS290 pen-injector for semaglutide 1.34 mg/ml:

Mitigations implemented for the pen:

- *The dose counter shows "0" to indicate when the user can stop pressing the dose button*
- *Supportive click that indicates when the dose counter shows "0"*

IFU section 4: "Inject your dose" describes the following in figures and text:

- *"Make sure you can see the dose counter. Don't cover it with your fingers. This could* (b) (4) *the injection."*
- *"Press and hold down the dose button until the dose counter shows 0. The 0 must line up with the dose pointer. You may then hear or feel a click."*
- *"Keep the needle in your skin after the dose counter has returned to 0 and count slowly to 6."*
- *Figure showing how to press down the dose button until the dose counter shows "0"*

Warning symbol and bold text in IFU section 4:

- *"Always watch the dose counter to know how many mg you inject. Hold the dose button down until the dose counter shows 0."*

Novo Nordisk has tested the mitigations implemented and evaluated that further mitigations would not provide significant improvements. Thus, the risk is reduced to 'as low as reasonably practicable' (ALARP) and meets the criteria of risk acceptability.

Reviewer Comment
The sponsor provided an adequate response. Additionally, injection time is not an essential performance requirement for pen injectors (tested in verification testing) as it is depended on the user. The sponsor has included several mitigations to mitigate the risk of premature release of the button.

7.3. Design Verification Review

The sponsor has provided a functional design requirements and verification activities in their essential performance and validation document. I have selected relevant design requirements for pen injectors in the below table; however, the table provided by the sponsor (in essential performance and safety requirements document) includes requirements other than what are listed in the below table. Please refer to section 3.2.P.7. container-closure-system-essential device performance document. I did not include the tables below because there was 24 pages of tables.

Essential Performance Requirement	Specification	Verification	Validation	Aging / Stability (Y/N)	Shipping/ Transportation (Y/N)	Lot Release Testing (Y/N)
Dose Accuracy	Dose accuracy after the test at Cool conditions, Normal conditions with Flow Check, Normal conditions without Flow Check, Warm conditions: (b) (4) Visual inspection after the test: The pen-	Extract of Verification Reports for PDS290 Pen-injector for Semaglutide 1.34 mg/ml (0.25 mg/0.5 mg/1.0 mg)	3a clinical studies	Y	Y	Y

	injectors shall not show significant defects					
Visual/Audible Feedback	During the dose setting and resetting sequence, the clicks should be audible During the injection phase, the clicks should be audible At the end of the injection phase, a distinct click should be audible	Reference data is generated on Norditropin® FlexPro® 15 mg/1.5 ml The rationale for reference data validity: identical components for the click functionalities as Norditropin® FlexPro® 15 mg/1.5 ml	Y	n/a	n/a	n/a
Activation Force	Activation force Min (b) (4) N Max (b) (4) N Activation travel Min: (b) (4) mm Max: mm	Reference data is generated on PDS290 pen-injector for insulin (FlexTouch®) The rationale for reference data validity: same dose button activation mechanism as PDS290 pen-injector for insulin (FlexTouch®)	Y	n/a	n/a	n/a
Needle Length	(b) (4) mm Labeling indicates pens come with 4 NovoFine Plus needs 510(k)s for NovoFine Plus needles appear to be within (b) (4)		Y	n/a	n/a	n/a

	(b) (4)					
Needle Gauge	No requirement but the Labeling indicates pens come with 4 NovoFine Plus needs Looking at NovoFine and (b) (4) needles, gauges are (b) (4) 32G	Y	Y	n/a	n/a	n/a
Needle Connection Type	No requirement but NovoFine and (b) (4) needles have been tested according to ISO 11608-2; additionally the sponsor included a mounting and unmounting requirement and verification testing using NovoFine (b) (4) needles (leveraging data from insulin FlexTouch-same platform)	Y	Y	n/a	n/a	n/a
Cap Removal Force	Removal cap: (b) (4) N Put on cap: Max (b) (4) N	Reference data is generated on Norditropin® FlexPro® 15 mg/1.5 ml The rationale for reference data validity: similar interface between cap	Y	n/a	n/a	n/a

		and cartridge holder as Norditropin® FlexPro® 15 mg/1.5 ml				

The Design Verification test was carried out according to ISO 11608-1 Needle-based injection systems for medical use – Requirements and test methods – Part 1: Needle-based injection systems. The Dose accuracy was tested at standard, cool and warm conditions for three dose sizes; dose 0.25 mg ((b) (4) , 0.5 mg (b) (4)), and 1.0 mg ((b) (4)) representing the minimum, midpoint and maximum dose, respectively.

Table 5 Acceptance criteria according to ISO 11608-1:2014

Drug Type	semaglutide 1.34 mg/ml
Temperature °C	(b) (4)
Dose size	
Limit	
Accepted Lower Limit	
Accepted Upper Limit	

Table 23 Acceptance criteria and results for dose accuracy for FR026

	Dose accuracy after drop at	Dose size (mg)	Acceptance criteria (µl)		Results (µl)	
			Minimum	Maximum	Minimum	Maximum
FR026	Standard conditions with flow check	0.25 mg	(b) (4)		182.1	192.1
		0.5 mg			357.8	373.7
		1.0 mg			719.3	747.8
	Standard conditions without flow check	0.25 mg			182.9	191.9
		0.5 mg			357.8	372.7
		1.0 mg			718.6	747.0
	Cool conditions	0.25 mg			181.3	191.9
		0.5 mg			356.6	373.9
		1.0 mg			721.3	743.3
	Warm conditions	0.25 mg			183.2	190.9
		0.5 mg			356.4	372.6
		1.0 mg			718.6	746.8

Based on the individual test results listed in this report it is concluded that all test results are within the specified acceptance criteria and that the PDS290 pen-injector for semaglutide 1.34 mg/ml meet the following requirements:

- FR009 - Maximum dose to be dialled
- FR011 - Dripping while setting and resetting a dose
- FR018 - Mean dosage flow
  - Cool conditions
  - Standard conditions
  - Warm conditions
- FR021 - Dripping after dosage of the maximum dose
- FR022 - Suction after a dosage of the maximum dose
- FR026 - Dose accuracy must comply after the pen-injector has been dropped from a height of 1000 mm
  - Cool conditions
  - Standard conditions
  - Warm conditions
- FR030 - The pen-injector must withstand the drug

Stability- Functional Performance

3.2.P.8.1- Shelf-Life Stability Studies Summary

A finalised long term stability study (36 months at 5°C ± 3°C) and a finalised accelerated stability study (6 months at 25°C ± 2°C) were performed on three primary stability batches for semaglutide drug product in order to establish a shelf life of 36 months at 5°C ± 3°C. The same stability programme is ongoing for additional three primary batches. Dose accuracy was tested for primary stability batches assembled into PDS290 pen-injector for semaglutide 1.34 mg/ml at long term conditions for up to 36 months. All available data support the proposed 36 months shelf life for semaglutide 1.34 mg/ml solution for injection at 5°C ± 3°C.

3.2.P.8.3- Stability Data

Study 1 has generated stability data covering 36 months at long term storage conditions and 6 months at accelerated storage conditions. The results are presented in Appendix A and Appendix B, respectively. Results for Dose accuracy testing are presented in Appendix E.

Appendix E Results from Dose accuracy testing (5°C ± 3°C/ambient humidity)

Test	Batch no.	Storage time (months)		
		0[a]	24	36
Dose accuracy	BV40251	Complies[b]	Complies[b]	Complies[b]
	BV40439	Complies[b]	Complies[b]	Complies[b,c]
	CV40259	Complies[d]	Complies[d]	[e]

[a] Results from release test are used for time zero

[b] Complies means that the acceptance criterion ± (b) (4) increments is fulfilled using ISO 3951-1 or ISO 3951-2 for sampling (acceptance criterion is in accordance with ISO 11608-1)

[c] Dose accuracy testing performed after (b) (4) months of storage

[d] Complies means that the acceptance criterion ± (b) (4) increments is fulfilled using ISO 3951-1 or ISO 3951-2 for sampling (acceptance criterion is in accordance with ISO 11608-1)

[e] Result is pending

The dose accuracy testing for stability batches was performed using (b) (4) increments for 2 batches and (b) (4) increments for the third patch (up to 24 months, results pending for 36 months).

Reviewer Notes

- The shelf-life of combination product (based on drug) is 36 months
- (b) (4) increments is max dose
-doses for the pen are .25 mg, .5 mg, and 1 mg

(b) (4) 1 mg

- **doses:**

(b) (4) increments = 1 mg
increments = 0.50 mg
(b) (4) increments = 0.25 mg

Reviewer Comments- IRs were sent to the sponsor on April 21, 2017

1. The sponsor has performed dose accuracy testing at ± (b) (4) increments and (b) (4) increments. IR sent to request stability testing and release testing with the lowest and highest dose.

2. Send IR for test protocols and reports.

3. There are two pens within the NDA, a pen labeled with 1mg dose only and a pen with options for 0.25 mg, 0.5 mg, and 1 mg doses. The sponsor should clarify which pen the stability studies were performed on and provide a rationale for why the testing is applicable for both pens.

4. The pen is able to dose at intervals not specified in labeling (unlabeled increments in between labeled doses). Request a risk analysis of incorrect dosing based on the user/patient setting the dose at one of the unlabeled increments.

5. It is unclear why the (b) (4) increment dose is used for stability studies, as that is not a labeled dose for this combination product. Also, dose accuracy testing should be performed with the highest and lowest intended doses. Request dose accuracy testing in your stability studies for the lowest and highest labeled doses.

6. Please clarify if the shelf-life of the pen-injector, prior to being incorporated into the combination product has been addressed in your stability studies. For example, if the pen-injector has a shelf-life of two years and the combination product has a shelf-life of three years, please clarify if you have provided testing demonstrating that the performance of the device remains acceptable considering the five years total shelf life/aging for the subassemblies.

Reviewer Comments- The reviewer still had concerns after the response to the above questions was provided on April 27, 2017. **Additional IRs were sent on May 16, 2017 to clarify the pens which pens were used in the stability studies, the phase III clinical program, and the to-be marketed pen injector and if there are any differences between the pens and/or drug products.**

The following information was included in the sponsor's response on May 27, 2017:

Table 1 provides the comparison of the five pen-injectors referenced in the stability studies. In this table, the relationships of the dose setting parameters are presented to clarify how Novo Nordisk has used them.

The information below aims to supplement the information provided in the original NDA209637 in 3.2.P.7 PDS290 Pen-injector for Semaglutide 1.34 mg/ml - Comparison to other PDS290 Peninjectors. To clarify that the PDS290 pen-injector for semaglutide used in phase 3a clinical trial programme and the to-be-marketed PDS290 pen-injector for semaglutide 1.34 mg/ml are identical except for:

- *the imprint on the scale drum*
- *the maximum dose stop*
- *the colour of the components*

These differences have been evaluated as having no impact for the dose accuracy of the peninjectors.

Table 1 Pen-injector comparison for dose setting parameters between the to-be-marketed PDS290 pen-injector for semaglutide 1.34 mg/ml, PDS290 pen-injector for semaglutide clinical trial and PDS290 pen-injector for insulin (FlexTouch®)

	To-be-marketed PDS290 pen-injector for semaglutide 1.34 mg/ml		PDS290 pen-injector for semaglutide used in phase 3a clinical trial programme		PDS290 pen-injector for insulin (FlexTouch®)
	PDS290 pen-injector for semaglutide 1.34 mg/ml (0.25 mg/0.5 mg/1.0 mg)	PDS290 pen-injector for semaglutide 1.34 mg/ml (1.0 mg)	PDS290 pen-injector for semaglutide used in phase 3a clinical trial programme (SUSTAIN 1-5)	PDS290 pen-injector for semaglutide used in phase 3a clinical trial programme (SUSTAIN 6)	
Pen configuration					
Solution for injection	Semaglutide 1.34 mg/ml solution for injection				Test medium
Concentration	1.34 mg /ml				N/A
Equivalent dose setting parameters and Scale drum graphics	(b) (4)				

	To-be-marketed PDS290 pen-injector for semaglutide 1.34 mg/ml		PDS290 pen-injector for semaglutide used in phase 3a clinical trial programme		PDS290 pen-injector for insulin (FlexTouch®)
	PDS290 pen-injector for semaglutide 1.34 mg/ml (0.25 mg/0.5 mg/1.0 mg)	PDS290 pen-injector for semaglutide 1.34 mg/ml (1.0 mg)	PDS290 pen-injector for semaglutide used in phase 3a clinical trial programme (SUSTAIN 1-5)	PDS290 pen-injector for semaglutide used in phase 3a clinical trial programme (SUSTAIN 6)	
	[redacted] (b) (4)				

*The imprint on the scale drum shown for the to-be-marketed PDS290 pen-injector for semaglutide 1.34 mg/ml (0.25 mg/0.5 mg/1.0 mg) and the PDS290 pen-injector for semaglutide used in phase 3a clinical trial programme (SUSTAIN 6) are different. The difference is related to the fact the study SUSTAIN 6 pen-injector used a scale drum component from an already existing pen-injector (see section 2.7.1 for detailed explanation). The difference in the reading on the scale drum was relevant for the clinical trial setting, where participants set the 0.25 mg, 0.5 mg and 1.0 mg semaglutide doses by dialling to [redacted] (b) (4) respectively.

Novo Nordisk would like to clarify that the concentrations of the semaglutide 1.34 mg/ml solution for injection used in the stability studies and clinical studies are exactly the same, i.e. 1.34 mg/ml.

Novo Nordisk would like to present the evidence to support that the PDS290 pen-injector for semaglutide 1.34 mg/ml is able to fulfil the dose accuracy specification for the proposed shelf life of 36 months. The evidence combines data from:

- *the similarity in viscosity and density of the test medium and the semaglutide 1.34 mg/ml solution for injection (presented in section 2.4.1.1)*
- *the combination of data from two stability studies on the PDS290 pen-injector portfolio (presented in section 2.4.1.2)*

  i. the dose accuracy data from the PDS290 pen-injector for semaglutide used in phase 3a clinical trial programme generated during stability (Table 3)
  ii. the dose accuracy data from the PDS290 pen-injector for insulin (FlexTouch®) generated during stability with test medium (Table 4, Table 5 and Table 6)

The comparability of the test medium and semaglutide 1.34 mg/ml solutions in combination with the results from the dose accuracy stability studies confirm the proposed shelf life of 36 months for the PDS290 pen-injector for semaglutide 1.34 mg/ml.

The data to support this conclusion is presented in the sections below.

Viscosity and density

Table 2 shows a comparison between the test medium (FlexTouch®) and semaglutide 1.34 mg/ml solution for injection. Data in Table 2 show an expected minor temperature dependency for the density for both test medium and semaglutide 1.34 mg/ml solution for injection. The effect of the differences between the two solutions at any one temperature is regarded as negligible.

Table 2 shows no difference in viscosity at 20°C for semaglutide 1.34 mg/ml solution for injection and test medium and negligible differences at 5°C and at 40°C. Hence viscosity of the two solutions is in this case also evaluated as having no influence on the dose accuracy performance if leveraged from the study on the PDS290 pen-injector for insulin (FlexTouch®) with test medium.

Table 2 Density and viscosity for semaglutide 1.34 mg/ml solution for injection and test medium, Time = 0

		PDS290 pen-injector for semaglutide 1.34 mg/ml	PDS290 pen-injector for insulin (FlexTouch®)
Drug product		Semaglutide 1.34 mg/ml solution for injection	Test medium
Density, [g/ml]	5°C	1.003	1.004
	20°C	1.001	1.002
	40°C	0.995	0.996
Viscosity, [mm²/s]	5°C	1.61	1.60
	20°C	1.07	1.07
	40°C	0.68	0.69

Stability data

Further to the fact that the differences in density and viscosity between the test medium and the semaglutide 1.34 mg/ml solution for injection are negligible, Novo Nordisk would also like to present the dose accuracy stability data as evidence of no change to the dose accuracy over time for both semaglutide 1.34 mg/ml solution for injection and test medium.

i. The shelf-life stability for the PDS290 pen-injector for semaglutide 1.34 mg/ml obtained fromthe PDS290 pen-injector for semaglutide used in phase 3a clinical trial programme show dose accuracy stability data throughout the shelf-life period of 36 months (Table 3)

The dose accuracy stability data in Table 3 demonstrate that the stability behaviour of the PDS290 pen-injector for semaglutide 1.34 mg/ml fulfils the dose accuracy specification according to ISO 11608-1 throughout the proposed shelf life of the product (36 months). No dose accuracy trend was observed in the results. The PDS290 pen-injectors for semaglutide used in phase 3a clinical trial programme is considered representative for the to-be-marketed PDS290 pen-injector for semaglutide 1.34 mg/ml, since the pen-injector differences presented in 2.1.1 are evaluated not to have an impact on dose accuracy.

Table 3 **Dose accuracy stability data, PDS290 pen-injector for semaglutide used in phase 3a clinical trial programme (SUSTAIN 6) and (SUSTAIN 1-5), at standard atmosphere**

		PDS290 pen-injector for semaglutide used in phase 3a clinical trial programme (SUSTAIN 6)		PDS290 pen-injector for semaglutide used in phase 3a clinical trial programme (SUSTAIN 1-5)
Cartridge batch No.		BW54755	BW55769	CW57300
Pen-injector batch No.		BV40251	BV40439	CV40259
Solution for injection		Semaglutide1.34 mg/ml solution for injection		
Concentration		1.34 mg/ml		
Dose setting as read on the scale drum for dose accuracy test (correspondence to equivalent names for dose setting parameters)		5.0 mg ((b) (4) solution for injection)*		0.5 mg (b) (4) = (b) (4) of solution for injection)
Dose accuracy Acceptance criteria ISO 11608-1 [mg of solution for injection]		LSL: (b) (4) USL:		LSL: (b) (4) USL:
Time = 0 months	Max [mg]	501.2	500.8	376.7
	Min [mg]	488.2	488.1	360.0
	Stdev. [mg]	2.98	2.89	3.12
	Mean [mg]	495.7	494.2	367.5
Time = 24 months	Max [mg]	502.6	501.7	367.1
	Min [mg]	492.1	486.1	361.1
	Stdev. [mg]	2.49	2.66	3.03
	Mean [mg]	497.6	495.4	367.5
Time = 36 months	Max [mg]	504.7	502.1	375.3**
	Min [mg]	477.2	488.4	352.5**
	Stdev. [mg]	4.61	2.82	3.55**
	Mean [mg]	496.7	496.0	367.1**

Abbreviations: Stdev. = Standard Deviation; LSL= Lower Specification Limit; USL= Upper Specification Limit.

* See response 2.7.1 for a clarification on the choice of dose setting of "5.0 mg ((b) (4) of solution for injection)"

**Data time point = 37 months

ii. The second source from which Novo Nordisk has leveraged shelf life data to support the PDS290 pen-injector for semaglutide 1.34 mg/ml is from the PDS290 pen-injector for insulin (FlexTouch®) with test medium.

The report for this stability study (t= 36 months) for FlexTouch® with test medium was provided to the Agency in Xultophy® (NDA 208583, (seq no. 0024)) and in Faster-acting insulin aspart (NDA 208751 (seq no. 0006)).

In addition, a summary of the same stability study for dose accuracy, now available up to four years (48 months), is provided in Table 4, Table 5 and Table 6.

Table 5 Dose accuracy stability data, PDS290 pen-injector for insulin (FlexTouch®), at standard atmosphere

			PDS290 pen-injector for insulin (FlexTouch®)					
Cartridge batch No.			AW50840					
Pen-injector batch No.			BP50051					
Solution for injection			Test medium					
Dose setting for dose accuracy test			(b) (4) / 10 µl		(b) (4) / 400 µl		(b) (4) / 800 µl	
Dose accuracy Acceptance criteria ISO 11608-1 [mg of solution for injection]			LSL:	USL:	LSL:	USL:	LSL:	USL: (b) (4)
Standard atmosphere as per ISO 11608-1	Time = 0 months	Results [mg]	9.25	10.99	391.63	406.41	786.42	809.25
		Stdev. [mg]	0.325		2.767		4.274	
		Mean [mg]	10.12		399.02		797.84	
Temp.: 23°C±5°C Humidity: 50%RH ± 25%RH	Time = 36 months	Results [mg]	8.57	11.73	392.11	405.29	785.95	808.06
		Stdev. [mg]	0.5930		2.4687		4.1402	
		Mean [mg]	10.15		398.70		797.01	
	Time = 48 months	Results [mg]	8.62	11.43	391.46	405.26	786.46	808.87
		Stdev. [mg]	0.5259		2.5840		4.1949	
		Mean [mg]	10.03		398.36		797.67	

Abbreviations: Temp.= Temperature; RH= relative humidity; Stdev. = Standard Deviation; LSL= Lower Specification Limit; USL: Upper Specification Limit.

Over time, Novo Nordisk observes no change in dose accuracy performance, thus fulfilling the dose accuracy specification according to ISO 11608-1 for up to 48 months.

The dose accuracy shelf-life data generated from the PDS290 pen-injector for insulin (FlexTouch®) with test medium, at three different temperature atmospheres, is considered representative for the shelf life for the PDS290 pen-injector for semaglutide 1.34 mg/ml. A final point to note is related to the mechanical design of the pen-injector, which has been shown to be sufficiently robust in terms of being able to provide dose accuracy results within the specifications across a temperature-dependent range of densities and viscosities as shown in Table 2.

Reviewer Comment
To demonstrate the dose accuracy post stability studies the sponsor is relying on:

a. the dose accuracy data from the PDS290 pen-injector for semaglutide used in phase 3a clinical trial program generated during stability (Table 3).
b. the dose accuracy data from the PDS290 pen-injector for insulin (FlexTouch®.

The sponsor has provided sufficient information on the comparison of the pens used on the clinical trial

and the to- be marketed pens for the dose for (a) and data comparing the viscosity and density of the test medium for (b).

3.2.P.8.1- In-use stability studies

In-use stability studies were performed on primary stability batches at 30°C ± 2°C for 56 days and at 5°C ± 3°C for 56 days. Primary stability batches were subjected to in-use simulation close to production date, at mid-shelf life, and near end of shelf life.

The in-use test is designed to simulate patient usage including penetration of the rubber closure, and movement. The product was monitored for Appearance (Macroscopy), as well as chemical and microbial stability during the test.

No change in Appearance of semaglutide drug product (Macroscopy) is observed during 56 days of in-use at 30°C ± 2°C or 56 days at 5°C ± 3°C including tempering (cold in-use).
Limited change is observed for the test parameters Content of semaglutide, HMWP, Hydrophilic impurities, Hydrophobic impurities 1, Hydrophobic impurities 2, and Sum of impurities. As expected, less formation of impurities was observed during cold in-use. All other test items remain at a constant level in the in-use studies.

Dose accuracy for PDS290 pen-injector for semaglutide 1.34 mg/ml complied with the defined acceptance criterion at end of in-use simulation. Based on the results, the proposed in-use time of 56 days (8 weeks) when stored below 30°C is justified for the semaglutide drug product. This includes storage at 5°C ± 3°C in-between applications.

8. DISCIPLINE SPECIFIC SUB-CONSULTED REVIEW

8.1. Biocompatibility

The intended use of the PDS290 semaglutide pen-injector implies brief, repeated contact to intact skin during handling of the device. According to *ISO 10993-1:2009* and the *FDA Guidance for Industry and Food and Drug Administration Staff, Use of International Standard ISO-10993" "Biological Evaluation of Medical Devices Part 1: Evaluation and Testing", June 16, 2016*, Appendix A for non-invasive devices, which will only be in user contact with intact skin, an evaluation of testing for the following biological hazards, shall be considered:

- Cytotoxicity
- Sensitization
- Irritation or intracutaneous reactivity

The biocompatibility evaluation of the final finished PDS290 semaglutide pen-injector was leveraged based on the previous FDA reviewed and approved PDS290 pen-injector for GLP-1(Saxenda®).

Table 1 Summary Biocompatibility Evaluation Information

Component	Biological evaluation tests		Material risk information	Rationale for why additional information is not needed
	Cytotoxicity	Irritation and sensitization	(b) (4)	
Housing and cap	Not tested	Not tested		Identical materials as in the approved PDS290 pen-injector for GLP-1 (Saxenda®). Manufacturing and processing is not considered to impact the biocompatibility of these components Appendix B
Cartridge holder	Not tested	Not tested		Identical (b) (4) as in the approved PDS290 pen-injector for GLP-1 (Saxenda®) Colour master batch does not contain any substances with a potential to cause irritation and/or sensitization. Manufacturing and processing is not considered to impact the biocompatibility of this component Appendix B
Dial	Not tested	Not tested		Identical material as in the approved PDS290 pen-injector for GLP-1 (Saxenda®) Manufacturing and processing is not considered to impact the biocompatibility of this components Appendix B
Dose button	Testing on final finished component manufactured without adding any master batch Appendix E	Not tested		Same class of (b) (4) as in the approved PDS290 pen-injector for GLP-1 (Saxenda®) Colour master batch does not contain any substances with a potential to cause irritation and/or sensitization. Manufacturing and processing is not considered to impact the biocompatibility of this component.

9. RISK ANALYSIS

9.1. Risk Analysis Attributes

Risk Analysis Attributes	Yes	No	N/A
Risk analysis conducted on the combination product	x		

Hazards adequately identified (e.g. FMEA, FTA, post-market data, etc.)	x		
Mitigations are adequate to reduce risk to health	x		
Version history demonstrates risk management throughout design / development activities			

9.2. Summary of Risk Analysis

The following IR was sent to the sponsor on June 27, 2017:

> You have not included a comprehensive risk analysis in this NDA. You state that the PDS290 pen-injector for semaglutide 1.34 mg/ml utilizes some generic PDS290 components and uses similar manufacturing processes to other marketed PDS290 pen-injectors and have been analysed with regard to risks related to the design and manufacturing processes by the use of the FMECA method. You also state that the conclusion of the design and manufacturing risk management analysis for the PDS290 pen-injector for semaglutide 1.34 mg/ml is that all risks have been analysed, assessed and reduced as documented in the FMECA document; however, this document has not been provided.
>
> Please clarify if there are any differences between the FMECA performed on the PDS290 semaglutide 1.34 mg/ml pen injector and the FMECA performed on previously approved PDS290 pen-injectors. If there are any differences, please provide a list of the differences and the corresponding risk analysis information.

The sponsor provided the following summary of their risk analysis approach following response on July 13, 2017 (SN # 0030, Quality Information 1.11.1):

> *The technical risk analysis of components and sub-assemblies with regards to design and manufacturing of the PDS290 pen-injectors portfolio is treated by the FMECA method in a centralized analysis. This analysis covers all components and sub-assemblies with their respective interfaces to other components and functions for the whole PDS290 pen-injector portfolio. In this FMECA each of the different drug products using the PDS290 pen-injector (e.g. insulin, human growth hormone, liraglutide and semaglutide) is assessed. All the potential hazards associated to components ("deviations/ failure modes" in the FMECA) and the associated consequences/effects (" user harms" in the FMECA) are treated and analysed with regards to severity and probability of harm. On the basis of these two factors, a Risk Priority Number ("RPN" in the FMECA) is calculated. The RPN is used to assess whether the hazard is acceptable or if there is a need for the hazard to be further mitigated in accordance with ISO 14971:2007 (and EN ISO 14971:2012). The RPN is calculated both before and after mitigations are implemented. The FMECA traces that design and manufacturing risks are mitigated to a risk level of either "Acceptable" or "ALARP" (As Low as Reasonably Practicable).*
>
> ***Differences between the PDS290 pen-injector for semaglutide 1.34 mg/ml and the PDS290 pen-injector portfolio***
>
> *The PDS290 pen-injector for semaglutide 1.34 mg/ml has been developed and designed by leveraging the existing information from the PDS290 pen-injector portfolio components and subassemblies from already*

approved PDS290 pen-injectors marketed in the U.S, such as the Saxenda® pen (NDA 206321) with liraglutide for weight management, the Norditropin® FlexPro® (NDA 021148/S-027, S-042) with human growth hormone and FlexTouch® for insulins (e.g. NovoLog® FlexTouch® (NDA 020986/S-061), Levemir® FlexTouch® (NDA 021536/S-033), Tresiba® FlexTouch® (NDA 203314)) and Xultophy® 100/3.6 (NDA 208583). The PDS290 pen-injector for semaglutide 1.34 mg/ml has some dedicated components. These components are:

- (b) (4)

The following sections provide the details of the differences between the components of the Saxenda® Pen (NDA 206321) with liraglutide for weight management, the Norditropin® FlexPro® (NDA 021148/S-027, S-042) with human growth hormone and an insulin drug product in FlexTouch®.

An accompanying analysis for new risk hazard lines is presented for each of the five components in the following sections. The new risk hazard lines are introduced into the relevant sections of the centralized analysis.

Conclusion

The conclusion from the centralized FMECA is that the PDS290 pen-injector for semaglutide 1.34 mg/ml can be produced safely and effectively and all the potential hazards associated to the five new components and the associated consequences/effects are mitigated to a risk level of "Acceptable" as demonstrated in the below sections.

Reviewer Comment
The sponsor has provided risk analysis information for the PDS290 platform and the PDS290 pen-injector for semaglutide 1.34 mg/ml for each of the hazards associated with each component that is different for the proposed injector (b) (4) The response is adequate. **The deficiency is resolved.**

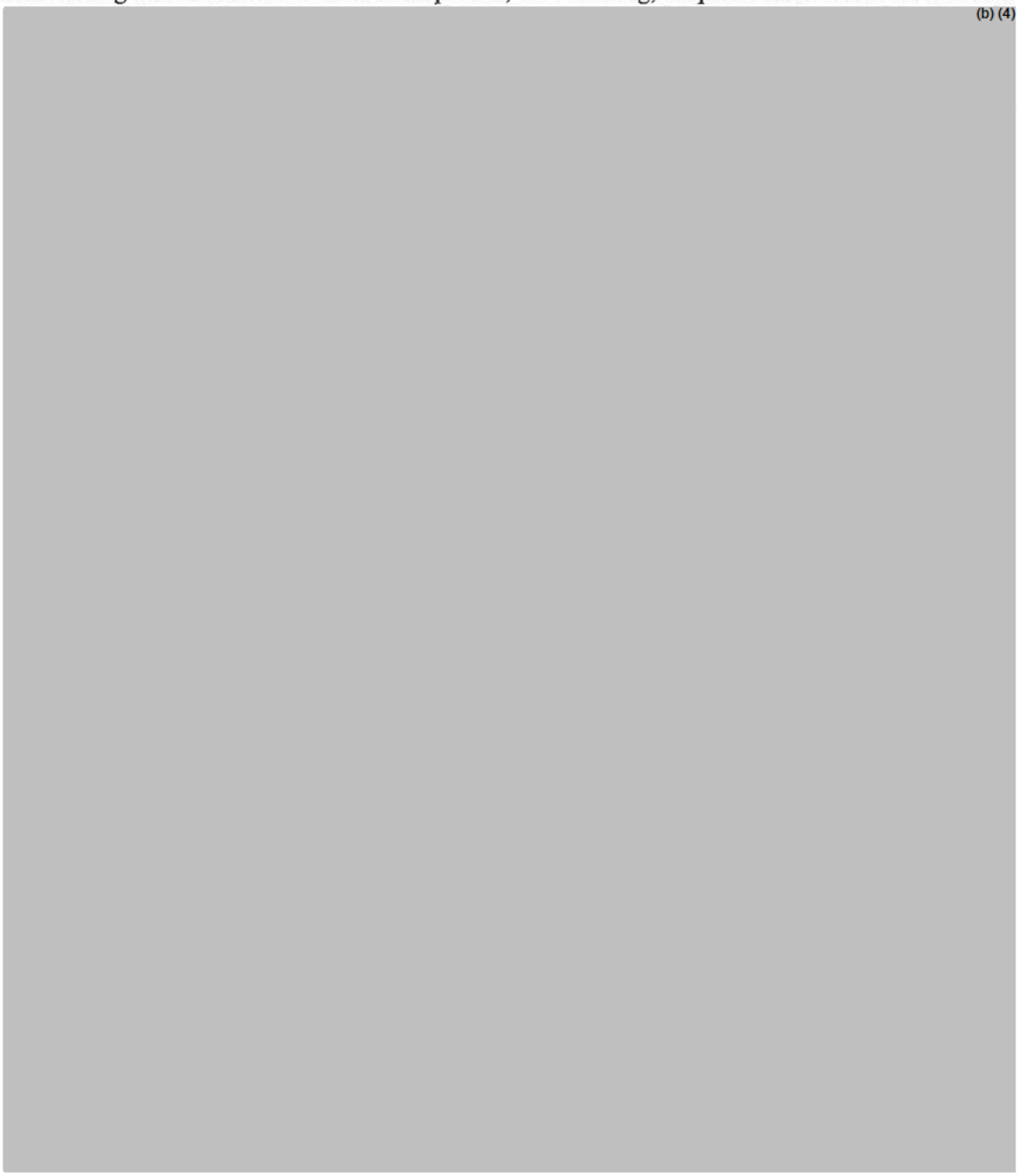
Table 2 **Extract from the PDS290 pen-injector FMECA and the risk analysis information of the differences for the PDS290 pen-injector for semaglutide 1.34 mg/ml – dose button**

Hazard ID number Deviation/ Failure mode	User Harm	S-class	RPN	Risk Class	Implemented mitigations	S-class	RPN	Risk Class	Conclusion

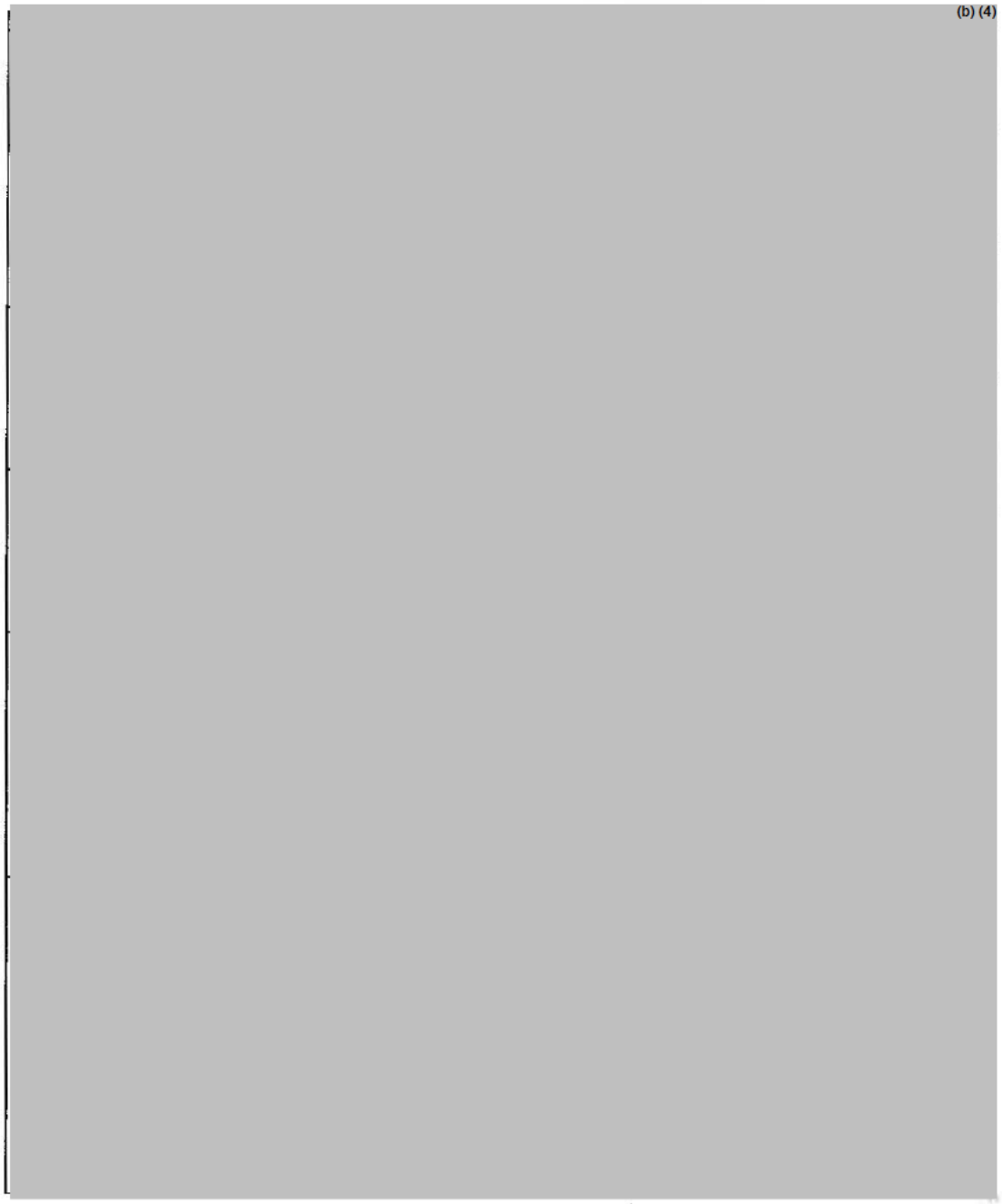
10.LABELING

The following instructions were found in Seq. 0001, 1.14 labeling; Proposed Instructions for Use 0.25-0.5-1 mg Pen

(b) (4)



3 Page(s) of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page



11.DESIGN TRANSFER ACTIVITIES – RELEASE SPECIFICATION

The following release specifications are included for the device constituent within eCTD Module 3.2.P.5 **(updated release specs in sequence 0013)**:

Dose accuracy	Weighing A332601a	Complies[5,6]

5: Complies means that the specification limit ± (b) (4) at a dose of 0.5 mg semaglutide (corresponding to (b) (4) solution for injection) for the PDS290 pen-injector for semaglutide 1.34 mg/ml (0.25 mg/0.5 mg/1.0 mg), item no. 5-9558-xx is fulfilled using ISO 3951-1:2005 or ISO 3951-2:2006

6: Complies means that the specification limit ± (b) (4) at a dose of 1.0 mg semaglutide (corresponding to (b) (4) solution for injection) for the PDS290 pen-injector for semaglutide 1.34 mg/ml (1.0 mg), item no. 5-9506-xx is fulfilled using ISO 3951-1:2005 or ISO 3951-2:2006

Reviewer Comments

1. Inclusion of .5 mg and 1.0 mg only, in the release specifications for dose accuracy is acceptable because 0.25 mg is not a clinical dose, it is used for titration up to the clinical doses included in the dose accuracy testing.

2. The sponsor has clarified that (b) (4) (.5 mg and 1.0 mg), respectively.

As an example, the calculated weight of a dose setting of (b) (4) increments (corresponding to a dose size of 0.5 mg semaglutide) is therefore:

(b) (4)

12. Change to the Pen

The sponsor provided an outline of a proposed modification to the PDS290 pen-injector for semaglutide 1.34 mg/ml from **0.25 mg/0.5 mg/1.0 mg** to **0.25 mg/0.5 mg** on June 7, 2017 submission (seq no. 0021). The sponsor's goal was to address DMEPA's concern about have two pens deliver 1.0 mg (and one of those pens also delivering 0.5 mg and 0.25 mg doses), while still being able to offer a 1.0 mg only pen patients.

On August 14, 2017, the sponsor provided information and testing to support the following 3 points and to demonstrate that the PDS290 pen-injector (0.25mg/0.5mg) design is safe and effective for its intended users, uses and use environment.

- the verification of the functional design associated to a modified maximum dose stop
- testing according to ISO 11608-1:2014– Needle-based injection system for medical use
- the verification of dose accuracy testing for batch release

The sponsor provided the following supportive information in SEQ 0035 of NDA 209637:

- PDS290 Pen-injector for Semaglutide 1.34 mg/ml(0.25 mg/0.5 mg)
  Summary of Comparison to the PDS290 Pen-injector for Semaglutide 1.34 mg/ml (0.25 mg/0.5 mg/1.0 mg)

  As outlined in our June 7, 2017 submission, the PDS290 semaglutide pen-injector (0.25 mg/0.5 mg) is identical to the PDS290 semaglutide pen-injector (0.25 mg/0.5 mg/1.0 mg) except for the differences presented in Table 1.

Table 1 **Differences between the PDS290 semaglutide pen-injector (0.25 mg/0.5 mg/1.0 mg) and the PDS290 semaglutide pen-injector (0.25 mg/0.5 mg)**

		PDS290 semaglutide pen-injector (0.25 mg/0.5 mg/1.0 mg)	PDS290 semaglutide pen-injector (0.25 mg/0.5 mg)
Pen-injector configuration			
Maximum dose stop position on housing		Maximum dose stop position at 74 increments 	Maximum dose stop position at 37 increments 
Imprint on the scale drum visible to the user	**Dose setting for 0.25 mg**		
	Dose setting for 0.5 mg		 Maximum dose stop
	Dose setting for 1.0 mg	 Maximum dose stop	Not Applicable

- PDS290 Pen-injector for Semaglutide 1.34 mg/ml (0.25 mg/0.5 mg) Dose Accuracy Data

Table 1 Release of batches according to Dose accuracy of PDS290 pen-injector for semaglutide 1.34 mg/ml (0.25 mg/0.5 mg)

Batch no. for assembled product	Drug product	Specification limit [(b) (4)] at a dose setting of 0.5 mg semaglutide (corresponding to [(b) (4)] i.e. [(b) (4)] mg solution for injection)	Mean value of solution for injection (mg)	Standard deviation (mg)	Result
GV40037	Semaglutide 1.34 mg/ml	[(b) (4)] mg	366.8	2.7	Complies
GV40038			366.1	2.6	Complies
GV40039			364.5	2.6	Complies

* According to ISO 11608-1 Needle-based injection systems for medical use - Requirements and test methods - Part 1: Needle-based injection systems.

The Dose Accuracy of the PDS290 pen-injector for semaglutide 1.34 mg/ml (0.25 mg/0.5 mg) is tested using the sampling procedures according to ISO 3951-1:2005 or ISO 3951-2:2006.

2 Results

The analytical testing program of dose accuracy testing has been performed in accordance with 3.2.P.5.2 Analytical Procedure A332601a Dose Accuracy. The results of the Dose accuracy test of the assembled batches "complies" i.e. the specification limits of ± [(b) (4)] at a dose setting of 0.5 mg semaglutide (corresponding to [(b) (4)] solution for injection) are fulfilled using ISO 3951-1:2005 or ISO 3951-2:2006.

- PDS290 Pen-injector for Semaglutide 1.34 mg/ml (0.25 mg/0.5 mg) Test Report According to ISO 11608-1 - Needle Based Injection Systems for Medical Use

  Objective: *The purpose of the test is to verify the performance and dose accuracy according to ISO 11608-1:2014 (1) of the PDS290 pen-injector for semaglutide 1.34 mg/ml (0.25 mg/0.5 mg), hereafter referred to as the PDS290 semaglutide pen-injector (0.25 mg/0.5 mg).*

  Overall conclusion: *The Design Verification testing of the PDS290 semaglutide pen-injector (0.25 mg/0.5 mg) complies with the dose accuracy tolerance limits according to ISO 11608-1:2014 (1). Furthermore, the PDS290 semaglutide pen-injector (0.25 mg/0.5 mg) meets the specifications for total content of device, dose accuracy of last dose, dose accuracy after free fall, and vibration pre-conditioning and visual inspection according to ISO 11608-1:2014 (1).*

- Updated release specifications under 3.2.P.5.1

Dose accuracy	Weighing A332601a	Complies[5,6]

5: Complies means that the specification limit ± [(b) (4)] at a dose of 0.5 mg semaglutide (corresponding to [(b) (4)] solution for injection) for the PDS290 pen-injector for semaglutide 1.34 mg/ml (0.25 mg/0.5 mg), item no. 5-9558-xx is fulfilled using ISO 3951-1:2005 or ISO 3951-2:2006

6: Complies means that the specification limit ± (b) (4) at a dose of 1.0 mg semaglutide (corresponding to (b) (4) solution for injection) for the PDS290 pen-injector for semaglutide 1.34 mg/ml (1.0 mg), item no. 5-9506-xx is fulfilled using ISO 3951-1:2005 or ISO 3951-2:2006

Table 5 shows the overview of the acceptance limits for dose accuracy on PDS290 semaglutide pen-injector (0.25 mg/0.5 mg) according to ISO 11608-1:2014 (1).

Table 5 Acceptance criteria according to ISO 11608-1:2014

Drug Type	semaglutide 1.34 mg/ml
Temperature °C	(b) (4)
Dose size	
Limit	
Accepted Lower Limit	
Accepted Upper Limit	

- Justification of specifications (3.2.P.5.6)

The specification limits are in accordance with ISO 11608-1 "Needle-based injection systems for medical use – Requirements and test methods – Part 1: Needle-based injection systems".

Reviewer Comment
The sponsor has provided adequate information to support the change of the dose stop from 1.0 mg to 0.5 mg in the 1.0 mg/0.5 mg/0.25 mg pen, which is now the 0.5 mg/0.25 mg pen.

13.INTERACTIVE REVIEW

Agency Information Request # 1 (sent on April 21, 2017)

1. In the document "Test Report According to ISO 11608-1 - Needle Based Injection Systems for Medical Use" (novoDOCS ID 002987428), you have included dose accuracy testing for the last dose. Table 8 shows the test results for the minimum dose, (b) (4) (0.25 mg). The pen-injector is able to dose (b) (4) In addition to the lowest dose, please provide the dose accuracy testing for the last dose for the highest dose (b) (4) 1.0 mg).

2. The Semaglutide 1.34 mg/ml (0.25 mg/0.5 mg/1.0 mg) Pen-injector is labeled for administration of three doses, 0.25 mg/0.5 mg/1.0 mg. However, the dose dial includes unlabeled increments in between the labeled doses. The user/patient is able to select and administer any of the unlabeled dose increments on the dose dial. Please provide a risk analysis of incorrect dosing based on the user/patient setting the dose at one of the unlabeled increments (therefore, over or under dosing). Please include in the risk analysis how the risk(s) to the patient if an unlabeled dose is selected, have been mitigated. For example, a human factors validation study including a critical task for users to select and administer the correct dose in which the user/patient has to select from multiple doses with increments in between doses unlabeled.
3. The injection time specification for the pen-injector is: (b) (4) seconds. The performance testing results for this specification ranged from (b) (4) seconds, depending on the gauge and length of needle; however, if the

maximum injection time specification is (b) (4) seconds, that injection time should be validated for the user population . Please provide validation data that the patient is able to understand that the injection is completed based on audible and visual feedback cues. Additionally, please provide validation that that the patient population is capable of holding the pen injector for (b) (4) seconds, if necessary. Alternatively, please tighten the injection time specification to be closer to the actual verification testing results.

4. Please provide a specification for the residual medication in the pen after last dose or provide a rationale for why a specification for the residual volume is not necessary.

5. The shelf-life of the combination product is 36 months. Appendix E of the document "Primary Stability Data for Semaglutide 1.34 mg/ml Solution for Injection Up to 36 Months at 5°C, 6 Months at 25°C" includes a summary of dose accuracy testing at (b) (4) % for the (b) (4) increment dose (2 batches) and (b) (4) increment dose (1 batch up to 24 months). It is unclear why the (b) (4) increment dose is used, as that is not a labeled dose for this combination product. It is also unclear how the testing for (b) (4) increments was performed given the scale drum is not labeled for a dose amount that corresponds to (b) (4) increments.

a. Please clarify why (b) (4) increments was chosen and how the testing was performed.
b. You have not included dose accuracy testing for the lowest (b) (4) increments) and highest (b) (4) increments) dose. Please provide dose accuracy testing in your stability studies for the lowest and highest labeled doses.
c. The reviewer is unable to locate the test protocols and test reports for the dose accuracy testing post stability studies. Please provide the location or the protocols and test reports for the verification testing of the dose accuracy testing post stability studies.
d. There are two pens within the NDA, a pen labeled with 1mg dose only and a pen with options for 0.25 mg, 0.5 mg, and 1 mg doses. Please clarify which pen the stability studies were performed on and provide a rationale for why the testing is applicable for both pens.
e. Please clarify if the shelf-life of the pen-injector, prior to being incorporated into the combination product has been addressed in your stability studies. For example, if the pen-injector has a shelf-life of X number of years and the combination product has a shelf-life of three years, please clarify if you have provided testing demonstrating that the performance of the device remains acceptable considering the X + 3 years total shelf life/aging for the pen-injector component.

6. You have included a dose accuracy specification within your release specification document (3.2.P.5.1) that states that the dose accuracy requirement "complies". Please see below:

Dose accuracy	*Weighing A332601a*	*Complies*[5,6]

5: specification limit ± (b) (4) at a dose of 0.5 mg semaglutide for the PDS290 pen-injector for semaglutide 1.34 mg/ml (0.25 mg/0.5 mg/1.0 mg), item no. 5-9558-xx is fulfilled using ISO 3951-1:2005 or ISO 3951- 2:2006
6: Complies means that the specification limit ± (b) (4) at a dose of 1.0 mg semaglutide for the PDS290 pen-injector for semaglutide 1.34 mg/ml (1.0 mg), item no. 5-9506-xx is fulfilled using ISO 3951-1:2005 or ISO 3951-2:2006

a. You can include that the device should conform to a standard in the release specifications; however, the specification acceptance criteria should state the actual dose accuracy specification within the release specifications (i.e. ± (b) (4) for the doses: (b) (4) or the range if acceptable doses: (b) (4) (b) (4) uL).
b. You have only included only a dose accuracy specification for the middle (0.5 mg) and highest dose (1.0 mg). The Agency recommends that you bracket the range of possible doses in your release specifications. Please include a dose accuracy specification for the lowest dose (0.25 mg) in the release specifications (3.2.P.5.1) in addition to the specifications currently included.

7. You have labeled the device for use with NovoFine needles. Please still include a specification for the length and gauge of the needles that should be used with your combination product within your essential performance and safety requirements document.

8. You have provided a Product Risk Management Summary for PDS290 Pen-injector for Semaglutide 1.34 mg/ml (novoDOCS ID: 003159739). The reviewer is unable to locate a comprehensive risk analysis for the device constituent of the combination product. The risk analysis should characterize and assess the potential risks posed to the user during correct normal use, probable misuse, and in situations where there is a potential device system failure that prevents the device from achieving its intended use. Specifically, the risk analysis should clearly describe the potential hazards that are apparent to your device, describe the safety mitigations you have implemented to address the identified hazards, explain why these mitigations are acceptable, and provide evidence that demonstrates the effectiveness of those mitigations. Furthermore, the risk analysis should include a scientific rationale and clinical justification regarding the acceptability of any residual risks posed within the final finished device system(s). Please provide the location of the risk analysis or provide the risk analysis document(s) that contains the above information.

Sponsor Response (received on April 27, 2017)

Reviewer Comments
The sponsor provided a number of the requested elements; however, further clarifications and additional information was needed. Please see below for the additional information requests.

Follow on Agency Information Request # 2 (sent on May 16, 2017) ADEQUATE

1.On April 21, 2017, the Agency asked for clarification for why (b)(4) increments was chosen for the assessment of dose accuracy post stability studies. Please provide the following clarifications for your response.

a.Table 1 "Supplementary PDS290 pen-injector comparison information with regard to the device used for testing of dose accuracy in the stability study" states that the dose accuracy testing at (b)(4)% is completed for (b)(4) increments (corresponding to (b)(4) mg) showing as '5.0 mg' (see footnote 1) on scale drum". It is unclear how (b)(4) increments equals (b)(4) mgs ((b)(4) is a typo) as the submission states that (b)(4) increment = (b)(4) ml drug product and the concentration of the drug is 1.34 mg/mL.

You state that the dose accuracy testing stability studies documented in 3.2.P.8.3 Primary Stability Data performed on the PDS290 pen-injector for semaglutide used in the phase 3a clinical trial programme (SUSTAIN 1-5) and (SUSTAIN 6) demonstrate that the PDS290 pen-injector for semaglutide 1.34 mg/ml meets the shelf life specifications for the dose accuracy.

Additionally, you state that the dose accuracy testing in the stability studies for the lowest and highest labelled doses are considered unnecessary and the dose accuracy test at dose setting at midpoint of (b)(4) increments is considered sufficient. This is based on the data leveraged from the PDS290 pen-injector for insulin (FlexTouch) as the dose accuracy for the PDS290 pen-injector for insulin (FlexTouch®)has been tested at (b)(4) increments, which are representative of the increments used in the semaglutide pen injector (i.e. (b)(4) increments). You reference supplement 61 of NDA 020986 for the Flextouch. This appears to be a labeling supplement and does not contain the stability data.

i.Please clarify the concentration of the Semaglutide used in the stability studies and the concentration of the Semaglutide used in the clinical studies.

ii. Footnote 1 could not be located in the response document. Please update the information provided to include footnote 1.

iii. To leverage data from the FlexTouch pen for stability studies, please provide a comparison of the drug products and provide a rationale for why any differences would not impact the dose accuracy testing after the stability protocols.

iv. Please provide the location of the stability testing for the FlexTouch combination product that you are leveraging as part of your assessment of the dose accuracy/stability studies.

b. In response to Question 5, you included the following information on the SUSTAIN 6 clincial trial:

PDS290 pen-injector for semaglutide used in the phase 3a clinical trial programme (SUSTAIN 6; 3297 participants for two years), with an imprint on the scale drum of (b) (4) mg with imprints every (b) (4) mg

The stability data provided in Appendix C, lists the dose accuracy in around (b) (4) mg). Footnote 2 includes the following information:

The dose settings appearing on the PDS290 pen-injector for semaglutide used in the phase 3a clinical trial programme (SUSTAIN 6) do not correspond to the actual number of milligram of active semaglutide 1.34 mg/ml solution for injection. In clinical trial SUSTAIN 6, a conversion table is used to dial the number of milligrams on the scale drum, which corresponds to the prescribed number of milligrams of active semaglutide 1.34 mg/ml solution for injection.

It is unclear how this relates to the drug product as (b) (4) increment = (b) (4) ml drug product and the concentration of the drug is 1.34 mg/mL.

i. Please clarify the concentration of Semaglutide in the PDS290 pen-injector for Semaglutide used in the phase 3a clinical trial programme (SUSTAIN 6).

ii. Please provide a rationale for why the dose accuracy testing using the (b) (4) mg pen injector is applicable for the to-be marketed combination product (1.34 mg/mL, 1.5 mL cartridge).

2. On April 21, 2017, the Agency requested that you include a dose accuracy specification for the lowest dose (0.25 mg) in your release specifications. The release specifications are included below:

Dose accuracy	Weighing A332601a	Complies[5,6]

5: Complies means that the specification limit = (b) (4) at a dose of 0.5 mg semaglutide (corresponding to (b) (4) solution for injection) for the PDS290 pen-injector for semaglutide 1.34 mg/ml (0.25 mg/0.5 mg/1.0 mg), item no. 5-9558-xx is fulfilled using ISO 3951-1:2005 or ISO 3951-2:2006

6: Complies means that the specification limit = (b) (4) at a dose of 1.0 mg semaglutide (corresponding to (b) (4) solution for injection) for the PDS290 pen-injector for semaglutide 1.34 mg/ml (1.0 mg), item no. 5-9506-xx is fulfilled using ISO 3951-1:2005 or ISO 3951-2:2006

Please clarify if (b) (4) mg is a typo and is meant to state (b) (4) uL. If so, please update your specifications document to include the correct units. If not, please clarify how

0.5 mg and 1.0 mg of Semaglutide corresponds to (b) (4) mgs of solution for injection, respectively.

Sponsor Response (received on May 29, 2017)

Reviewer Comments
The sponsor provided the requested information. The response is adequate. The sponsor's responses have been incorporated into the appropriate sections of the review memo.

Information Request # 3 (sent on June 8, 2017) ADEQUATE

On June 7, 2017, the sponsor submitted a proposal to change the to-be marketed pen (see section 12). The following IRs were sent to determine if the change would impact the review timeline.

1. Please provide a more detailed description of the proposed modification.

    a. Please include the mechanism of the dose stop and technical drawings.
    b. Please clarify if the dose stop is right at .5 mg.

2. Please clarify how you plan to verify that the dose stop works after shipping, dropping, etc.

Sponsor Response (received on June 12, 2017)

Reviewer Comments
Based on the information provided, it was determined that the change should not impact the review timeline.

Follow on to IR #1 (deficiency #8) Agency Information Request # 4 (sent on June 13, 2017) - ADEQUATE

1. You have not included a comprehensive risk analysis in this NDA. You state that the PDS290 peninjector for semaglutide 1.34 mg/ml utilizes some generic PDS290 components and (b) (4) to other marketed PDS290 pen-injectors and have been analysed with regard to risks related to the design and manufacturing processes by the use of the FMECA method. You also state that the conclusion of the design and manufacturing risk management analysis for the PDS290 pen-injector for semaglutide 1.34 mg/ml is that all risks have been analysed, assessed and reduced as documented in the FMECA document; however, this document has not been provided.

Please clarify if there are any differences between the FMECA performed on the PDS290 semaglutide 1.34 mg/ml pen injector and the FMECA performed on previously approved PDS290 pen-injectors. If there are any differences, please provide a list of the differences and the corresponding risk analysis information.

Sponsor Response (received on June 27, 2017)

Reviewer Comments
The sponsor provided the requested information. The deficiency is resolved.

14.RECOMMENDATION

The device is approvable based on the design and performance review of the device constituent of the combination product.

APPEARS THIS WAY ON ORIGINAL

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Devices and Radiological Health
Office of Compliance, TPLC Division 2
Respiratory, ENT, General Hospital, Ophthalmic (REGO) Device Team

DATE: July 28, 2017

TO: Suong Tran, OMPT/CDER/OPQ/ONDP/DNDPI/NDPBII
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Through: Nazia Rahman, DMQ/OC/CDRH
Nazia Rahman -S
2017.08.09 17:04:00 -04'00'

From: Christopher J Brown, P.E., REGO/D2/OC/CDRH

Applicant: Novo Nordisk, Inc.
P.O. Box 846
800 Scudder Mill Rd
Plainsboro NJ 08536
FEI: 3010446981

Application # NDA 209637

Consult # ICC1600855

Product Name: Semaglutide 1.34 mg/ml solution for assembled in a PDS290 pen-injector

Inspection Needed: Yes (Post Approval)

Documentation Review: No Additional Information Required

Final Recommendation: **APPROVAL**

The Office of Compliance at CDRH received a consult request from CDER to evaluate the applicant's compliance with applicable Quality System Requirements for the approvability of NDA 209637.

PRODUCT DESCRIPTION

Per the firm, Semaglutide is a novel glucagon-like peptide-1 (GLP-1) analogue for once-weekly subcutaneous (s.c.) administration in patients with type 2 diabetes. Patients are required to follow a fixed dose escalation regimen, with an initiation dose of 0.25 mg once-weekly. After 4 weeks, the dose should be increased to 0.5 mg once-weekly. After at least 4 weeks with a dose of 0.5 mg once-weekly, the dose may be increased to 1.0 mg once-weekly for additional glycemic control. The maximum recommended dose is 1.0 mg once-weekly.

Semaglutide is delivered in a prefilled disposable pen-injector belonging to the PDS290 technology platform (already approved for Saxenda®, Levemir®, Tresiba®, Ryzodeg®, and Norditropin®). Semaglutide solution for injection is supplied as an (b) (4) solution ready for injection with a pH of 7.4 and a concentration of 1.34 mg/ml.

The PDS290 pen-injector for Semaglutide 1.34 mg/ml has two variants, both containing Semaglutide 1.34 mg/ml solution for injection filled in a 1.5 ml cartridge. There is no direct contact between the PDS290 pen-injector and the product. The two variants of the PDS290 pen-injector for Semaglutide 1.34 mg/ml are as follows:

- PDS290 pen-injector for Semaglutide 1.34 mg/ml (0.25 mg/0.5 mg/1.0 mg), which can deliver doses of 0.25 mg, 0.5 mg or 1.0 mg.
- PDS290 pen-injector for Semaglutide 1.34 mg/ml (1.0 mg), which can only deliver doses of 1.0 mg

The difference between the two variants of the PDS290 pen-injector for Semaglutide 1.34 mg/ml is limited to the imprint on the scale drum.

Figure 1. Figure 1 PDS290 pen-injector for Semaglutide 1.34 mg/ml

REGULATORY HISTORY

The following facilities were identified as being involved in the manufacturing and/or development of the Semaglutide 1.34 mg/ml solution for assembled in a PDS290 pen-injector in NDA 209637

1. Novo Nordisk, Inc.
   P.O. Box 846
   800 Scudder Mill Rd
   Plainsboro NJ 08536
   FEI: 3010446981

Responsibility - The firm is the applicant and ultimately responsible for the Combination Product Part 4, requirements.

Inspectional History – An analysis of the firm's inspection history over the past 2 years showed that an inspection was conducted 03/21/2016 to 04/12/2016. The inspection covered drug GMP and was classified NAI. The inspection did not cover device GMP.

Inspection Recommendation:
A preapproval inspection is not required because a recent drug inspection of the firm was acceptable. A post-approval inspection covering the 21 CFR 820 quality system requirements for a combination product, as defined in 21 CFR 4.4(b)(1), is requested.

2. Novo Nordisk A/S
   Brennum Park
   Hillerød Hovedstaden 3400
   Denmark
   FEI: 3003131673
   (Owner and Location of Design History File)

Responsibility - Facility responsible for developing the PDS290 pen-injector for Semaglutide 1.34 mg/ml design specifications, maintaining the design history file, and for pre-assembly for the PDS290 pen-injector for Semaglutide 1.34 mg/ml. This facility is responsible for the assembly, labelling and packaging of finished product (Semaglutide 1.34 mg/ml solution for injection, PDS290 pen-injector).

Inspectional History – An analysis of the firm's inspection history over the past 2 years showed that an inspection was conducted 01/11/2016 to 01/22/2016. The inspection covered drug GMP and was classified VAI. The inspection did not cover device GMP.

Inspection Recommendation:
A preapproval inspection is not required because a recent drug inspection of the firm was acceptable. A post-approval inspection covering the 21 CFR 820 quality system requirements for a combination product, as defined in 21 CFR 4.4(b)(1), is requested.

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(b) (4)

[redacted]

Documentation Review Recommendation

The application was searched for documents pertaining to the manufacturing of the combination product. The documentation review of the application for compliance with the applicable Quality System Requirements showed no deficiencies. No additional information is required for the documentation review

RECOMMENDATION

The Office of Compliance at CDRH has completed the evaluation of NDA 209637 and has the following recommendations:

The application for Semaglutide 1.34 mg/ml solution for assembled in a PDS290 pen-injector NDA 209637 is approvable from the perspective of the applicable Quality System Requirements:

(1) The documentation review of the application for compliance with the Quality System Requirements showed no deficiencies.

(2) There were no facility inspections for compliance with applicable Quality System Requirements needed for approvability determination. However, CDRH recommends that the applicant and manufacturer that are listed in the inspectional guidance that follows be inspected post approval since they are subject to, but have not been inspected for 21CFR820, Part 4 regulatory requirements for Combination Products.

Christopher J. Brown -S

Digitally signed by Christopher J. Brown -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000986478, cn=Christopher J. Brown -S
Date: 2017.08.09 17:13:37 -04'00'

Christopher J Brown, P.E.

Prepared: CJBrown: 07/28/2017
Reviewed: NRahman 08/09/2017

CTS No.: ICC160855
NDA 209637

Review Cycle Meeting Attendance:
N/A

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/s/

ANIKA A LALMANSINGH
08/10/2017
Uploaded on behalf of Christopher J Brown, PE

Interim Clinical Inspection Summary

Date	8/1/2017
From	Cynthia F. Kleppinger, M.D., Senior Medical Officer Janice Pohlman, M.D., M.P.H., 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 William Chong, M.D., Team Leader Peter Franks, Regulatory Project Manager Division of Metabolism and Endocrinology Products (DMEP)
NDA/BLA #	NDA 209637
Applicant	Novo Nordisk, Inc.
Drug	Semaglutide
NME (Yes/No)	Yes
Therapeutic Classification	Antidiabetic
Proposed Indication(s)	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (b) (4)
Consultation Request Date	1/25/2017
Summary Goal Date	8/2/2017
Action Goal Date	12/5/2017
PDUFA Date	12/5/2017

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The inspection for this NDA consisted of five domestic and five foreign clinical sites as well as the sponsor. The inspection of the contract research organization is pending. The inspection of two clinical investigators listed below revealed regulatory violations. The inspection of the sponsor and the remaining clinical investigators revealed no regulatory violations.

In general, based on the inspections of the 10 clinical sites and the sponsor, the inspectional findings support validity of data as reported by the sponsor under this NDA. However, Novo Nordisk informed FDA July 5, 2017 during the review of application NDA 209637 that the Event Adjudication Committee (EAC) adjudicators were unblinded to treatment in four open-label trials in the SUSTAIN program. This was not revealed nor discovered during the sponsor inspection

(See background section). It was decided that the contract research organization tasked for handling the adjudication packages (b) (4) should be inspected to access the mistake, verify the number of unblinded packages, and confirm that only the four open-label trials were affected. The Clinical Inspection Summary will be updated once this CRO inspection has been completed.

The classification for Drs. Armas and Frechtel is Voluntary Action Indicated (VAI). Although regulatory violations were noted (as described below), they are unlikely to significantly impact primary safety and efficacy analyses. Reliability of data from these sites is acceptable for use in support of the indication for this application. The full Establishment Inspection Reports (EIRs) were submitted for review.

The classification for Drs. Busch, Cannon, Cheung, Deshpande, Duckor, Kiyosue, Maffei, Matsuoka and the sponsor is No Action Indicated (NAI). Data from these sites are considered reliable based on the available information. The full Establishment Inspection Report (EIR) was submitted for review for Drs. Cannon, Deshpande, Maffei, Busch, and the sponsor. The full Establishment Inspection Report (EIR) was not available for review for Drs. Cheung, Duckor, Kiyosue, and Matsuoka. Preliminary inspection results were communicated by the FDA ORA field investigator.

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 EIRs.

II. BACKGROUND

Novo Nordisk is seeking approval of a New Drug Application (NDA) for Ozempic® (semaglutide) injection indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (b) (4)

Inspections were requested for the following four studies:

- **NN9535-3623** SUSTAIN 1: Efficacy and safety of semaglutide once-weekly versus placebo in drug-naïve subjects with type 2 diabetes

The trial began February 3, 2014 and completed May 8, 2015. Database lock was June 22, 2015. There were 72 sites in 8 countries that randomized subjects. There were 652 subjects screened and 388 subjects randomized. The primary endpoint was change from baseline to week 30 in HbA1c.

- **NN9535-3625** SUSTAIN 4: Efficacy and safety of semaglutide once weekly versus insulin glargine once daily as add on to metformin with or without sulphonylurea in insulin-naïve subjects with type 2 diabetes

The study began August 4, 2014 and completed September 3, 2015. Database lock was October

23, 2015. There were 196 sites in 14 countries that randomized subjects. There were 1610 subjects screened and 1089 subjects were randomized. The primary endpoint was change from baseline in HbA1c at week 30.

- **NN9535-3627** Efficacy and safety of semaglutide once-weekly versus placebo as add-on to basal insulin alone or basal insulin in combination with metformin in subjects with type 2 diabetes (T2D)

The study began December 1, 2014 and completed November 21, 2015. Database lock was January 21, 2016. There were 90 sites in five countries that randomized subjects. There were 534 subjects screened and 397 subjects randomized. The primary endpoint was change from baseline in HbA1c at week 30.

- **NN9535-3744** SUSTAIN 6 – Long-term Outcomes A long-term, randomized, double-blind, placebo-controlled, multinational, multi-center trial to evaluate cardiovascular and other long-term outcomes with semaglutide in subjects with type 2 diabetes.

The study began February 21, 2013 and completed March 15, 2016. There were 229 sites in 20 countries that randomized subjects. The primary endpoint was time from randomization to first occurrence of a major adverse cardiovascular event (MACE), defined as cardiovascular (CV) death, non-fatal myocardial infarction (MI), or non-fatal stroke.

Novo Nordisk informed FDA July 5, 2017 during the review of application NDA 209637 that a deviation had been identified from the predefined adjudication process for the four open-label trials in the semaglutide phase 3a program (SUSTAIN). The four affected open-label trials are Study 3624, Study 3625 and two local Japanese trials (Studies 4091 and 4092).

According to the Event Adjudication Committee (EAC) charter, the adjudicators were to be blinded to treatment in all trials in the SUSTAIN program, regardless of whether the trials were double-blind or open-label, and even though treatment allocation was known by investigators and site personnel in the open-label trials. To maintain blinding, all information that could potentially unblind the EAC members was to be redacted before sending the packages to the EAC members. The adjudication process was handled by the external, independent contract research organization, (b) (4), who managed the collection and verification of relevant information from the clinical trial sites for events sent for adjudication, and ensured that the information was blinded with respect to treatment assignment and anonymized before forwarding it to the EAC members.

In addition to source data from the clinical sites, all events sent for adjudication had information from the electronic case report form (eCRF) provided from Novo Nordisk. The eCRF in the open label trials contains information on trial product, dose and/or route of administration, which is not the case in the double-blinded trials. Novo Nordisk discovered on June 1, 2017 that the eCRF information was not consistently redacted by (b) (4) and was inadvertently included in the packages sent to the EAC members. In the four affected trials, the redaction of treatment assignment, dose or administration route was not consistently implemented in the supporting eCRF. The eCRFs were provided to the independent EAC members in addition to source data from investigators in the open-label trials, thereby leading to potential unblinding of EAC members.

A total of 2,994 events were sent for adjudication in all trials in the SUSTAIN phase 3a program. After an investigation by the sponsor, it was determined that 275 packages (from 185 patients) included unredacted information in the eCRF where the EAC members could have been unblinded to treatment information. Novo Nordisk is in the process of forming a new EAC to reassess the 275 cases in a blinded manner. As the trials have been completed, the contract research organization will need to re-open the event adjudication system. The blinded adjudication will be performed using the same process and definitions as the original adjudication, however, additional source data cannot be requested and new events cannot be identified. Novo Nordisk will submit the outcome of the blinded adjudication, including an evaluation of any differences in adjudication outcome.

Assessment by FDA of the unblinding incident is pending inspection of (b) (4)

III. RESULTS (by Site):

Name of CI/ Address Site#	**Protocol # and # of Subjects Randomized**	**Inspection Date**	**Classification**
Mayura Deshpande MeDiNova North London Clinical Studies Centre Mount Vernon Hospital Rickmansworth Road Northwood, NA HA6 2RN Great Britain Site 111 and Site 528	P3625 Site 111 15 subjects P3744 Site 528 12 subjects	04/28 – 05/05/2017	No Action Indicated (NAI)
Gustavo Frechtel Fernandez de Enciso 4620 CABA, NA C1419AHN Argentina Site 122	P3744 30 subjects	05/29 – 06/02/2017	Voluntary Action Indicated (VAI)*
Laura Maffei Consultorios Asociados de Endocrinologia Cerviño 3365/75, Piso 1, Office 2 Buenos Aires, NA C1425AGC Argentina Site 804	P3625 16 subjects	06/05 – 06/08/2017	No Action Indicated (NAI)
Arihiro Kiyosue 3-3-14, Nihombashi Chuo-ku, Tokyo, NA 103 0027 Japan Site 901 and Site 152	P3623 Site 901 15 subjects P3627 Site 152 11 subjects	05/29 – 06/02/2017	No Action Indicated (NAI)*
Osamu Matsuoka 6-26-8, Shinjuku Shinjuku-ku, Tokyo, NA 160-0022 Japan Site 903	P3623 14 subjects	06/05 – 06/08/2017	No Action Indicated (NAI)*
Eddie Armas 7000 SW 62nd Ave Suite 100 Miami, FL 33143-4717 Site 412	P3623 11 subjects	04/26 – 05/02/2017	Voluntary Action Indicated (VAI)*

Robert Busch 1365 Washington Avenue Suite 300 Albany, NY 12206 Site 604	P3744 33 subjects	06/26 – 06/29/2017	No Action Indicated (NAI)
Kevin Cannon PMG Research of Wilmington 1907 Tradd Court Wilmington, NC 28401 Site 692 and 683	P3625 Site 692 6 subjects P3744 Site 683 30 subjects	05/08 – 05/11/2017	No Action Indicated (NAI)
Deanna Cheung 3745 Long Beach Blvd. Suite 100 Long Beach, CA 90807 Site 728	P3625 7 subjects	07/13 – 07/20/2017	No Action Indicated (NAI)*
Steven Duckor 1085 N. Harbor Blvd Anaheim, CA 92801 Site 734 and Site 309 and Site 610	P3625 Site 734 8 subjects P3627 Site 309 8 subjects P3744 Site 610 16 subjects	07/24 – 07/28/2017	No Action Indicated (NAI)*
Novo Nordisk A/S Vandtaarnsvej 114 DK 2860 Soeborg Denmark	P3623 P3625 P3627 P3744	06/12 – 06/15/2017	No Action Indicated (NAI)
(b) (4)	P3623 P3624 P3625 P3627 P3744 P4091 P4092	PENDING	

Key to Compliance Classifications
NAI = No deviation from regulations
VAI = Deviation(s) from regulations
OAI = Significant deviations from regulations; data unreliable.
*Pending = Preliminary classification based on information in 483 (if applicable) and preliminary communication with the field; final classification is pending letter to site.

NOTE: Site inspections focused on 100% 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.

The non-U.S. sites were not conducted under IND.

1. Mayura Deshpande/ Site 111 P3625 / Site 528 P3744

The MeDiNova North London Clinical Studies Centre is a dedicated clinical research center since 1997 physically located on the Mount Vernon Hospital campus in Northwood (North London), U.K. Dr. Mayura Deshpande, M.D. was the Principal Investigator (PI) responsible for both clinical trials at the time of completion. Dr. Deshpande is no longer employed at the site. She accepted a position at another institution in April 2016. Dr. Ronnie Beboso, M.D. was assigned as the PI of record for record/document access and inspection purposes. He was not involved in either clinical trial inspected. Three different PIs were involved in the conduct of P3625 at the inspected site. There were two different PIs involved in the conduct of P3744 at the inspected site.

For Study P3625, there were 20 subjects screened and 15 subjects enrolled into the study; 11 subjects completed the study (two subjects were enrolled and randomized but withdrew consent at the time of randomization and two subjects were discontinued from participation due to adverse events as required by the protocol). There were 20 subject records reviewed.

The central Research Ethics Committee (REC) of record is (b) (4)

For Study P3744, there were 21 subjects screened and 12 subjects enrolled into the study; six subjects completed the study (one subject died, four subjects withdrew due to serious adverse events and one additional subject was withdrawn due to protocol non-compliance). There were 21 subject records reviewed.

The central Research Ethics Committee (REC) of record is (b) (4)

For both studies, study records were orderly and available for inspection. There were dedicated Site Files or Trial Master File binders that included general and regulatory type records. The files for both trials were similar and included much of the same sections and information pertaining to the respective trial. Source records verified all inclusion/ exclusion criteria. Clinical trial activities and conduct was well documented. There was no under-reporting of adverse events. The primary efficacy endpoints were verifiable as well as the secondary efficacy endpoints reviewed. Data was verifiable by comparing the source documents to the eCRFs and/or the sponsor data listings/tables.

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. Gustavo Frechtel/ Site 122 P3744

There were 34 subjects screened and 30 subjects enrolled into the study; 30 subjects completed the study. There were 11 subject records reviewed.

The study was conducted at an office affiliated with the hospital about three blocks away. Dr. Frechtel has a private practice adjacent to the hospital and devotes about 50 percent of his time to clinical studies. The subjects recruited for these studies were already patients of the hospital, his private practice and/or from referring physicians who are subinvestigators.

There were two Ethics Committees (ECs) for the study as there were new regulations that were passed for ECs in Argentina. The original EC that approved the study was (b) (4) (b) (4) The subsequent EC was .

There was a sponsor audit performed at the site on 6/30/2015 which identified a high number of protocol deviations and laboratory reports with evaluations documented out of timelines. Corrective actions were instituted and the sponsor retrained the staff.

The study files were well organized and available. There was no under-reporting of adverse events. The primary endpoint was verifiable. All protocol deviations were captured and reported. The source records confirmed the data in the sponsor data line listings except for the inspectional observations noted of missing concomitant medications.

At the conclusion of the inspection, a Form FDA-483, Inspectional Observations, was issued for the following deficiencies:

1. Failure to ensure that an investigation was conducted in accordance with the general investigational plan and protocols as specified in the IND. Specifically, the following concomitant medications found in the source records were not listed in the eCRF/data submitted to the sponsor:

Subject #	Date taking medication and/or listed on source	Concomitant Medications listed on source document
122-019	04/08/2014	Brimonidina, Timolol 0.50%, Travoprost, Terazosina 5mg, and Alprazolam
122-028	09/26/2013	Aspirina 100 mg

In addition, while reviewing the medical notes for subject 122-001, there is a date entry 5/7/2014 for a flu vaccine that was also not listed as a concomitant medication.

Dr. Frechtel responded to the observations on 6/15/2017 with appropriate corrective and preventive actions.

3. Laura Maffei/ Site 804 P3625

There were 26 subjects screened and 16 subjects enrolled into the study; 16 subjects completed the study. There were 16 subject records reviewed.

Dr. Maffei devotes about 65 % of her time to clinical studies and 35 % to her private practice. The subjects were recruited from the site's database and also had patients that were referred to the site.

The IRB for this study was (b) (4)

Documents were orally translated during the inspection. The study files were available and organized. Source records were compared to the sponsor data line listings and there were no discrepancies. There was no under-reporting of adverse events. The primary efficacy endpoint was verifiable.

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. Arihiro Kiyosue/ Site 901 P3623/ Site 152 P3627

For Study P3623, there were 16 subjects screened and 15 subjects enrolled into the study; 15 subjects completed the study. There were 16 subject records reviewed.

Records were adequate and very well organized. There was no evidence of under-reporting of AEs. The primary endpoints were verifiable. There were no discrepancies with source data and sponsor's data line listings.

For Study P3627, there were 13 subjects screened and 11 subjects enrolled into the study; 10 subjects completed the study. There were 13 subject records reviewed.

Records were adequate and very well organized. There was no evidence of under-reporting of AEs. The primary endpoints were verifiable. There were no discrepancies with source data and sponsor's data line listings.

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. Osamu Matsuoka/ Site 903 P3623

There were 16 subjects screened and 14 subjects enrolled into the study; 13 subjects

completed the study. There were 16 subject records reviewed. Of note, only one woman was entered into the trial. The clinical investigator indicated that women are reluctant to enter into clinical studies in Japan.

Records were adequate and very well organized. There was no evidence of under-reporting of AEs. The primary endpoints were verifiable. There were no discrepancies with source data and sponsor's data line listings.

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. Eddie Armas/ Site 412 P3623

There were 16 subjects screened and 11 subjects enrolled into the study; 10 subjects completed the study. There were 11 subject records reviewed.

The clinical trial took place at Well Pharma Medical Research, which is a site management organization partly owned by Dr. Armas and also serves as Dr. Armas' private practice. The subjects enrolled were recruited mostly through his private practice, but some were also referred to him by physician assistants that he works with.

The IRB used for the clinical trial was (b) (4)

A review of the source documents showed no major deviations from the protocol and all instances were documented and communicated to the sponsor. There were no major discrepancies noted between the source documents and data listings. There was no under-reporting of adverse events. The primary efficacy endpoint was verifiable. The subject records were found to be organized and complete except for the documentation of patient compliance with taking the investigational product.

At the conclusion of the inspection, a Form FDA-483, Inspectional Observations, was issued for the following deficiencies:

1. Failure to prepare or maintain adequate and accurate case histories with respect to observations and data pertinent to the investigation. The site created its own source documentation templates based on the protocol requirements. According to the source documents, the site verifies subject compliance with taking their weekly injection by reviewing the subject diary where subjects record the date they took each injection. However, the subject diary does not have a space for every dose that is required to be taken, therefore this method is ineffective in verifying subject compliance.

The study coordinator for the study stated that the source documents were incorrect in that the subject compliance was not based solely on the entries in the subject diary. She stated

she used the subject diaries as well as subject interviews to ensure that the subjects were compliant. It was difficult to document compliance because the injector pens did not have a counter which would countdown the amount of product left in the pen, so the only way they could document compliance is through the subject diary and subject interviews.

> *OSI Reviewer Comment: The root cause of the problem was that the diary was improperly designed and did not capture all doses. Dr. Armas responded to the observations May 10, 2017 with corrective and preventive actions deemed to be acceptable.*

7. Robert Busch/ Site 604/ P3744

There were 38 subjects screened and 33 subjects enrolled into the study; 33 subjects completed the study (25 subjects who completed the study on study medication and eight subjects who completed off study medication). There were 24 subject records reviewed.

Dr. Busch is the Director of Clinical Research of the Endocrine Group which is comprised of multiple endocrinologists and ancillary staff and is part of the Albany Medical Faculty Physicians. Potential subjects were identified within the electronic data base of patients at his endocrinology practice.

The IRB of record is the centralized (b) (4).

The study files were well organized and available. There was no under-reporting of adverse events. The primary endpoint was verifiable. All protocol deviations were captured and reported. The source records confirmed the data in the sponsor data line listings.

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. Kevin Cannon/ Site 692 P3625/Site 683 P3744

For Study P3625, there were eight subjects screened and six subjects enrolled into the study; six subjects completed the study. There were eight subject records reviewed.

For Study P3744, there were 48 subjects screened and 30 subjects enrolled into the study; 28 subjects completed the study (two withdrew consent). There were 12 subject records reviewed.

The IRB used for the studies is (b) (4).

For both studies, the inspection found no significant deficiencies. All subjects appeared to have met eligibility criteria. Data listings were compared to and found consistent with source documents. Primary efficacy endpoint data were verifiable. There was no evidence of under-reporting of AEs.

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. Deanna Cheung/ Site 728 P3625

There were 13 subjects screened and seven subjects enrolled into the study; four subjects completed the study. There were 13 subject records reviewed.

Study records were available, organized and legible. The inspection found no significant deficiencies. All subjects appeared to have met eligibility criteria. Data listings were compared to and found consistent with source documents. Primary efficacy endpoint data were verifiable. There was no evidence of under-reporting of AEs.

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. Steven Duckor/ Site 734 P3625/ Site 309 P3627/ Site 610 P3744

For Study P3625, there were 11 subjects screened and eight subjects enrolled into the study; seven subjects completed the study. There were 11 subject records reviewed.

For Study P3627, there were 12 subjects screened and eight subjects enrolled into the study; eight subjects completed the study. There were 12 subject records reviewed.

For Study P3744, there were 19 subjects screened and 16 subjects enrolled into the study; 15 subjects completed the study. There were 19 subject records reviewed.

For all three studies, all subject records were organized, legible, and available. There were no discrepancies noted in comparing the source documents to the data listings. There was no under-reporting of adverse events. The primary efficacy endpoints for the three studies were verifiable. No issues were noted regarding the eligibility criteria, test article accountability or randomization procedures.

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.

11. Novo Nordisk A/S/ Sponsor

The inspection consisted of reviewing the organizational structure and responsibilities, transfer of obligations, contractual agreements, selection of sites, training, investigational product accountability, the evaluation of the adequacy of monitoring and corrective actions taken by the sponsor/monitor/CRO, deviations related to key safety and efficacy endpoints, quality assurance and audits, adverse events evaluation and reporting, 1572s and

investigator agreements, the interactive voice/web response system, financial disclosures, standard operating procedures (SOPs), trial master file review, record retention, selection criteria for all committee members, oversight of committees, data management, escalation of issues, and clinical trial oversight.

Several trial-level issues were also assessed, including the following:

1. Source documents for Medical Events of Special Interest (MESIs) requiring event adjudication were to be loaded within four weeks of event identification by the sites into (b) (4) (b) (4) (b) (4) Event Adjudication System (EAS). Requesting access to the database and the timeline for upload of source documents within four weeks of event identification had not been possible in the period of January 23, 2014 to March 17, 2014 due to technical issues. As the Site IDs (Site numbers) in the SUSTAIN program are not unique, (b) (4) had to correct the Site list by adding the Trial ID to all the Site numbers created in the (b) (4) EAS database. The database was not available for uploading during the time of the corrections. Data transfer from the FTP server used for the transfer of events from Novo Nordisk to (b) (4) EAS had not been possible. It was confirmed that this had no impact on MESIs/SAEs reporting as there was monitoring of the adverse events reported by the investigator in the eCRF (Inform).
2. For the time period of June 17, 2014 until September 30, 2014, SUSAR reports in Mexico were delivered late (105 days delayed) mainly owing to missing oversight from the responsible clinical trial administrator and the loss of airway bills from the SUSAR packages by the courier. This issue was captured in a country level protocol deviation. The sponsor assessed the deviation when it was discovered. No safety issues warranting actions were identified based on review of safety information reported. No actions were recommended by the DMC based on safety data reported. The SUSAR reports in question did not change the overall safety profile of semaglutide from the IB versions 9 and 10 effective before and after the late SUSAR reporting to investigators; no updates were made based on the SUSARs in question.
3. A total of 25 subjects had been treated with investigational medicinal product (IMP) stored at an incorrect temperature. There were 18 deviations between April 23, 2014 and June 11, 2014 related to US Site 415. An investigation was done by the sponsor. The site used a back-up thermometer only during this period that only recorded actual temperatures. The site misunderstood how to properly monitor and document temperature recordings with the back-up device. This was not picked up by the site monitor. Therefore, trial product was stored at an unknown temperature, and quality was not supported by stability data. This was discovered during a site audit on April 1, 2015. Out of the 18 subject level protocol deviations the trial product was deemed acceptable for use for 10 subjects after review of available documentation by the clinical supply temperature deviation team. The remaining eight deviations cover six subjects that had trial product dispensed which was deemed unacceptable for use. Some were returned and some were lost by the subject. There have been no AEs. The site staff was retrained to ensure correct use and reading of temperature devices.
4. Dr. Uzoaga was an investigator for US Site 697 that was activated on August 13, 2013. Nine patients were enrolled at this site. Dr. Uzoaga was found guilty of health care fraud and conspiracy to commit health care fraud in November 2015 and sentenced to 42 months prison in March 2016. The sponsor learned of the indictment of Dr. Uzoaga on October 22, 2014.

The FDA inspector reviewed all of the Uzoaga monitoring visit reports and confirmed that there were no issues identified during those visits. It was asked why it was not possible to transfer the subjects or get a new investigator. It was explained that there was only one site within reasonable travel distance from Dr. Uzoaga's site. It was determined that this other site was not a viable option as the site already had 21 ongoing patients and not adequate resources for a transfer of more subjects. Also, the trial was near to completion at the Dr. Uzoaga site with only off-study drug follow-up visits remaining. Based on the internal evaluation of the charges against Dr. Uzoaga along with the outcome of the Quality Assessment visit (Dec-2014), Novo Nordisk determined that it was not necessary to either transfer the subjects or change investigators. It was confirmed that there were four remaining subjects at the time the sponsor learned of the conviction. All patients were off trial product and the four patients were scheduled for the final visit.

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.

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08/01/2017

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Ophthalmology Consult Review of NDA 209-637

Consult Request Date: January 26, 2017
Submission Date: December 5, 2016
Review completed: July 4, 2017

Product name: Semaglutide

Applicant: Novo Nordisk
Related IND: IND 79,754

Requested: On December 5, 2016, Novo Nordisk submitted original NDA 209637 for semaglutide (s.c.). Semaglutide injection is a long-acting glucagon-like peptide-1 (GLP-1) agonist. The proposed indications are as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitu (b) (4) The sponsor is pursuing approval of semaglutide through the 505(b)(1) pathway.

The Applicant noticed an imbalance in retinopathy events with semaglutide compared to placebo. This was mainly observed in the cardiovascular outcomes study (3744), the largest study in the development program, and also including the patients with longer diabetes duration and more complications. In study 3744 retinopathy events were systematically assessed and adjudicated. The imbalance was noted early, and was maintained throughout the course of the study.

The DMEP would appreciate the opinion of the DTOP on the following:

1. In your opinion, were the processes in place for capturing retinopathy events adequate and appropriate to capture events and assess the clinical significance of these events? Do you have any concerns regarding the processes in place for identifying and adjudicating retinopathy events in the semaglutide program (and specifically study 3744)?

2. Given the available data, how seriously would you view the reported ophthalmologic events (i.e., progression, need for intervention)?

3. Our understanding is that sudden changes in glucose control are associated with progression of diabetic retinopathy, though we note that we have not previously observed an increased incidence in retinopathy with previous antidiabetic drugs. We would appreciate your expertise in considering this potential safety signal and implications for use of semaglutide in this patient population. Given the timing of the events, what is your opinion with regard to the reason for the observed difference between treatment arms? Do you think that the observed increase in the incidence of retinopathy events could be due to a rapid reduction in glucose with semaglutide, or could it be a drug-related toxicity/adverse event?

4. Based on the available data, do you have any recommendations with regard to the use of semaglutide (e.g., restricted population, alternative dosing schedule, recommendations on retinal exam schedules, etc.)?

5. Do the findings of an increased incidence in progression of retinopathy raise any other concerns?

Meeting dates:
Filing meeting: January 19, 2017
Mid-Cycle Meeting: May 11, 2017
Labeling Planning Meeting: June 1, 2017
Labeling Meetings: September 27, 2017, October 17, 2017
Wrap-up Meeting: October 10, 2017
Link to electronic submission (if available): \\CDSESUB1\EVSPROD\NDA209637\209637.enx

Note: This is a Consult Review and comments in this review are limited to areas of Ophthalmologic Concern.

Clinical Trial: Trial ID: NN9535-3744 SUSTAIN 6 – Long-term Outcomes
A long-term, randomised, double-blind, placebo-controlled, multinational, multi-centre trial to evaluate cardiovascular and other long-term outcomes with semaglutide in subjects with type 2 diabetes.

The trial was double-blinded, and eligible subjects were randomized 1:1:1:1 to receive once-weekly doses of semaglutide 0.5 mg, or semaglutide 1.0 mg, or volume-matched placebo, as an add-on to their standard-of-care treatment.

Population:
Of the 4346 subjects screened, 1049 subjects were screening failures. The majority of screening failures (668/1049) were due to subjects not meeting the inclusion criterion of an HbA1c ≥7% at screening. 3297 subjects were randomized (1:1:1:1) to receive semaglutide 0.5 mg (826 subjects), semaglutide 1.0 mg (822 subjects), placebo 0.5 mg (824 subjects) or placebo 1.0 mg (825 subjects).

Primary objective
To confirm that treatment with semaglutide does not result in an unacceptable increase in cardiovascular risk as compared to placebo in adults with type 2 diabetes. This is done by demonstrating that the upper limit of the two-sided 95% confidence interval (CI) of the hazard ratio for semaglutide versus placebo is less than 1.8 when comparing time to first occurrence of a major adverse cardiovascular event (MACE).

The primary objective was changed in global protocol amendment no. 4, implemented after FSFV, from the original: To confirm that treatment with semaglutide does not result in an unacceptable increase in cardiovascular risk as compared to a pooled comparator group (including placebo and active comparators) in adults with type 2 diabetes. This is done by demonstrating that the upper limit of the 95% CI of the hazard ratio for semaglutide versus comparators is less than 1.8 when comparing in a meta-analysis time to first occurrence of a major adverse cardiovascular event (MACE) using all MACEs accrued from all subjects included in all of the confirmatory phase 3a clinical trials.

Secondary objectives/endpoints
In order to address the primary and secondary objectives of the trial, the following parameters were assessed: CV and microvascular outcomes, AEs including MESI, episodes of hypoglycaemia, safety laboratory measures (haematology, biochemistry, urinalysis, antibodies), ECG, glycaemic control parameters, body weight and waist circumference, pulse rate, BP, PRO and population PK (in a subgroup).

Within multiple secondary objectives was the following time-to event:

- time from randomization to first occurrence of a composite microvascular outcome, defined as any one of the following:
  - need for retinal photocoagulation or treatment with intravitreal agents
  - vitreous hemorrhage
  - onset of diabetes-related blindness (defined as Snellen visual acuity of 20/200 [6/60] or less, or visual field of <20 degrees in the better eye with best correction possible)
  - new or worsening nephropathy (defined as new onset of persistent urine albumin ≥300 mg/g creatinine (macro-albuminuria), or persistent doubling of serum creatinine level and eGFR ≤ 45 mL/min/1.73 m2 per MDRD
  - need for continuous renal replacement therapy in the absence of an acute reversible cause
  - death due to renal disease
- time from randomization to each individual component of the composite microvascular outcome and to the retinopathy and nephropathy composite outcomes separately.

Reviewer's Comment:

1. *The composite microvascular outcome as defined in this protocol is not recommended to be used as an outcome measure. It combines equally events which are of unequal clinical severity, unequal clinical significance, and unequal expected frequency. The endpoint is more of a measure of an effect on the kidneys and does not represent a complete picture of microvascular outcomes.*

2. *The "need for retinal photocoagulation or treatment with intravitreal agents" is not a good endpoint. In spite of clinical trials demonstrating the clinical benefits and clinical consequences of retinal photocoagulation, there is not uniform agreement on the clinical characteristics that should dictate the timing of photocoagulation treatment. Up until the advent of Vascular Endothelial Growth Factor (VEGF) inhibitor use, clinical trials would have suggested that the use be based on having proliferative retinopathy. Presently, VEGF inhibitors can be used to treat proliferative retinopathy. In addition, cost, reimbursement, medical alternatives and a variety of individual interests can influence the "need" or "actual" retinal photocoagulation treatment. There are examples in clinical trials over the past 15 years of specific retinopathy treatment criteria for photocoagulation being defined at the start of a clinical trial, yet multiple investigators choose to either perform photocoagulation before the criteria was met or choose to not perform photocoagulation even though the predefined criteria was met.*

   There are clinical trials demonstrating the clinical benefits and potential clinical consequences of intravitreal injections, but like retinal photocoagulation, there is not uniform agreement on the timing for administering intravitreal agents. In addition, cost,

reimbursement, and a variety of individual interests can influence the "need" or "actual" administration of intravitreal agents.

3. *While the protocol described this measure as the "need for treatment," it appears that the Event Adjudication Committee Charter required actual treatment in order to valid this endpoint. This could have resulted in some events being counted when they were not actually needed and some events not being counted because the treatment was not performed.*

4. *The onset of diabetes-related blindness (defined as Snellen visual acuity of 20/200 [6/60] or less, or visual field of <20 degrees in the better eye with best correction possible) is not a good endpoint because it is difficult to judge whether the blindness was diabetes related. There are increased frequencies of many ocular conditions (e.g., cataracts, macular edema, retinal vein occlusions) leading to a loss of visual acuity in patients with diabetes. This does not necessarily mean that any loss of vision due to one of these conditions is necessarily due to the diabetes. Some of the conditions leading to a visual acuity of 20/200 or worse are potentially reversible (i.e., cataracts, macular edema, vitreous hemorrhage) and some are not. The clinical significance of this endpoint depends on whether the blindness is reversible or not.*

5. *Vitreous hemorrhage could have been a reasonable endpoint, particularly if it was qualified by the duration that it was present. However, the frequency of the event is often low even in an untreated group, and therefore the endpoint is of limited utility unless the number of enrolled subjects is very large (i.e., larger than this trial). Vitreous hemorrhages which do not resolve within 3 months (often leading to a need for a vitrectomy) are much more significant than those which resolve more quickly without any significant intervention.*

6. *"Time to" events involving retinopathy, even when measured on an accepted retinopathy scale (i.e., ETDRS [Early Treatment Diabetic Retinopathy Study]) are problematic because rapid drops in Hemoglobin A1c (HbA1c) result in an increase in diabetic retinopathy during the first year in which the HbA1c decreased. The most well-known of the studies to demonstrate this was the Diabetic Control and Complications Trial (DCCT). The DCCT study demonstrated that rapid decreases in HbA1c resulted in increased retinopathy. The control group did not catch up until Year 3. While the DCCT demonstrated this finding in Type 1 diabetics, it is true for both Type 1 and Type 2 diabetics [Literature examples include by are not limited to Arch Ophthalmol. 2006;124:38-45. and Diabetes Research and Clinical Practice. 2014;103(3):e37-39.]*

Fundoscopy/fundus photography
Fundoscopy/fundus photography was to be performed at visit 2 or within 90 days prior to visit 2 if the fundoscopy/fundus photography had been performed for any reason unrelated to this trial.

In this case the fundoscopy/fundus photography did not need to be repeated, unless visual function had worsened since the last examination. It was to be documented in the medical records that the reason for performing the fundoscopy/fundus photography was not related to this trial.

Furthermore, fundoscopy/fundus photography was to be performed at visits 11 and 25 (Weeks 56 and 104) or within 14 days prior to these visits.

In case of premature discontinuation of trial product, fundoscopy/fundus photography was to be performed at visit 25A. It was acceptable to perform the fundoscopy/fundus photography after visit 25A provided the results were available at visit 26A.

Fundoscopy/fundus photography was to be performed by the investigator, a local ophthalmologist or an optometrist according to local practice. Dilation was not a requirement. Result of the fundoscopy/fundus photography was to be interpreted locally by the investigator. The interpretation followed the categories:

- Normal
- Abnormal, not clinically significant
- Abnormal, clinically significant.

To ensure fundoscopy/fundus photography was performed timely, the investigator was to assist the subject in making appointments for fundoscopy/fundus photography.

Reviewer's Comment: *The lack of standardized fundus evaluations at baseline and throughout the study is problematic in trying to assess whether the groups were equal at baseline and whether there was any progression. It is hoped that the randomization provided equal baselines between groups. The absence of formal grading (readings of retinal fundus photography) of the level of retinopathy in this trial severely limits the ability to evaluate the effect of treatment intervention on ophthalmic endpoints in this population. While photography can sometimes be performed without dilation, funduscopy without dilation is not a reliable method of assessment diabetic retinopathy.*

History of diabetic complications at baseline

	Semaglutide	Placebo
Number of subjects in FAS	1648	1649
Diabetic retinopathy		
Yes	510 (31%)	459 (28%)
Nonproliferative [a]	402 (24%)	348 (21%)
Macular oedema	31 (2%)	33 (2%)
Laser therapy/intravitreal agents	57 (4%)	43 (3%)
Surgical treatment	5 (0.3%)	5 (0.3%)
Proliferative [a]	103 (6%)	99 (6%)
Macular oedema	16 (1%)	15 (1%)
Laser therapy/intravitreal agents	59 (4%)	53 (3%)
Surgical treatment	14 (0.8%)	10 (0.6%)
Unknown	5 (0.3%)	12 (0.7%)
Macular oedema	0	1 (0.1%)
Laser therapy/intravitreal agents	2 (0.1%)	2 (0.1%)
No	1023 (62%)	1089 (66%)
Unknown	115 (7%)	101 (6%)

Notes: [a] For neuropathy, nonproliferative diabetic retinopathy and proliferative diabetic retinopathy a subject might have more than one filled out.

Reviewer's Comment: *Standard grading procedures for diabetic retinopathy include multiple levels of nonproliferative diabetic retinopathy and multiple layers of proliferative diabetic retinopathy. Macular edema, laser therapy and/or use of intravitreal agents are not part of that grading system. The study failed to capture the particular level of diabetic retinopathy.*

Results of Fundoscopy

	Sema 0.5	Sema 1	Placebo 0.5	Placebo 1
Number of subjects	823	819	819	825
Right eye ophthalmoscopy - Observed 'on-treatment' data				
Visit 2 (week 0)				
Normal	388 (48%)	432 (54%)	434 (54%)	433 (53%)
Abnormal and not clinically significant	332 (41%)	292 (37%)	291 (36%)	305 (38%)
Abnormal and clinically significant	85 (11%)	75 (9%)	84 (10%)	74 (9%)
Visit 11 (week 56)				
Normal	346 (50%)	352 (53%)	381 (55%)	383 (54%)
Abnormal and not clinically significant	273 (40%)	246 (37%)	262 (38%)	255 (36%)
Abnormal and clinically significant	68 (10%)	68 (10%)	55 (8%)	71 (10%)
Visit 25 (week 104)				
Normal	302 (50%)	311 (54%)	332 (55%)	307 (51%)
Abnormal and not clinically significant	263 (44%)	231 (40%)	233 (38%)	255 (42%)
Abnormal and clinically significant	35 (6%)	36 (6%)	43 (7%)	45 (7%)
Left eye ophthalmoscopy - Observed 'on-treatment' data				
Visit 2 (week 0)				
Normal	394 (49%)	432 (54%)	444 (55%)	436 (54%)
Abnormal and not clinically significant	325 (41%)	290 (36%)	278 (34%)	310 (38%)
Abnormal and clinically significant	84 (10%)	78 (10%)	88 (11%)	65 (8%)
Visit 11 (week 56)				
Normal	348 (51%)	358 (54%)	380 (55%)	387 (55%)
Abnormal and not clinically significant	268 (39%)	247 (37%)	258 (37%)	258 (36%)
Abnormal and clinically significant	69 (10%)	63 (9%)	58 (8%)	63 (9%)
Visit 25 (week 104)				
Normal	305 (51%)	313 (54%)	330 (54.2)	313 (52%)
Abnormal and not clinically significant	255 (43%)	232 (40%)	236 (38.8)	253 (42%)
Abnormal and clinically significant	38 (6%)	34 (6%)	43 (7%)	40 (7%)

Reviewer's Comment: *The table does not provide a meaningful comparison between groups because of a lack of standardization for the amount of retina that needed to be observed and the failure to differentiate in a meaningful way abnormal retinal findings.*

Physical Exam
Head, Ears, Eyes, Nose, Throat, Neck - Observed 'on-treatment' data

	Sema 0.5 N (%)	Sema 1 N (%)	Placebo 0.5 N (%)	Placebo 1 N (%)
Visit 1 (week -2)				
Normal	754 (92%)	732 (90%)	729 (89%)	751 (91%)
Abnormal and not clinically significant	62 (8%)	76 (9%)	79 (10%)	66 (8%)
Abnormal and clinically significant	4 (0.5%)	8 (1%)	10 (1%)	8 (1%)
Visit 25 (week 104)				
Normal	586 (92%)	573 (92%)	573 (90%)	582 (90%)
Abnormal and not clinically significant	43 (7%)	46 (7%)	61 (9%)	54 (8%)
Abnormal and clinically significant	7 (1%)	3 (0.5%)	5 (0.8%)	8 (1%)

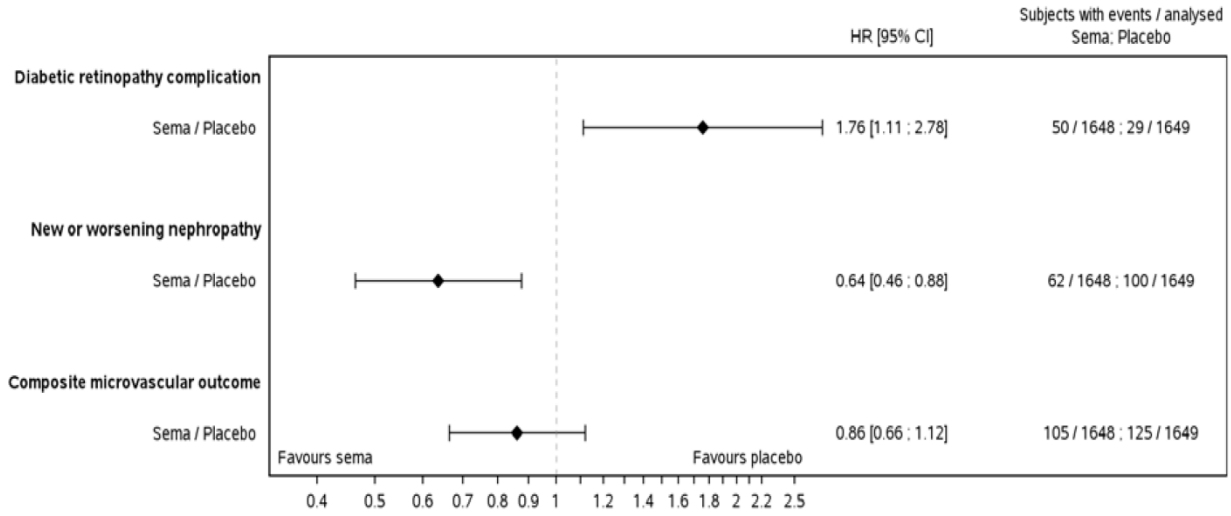
Reviewer's Comment: *The physical exams provide an example of the inconsistencies in ocular examinations and/or the reporting of ocular examinations.*

Subject ID 106021 was a 61 YO listed as having a normal HEENTN examination.
Subject ID 105009 is a 70 YO listed as having normal HEENTN examination.
Subject ID 121011 is a 70 YO listed as having a normal HEENTN examination.
Subject ID 1060071 is a 70 YO listed as having a normal HEENTN examination
Subject ID 102002 is a 76 YO, listed as having presbyopia on his HEENTN exam.
Subject ID 102005 is a 62 YO listed as having presbyopia on his HEENTN exam.
Subject ID 601002 is a 62 YO listed as having presbyopia and a cataract on his HEENTN exam.

Considering that presbyopia is a normal aging process and that all patients would have presbyopia by the age of 50, it is not reasonable to expect that 61 and 70 year olds would not have presbyopia. It is also highly unlikely that 70 year olds would not have had cataracts.

This is not an exhaustive list of the ocular inconsistencies reported in the baseline examination. It suggests that the definition of normal was not consistent between investigators or potentially between subjects.

Composite microvascular outcome



HR: Estimated hazard ratio CI: confidence interval. Summary of results from analyses of time to components of composite microvascular outcome. Estimated hazard ratios and associated confidence intervals are from a Cox proportional hazards model with treatment (semaglutide, placebo) as fixed factor and stratified by all possible combinations of the three stratification factors used in the randomisation procedure (in total 9 levels).

First Event Adjudication Committee (EAC)-confirmed composite microvascular outcome, semaglutide versus placebo Full Analysis Set (FAS)

	Sema 0.5 N (%)	Sema 1.0 N (%)	Placebo 0.5 N (%)	Placebo 1.0 N (%)
Number of subjects	826	822	824	825
First Composite Microvasc. Outcome	57 (7%)	48 (6%)	68 (8%)	57 (7%)
New or worsening nephropathy	36 (4%)	23 (3%)	54 (7%)	45 (6%)
Persistent macroalbuminuria	22 (3%)	19 (2%)	42 (5%)	38 (5%)
Persistent doubling of serum creatinine level and creatinine clearance	8 (1%)	1 (0.1%)	8 (1%)	2 (0.2%)
Need for continuous renal- replacement therapy	6 (0.7%)	3 (0.4%)	4 (0.5%)	5 (0.6%)
Diabetic retinopathy complications	21 (3%)	25 (3%)	14 (2%)	12 (1%)
Need for retinal photocoagulation	11 (1%)	12 (1%)	10 (1%)	3 (0.4%)
Vitreous hemorrhage	4 (0.5%)	8 (1%)	1 (0.1%)	5 (0.6%)
Need for treatment with intravitrealagents	2 (0.2%)	4 (0.5%)	2 (0.2%)	4 (0.5%)
Onset of diabetes-related blindness	4 (0.5%)	1 (0.1%)	1 (0.1%)	0

Reviewer's Comment: *The composite microvascular outcome as defined in this protocol is not recommended to be used as an outcome measure. It combines equally events which are of unequal clinical severity, unequal clinical significance, and unequal expected frequency. The endpoint is more of a measure of an effect on the kidneys and does not represent a complete picture of microvascular outcomes.*

Applicant Reported EAC-confirmed events of diabetes-related blindness (Applicant's Table 13-47)

Subject ID: 144007, 0.5 Semaglutide
57 YO, male subject had a 13.5 year duration of diabetes at baseline and a history of proliferative diabetic retinopathy, macular edema with laser therapy and intravitreal agents. On day 15, he was reported to have EAC confirmed blindness, photocoagulation and intravitreal agents with a visual acuity of 6/60 in each eye. He was reported to have blindness in the better eye on the day of event.

Reviewer's Comment: *Concur that this patient meets protocol definition of blindness.*

Subject ID: 524008, 1.0 Semaglutide
70 YO, male subject had a 13.2 year duration of diabetes at baseline and a history of proliferative diabetic retinopathy with laser therapy and intravitreal agents. On day 60, he was reported to have EAC confirmed blindness, vitreous hemorrhage and photocoagulation with a visual acuity of hand motion in the right eye and 6/9 in the left eye. The subject is reported to not have blindness in the better eye on the day of the event. Eighteen months later, after cataract surgery, the visual acuity improved to 6/9 in the right eye and 6/5-3 in the left eye.

Reviewer's Comment: *This patient should not be included in the category of diabetes-related blindness because they have a visual acuity in the left eye of better than 20/200.*

Subject ID: 681004, 0.5 Semaglutide
62 YO, male subject had a 20.5 year duration of diabetes at baseline and a history of proliferative diabetic retinopathy. On day 121, he was reported to have EAC confirmed blindness and photocoagulation with a visual acuity of 20/30+ in the right eye and 20/50 in the left eye. The subject is reported to not have blindness in the better eye on the day of the event.

Reviewer's Comment: *This patient should not be included in the category of diabetes-related blindness because they have a visual acuity in the left eye of better than 20/200.*

Subject ID: 663010, 0.5 Semaglutide
67 YO, male subject had a 20.5 year duration of diabetes at baseline and a history of laser therapy and intravitreal agents. On day 304, he was reported to have EAC confirmed blindness, vitreous hemorrhage and photocoagulation with a visual acuity of counting fingers in the right eye and 20/60 in the left eye. The subject is reported to not have blindness in the better eye on the day of the event. The subject had a vitrectomy for a retinal detachment the same day as the event and had an EAC-confirmed event of treatment with intravitreal agents 6 weeks later for a macular hole.

Reviewer's Comment: *This patient should not be included in the category of diabetes-related blindness because they have a visual acuity in the left eye of better than 20/200.*

Subject ID: 604015, 0.5 Semaglutide
71 YO, female subject had a 43.3 year duration of diabetes at baseline and a history of proliferative diabetic retinopathy, laser therapy and intravitreal agents. On day 239, she was reported to have EAC confirmed blindness with no eye examinations because the patient had been hospitalized. It is reported that it is unknown whether the patient had blindness because the patient was hospitalized and subsequently died.

Reviewer's Comment: *This patient should not be included in the category of diabetes-related blindness because there was no examination of the patient at the time of the event or subsequently.*

Subject ID: 649001, Placebo
52 YO, female subject had a 25.2 year duration of diabetes at baseline and no history of diabetic retinopathy. On day 239, she was reported to have EAC confirmed blindness, photocoagulation and intravitreal agents with a visual acuity of counting fingers at 3 feet in each eye. She was reported to have blindness in the better eye on the day of event.

Reviewer's Comment: *Concur that this patient meets protocol definition of blindness.*

Reviewer's Comment: *As described above, of the six subjects classified by the event adjudication committee as being blind, only two met the protocol definition of blindness, one in the semaglutide 0.5mg group and one in the placebo group. The protocol definition of blindness is the same as the United States legal definition of blindness. The analyses in the study report are not correct with respect to the number of patients classified as blind.*

Vitreous Hemorrhage Events

History at Baseline

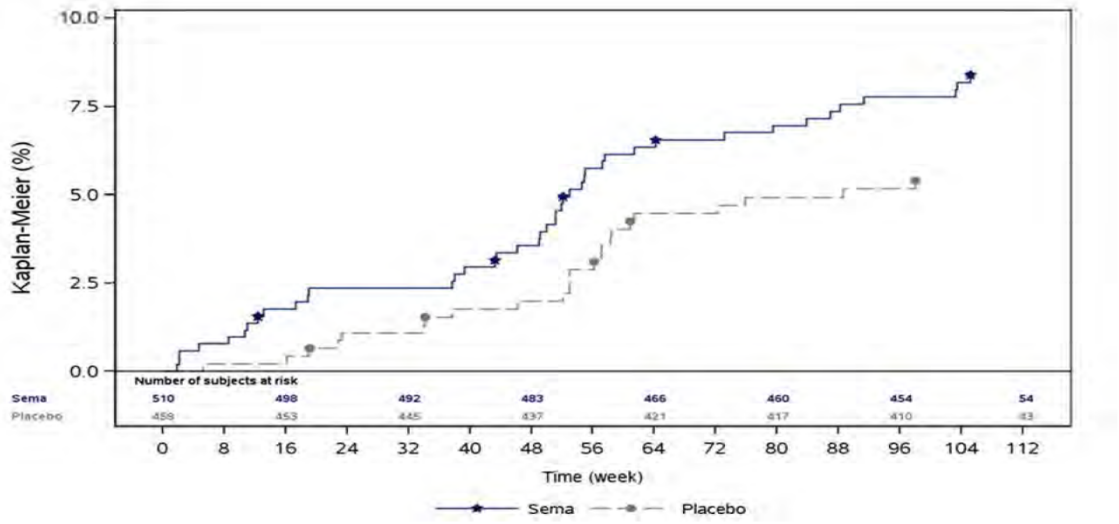
	Sema 0.5	Sema 1	Placebo 0.5	Placebo 1
Retina, choroid and vitreous haemorrhages and vascular disorders	6 (0.7%)	9 (1.1%)	3 (0.4%)	5 (0.6%)
Vitreous haemorrhage	1 (0.1%)	5 (0.6%)	2 (0.2%)	1 (0.1%)
Retinopathy	1 (0.1%)	1 (0.1%)	1 (0.1%)	2 (0.2%)
Diabetic retinopathy	3 (0.4%)			
Arteriosclerotic retinopathy	1 (0.1%)			1 (0.1%)
Retinopathy hypertensive		1 (0.1%)		1 (0.1%)
Retinal haemorrhage		1 (0.1%)		
Retinal vein occlusion		1 (0.1%)		

Concomitant illness ongoing at baseline

	Sema 0.5	Sema 1	Placebo 0.5	Placebo 1
Retina, choroid and vitreous haemorrhages and vascular disorders	100 (12.1)	94 (11.4%)	84 (10.2%)	91 (11.0%)
Diabetic retinopathy	41 (5.0%)	43 (5.2%)	30 (3.6%)	40 (4.8%)
Retinopathy hypertensive	17 (2.1%)	18 (2.2%)	18 (2.2%)	22 (2.7%)
Retinopathy	15 (1.8%)	14 (1.7%)	16 (1.9%)	22 (2.7%)
Arteriosclerotic retinopathy	19 (2.3%)	12 (1.5%)	12 (1.5%)	6 (0.7%)
Retinal vascular disorder	4 (0.5%)	2 (0.2%)	6 (0.7%)	1 (0.1%)
Retinal haemorrhage	2 (0.2%)		5 (0.6%)	2 (0.2%)
Retinal aneurysm		3 (0.4%)	1 (0.1%)	4 (0.5%)
Vitreous haemorrhage	3 (0.4%)	3 (0.4%)	1 (0.1%)	1 (0.1%)
Retinal vein occlusion	1 (0.1%)	1 (0.1%)	1 (0.1%)	1 (0.1%)
Retinal exudates	2 (0.2%)	1 (0.1%)		
Retinal artery embolism				2 (0.2%)
Retinal artery occlusion	2 (0.2%)			
Retinopathy proliferative				2 (0.2%)
Macular ischaemia	1 (0.1%)			
Retinal artery thrombosis				1 (0.1%)
Retinal vascular occlusion				1 (0.1%)
Retinal vascular thrombosis			1 (0.1%)	
Retinal vein thrombosis		1 (0.1%)		

Reviewer's Comment: *There are many overlapping terms in these tables. However, there was a tendency to have more subjects at baseline with a prior history or with concomitant retinal/vitreous vascular events in the semaglutide groups. This may have led to the reporting of a greater number of similar events in the clinical trial.*

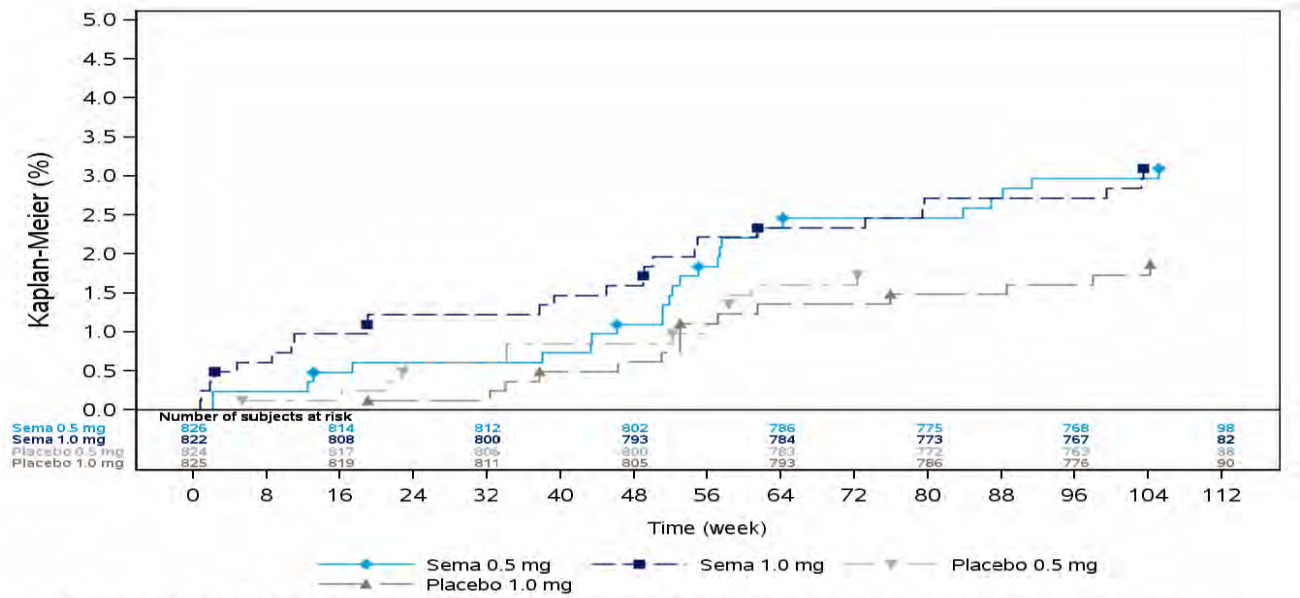
Time to first EAC confirmed diabetic retinopathy complication - Kaplan-Meier plot for individual dose arms - in-trial - full analysis set



Note: Kaplan Meier estimates: Analysis of time from randomisation to first EAC-confirmed event of diabetic retinopathy complications. Subjects are censored at their planned end-of-trial visit, last direct subject-site contact, all-cause death of the subject, whichever comes first. Numbers below the figure are subjects at risk.
Abbreviations: FAS: full analysis set; sema: semaglutide.

Cross-reference: EOT Figure 15.2.131

Kaplan-Meier Time to First Retinopathy Endpoint by Treatment Group

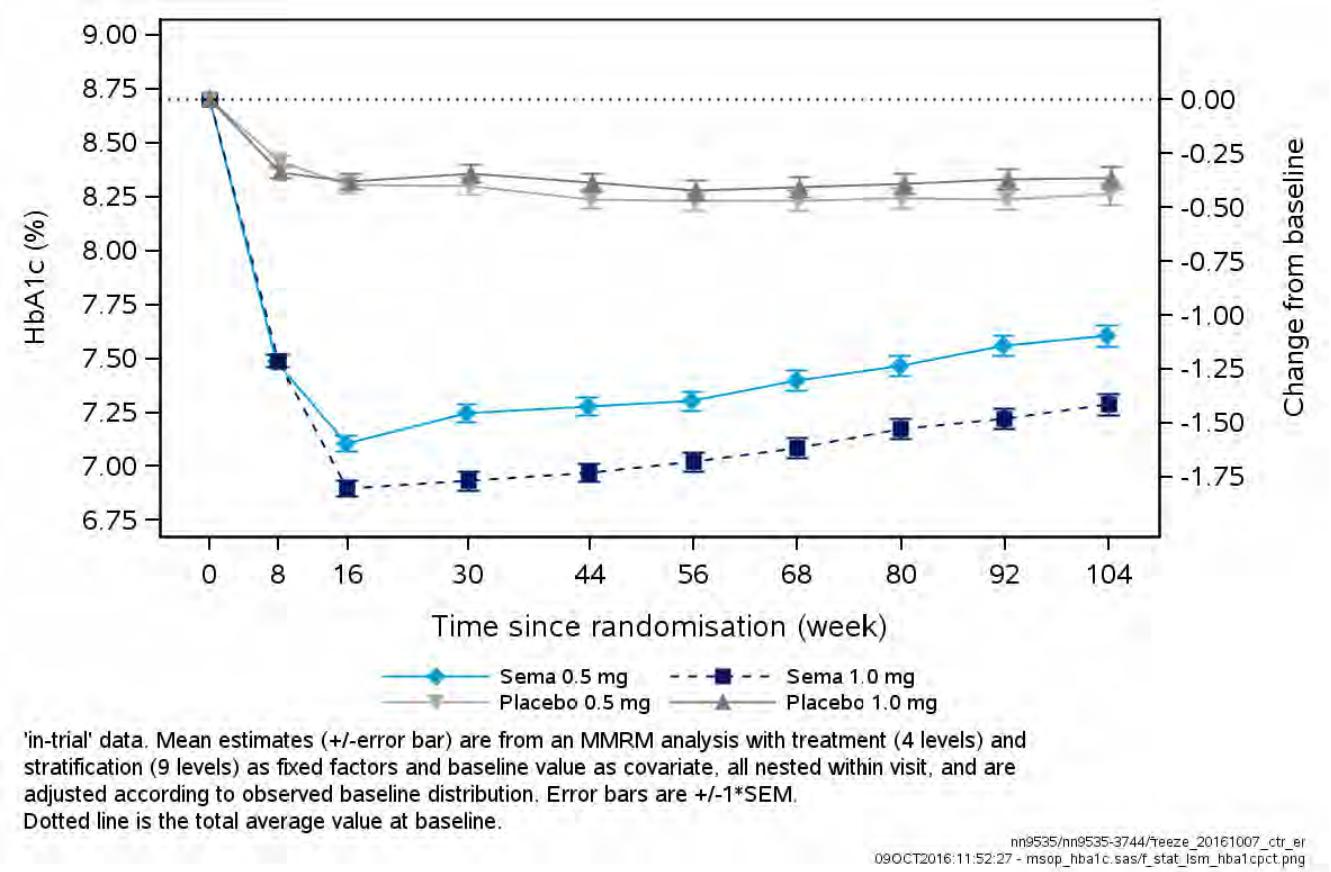


Kaplan-Meier estimates: Analysis of time from randomisation to first retinal photocoagulation or treatment with intravitreal agents, vitreous haemorrhage or onset of diabetes-related blindness. Subjects are censored at their planned end-of-trial visit, last direct subject-site contact or all-cause death of the subject, whichever comes first.
Numbers below the graph are subjects at risk.

nn9535/nn9535-3744/freeze_20161007_ctr_er
09OCT2016:13:26:06 - t_time2microut.sas/f_time2retinopathy_trt_km.png

Reviewer's Comment: *There was a statistically significant difference between groups treated with semaglutide versus placebo. The semaglutide 1mg group contributes more events than the semaglutide 0.5 mg group. However, as noted above, the ophthalmic endpoints measured in this study are not accurate representations of diabetic complications in the eye, nor are they measures of improvement in ophthalmic parameters of diabetic disease.*

Hemoglobin A1c



'in-trial' data. Mean estimates (+/-error bar) are from an MMRM analysis with treatment (4 levels) and stratification (9 levels) as fixed factors and baseline value as covariate, all nested within visit, and are adjusted according to observed baseline distribution. Error bars are +/-1*SEM.
Dotted line is the total average value at baseline.

nn9535/nn9535-3744/freeze_20161007_ctr_er
09OCT2016:11:52:27 - msop_hba1c.sas/f_stat_lsm_hba1cpct.png

Reviewer's Comment: *As noted in the graph above, there was at least a 3 times greater decrease in HbA1c in the semaglutide groups than in the placebo groups within the first 4 months of treatment. Progression of diabetic retinopathy is known to be positively correlated when patients with elevated HbA1c have a rapid (i.e., within 3 month period) decreases in HbA1c. The mean HbA1c in this trial suggests that there would be an increase in retinopathy expected to be seen in a significant number of patients. Based on literature studies, the patients at greatest risk for increasing their retinopathy levels are subjects with at least early retinopathy changes and HbA1c decreases of at least 2 to 3 percentage points in 3 months. In this study, about 22% of patients in the semaglutide 1 mg group and 16% in the semaglutide 0.5 mg group demonstrated a 2.5 point or more decrease in HbA1c in the first four months. Less than 5% of the patients of the placebo demonstrated a 2.5 point or more decrease in HbA1c.*

Relationship between HbA1c and Retinopathy events

Baseline HbA1c and change from baseline in HbA1c at weeks 8, 16 and 104 in subjects with and without first EAC-confirmed events of diabetic retinopathy complications – FAS in-trial

	Sema 0.5	Sema 1	Placebo 0.5	Placebo 1
Number of subjects				
Retinopathy	25	25	14	15
No retinopathy	801	797	810	810
Week 0 – baseline HbA1c				
Mean (SD)-retinopathy	9.38 (1.96)	8.98 (1.95)	10.04 (1.80)	9.40 (1.86)
Mean (SD)-no retinopathy	8.65 (1.37)	8.72 (1.50)	8.68 (1.48)	8.69 (1.44)
Week 8 – change from baseline in HbA1c				
Mean (SD)-retinopathy	-1.33 (1.30)	-1.66 (1.10)	-0.53 (1.62)	-0.75 (1.13)
Mean (SD)-no retinopathy	-1.21 (0.92)	-1.22 (0.97)	-0.29 (0.93)	-0.34 (1.04)
Week 16 – change from baseline in HbA1c				
Mean (SD)-retinopathy	-1.87 (1.69)	-2.47 (1.94)	-0.88 (1.89)	-1.27 (1.74)
Mean (SD)-no retinopathy	-1.59 (1.20)	-1.82 (1.37)	-0.38 (1.17)	-0.36 (1.25)
Week 104/end-of-trial – change from baseline in HbA1c				
Mean (SD)-retinopathy	-1.40 (1.72)	-1.81 (2.28)	-1.12 (2.24)	-0.66 (1.64)
Mean (SD)-no retinopathy	-1.06 (1.52)	-1.43 (1.68)	-0.40 (1.55)	-0.36 (1.58)

Reviewer's Comment: *While there is a greater decrease in the HbA1c group in the patients with EAC confirmed retinopathy, the classification of EAC retinopathy is of questionable value.*

First EAC confirmed diabetic retinopathy complication - observed risk times and incidence rates - summary by treatment, baseline retinopathy and reduction in HbA1c (%-points) at week 16 - in-trial - full analysis set

Treatment	Baseline Retinopathy	HbAlc Reduction	Number with event	Number at risk	Risk time (years)	Rate per 100 PYR
Semaglutide	No	< 0.5%	0	131	272	0.00
Semaglutide	Unknown	< 0.5%	0	9	19	0.00
Semaglutide	Yes	< 0.5%	4	61	123	3.26
Semaglutide	No	0.5-1.5%	2	399	817	0.24
Semaglutide	Unknown	0.5-1.5%	0	31	56	0.00
Semaglutide	Yes	0.5-1.5%	15	213	427	3.51
Semaglutide	No	> 1.5%	3	493	1026	0.29
Semaglutide	Unknown	> 1.5%	3	75	150	2.00
Semaglutide	Yes	> 1.5%	23	236	459	5.02
Placebo	No	< 0.5%	2	658	1357	0.15
Placebo	Unknown	< 0.5%	0	57	119	0.00
Placebo	Yes	< 0.5%	9	245	499	1.80
Placebo	No	0.5-1.5%	2	291	602	0.33
Placebo	Unknown	0.5-1.5%	1	31	62	1.60
Placebo	Yes	0.5-1.5%	7	138	271	2.59
Placebo	No	> 1.5%	0	140	288	0.00
Placebo	Unknown	> 1.5%	0	13	25	0.00
Placebo	Yes	> 1.5%	8	76	143	5.58

Reviewer's Comment: *As expected, the highest risk for an event is in the subjects with a prior history of retinopathy and the highest HbA1c reduction early in the trial.*

Adverse events of diabetic retinopathy (PT) – FAS in-trial

	Sema 0.5			Sema 1.0			Placebo		
	N (%)	E	R	N (%)	E	R	N (%)	E	R
Number of subjects	826			822			1649		
Exposure time (year)	1708.4			1699.8			3401.1		
Events	50 (6.1)	54	3.2	58 (7.1)	66	3.9	83 (5.0)	88	2.6
SAEs	4 (0.5)	4	0.2	2 (0.2)	3	0.2	6 (0.4)	6	0.2
Severity									
Severe	4 (0.5)	4	0.2	3 (0.4)	3	0.2	6 (0.4)	6	0.2
Moderate	22 (2.7)	23	1.3	16 (1.9)	16	0.9	19 (1.2)	19	0.6
Mild	25 (3.0)	27	1.6	41 (5.0)	47	2.8	59 (3.6)	63	1.9
Leading to premature treatment discontinuation									
Yes	0			0			0		
No	50 (6.1)	54	3.2	58 (7.1)	66	3.9	83 (5.0)	88	2.6

N=number of subjects, E=number of events, R= Rate per 100 years of exposure.

Reviewer's Comment: *The differences between groups were minimal.*

Division's Question:

1. In your opinion, were the processes in place for capturing retinopathy events adequate and appropriate to capture events and assess the clinical significance of these events? Do you have any concerns regarding the processes in place for identifying and adjudicating retinopathy events in the semaglutide program (and specifically study 3744)?

Response to Question: *The processes in place for capturing retinopathy events in this trial were not adequate to be able to appropriately capture clinically significant events and analyze them. The "need for retinal photocoagulation or treatment with intravitreal agents" is not a good endpoint. There is not uniform agreement on the clinical characteristics that should dictate the timing of photocoagulation treatment or the use of Vascular Endothelial Growth Factor (VEGF) inhibitors. Cost, reimbursement, medical alternatives and a variety of individual interests can influence the "need" or "actual" retinal photocoagulation treatment and/or intravitreal treatment.*

While the protocol described this measure as the "need for treatment," it appears that the Event Adjudication Committee Charter required actual treatment in order to valid this endpoint. This could have resulted in some events being counted when they were not actually needed and some events not being counted because the treatment was not performed.

The onset of diabetes-related blindness (defined as Snellen visual acuity of 20/200 [6/60] or less, or visual field of <20 degrees in the better eye with best correction possible) is not a good endpoint because it is difficult to judge whether the blindness was diabetes related. There are increased frequencies of many ocular conditions (e.g., cataracts, macular edema, retinal vein occlusions) leading to a loss of visual acuity in patients with diabetes. This does not necessarily mean that any loss of vision due to one of these conditions is necessarily due to the diabetes. Some of the conditions leading to a visual acuity of 20/200 or worse are potentially reversible (i.e., cataracts, macular edema, vitreous hemorrhage) and some are not. The clinical significance of this endpoint depends on whether the blindness is reversible or not.

While visual acuity was captured in this trial and there is agreement that the definition of blindness was appropriate, the definition of blindness was not followed in identifying patients considered to be blind. This raises a question about the adjudication process for ophthalmic events.

Vitreous hemorrhage could have been a reasonable endpoint, particularly if it was qualified by the duration that it was present. However, the frequency of the event is often low even in an untreated group and therefore the endpoint is of limited utility unless the number of enrolled subjects is very large (i.e., larger than this trial). Vitreous hemorrhages which do not resolve within 3 months (often leading to a need for a vitrectomy) are much more significant than those which resolve more quickly without any significant intervention.

"Time to" events involving retinopathy, even when measured on an accepted retinopathy scale (i.e., ETDRS [Early Treatment Diabetic Retinopathy Study]) are problematic because rapid drops in Hemoglobin A1c (HbA1c) result in an increase in diabetic retinopathy during

the first year in which the HbA1c decreased. The most well-known of the studies to demonstrate this was the Diabetic Control and Complications Trial (DCCT). The DCCT study demonstrated that rapid decreases in HbA1c resulted in increased retinopathy. The control group did not catch up until Year 3. While the DCCT demonstrated this finding in Type 1 diabetics, it is true for both Type 1 and Type 2 diabetics [Literature examples include by are not limited to Arch Ophthalmol. 2006;124:38-45. and Diabetes Research and Clinical Practice. 2014;103(3):e37-39.]

2. Given the available data, how seriously would you view the reported ophthalmologic events (i.e., progression, need for intervention)?

Response to Question: *The methods used to evaluate diabetic retinopathy are not sufficient to draw definitive conclusions. To the extent that the data suggest a signal that there was progression of diabetic retinopathy in patients with significant decreases in HbA1c, these events should be expected because they are consistent with treatments which decrease HbA1c. While this decrease may result in an initial increase in retinopathy, ocular health is ultimately benefited by decreasing HbA1c. Based on clinical trials such as the DCCT, it is better to reduce HbA1c as soon as possible, regardless of whether or not it results in an initial increase in the progression of retinopathy.*

3. Our understanding is that sudden changes in glucose control are associated with progression of diabetic retinopathy, though we note that we have not previously observed an increased incidence in retinopathy with previous antidiabetic drugs. We would appreciate your expertise in considering this potential safety signal and implications for use of semaglutide in this patient population. Given the timing of the events, what is your opinion with regard to the reason for the observed difference between treatment arms? Do you think that the observed increase in the incidence of retinopathy events could be due to a rapid reduction in glucose with semaglutide, or could it be a drug-related toxicity/adverse event?

Response to Question: *If the methods used to evaluate diabetic retinopathy in this program are similar or better than other programs used to evaluate previous antidiabetic drugs, it is unlikely that the methodology would have been sufficient to provide an interpretable result based purely on the ocular examinations. To the extent that this drug product provides a greater and/or more rapid HbA1c response, it is likely that more initial progression of diabetic retinopathy would have been observed.*

4. Based on the available data, do you have any recommendations with regard to the use of semaglutide (e.g., restricted population, alternative dosing schedule, recommendations on retinal exam schedules, etc.)?

Reviewer's Comment: *Based on the ophthalmic data in this program, there is no reason to restrict semaglutide with respect to population or dosing schedule. There is also no reason to require any more or less ophthalmic follow-up.*

5. Do the findings of an increased incidence in progression of retinopathy raise any other concerns?

Response to Question: *To the extent that the increased incidence in progression of retinopathy is real in this program, it does not raise any ophthalmic concerns.*

Wiley A. Chambers, M.D.,
Supervisory Medical Officer, Ophthalmology

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/s/

WILEY A CHAMBERS
07/05/2017

Interdisciplinary Review Team for QT Studies Consultation: Thorough QT Study Review

IND or NDA	NDA 209637
Brand Name	OZEMPIC
Generic Name	Semaglutide
Sponsor	Novo Nordisk
Indication	As an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus
Dosage Form	Subcutaneous injection
Drug Class	Glucagon-like peptide (GLP-1) receptor agonist
Therapeutic Dosing Regimen	Start at 0.25 mg subcutaneously once weekly. After 4 weeks the dose should be increased to 0.5 mg once weekly. After 4 weeks dose can be increased to 1 mg once weekly for additional glycemic control.
Duration of Therapeutic Use	Chronic
Maximum Tolerated Dose	The maximum multiple dose tested was 1.5 mg OW
Submission Number and Date	SDN 001; 05 Jan 2017
Review Division	DMEP

Note: Any text in the review with a light background should be inferred as copied from the sponsor's document.

1 SUMMARY

1.1 OVERALL SUMMARY OF FINDINGS

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

In this randomized, blinded, 3-arm parallel study with a nested crossover design for positive control, 168 healthy subjects were randomized to receive semaglutide (dose escalation regimen of 0.25 mg, 0.5 mg, 1.0 mg, and 1.5 mg), semaglutide placebo, moxifloxacin placebo, and a single dose of moxifloxacin 400 mg. ECG sampling was done for 0.5 mg, 1.0 mg, and 1.5 mg dose levels. Overall summary of findings is presented in Table 1.

Table 1: The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for Semaglutide (0.5 mg, 1 mg, and 1.5 mg) and the Largest Lower Bound for Moxifloxacin (FDA Analysis)

Treatment	Time (hour)	ΔΔQTcF (ms)	90% CI (ms)
Semaglutide 1.5 mg	0	0.2	(-2.8, 3.2)
Semaglutide 1.0 mg	0	0.5	(-2.7, 3.7)
Semaglutide 0.5 mg	24	-1.8	(-4.7, 1.1)
Moxifloxacin 400 mg*	3	14.0	(12.1, 15.9)

* Multiple endpoint adjustment of 3 time points was applied.

The supratherapeutic exposures of semaglutide were attained after multiple doses of semaglutide, escalated up to 1.5 mg in the TQT study. C_{max} and AUC values in the thorough QT study were approximately 2.2- and 2.1- fold higher, respectively, following administration of 1.5 mg semaglutide in healthy subjects compared with 1.0 mg semaglutide, the intended clinical dose, in patients with T2D. These concentrations are above those for the predicted worst case scenario (patients with T2D with low body weights) and are likely to cover supra-therapeutic exposure level of semaglutide in the treatment setting. Within the studied exposure range (2.2-fold of normal therapeutic exposure), no exposure-response relationship was seen between baseline- and placebo-adjusted QTcF and QTcI intervals and semaglutide concentrations.

2 PROPOSED LABEL

12.2 Pharmacodynamics

Cardiac electrophysiology (QTc) effect of semaglutide on cardiac repolarization was tested in a through QTc trial. (b) (4)

The following is QT-IRT's proposed labeling language which is a suggestion only. We defer final labeling decisions to the Division.

12.2 Pharmacodynamics

Cardiac electrophysiology

The effect of semaglutide on cardiac repolarization was tested in a through QTc trial. At a dose 1.5 times the maximum approved recommended dose, semaglutide does not prolong the QT interval to any clinically relevant extent.

3 BACKGROUND

3.1 Product Information

Semaglutide is a GLP-1 (glucagon like protein-1) receptor agonist (RA) with 94% structural homology to native GLP-1. It is structurally similar to another GLP-1 RA liraglutide but modified to have a longer half-life suitable for once-weekly dosing. Semaglutide is currently being developed to improve glycaemic control in patients with

type 2 diabetes mellitus (T2D) [redacted] (b) (4)

3.2 Market approval status

Semaglutide is not approved for marketing in any country.

3.3 Preclinical Information

In vitro studies on the potential of semaglutide for inhibition of the cardiac potassium channel (hERG) and the action potential recordings from isolated rabbit Purkinje fibres were used for assessment of the potential for QT prolongation. It was concluded that treatment with semaglutide 7.8 µmol/L (corresponding to a 242-fold higher concentration than the mean maximal plasma concentration at the maximal recommended human dose (MRHD) of 1 mg/week) produced no inhibition of hERG tail current. In addition, no effects of semaglutide were detected on action potential parameters (RMP, UA, MRD, APD60, APD90 or triangulation) in this test system up to and including free plasma concentrations of 8.2 µmol/L (nominal 10 µmol/L). Semaglutide is therefore not expected to have direct effects on cardiac ion channels generating the action potential. The concentration tested corresponds to 255-fold above the maximal mean plasma concentration at the MRHD of 1 mg/week.

[redacted] (b) (4)

3.4 Previous Clinical Experience

As of 31 July 2013, 5 clinical pharmacology trials (NN9535-1820, -3679, -3633, -3616 and -3819) and 1 phase 2 trial (NN9535-1821) have been completed with semaglutide.

In the completed trials a total of 519 subjects have been exposed to semaglutide: 164 healthy subjects (both single and multiple dosing), 313 patients with type 2 diabetes (up to 12 weeks of treatment) and 42 subjects with varying degrees of renal impairment (single dosing).

[redacted] (b) (4)

3.5 Clinical Pharmacology

Appendix 6.1 summarizes the key features of semaglutide's clinical pharmacology.

4 SPONSOR'S SUBMISSION

4.1 OVERVIEW

The QT-IRT reviewed the protocol prior to conducting this study under IND 79754. The QT-IRT agreed that the proposed design of the NN9535-3652 trial would fulfill the FDA requirement for a TQT trial, but required enough subjects to be enrolled to ensure the number of subjects completing the 1.5mg dose is sufficient to have enough power for primary hypothesis testing (Reference ID: 3330446). The sponsor submitted the study report NN9535-3652 for semaglutide, including electronic datasets and waveforms to the ECG warehouse.

4.2 TQT STUDY

4.2.1 Title

A thorough QTc evaluation of the effect of semaglutide on cardiac repolarisation in healthy subjects: A randomized, double-blind, placebo-controlled, three-arm parallel trial with a nested cross-over design for positive control with moxifloxacin administration.

4.2.2 Protocol Number

NN9535-3652

4.2.3 Study Dates

26 February 2014 - 23 April 2015

4.2.4 Objectives

Primary objective:

- To confirm that treatment with semaglutide does not result in an unacceptable prolongation in cardiac repolarization compared to placebo. This is done by demonstrating that the upper limit of the one-sided 95% confidence interval (CI) of the maximum mean time-matched difference in QTcI (i.e. baseline adjusted QT interval corrected individually for heart rate) for semaglutide 1.5 mg versus placebo is less than 10 msec.

Secondary objective:

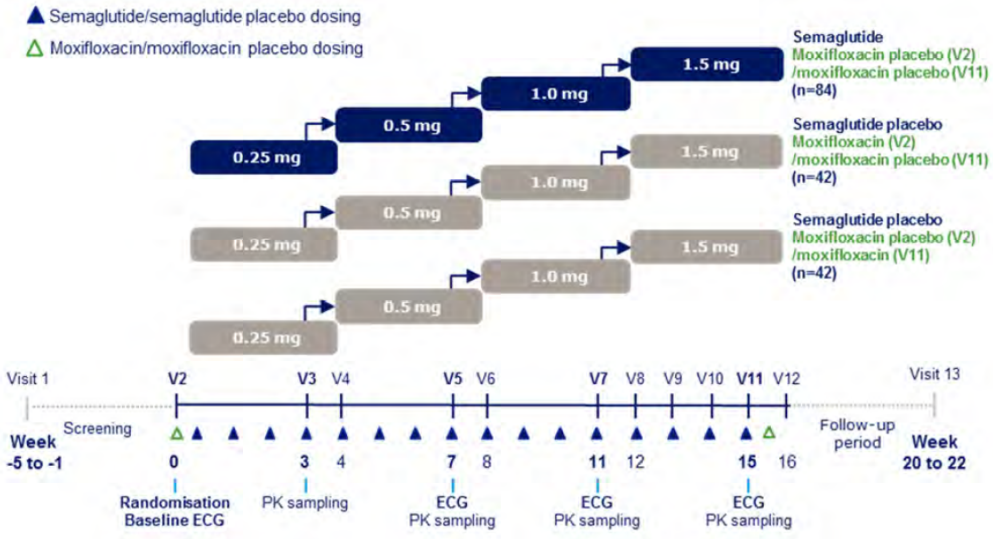
- To establish QT assay sensitivity of the trial by investigating the effects of a single dose moxifloxacin (positive control) vs placebo. This is done by demonstrating that the lower limit of the one-sided 95% CI of the maximum mean time-matched difference in baseline adjusted QTcI for moxifloxacin versus placebo is above 5 msec.
- To compare other electrocardiogram (ECG) parameters between semaglutide treatment (0.5, 1.0 and 1.5 mg), and placebo, including heart rate and PR interval
- To assess exposure-response relationship between semaglutide concentration and any changes in QTcI
- To assess dose proportionality of semaglutide
- To assess safety and tolerability of semaglutide throughout the exposure period

4.2.5 Study Description

4.2.5.1 Design

This trial was a single-center, parallel, three-arm, randomized, double-blind, and placebo-controlled trial with multiple doses of semaglutide, escalated up to 1.5 mg, and a single dose of moxifloxacin 400 mg as a positive control. The semaglutide placebo group was divided into two subgroups (Arm 2A and 2B), using a nested cross-over design, as shown in Figure 1.

Figure 1: Trial Design



4.2.5.2 Controls

The sponsor used both placebo and positive (moxifloxacin) controls. To assess the QT assay sensitivity the placebo group was divided into two subgroups (Arm 2A and 2B) using a nested cross-over design.

4.2.5.3 Blinding

All treatment arms were administered blinded using a double dummy approach. Moxifloxacin tablets were over-encapsulated.

4.2.6 Treatment Regimen

4.2.6.1 Treatment Arms

The subjects were randomized in a 2:1:1 manner as follows:

Arm 1: Treatment with semaglutide + moxifloxacin placebo.

Subjects received moxifloxacin placebo both before the start of semaglutide treatment and at the end of the semaglutide treatment.

Arm 2A: Treatment with semaglutide placebo + moxifloxacin/moxifloxacin placebo.

Subjects received moxifloxacin before the start of semaglutide placebo treatment and moxifloxacin placebo at the end of the semaglutide placebo treatment.

Arm 2B: Treatment with semaglutide placebo + moxifloxacin placebo/moxifloxacin.

Subjects received moxifloxacin placebo before the start of semaglutide placebo treatment and moxifloxacin at the end of the semaglutide placebo treatment.

4.2.6.2 Sponsor's Justification for Doses

Dosing with semaglutide 1.5 mg for 4 weeks was used in this trial to obtain supra-therapeutic exposure levels of semaglutide in this trial. Due to unacceptable adverse effects, that may affect the endpoints, administration with semaglutide 1.5 mg or higher would not be feasible without dose escalation.

Based on these previous experiences and in accordance with intended clinical use, a 4-weekly dose escalation regimen was applied in the present trial to reach supra-therapeutic exposure levels of semaglutide. Treatment was initiated with semaglutide 0.25 mg administered once-weekly in the first 4 weeks, 0.5 mg once-weekly the next 4 weeks, 1.0 mg once-weekly in the third 4 week period, and 1.5 mg once-weekly (highest dose) in the last 4 weeks of the treatment period, resulting in approximately 16 weeks between baseline measurements and the semaglutide 1.5 mg steady state measurements. Based on the PK characteristics of semaglutide, the 4-week dosing schedule at each dose level will lead to approximately 94% of the expected exposure obtained at steady state. A dose level of semaglutide 1.5 mg will result in approximately 1.5 times higher exposure than during the highest planned therapeutic maintenance dose of 1.0 mg.

Furthermore, it is expected that the use of healthy subjects will, due to a lower mean body weight, ensure a higher/supra-therapeutic exposure level of semaglutide than in subjects with T2D. Based on PK simulations it is expected that the supra-therapeutic dose of semaglutide 1.5 mg once-weekly will cover the expected exposure in subjects with a lower body weight compared to a typical Caucasian subject with T2D. Also subjects suffering from severe renal impairment may have a slightly higher semaglutide exposure than subjects with normal renal function, as indicated by data obtained after a single dose (trial NN9535-3616). This higher exposure is also expected to be covered by the 1.5 mg dose.

Reviewer's Comment: Semaglutide 1.5 mg is the maximum tolerated dose studied. The geometric mean AUC_{0-168h} at steady state for semaglutide 1.5mg in healthy subjects in the TQT study was 9928 nmol.h/L (18% CV), approximately 2 fold higher than the exposure of therapeutic maintenance dosing 1.0 mg in patients with T2D (median geometric mean 4700 nmol.h/L). Pop-PK analysis identified body weight as the only covariate of clinical importance for semaglutide exposure. The results of model-based covariate analysis showed that a patient with 55 kg would have 1.40 (90% CI: 1.38, 1.42) fold higher dose-normalized semaglutide exposure at steady-state compared to a patient with median body weight (85 kg). Therefore the reviewer agrees with the applicant that Semaglutide 1.5 mg in the TQT study is likely to cover the supra-therapeutic exposure level of semaglutide in the treatment setting.

4.2.6.3 Instructions with Regard to Meals

For Visits in which intensive ECGs will be collected (2, 5, 7 and 9), subjects will come to the trial site on the evening before to have dinner at approximately 6 P.M. Meals will be standardized to the extent possible for the visits.

Reviewer's Comment: Semaglutide is administered via subcutaneous injection. Therefore, an effect of food on its pharmacokinetics is not anticipated.

4.2.6.4 ECG and PK Assessments

The ECGs were collected at the following pre-specified time points:

- 0−48 hours (days 1−3) at baseline and after 8, 12 and 16 weeks treatment with semaglutide/semaglutide placebo: Prior to dosing (time = 0), 12, 18, 24, 25, 26, 27, 30, 36, 42, 48 hours post dosing (baseline and semaglutide/semaglutide placebo 0.5, 1.0 and 1.5 mg, respectively).
- 0−24 hours (days 3−4) at baseline and after 16 weeks treatment with semaglutide/semaglutide placebo: Prior to dosing (time = 0), 1, 2, 3, 6, 12, 18, 24 hours post dosing (moxifloxacin/moxifloxacin placebo).

Blood sampling for the bioanalysis of semaglutide was done during the 48 hours ECG collection at visits 5, 7 and 11 (steady state of semaglutide/semaglutide placebo 0.5, 1.0 and 1.5 mg) at the following time points: 0 (= pre-dose), 12, 18, 24, 25, 26, 27, 30, 36, 42, 48 hours post dosing. A similar blood sampling schedule was applied for semaglutide PK profile at visit 3 during the fourth dose of semaglutide/semaglutide placebo 0.25 mg.

For details on the schedule of ECG/PK collection time refer to Table 2.

Table 2: Dosing, ECG-recordings and PK-Sampling during All In-House Visits

Day within visit	Nominal Time[d] (h)	Dosing (active drug/placebo), ECG recording (=ECG)[a], semaglutide PK blood sampling (=PK)[b] and moxifloxacin PK blood sampling (=PK Mox)				
		Visit 2, days1−4 Baseline & Positive control	Visit 3, days1−3 PK-sema (0.25 mg)	Visit 5, days1−3 PK-sema (0.5 mg)	Visit 7, days1−3 PK-sema (1.0 mg)	Visit 11, days1−4 PK-sema (1.5 mg) & Positive control
1	0	ECG No dosing	PK Sema Dose: Sema 0.25 mg	ECG+PK Sema Dose: Sema 0.5 mg	ECG+PK Sema Dose: Sema 1.0 mg	ECG+PK Sema Dose: Sema 1.5 mg
	12	ECG	PK	ECG + PK	ECG + PK	ECG + PK
2	18	ECG	PK	ECG + PK	ECG + PK	ECG + PK
	24	ECG	PK	ECG + PK	ECG + PK	ECG + PK
	25	ECG	PK	ECG + PK	ECG + PK	ECG + PK
	26	ECG	PK	ECG + PK	ECG + PK	ECG + PK
	27	ECG	PK	ECG + PK	ECG + PK	ECG + PK
	30	ECG	PK	ECG + PK	ECG + PK	ECG + PK
	36	ECG	PK	ECG + PK	ECG + PK	ECG + PK
3	42	ECG	PK	ECG + PK	ECG + PK	ECG + PK
	48	ECG[c] PK Mox Dose: Mox/Mox placebo	PK	ECG + PK	ECG + PK	ECG[c] 2xPK (Mox, Sema) Dose: Mox/Mox placebo
	49	ECG + PK Mox	-	-	-	ECG + PK Mox
	50	ECG + PK Mox	-	-	-	ECG + PK Mox
	51	ECG + PK Mox	-	-	-	ECG + PK Mox
	54	ECG + PK Mox	-	-	-	ECG + PK Mox
	60	ECG + PK Mox	-	-	-	ECG + PK Mox
4	66	ECG + PK Mox	-	-	-	ECG + PK Mox
	72	ECG + PK Mox	-	-	-	ECG + PK Mox

Source: Sponsor's clinical study report, Table 9-4, page 63.

Reviewer's Comment: The sponsor's timing of PK/ECG collection is acceptable, since it captures the effects at Tmax (range 26-60 hours) and any potential delayed effects.

4.2.6.5 Baseline

Time-matched QT/QTc values at Visit 2 were used as baselines for primary analysis. The predose QT/QTc value before moxifloxacin/moxifloxacin placebo administration was used as baseline for assay sensitivity analysis.

4.2.7 ECG Collection

Intensive 12-Lead Holter monitoring was used to obtain digital ECGs. Standard 12-Lead ECGs were obtained while subjects were recumbent.

4.2.8 Sponsor's Results

4.2.8.1 Study Subjects

A total of 168 healthy subjects were planned and randomized to the study. Overall, 166 subjects (67 females and 99 males) were exposed to trial drugs, and all of the 166

subjects were included in the full analysis set and the safety analysis set. Sixteen subjects withdrew after randomization and 152 subjects completed the study.

The average age (SD) of the 166 subjects was 38.2 (10.2) years, ranging from 19.0 to 55.0 years. Most subjects (160/166, 96.4%) were White; 2 subjects were American Indian or Alaska Native; 4 subjects were of race Other. The majority of the subjects were Not Hispanic or Latino (164/166, 98.8%).

4.2.8.2 Statistical Analyses

4.2.8.2.1 Primary Analysis

The primary endpoints consisted of the 11 time-matched QTcI measurements during the 48-hour post-dose recording at steady state of the 1.5 mg semaglutide/placebo dose level, assessed at visit 11.

Estimated mean treatment differences between subjects treated with semaglutide 1.5 mg and placebo in baseline-adjusted QTcI appeared steady over the 48-hour time course post dosing.

The primary statistical analysis showed no unacceptable prolongation of QTcI at steady state of semaglutide 1.5 mg; the upper limits of the 11 two-sided 90% CIs (equivalent to the upper limits of the one-sided 95% CIs) for the estimated mean treatment differences were all below 10 msec. The upper limit of the two-sided 90% CI for the maximum time matched estimated mean treatment difference in QTcI was 0.29 msec. The estimated mean treatment differences ranged from −6.56 msec to −3.16 msec.

The sponsor's primary analysis results are displayed in the following Table 3.

Table 3: QTcI Interval 0-48 Hours at Steady State - Semaglutide/placebo 1.5 mg (Sponsor's Results based on Full Analysis Set)

	Number of subjects in full analysis set	N	Estimate	90% CI	p-value
QTcI interval (msec)					
Mean baseline-adjusted					
sema 1.5 mg					
0 hour	83	76	-0.46	[-2.91 ; 1.98]	
12 hours	83	76	-4.34	[-6.91 ; -1.76]	
18 hours	83	76	-0.04	[-2.69 ; 2.61]	
24 hours	83	76	-3.41	[-5.90 ; -0.92]	
25 hours	83	76	-3.74	[-6.21 ; -1.27]	
26 hours	83	76	-5.07	[-7.44 ; -2.71]	
27 hours	83	76	-5.43	[-7.87 ; -2.98]	
30 hours	83	76	-8.09	[-10.43 ; -5.76]	
36 hours	83	76	-6.62	[-9.18 ; -4.07]	
42 hours	83	76	-3.51	[-6.06 ; -0.95]	
48 hours	83	76	-4.56	[-6.79 ; -2.34]	
placebo					
0 hour	83	76	2.70	[0.25 ; 5.15]	
12 hours	83	76	-0.95	[-3.53 ; 1.63]	
18 hours	83	76	5.10	[2.47 ; 7.74]	
24 hours	83	76	1.40	[-1.10 ; 3.89]	
25 hours	83	76	0.52	[-1.95 ; 2.99]	
26 hours	83	76	0.73	[-1.64 ; 3.10]	
27 hours	83	76	-0.14	[-2.59 ; 2.31]	
30 hours	83	76	-4.21	[-6.57 ; -1.85]	
36 hours	83	76	-0.73	[-3.28 ; 1.82]	
42 hours	83	76	3.05	[0.51 ; 5.59]	
48 hours	83	76	0.57	[-1.66 ; 2.79]	
Treatment difference, sema 1.5 mg - placebo					
0 hour			-3.16	[-6.62 ; 0.29]	<.0001
12 hours			-3.38	[-7.03 ; 0.26]	<.0001
18 hours			-5.15	[-8.84 ; -1.45]	<.0001
24 hours			-4.80	[-8.33 ; -1.28]	<.0001
25 hours			-4.26	[-7.75 ; -0.77]	<.0001
26 hours			-5.81	[-9.16 ; -2.45]	<.0001
27 hours			-5.29	[-8.75 ; -1.83]	<.0001
30 hours			-3.88	[-7.14 ; -0.63]	<.0001
36 hours			-5.89	[-9.50 ; -2.28]	<.0001
42 hours			-6.56	[-10.14 ; -2.98]	<.0001
48 hours			-5.13	[-8.27 ; -1.99]	<.0001

N: Number of subjects contributing to analysis, CI: Confidence interval
The endpoint is analysed using a linear mixed model for repeated measures, where all eleven time-matched sampling time points enter as dependent variables with treatment as fixed factor and baseline measurements as covariate. The treatment and covariate are nested within time points. An unstructured covariance matrix is applied.
The estimates are presented with corresponding two-sided 90% CI.
The p-value is for the one-sided test of a mean difference greater than 10 msec.

Source: the sponsor's clinical study report, Table 11-1, page 109

Reviewer's Comments: Please see the reviewer's analysis in section 5.2.

4.2.8.2.2 Assay Sensitivity

A single dose of moxifloxacin 400 mg was used as a positive control to establish QT assay sensitivity in this trial. The assessment was made as a cross-over in the placebo arms at day 3−4 of visits 2 and day 3−4 of visit 11. The QTcI at 3 and 6 hours post dosing during the 24-hour recording period after moxifloxacin/moxifloxacin placebo administration were considered confirmatory endpoints.

A prolongation in QTcI was induced by administration of moxifloxacin compared to moxifloxacin placebo and QT assay sensitivity was established; the lower limits of the 95% CIs for the estimated mean treatment differences were greater than 5 msec at both confirmatory time points. The estimated mean treatment difference in QTcI at 3 and 6 hours post dosing between subjects treated with moxifloxacin and moxifloxacin placebo were 12.29 msec [10.97; 13.61]95% CI and 8.87 msec [7.12; 10.61]95% CI, respectively.

The sponsor's results for assay sensitivity analysis are displayed in the following Table 4.

Table 4: QTcI Interval at 3 and 6 Hours after Single Dose of Moxifloxacin
(Sponsor's Results based on Full Analysis Set)

	Number of subjects in full analysis set	N	Estimate	95% CI	p-value
QTcI interval (msec)					
At 3 hours					
Mean					
moxifloxacin	83	77	406	[405 ; 407]	
placebo	83	82	394	[393 ; 395]	
Treatment difference					
moxifloxacin - placebo			12.29	[10.97 ; 13.61]	<.0001
At 6 hours					
Mean					
moxifloxacin	83	77	396	[395 ; 397]	
placebo	83	82	387	[386 ; 388]	
Treatment difference					
moxifloxacin - placebo			8.87	[7.12 ; 10.61]	<.0001

N: Number of subjects contributing to analysis, CI: Confidence interval
The endpoint is analysed using an analysis of variance model with treatment, period and subject as fixed factors and pre-dose QTcI interval as covariate. The estimates are presented with corresponding two-sided 95% CI.
The p-value is for the one-sided test of a mean difference less than 5 msec.

Source: the sponsor's clinical study report, Table 11-2, page 112

Reviewer's Comments: Please see the reviewer's analysis in section 5.2.

4.2.8.2.3 Categorical Analysis

From the sponsor's table in report, no subjects had QTcI >480 ms. In the placebo treatment group, 2 subjects (2.6%) at 0.5 mg dose level, 1 subject (1.3%) at 1.0 mg dose level, and 1 subject (1.3%) at 1.5 mg dose level had QTcI >450 ms. In the semaglutide treatment group, only 1 subject (1.3%) at 1.5 mg dose level had QTcI >450 ms.

No subjects had change from baseline in QTcI (ΔQTcI) >60 ms. In the placebo treatment group, 2 subjects (2.6%) at 0.5 mg dose level and 1 subject (1.3%) at 1.0 mg dose level had ΔQTcI >30 ms. No subjects had ΔQTcI >30 ms in the semaglutide treatment group.

4.2.8.3 Safety Analysis

No deaths occurred in this study. Six subjects withdrew from the study due to adverse events (AEs); 2 of the 6 subjects were treated with semaglutide and 4 subjects were treated with placebo.

During this trial, 1 serious adverse event (SAE) of 'clavicle fracture' in the SOC 'injury, poisoning and procedural complications' was reported for a subject treated with semaglutide. Onset of the event was 23 days after the subject had received the fourth and last dose of semaglutide 1.5 mg. The SAE was moderate in severity; the subject

recovered and the event was assessed as unlikely related to trial products by the investigator. No SAEs were reported for subjects treated with placebo.

4.2.8.4 Clinical Pharmacology

4.2.8.4.1 Pharmacokinetic Analysis

The steady state PK properties are presented in Table 5. C_{max} and AUC values in the thorough QT study were approximately 2.2- and 2.1- fold higher, respectively, following administration of 1.5 mg Semaglutide in healthy subjects compared with 1.0 mg Semaglutide, the intended clinical dose, in patients with T2D.

Table 5: Steady State Pharmacokinetics for Semaglutide in Subjects with T2D, Subjects with Obesity and in Healthy Subjects

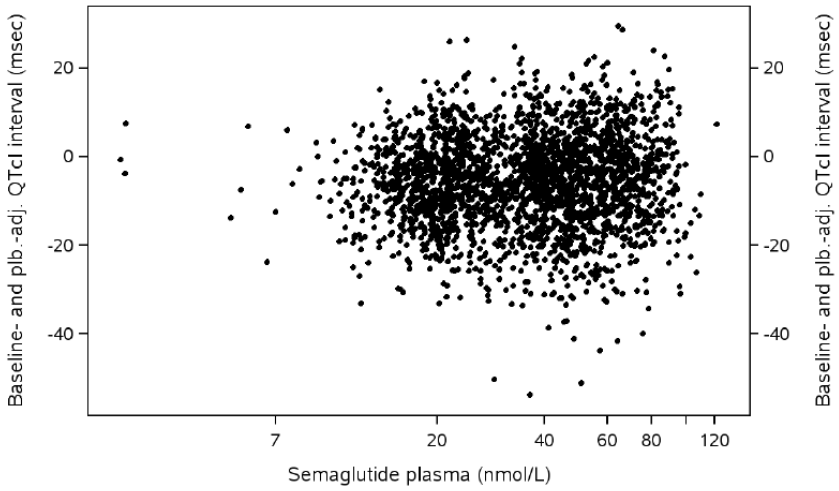
	Trial	N	Dose (mg)	AUC_{0-168h} (nmol·h/L) geometric mean (CV [%])	C_{max} (nmol/L) geometric mean (CV [%])	t_{max} (h) median (min-max)
T2D	3819 (a)	40	1.0	4602 (16.8)	33.8 (15.5)	36 (12-167)
	3635	36	1.0	4684 (18.8)	32.2 (19.1)	36 (4-165)
	3684	37	1.0	4811 (20.2)	33.3 (20.8)	60 (18-121)
Obesity	3685	30	1.0	4467 (17.7)	32.0 (19.1)	35 (12- 84)
Healthy	3652	82 (b)	0.25	1589 (18.0)	11.9 (19.3)	26 (12- 48) (c)
	3652	81	0.5	3081 (20.0)	22.1 (20.7)	27 (12- 48) (c)
	3634 (d)	7	0.5	3371 (2.4)	23.7 (7.5)	36 (24- 72)
	3634 (e)	8	0.5	3583 (17.8)	25.1 (17.8)	30 (12- 72)
	3817	22	1.0	5877 (31.5)	43.1 (31.3)	36 (12- 72)
	3818	26	1.0	7020 (20.9)	48.6 (22.4)	36 (12- 96)
	3652	80 (f)	1.0	6077 (20.0)	42.7 (20.9)	27 (12- 48) (c)
	3634 (d)	6	1.0	7490 (17.9)	50.6 (17.5)	30 (24- 72)
	3634 (e)	8	1.0	7449 (12.2)	51.6 (11.1)	36 (18- 96)
	3652	76	1.5	9928 (18.0)	72.6 (20.8)	27 (12- 48) (c)

Source: Sponsor's summary of clinical pharmacology, Table 3-3, page 37.

4.2.8.4.2 Exposure-Response Analysis

The exposure-response relationship was assessed by baseline- and placebo-adjusted QTcI at steady state of semaglutide 0.5, 1.0 and 1.5 mg versus corresponding semaglutide plasma concentrations (Figure 2). Statistical analysis did not show any indication of a dose-dependency between baseline- and placebo-adjusted QTcI intervals and semaglutide concentration, as shown in Table 6.

Figure 2: Scatter Plots of Baseline- and Placebo-Adjusted QTcI Versus Semaglutide Concentrations.



Source: Sponsor's clinical study report, Figure 11-12, page 134.

Table 6: Results of Semaglutide Concentration-ΔΔQTcI Analysis

	Number of subjects in full analysis set	N	Estimate of slope	95% CI	p-value
log(sema concentration)	83	81	0.43	[-0.03 ; 0.89]	0.0650

N: Number of subjects contributing to analysis, CI: Confidence interval
The concentration-response relation is analysed by a linear mixed model with the placebo-subtracted QTcI measurements as the dependent variable, the log-transformed semaglutide plasma concentrations and the baseline QTcI measurements as covariates and subject as a random effect.

Source: Sponsor's clinical study report, Table 11-9, page 135.

Reviewer's Analysis: Independent analyses for the relationship between ΔΔQTcI and Semaglutide concentrations were conducted by the reviewer (

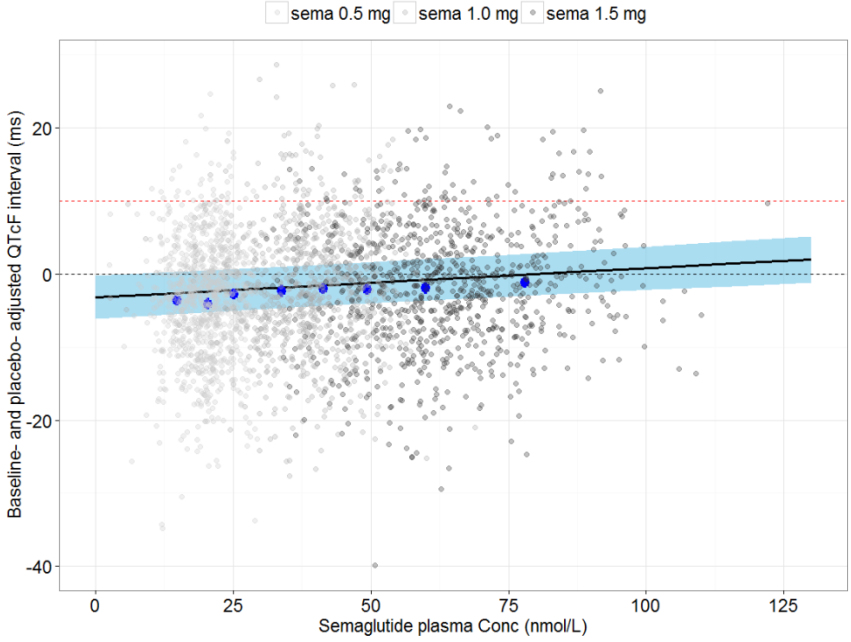


Figure 8*). Consistent with the sponsor's results, no significant exposure-response relationship was identified between ΔΔQTcI and semaglutide concentrations.*

5 REVIEWERS' ASSESSMENT

5.1 EVALUATION OF THE QT/RR CORRECTION METHOD

In addition to QTcB and QTcF, the sponsor derived exponential correction QTcI and linear regression correction QTcL.

$$QTcI = QT/RR^{\beta}$$

The individual coefficient β was derived by fitting all baseline QT/RR in a model form $\log QT_{ij} = \alpha_{i\_} + \beta_i \log RR_{ij} + e_{ij}$, where QT_{ij} denoted the QT value for subject i recording j.

$$QTcL = QT - \gamma\,(1\text{-}RR)$$

The coefficient γ was determined using all baseline QT/RR in a model form $QT_k = \alpha + \gamma(1 - RR_k) + e_k$, where QT_k denoted the QT value for recording k.

A heart rate increasing effect was detected for semaglutide and the sponsor used QTcI as the primary endpoint. We evaluated the appropriateness of the correction methods (QTcF, QTcI, and QTcL). Baseline values were excluded in the validation. Ideally, a good correction QTc would result in no relationship of QTc and RR intervals.

We used the criterion of Mean Sum of Squared Slopes (MSSS) from individual regressions of QTc versus RR. The smaller this value is, the better the correction. Based on the results listed in Table 7 and Figure 4, QTcF was used for the primary statistical analysis.

Table 7: Average of Sum of Squared Slopes for Different QT-RR Correction Methods

	QTcF		QTcI		QTcL	
Treatment Group	**N**	**MSSS**	**N**	**MSSS**	**N**	**MSSS**
Moxifloxacin 400 mg	77	0.00362	77	0.00604	77	0.00649
Moxifloxacin placebo	165	0.00150	165	0.00322	165	0.00307
Semaglutide 0.5 mg	81	0.00260	81	0.00527	81	0.00506
Semaglutide 1.0 mg	80	0.00315	80	0.00638	80	0.00628
Semaglutide 1.5 mg	76	0.00286	76	0.00606	76	0.00610
Semaglutide placebo	77	0.00099	77	0.00227	77	0.00244
All	166	0.00077	166	0.00256	166	0.00243

The relationship between different correction methods and RR is presented in Figure 3. Dose-dependent heart rate increasing effect was observed for semaglutide. The boxplots of baseline and post-baseline HR across treatment and placebo groups were shown in Figure 4, which suggests that the collected baseline data is not sufficient to describe the QT changes on treatment. However, as noted in the summary it is unlikely that the imprecision resulting from the lack of proper QTc correction would have altered the interpretation of the study results.

Figure 3: QTcF, QTcI and QTcL vs. RR

(Each Subject's Data Points are Connected with a Line)

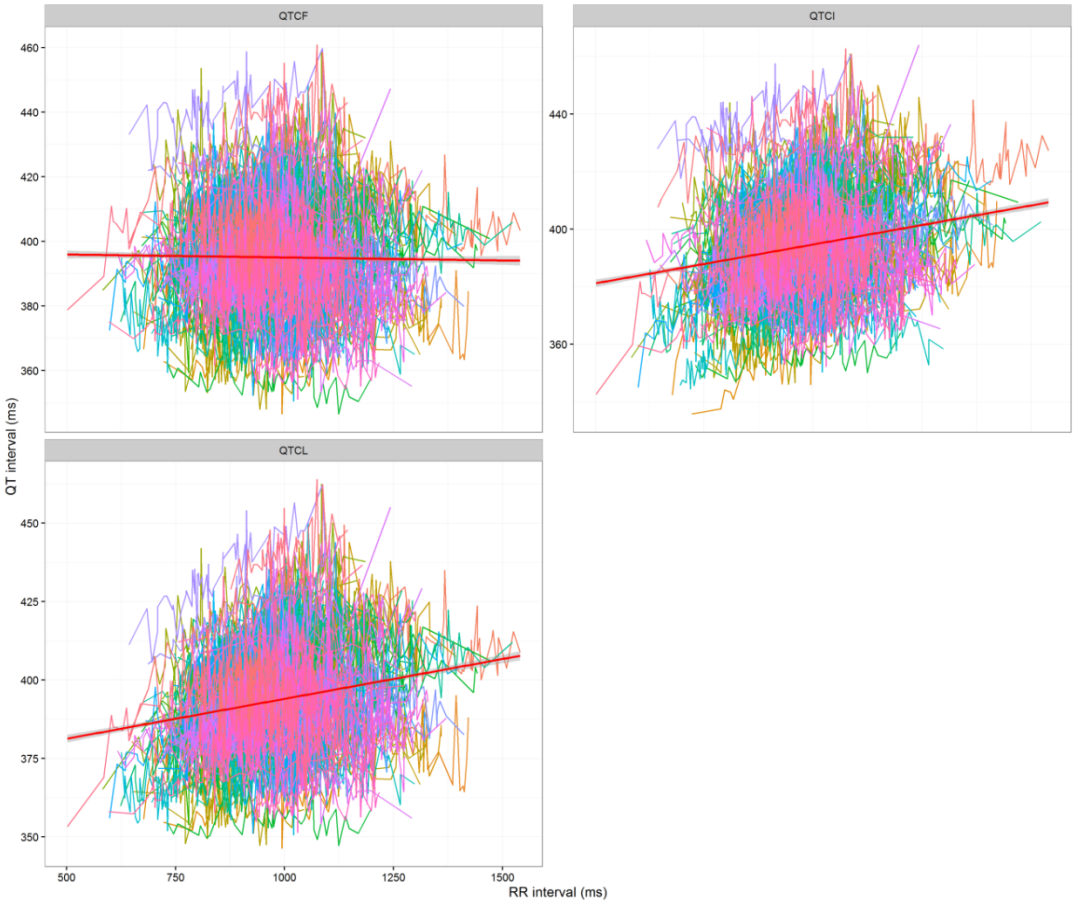
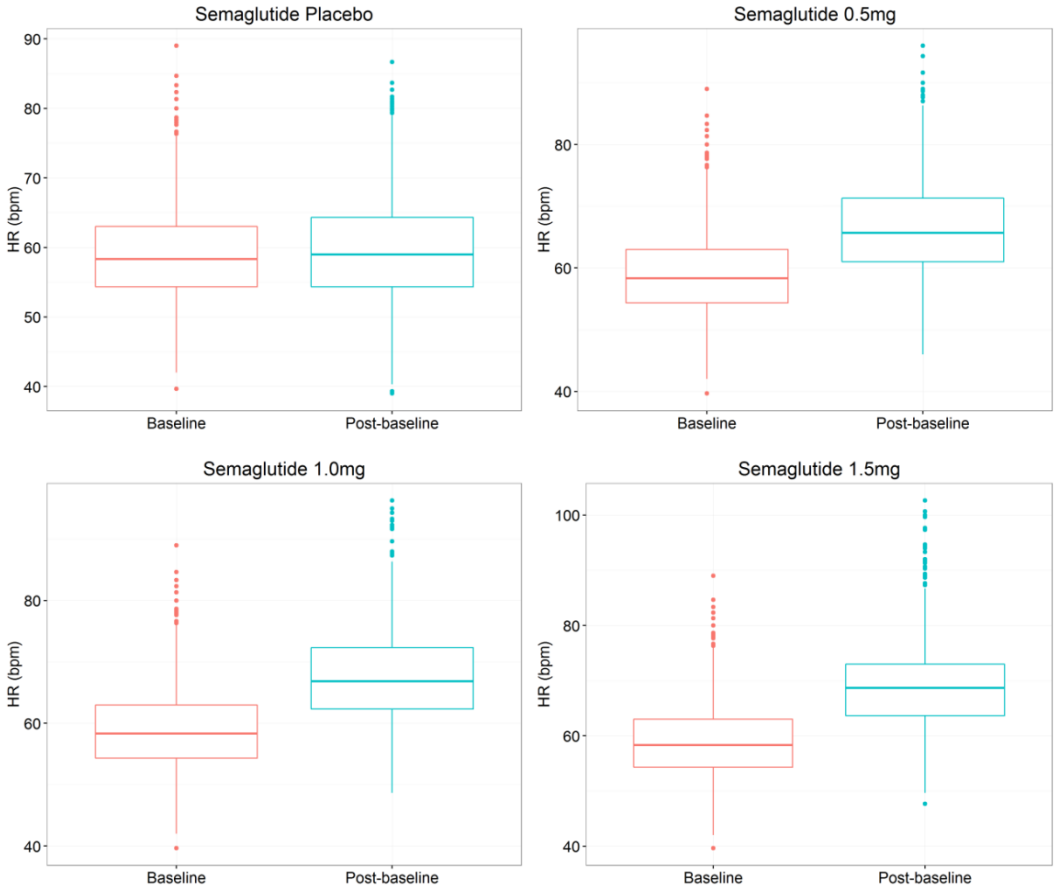


Figure 4: Comparisons of baseline and post-baseline Heart Rates across Semaglutide Treatment and Placebo Groups.



5.2 STATISTICAL ASSESSMENTS

5.2.1 QTc Analysis

5.2.1.1 The Primary Analysis for Semaglutide

The statistical reviewer used mixed model to analyze the ΔQTcF effect by visit. Baseline values are also included in the model as a covariate. The analysis results are listed in the following tables.

Table 8: Analysis Results of ΔQTcF and ΔΔQTcF for Semaglutide 1.5 mg

	ΔQTcF (ms) Semaglutide 1.5 mg			ΔQTcF (ms) Semaglutide Placebo			ΔΔQTcF (ms) Semaglutide 1.5 mg	
Time (hour)	N	LSmean	SD	N	LSmean	SD	LSmean	90% CI
0	76	3.0	1.3	76	2.8	1.3	0.2	(-2.8, 3.2)
12	76	-0.2	1.3	76	0.6	1.3	-0.8	(-3.8, 2.2)

	ΔQTcF (ms) Semaglutide 1.5 mg			ΔQTcF (ms) Semaglutide Placebo			ΔΔQTcF (ms) Semaglutide 1.5 mg	
Time (hour)	**N**	**LSmean**	**SD**	**N**	**LSmean**	**SD**	**LSmean**	**90% CI**
18	76	3.2	1.3	76	4.9	1.3	-1.7	(-4.7, 1.3)
24	76	1.0	1.3	76	0.9	1.3	0.1	(-3.0, 3.1)
25	76	0.2	1.3	76	0.6	1.3	-0.4	(-3.4, 2.7)
26	76	-0.3	1.3	76	1.1	1.3	-1.3	(-4.4, 1.7)
27	76	-0.5	1.3	76	0.6	1.3	-1.1	(-4.1, 1.9)
30	76	-3.2	1.3	76	-1.9	1.3	-1.3	(-4.3, 1.7)
36	76	-2.2	1.3	76	0.5	1.3	-2.7	(-5.8, 0.3)
42	76	1.0	1.3	76	3.6	1.3	-2.6	(-5.6, 0.4)
48	76	0.4	1.3	76	0.8	1.3	-0.4	(-3.4, 2.6)

Table 9: Analysis Results of ΔQTcF and ΔΔQTcF for Semaglutide 1.0 mg

	ΔQTcF (ms) Semaglutide 1.0 mg			ΔQTcF (ms) Semaglutide Placebo			ΔΔQTcF (ms) Semaglutide 1.0 mg	
Time (hour)	**N**	**LSmean**	**SD**	**N**	**LSmean**	**SD**	**LSmean**	**90% CI**
0	80	3.6	1.4	77	3.0	1.4	0.5	(-2.7, 3.7)
12	80	0.0	1.4	77	1.8	1.4	-1.7	(-4.9, 1.4)
18	80	3.0	1.4	77	5.4	1.4	-2.4	(-5.6, 0.8)
24	80	1.2	1.4	77	1.7	1.4	-0.4	(-3.6, 2.8)
25	80	0.7	1.4	77	1.3	1.4	-0.6	(-3.8, 2.6)
26	80	-0.9	1.4	77	0.9	1.4	-1.8	(-5.0, 1.4)
27	80	-0.9	1.4	77	0.7	1.4	-1.6	(-4.8, 1.6)
30	80	-3.3	1.4	77	-2.2	1.4	-1.1	(-4.3, 2.1)
36	80	-4.1	1.4	77	1.9	1.4	-5.9	(-9.1, -2.7)
42	80	1.3	1.4	77	4.0	1.4	-2.7	(-5.9, 0.5)
48	80	-0.2	1.4	77	-0.2	1.4	0.0	(-3.2, 3.2)

Table 10: Analysis Results of ΔQTcF and ΔΔQTcF for Semaglutide 0.5 mg

	ΔQTcF (ms) Semaglutide 0.5 mg			ΔQTcF (ms) Semaglutide Placebo			ΔΔQTcF (ms) Semaglutide 0.5 mg	
Time (hour)	N	LSmean	SD	N	LSmean	SD	LSmean	90% CI
0	81	1.0	1.2	77	3.4	1.3	-2.3	(-5.2, 0.6)
12	81	-2.1	1.2	77	2.0	1.3	-4.1	(-7.0, -1.2)
18	81	0.8	1.2	77	4.6	1.3	-3.8	(-6.7, -0.8)
24	81	-0.9	1.2	77	0.9	1.3	-1.8	(-4.7, 1.1)
25	81	-2.1	1.2	77	1.3	1.3	-3.3	(-6.3, -0.4)
26	81	-2.1	1.2	77	0.2	1.3	-2.3	(-5.3, 0.6)
27	81	-1.8	1.2	77	0.1	1.3	-1.9	(-4.8, 1.0)
30	81	-5.4	1.2	77	-2.6	1.3	-2.8	(-5.7, 0.2)
36	81	-4.8	1.2	77	2.0	1.3	-6.8	(-9.8, -3.9)
42	81	0.1	1.2	77	3.2	1.3	-3.0	(-6.0, -0.1)
48	81	-1.9	1.2	77	1.0	1.3	-2.9	(-5.9, -0.0)

No significant mean difference between semaglutide 1.5 mg and placebo was observed. The largest upper bound of the 2-sided 90% CI for the mean difference between semaglutide 1.5 mg and placebo was 3.2 ms. No QTcF prolongation effect was observed for semaglutide 1.0 mg and semaglutide 0.5 mg dose levels either.

5.2.1.2 Assay Sensitivity Analysis

The statistical reviewer used mixed model for a cross-over design to analyze moxifloxacin and placebo data. The results are presented in Table 11. The largest unadjusted 90% lower confidence interval was 12.6 ms. By considering Bonferroni multiple endpoint adjustment, the largest lower confidence interval was 12.1 ms, which indicates that an at least 5 ms QTcF effect due to moxifloxacin can be detected from the study.

Table 11: Analysis Results of ΔQTcF and ΔΔQTcF for Moxifloxacin

	ΔQTcF (ms) Moxifloxacin 400 mg			ΔQTcF (ms) Moxi Placebo			ΔΔQTcF (ms) Moxifloxacin 400 mg		
Time (hour)	N	LSmean	SD	N	LSmean	SD	LSmean	CI	Adjust 90% CI*
1	77	12.0	0.6	82	0.0	0.6	12.0	(10.6, 13.3)	(10.2, 13.7)

	ΔQTcF (ms) Moxifloxacin 400 mg			ΔQTcF (ms) Moxi Placebo			ΔΔQTcF (ms) Moxifloxacin 400 mg		
Time (hour)	N	LSmean	SD	N	LSmean	SD	LSmean	CI	Adjust 90% CI*
2	77	14.2	0.6	82	0.9	0.6	13.3	(12.1, 14.5)	(11.7, 14.9)
3	77	13.5	0.7	82	-0.6	0.6	14.0	(12.6, 15.5)	(12.1, 15.9)
6	77	5.5	0.8	82	-4.0	0.8	9.5	(7.6, 11.3)	(7.1, 11.9)
12	77	12.1	0.8	82	1.9	0.8	10.2	(8.3, 12.1)	(7.8, 12.7)
18	77	12.9	0.8	82	5.5	0.8	7.4	(5.7, 9.1)	(5.1, 9.6)
24	77	6.6	0.7	82	0.3	0.7	6.2	(4.7, 7.8)	(4.2, 8.3)

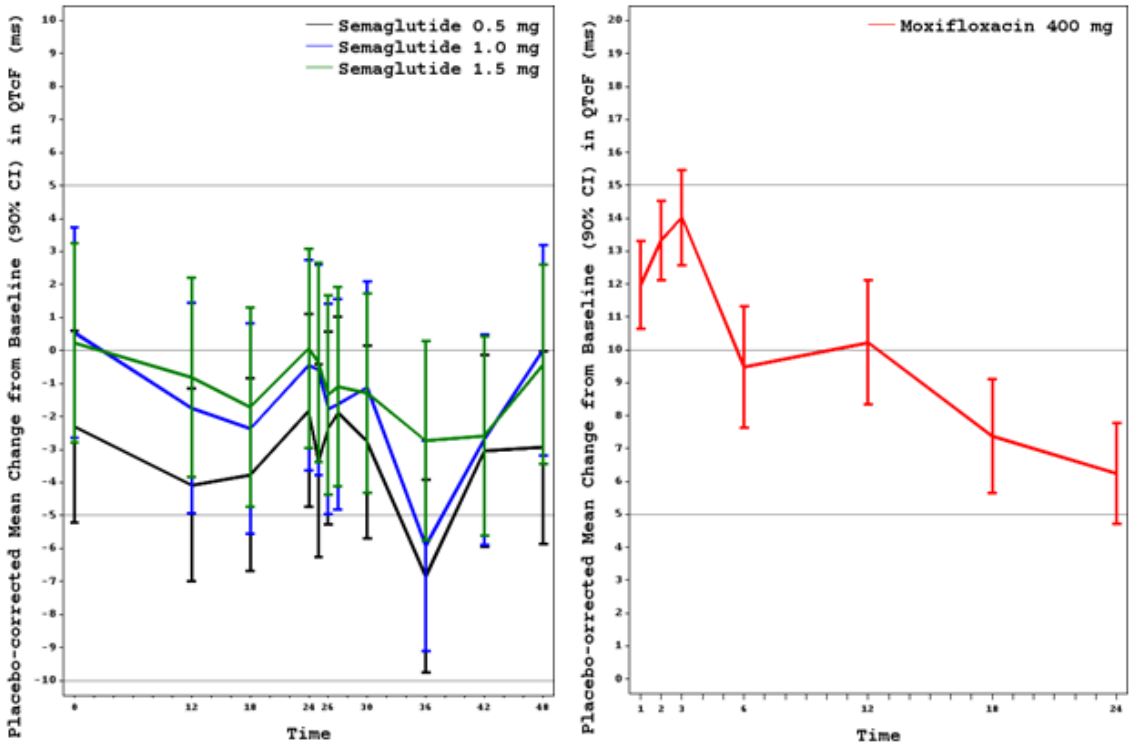
* Bonferroni method was applied to all time points to adjust for multiple endpoint evaluation at 3 time points around moxifloxacin C_{max}.

5.2.1.3 Graph of ΔΔQTcF Over Time

The following figure displays the time profile of ΔΔQTcF for different treatment groups.

(Note: CIs are all unadjusted including moxifloxacin)

Figure 5: Mean and 90% CI ΔΔQTcF Timecourse



5.2.1.4 Categorical Analysis

Table 12 lists the number of subjects as well as the number of observations whose QTcF values were ≤ 450 ms and between 450 ms and 480 ms. No subject's QTcF was above 480 ms.

Table 12: Categorical Analysis for QTcF

	Total N		QTcF<=450 ms		450<QTcF<=480 ms	
Treatment Group	**Subj. #**	**Obs. #**	**Subj. #**	**Obs. #**	**Subj. #**	**Obs. #**
Moxifloxacin 400 mg	77	539	77 (100%)	539 (100%)	0 (0.0%)	0 (0.0%)
Moxi placebo	165	1687	163 (98.8%)	1683 (99.8%)	2 (1.2%)	4 (0.2%)
Semaglutide/Semaglutide placebo Baseline	166	1826	165 (99.4%)	1824 (99.9%)	1 (0.6%)	2 (0.1%)
Semaglutide 0.5 mg	81	890	81 (100%)	890 (100%)	0 (0.0%)	0 (0.0%)
Semaglutide 1.0 mg	80	880	79 (98.8%)	879 (99.9%)	1 (1.3%)	1 (0.1%)
Semaglutide 1.5 mg	76	836	75 (98.7%)	835 (99.9%)	1 (1.3%)	1 (0.1%)
Semaglutide placebo	77	2530	75 (97.4%)	2527 (99.9%)	2 (2.6%)	3 (0.1%)

Table 13 lists the categorical analysis results for ΔQTcF. No subject's change from baseline in QTcF was above 60 ms.

Table 13: Categorical Analysis of ΔQTcF

	Total N		ΔQTcF<=30 ms		30<ΔQTcF<=60 ms	
Treatment Group	**Subj. #**	**Obs. #**	**Subj. #**	**Obs. #**	**Subj. #**	**Obs. #**
Moxifloxacin 400 mg	77	539	77 (100%)	539 (100%)	0 (0.0%)	0 (0.0%)
Moxi placebo	165	1687	165 (100%)	1687 (100%)	0 (0.0%)	0 (0.0%)
Semaglutide 0.5 mg	81	890	81 (100%)	890 (100%)	0 (0.0%)	0 (0.0%)
Semaglutide 1.0 mg	80	880	79 (98.8%)	879 (99.9%)	1 (1.3%)	1 (0.1%)
Semaglutide 1.5 mg	76	836	76 (100%)	836 (100%)	0 (0.0%)	0 (0.0%)
Semaglutide placebo	77	2530	76 (98.7%)	2529 (100%)	1 (1.3%)	1 (0.0%)

5.2.2 HR Analysis

The same statistical method used in primary analysis was applied to HR analysis. The point estimates and the 90% confidence intervals are presented in Table 14, Table 15, and Table 16. The largest HR mean differences between semaglutide 1.5 mg and placebo was 11.2 bpm with a 90% CI of 9.4 bpm to 12.9 bpm. A dose-dependent HR increasing effect was observed for all semaglutide.

The outlier analysis results for HR are presented in Table 17.

Table 14: Analysis Results of ΔHR and ΔΔHR for Semaglutide 1.5 mg

	ΔHR (bpm) Semaglutide 1.5 mg			ΔHR (bpm) Semaglutide Placebo			ΔΔHR (bpm) Semaglutide 1.5 mg	
Time (hour)	N	LSmean	SD	N	LSmean	SD	LSmean	90% CI
0	76	7.9	0.8	76	-0.2	0.8	8.1	(6.3, 9.9)
12	76	9.8	0.8	76	1.6	0.8	8.1	(6.3, 9.9)
18	76	9.3	0.8	76	-0.6	0.8	9.8	(8.0, 11.6)
24	76	9.4	0.8	76	-1.1	0.8	10.5	(8.8, 12.3)
25	76	9.1	0.8	76	-1.0	0.8	10.0	(8.3, 11.8)
26	76	10.3	0.8	76	-0.3	0.8	10.6	(8.8, 12.4)
27	76	10.8	0.8	76	0.6	0.8	10.2	(8.4, 12.0)
30	76	12.3	0.8	76	4.5	0.8	7.8	(6.0, 9.6)
36	76	10.9	0.8	76	2.1	0.8	8.8	(7.0, 10.6)
42	76	10.1	0.8	76	-0.3	0.8	10.4	(8.6, 12.2)
48	76	11.5	0.8	76	0.3	0.8	11.2	(9.4, 12.9)

Table 15: Analysis Results of ΔHR and ΔΔHR for Semaglutide 1.0 mg

	ΔHR (bpm) Semaglutide 1.0 mg			ΔHR (bpm) Semaglutide Placebo			ΔΔHR (bpm) Semaglutide 1.0 mg	
Time (hour)	N	LSmean	SD	N	LSmean	SD	LSmean	90% CI
0	80	6.2	0.7	77	-0.6	0.7	6.7	(5.1, 8.3)
12	80	8.0	0.7	77	0.2	0.7	7.8	(6.2, 9.4)
18	80	7.9	0.7	77	-0.5	0.7	8.4	(6.8, 10.0)
24	80	6.7	0.7	77	-0.8	0.7	7.6	(5.9, 9.2)
25	80	7.6	0.7	77	-1.2	0.7	8.8	(7.2, 10.4)
26	80	8.9	0.7	77	-0.8	0.7	9.7	(8.1, 11.3)
27	80	8.9	0.7	77	-0.6	0.7	9.4	(7.8, 11.0)
30	80	10.8	0.7	77	3.9	0.7	6.9	(5.2, 8.5)
36	80	9.8	0.7	77	1.1	0.7	8.7	(7.1, 10.3)

	ΔHR (bpm) Semaglutide 1.0 mg			ΔHR (bpm) Semaglutide Placebo			ΔΔHR (bpm) Semaglutide 1.0 mg	
Time (hour)	**N**	**LSmean**	**SD**	**N**	**LSmean**	**SD**	**LSmean**	**90% CI**
42	80	9.6	0.7	77	-0.1	0.7	9.7	(8.1, 11.3)
48	80	12.5	0.7	77	3.5	0.7	9.0	(7.4, 10.6)

Table 16: Analysis Results of ΔHR and ΔΔHR for Semaglutide 0.5 mg

	ΔHR (bpm) Semaglutide 0.5 mg			ΔHR (bpm) Semaglutide Placebo			ΔΔHR (bpm) Semaglutide 0.5 mg	
Time (hour)	**N**	**LSmean**	**SD**	**N**	**LSmean**	**SD**	**LSmean**	**90% CI**
0	81	5.3	0.7	77	-1.1	0.7	6.5	(4.8, 8.1)
12	81	7.0	0.7	77	1.5	0.7	5.5	(3.8, 7.2)
18	81	5.8	0.7	77	-0.4	0.7	6.1	(4.5, 7.8)
24	81	6.4	0.7	77	-1.7	0.7	8.1	(6.4, 9.8)
25	81	5.6	0.7	77	-1.8	0.7	7.4	(5.8, 9.1)
26	81	6.3	0.7	77	-0.4	0.7	6.7	(5.0, 8.4)
27	81	7.1	0.7	77	-0.3	0.7	7.3	(5.6, 9.0)
30	81	9.4	0.7	77	4.1	0.7	5.3	(3.6, 7.0)
36	81	9.0	0.7	77	1.4	0.7	7.6	(5.9, 9.3)
42	81	8.4	0.7	77	-0.0	0.7	8.4	(6.7, 10.1)
48	81	11.0	0.7	77	3.3	0.7	7.7	(6.0, 9.4)

Table 17: Categorical Analysis for HR

	Total N	**HR<=100 bpm**	**HR>100 bpm**	**HR>45 bpm**	**HR<=45 bpm**
Treatment Group	**Subj. #**	**Subj. #**	**Subj. #**	**Subj. #**	**Subj. #**
Moxifloxacin 400 mg	77	77 (100%)	0 (0.0%)	75 (97.4%)	2 (2.6%)
Moxi placebo	165	164 (99.4%)	1 (0.6%)	156 (94.5%)	9 (5.5%)
Semaglutide/Semaglutide placebo Baseline	166	166 (100%)	0 (0.0%)	159 (95.8%)	7 (4.2%)

	Total N	HR<=100 bpm	HR>100 bpm	HR>45 bpm	HR<=45 bpm
Treatment Group	**Subj. #**	**Subj. #**	**Subj. #**	**Subj. #**	**Subj. #**
Semaglutide 0.5 mg	81	81 (100%)	0 (0.0%)	81 (100%)	0 (0.0%)
Semaglutide 1.0 mg	80	80 (100%)	0 (0.0%)	80 (100%)	0 (0.0%)
Semaglutide 1.5 mg	76	74 (97.4%)	2 (2.6%)	76 (100%)	0 (0.0%)
Semaglutide placebo	77	77 (100%)	0 (0.0%)	72 (93.5%)	5 (6.5%)

5.2.3 PR Analysis

The same statistical method used in primary analysis was applied to PR analysis. The point estimates and the 90% confidence intervals are presented in Table 18, Table 19, and Table 20. Mean PR prolongation effect of 4.6 ms to 10.1 ms, 3.5 ms to 9.2 ms, 6.3 ms to 10.7 ms was observed for semaglutide 1.5 mg, semaglutide 1.0 mg, and semaglutide 0.5 mg, respectively.

The outlier analysis results for PR are presented in Table 21.

Table 18: Analysis Results of ΔPR and ΔΔPR for Semaglutide 1.5 mg

	ΔPR (ms) Semaglutide 1.5 mg			ΔPR (ms) Semaglutide Placebo			ΔΔPR (ms) Semaglutide 1.5 mg	
Time (hour)	**N**	**LSmean**	**SD**	**N**	**LSmean**	**SD**	**LSmean**	**90% CI**
0	76	5.5	1.8	76	-0.3	1.8	5.8	(1.5, 10.1)
12	76	4.7	1.8	76	-2.2	1.8	6.9	(2.6, 11.1)
18	76	7.8	1.8	76	-0.4	1.8	8.2	(4.0, 12.4)
24	76	4.9	1.8	76	-0.7	1.8	5.6	(1.5, 9.8)
25	76	4.4	1.7	76	-0.6	1.7	5.1	(1.1, 9.1)
26	76	4.8	1.6	76	-1.7	1.6	6.6	(2.7, 10.4)
27	76	4.1	1.7	76	-0.5	1.7	4.6	(0.6, 8.6)
30	76	5.3	1.7	76	-4.8	1.7	10.1	(6.1, 14.1)
36	76	5.1	1.7	76	-2.0	1.7	7.2	(3.2, 11.2)
42	76	7.5	1.8	76	-0.2	1.8	7.8	(3.6, 12.0)
48	76	6.9	2.1	76	-0.8	2.1	7.6	(2.7, 12.5)

Table 19: Analysis Results of ΔPR and ΔΔPR for Semaglutide 1.0 mg

	ΔPR (ms) Semaglutide 1.0 mg			ΔPR (ms) Semaglutide Placebo			ΔΔPR (ms) Semaglutide 1.0 mg	
Time (hour)	N	LSmean	SD	N	LSmean	SD	LSmean	90% CI
0	80	5.6	1.9	77	0.6	2.0	5.0	(0.5, 9.6)
12	80	5.6	1.9	77	-0.8	1.9	6.4	(2.0, 10.9)
18	80	9.9	1.9	77	0.7	1.9	9.2	(4.7, 13.6)
24	80	6.9	1.8	77	0.6	1.9	6.3	(1.9, 10.6)
25	80	7.7	1.8	77	0.0	1.9	7.7	(3.4, 12.0)
26	80	6.0	1.8	77	-1.6	1.8	7.6	(3.3, 11.9)
27	80	5.9	1.8	77	-1.7	1.8	7.6	(3.4, 11.9)
30	80	3.8	1.7	77	-5.5	1.7	9.2	(5.3, 13.2)
36	80	6.9	1.9	77	-1.5	1.9	8.3	(3.8, 12.9)
42	80	9.8	1.9	77	0.6	1.9	9.2	(4.8, 13.6)
48	80	2.7	1.8	77	-0.8	1.8	3.5	(-0.7, 7.6)

Table 20: Analysis Results of ΔPR and ΔΔPR for Semaglutide 0.5 mg

	ΔPR (ms) Semaglutide 0.5 mg			ΔPR (ms) Semaglutide Placebo			ΔΔPR (ms) Semaglutide 0.5 mg	
Time (hour)	N	LSmean	SD	N	LSmean	SD	LSmean	90% CI
0	81	6.2	1.9	77	-0.0	1.9	6.3	(1.8, 10.7)
12	81	4.9	1.8	77	-2.5	1.9	7.4	(3.1, 11.7)
18	81	9.5	1.9	77	0.7	2.0	8.8	(4.2, 13.3)
24	81	7.9	1.9	77	0.2	1.9	7.8	(3.3, 12.2)
25	81	7.6	1.9	77	-1.0	1.9	8.5	(4.0, 13.0)
26	81	7.1	1.9	77	-0.7	1.9	7.8	(3.3, 12.2)
27	81	6.6	1.8	77	-0.9	1.9	7.6	(3.3, 11.9)
30	81	3.7	1.7	77	-5.4	1.7	9.1	(5.1, 13.1)
36	81	6.3	1.9	77	-2.3	2.0	8.6	(4.0, 13.2)
42	81	10.9	1.9	77	0.2	2.0	10.7	(6.2, 15.3)
48	81	5.8	1.9	77	-1.2	1.9	7.0	(2.5, 11.5)

Table 21: Categorical Analysis for PR

	Total N		PR<=200 ms		PR>200 ms	
Treatment Group	**Subj. #**	**Obs. #**	**Subj. #**	**Obs. #**	**Subj. #**	**Obs. #**
Moxifloxacin 400 mg	77	539	70 (90.9%)	518 (96.1%)	7 (9.1%)	21 (3.9%)
Moxi placebo	165	1687	146 (88.5%)	1598 (94.7%)	19 (11.5%)	89 (5.3%)
Semaglutide/Semaglutide placebo Baseline	166	1826	149 (89.8%)	1731 (94.8%)	17 (10.2%)	95 (5.2%)
Semaglutide 0.5 mg	81	890	68 (84.0%)	800 (89.9%)	13 (16.0%)	90 (10.1%)
Semaglutide 1.0 mg	80	880	69 (86.3%)	809 (91.9%)	11 (13.8%)	71 (8.1%)
Semaglutide 1.5 mg	76	836	64 (84.2%)	772 (92.3%)	12 (15.8%)	64 (7.7%)
Semaglutide placebo	77	2530	69 (89.6%)	2402 (94.9%)	8 (10.4%)	128 (5.1%)

5.2.4 QRS Analysis

The same statistical method used in primary analysis was applied to QRS analysis. The point estimates and the 90% confidence intervals are presented in Table 22, Table 23, and Table 24. The effect of semaglutide (1.5 mg, 1.0 mg, and 0.5 mg) on QRS interval was clinically small and statistically insignificant for almost all time points.

The outlier analysis results for QRS are presented in

Table 25.

Table 22: Analysis Results of ΔQRS and ΔΔQRS for Semaglutide 1.5 mg

	ΔQRS (ms) Semaglutide 1.5 mg			ΔQRS (ms) Semaglutide Placebo			ΔΔQRS (ms) Semaglutide 1.5 mg	
Time (hour)	**N**	**LSmean**	**SD**	**N**	**LSmean**	**SD**	**LSmean**	**90% CI**
0	76	-0.6	0.8	76	0.6	0.8	-1.1	(-3.0, 0.7)
12	76	-0.8	0.8	76	0.7	0.8	-1.4	(-3.3, 0.4)
18	76	-0.3	0.8	76	1.2	0.8	-1.5	(-3.4, 0.4)
24	76	-0.9	0.8	76	0.5	0.8	-1.4	(-3.2, 0.5)
25	76	-0.9	0.8	76	0.3	0.8	-1.3	(-3.1, 0.6)
26	76	-1.2	0.8	76	0.5	0.8	-1.7	(-3.5, 0.1)
27	76	-1.2	0.8	76	0.4	0.8	-1.6	(-3.4, 0.2)
30	76	-0.8	0.8	76	1.3	0.8	-2.0	(-3.8, -0.2)
36	76	-1.0	0.8	76	0.5	0.8	-1.5	(-3.3, 0.4)

	ΔQRS (ms) Semaglutide 1.5 mg			ΔQRS (ms) Semaglutide Placebo			ΔΔQRS (ms) Semaglutide 1.5 mg	
Time (hour)	**N**	**LSmean**	**SD**	**N**	**LSmean**	**SD**	**LSmean**	**90% CI**
42	76	-0.6	0.8	76	1.2	0.8	-1.8	(-3.7, 0.0)
48	76	-0.9	0.8	76	0.4	0.8	-1.3	(-3.1, 0.5)

Table 23: Analysis Results of ΔQRS and ΔΔQRS for Semaglutide 1.0 mg

	ΔQRS (ms) Semaglutide 1.0 mg			ΔQRS (ms) Semaglutide Placebo			ΔΔQRS (ms) Semaglutide 1.0 mg	
Time (hour)	**N**	**LSmean**	**SD**	**N**	**LSmean**	**SD**	**LSmean**	**90% CI**
0	80	-0.5	0.7	77	0.6	0.7	-1.1	(-2.8, 0.6)
12	80	-0.5	0.7	77	0.5	0.7	-1.0	(-2.7, 0.6)
18	80	-0.0	0.7	77	1.1	0.7	-1.1	(-2.8, 0.6)
24	80	-0.6	0.7	77	0.4	0.7	-1.0	(-2.6, 0.6)
25	80	-0.8	0.7	77	0.4	0.7	-1.3	(-2.9, 0.4)
26	80	-1.1	0.7	77	0.3	0.7	-1.4	(-3.0, 0.2)
27	80	-1.1	0.7	77	0.3	0.7	-1.4	(-3.0, 0.2)
30	80	-0.6	0.7	77	0.8	0.7	-1.4	(-3.0, 0.3)
36	80	-0.9	0.7	77	0.4	0.7	-1.4	(-3.0, 0.3)
42	80	-0.6	0.7	77	0.8	0.7	-1.4	(-3.1, 0.3)
48	80	-0.8	0.7	77	0.2	0.7	-1.0	(-2.7, 0.6)

Table 24: Analysis Results of ΔQRS and ΔΔQRS for Semaglutide 0.5 mg

	ΔQRS (ms) Semaglutide 0.5 mg			ΔQRS (ms) Semaglutide Placebo			ΔΔQRS (ms) Semaglutide 0.5 mg	
Time (hour)	**N**	**LSmean**	**SD**	**N**	**LSmean**	**SD**	**LSmean**	**90% CI**
0	81	-0.2	0.7	77	0.5	0.7	-0.7	(-2.3, 1.0)
12	81	-0.4	0.7	77	0.5	0.7	-1.0	(-2.6, 0.7)
18	81	0.1	0.7	77	1.0	0.7	-0.9	(-2.6, 0.8)
24	81	-0.3	0.7	77	0.3	0.7	-0.6	(-2.3, 1.0)
25	81	-0.7	0.7	77	0.3	0.7	-1.0	(-2.6, 0.6)

	ΔQRS (ms) Semaglutide 0.5 mg			ΔQRS (ms) Semaglutide Placebo			ΔΔQRS (ms) Semaglutide 0.5 mg	
Time (hour)	**N**	**LSmean**	**SD**	**N**	**LSmean**	**SD**	**LSmean**	**90% CI**
26	81	-0.8	0.7	77	0.3	0.7	-1.1	(-2.7, 0.5)
27	81	-0.7	0.7	77	0.3	0.7	-1.0	(-2.6, 0.6)
30	81	-0.6	0.7	77	0.8	0.7	-1.4	(-3.0, 0.3)
36	81	-0.5	0.7	77	0.5	0.7	-1.0	(-2.6, 0.6)
42	81	-0.3	0.7	77	0.8	0.7	-1.1	(-2.7, 0.6)
48	81	-0.7	0.7	77	0.2	0.7	-0.9	(-2.6, 0.7)

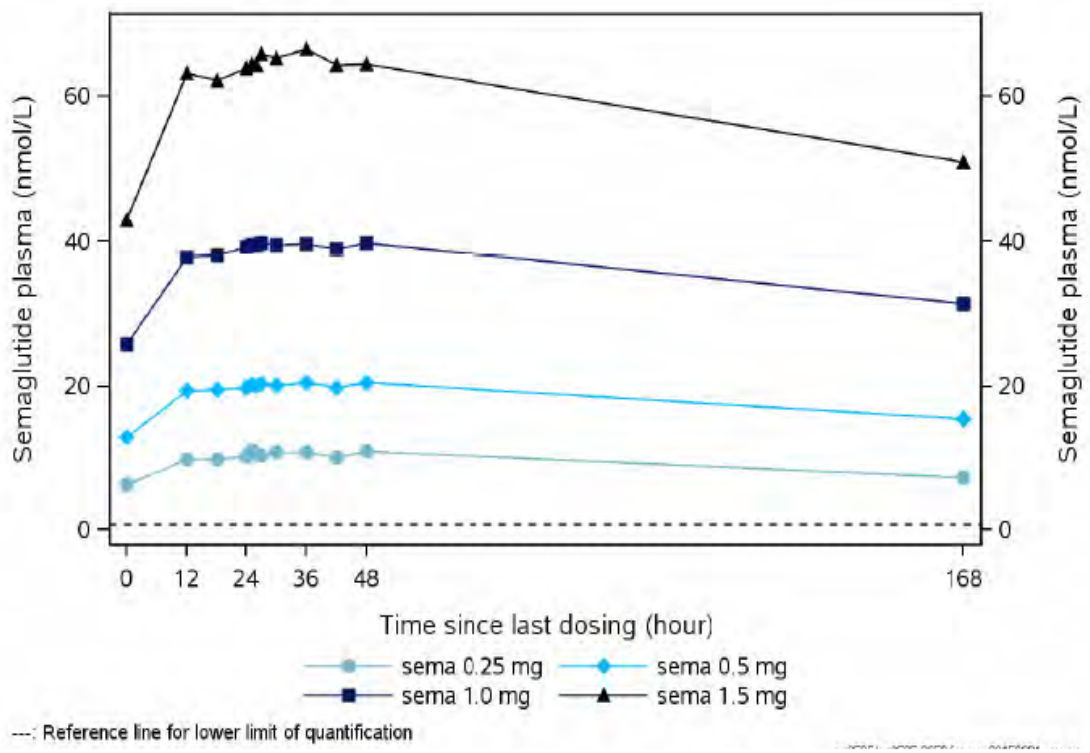
Table 25: Categorical Analysis for QRS

	Total N		QRS<=110 ms		QRS>110 ms	
Treatment Group	**Subj. #**	**Obs. #**	**Subj. #**	**Obs. #**	**Subj. #**	**Obs. #**
Moxifloxacin 400 mg	77	539	71 (92.2%)	501 (92.9%)	6 (7.8%)	38 (7.1%)
Moxifloxacin placebo	165	1687	157 (95.2%)	1635 (96.9%)	8 (4.8%)	52 (3.1%)
Semaglutide/Semaglutide placebo Baseline	166	1826	157 (94.6%)	1754 (96.1%)	9 (5.4%)	72 (3.9%)
Semaglutide 0.5 mg	81	890	78 (96.3%)	869 (97.6%)	3 (3.7%)	21 (2.4%)
Semaglutide 1.0 mg	80	880	79 (98.8%)	872 (99.1%)	1 (1.3%)	8 (0.9%)
Semaglutide 1.5 mg	76	836	75 (98.7%)	825 (98.7%)	1 (1.3%)	11 (1.3%)
Semaglutide placebo	77	2530	71 (92.2%)	2361 (93.3%)	6 (7.8%)	169 (6.7%)

5.3 CLINICAL PHARMACOLOGY ASSESSMENTS

The mean semaglutide profile after the fourth (and last) dosing at each dose level (0−168 hours) in the TQT study is shown in Figure 6.

Figure 6: Geometric Mean Plasma Concentration-Time Profiles of Semaglutide after Fourth Doing at Each Dose Level



Source: Sponsor's clinical study report, Table 11-14, page 137.

The relationship between ΔQTc and semaglutide was investigated by linear mixed-effects modeling. The model used QTcF change from baseline (ΔQTcF), as well as QTcI change from baseline (ΔQTcF), as the dependent variable and observed drug concentrations as the continuous variable (0 for placebo group), treatment (1 for treatment or 0 for placebo), nominal time of data collection as categorical factors, and random effects on intercept and slope. The general model formula is shown below.

$\Delta QT_{c\,l,,} = \mu_l + p_t + qC_{l,k,t} + V_k\,C_{l,k,t} + W_k + \varepsilon_{l,k,t}$

μ_l = Fixed effect, treatment specific (l) intercept (active (l=1), placebo (l=0))
p_t = Fixed effect, Study Time (t) specific intercept (as categorical factor)
q = Fixed effect, slope parameter
$C_{l,,}$ = Independent variable, Concentration for time point(t), treatment(l), and subject (k)
V_k = Random effect, random subject level (k) effect on slope (q)
W_k = Random effect, random subject level (k) effect on intercept (μ)
$\varepsilon_{l,,}$ = Random effect, residual error for time point(t), treatment(l), and subject (k)

The relationships between ΔQTc and semaglutide concentrations are listed in The relationships between ΔΔQTcF and ΔΔQTcI and semaglutide concentrations were shown in Figure 7 and Figure 8. The mean (90% CI) ΔΔQTcF and ΔΔQTcI at mean steady-state

$\mathbf{C_{max}}$ of 74.19 nmol/L following surpatherapeutic dosing regimen 1.5 mg once weekly is estimated to be -0.22 (-3.07, 2.63) and -5.11 (-7.77, -2.46) ms, respectively. Based on the concentration-QTc analysis, no QTc interval prolongation of clinical concern is expected at the therapeutic concentration range of semaglutide.

Table 26. According to the final model, a shallow but statically significant exposure-response relationship was identified between ΔQTcF and semaglutide concentrations, while no significant relationship was found between ΔQTcI and semaglutide concentrations.

The relationships between ΔΔQTcF and ΔΔQTcI and semaglutide concentrations were shown in

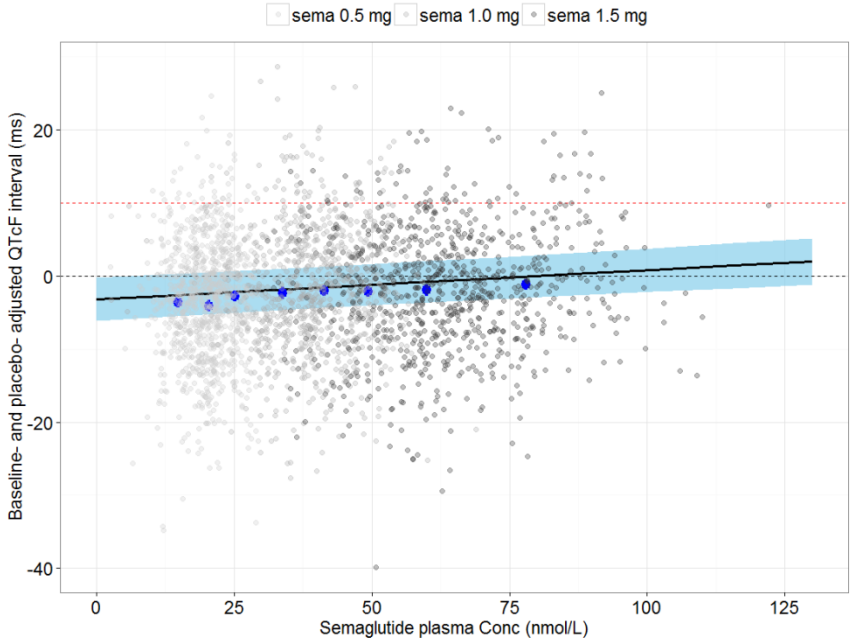


Figure 8 and

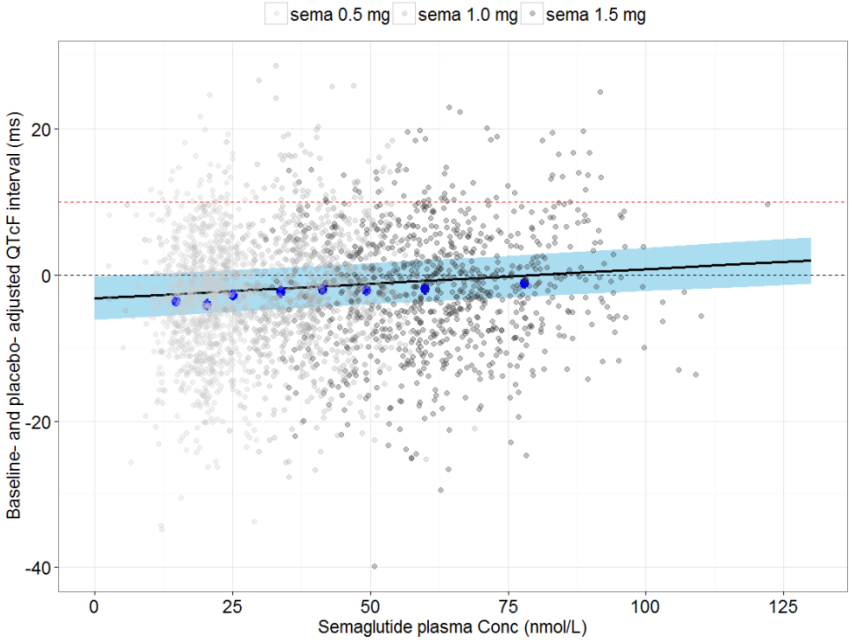


Figure 8. The mean (90% CI) ΔΔQTcF and ΔΔQTcI at mean steady-state $\mathbf{C_{max}}$ of 74.19 nmol/L following surpatherapeutic dosing regimen 1.5 mg once weekly is estimated to be

-0.22 (-3.07, 2.63) and -5.11 (-7.77, -2.46) ms, respectively. Based on the concentration-QTc analysis, no QTc interval prolongation of clinical concern is expected at the therapeutic concentration range of semaglutide.

Table 26: Concentration-QTc Effect Analysis. Estimates from Linear Mixed Model – QTc Individual and QTc Fridericia Pharmacokinetic-Pharmacodynamic Population

Parameters	Slope of Plasma Conc. (10nmol/L) Effect on ΔQTc	Standard error of slope effect on ΔQTc	P-value
ΔQTcF	0.398	0.115	0.001
ΔQTcI	0.134	0.136	0.329

Figure 7: ΔΔQTcF vs. Semaglutide Concentrations

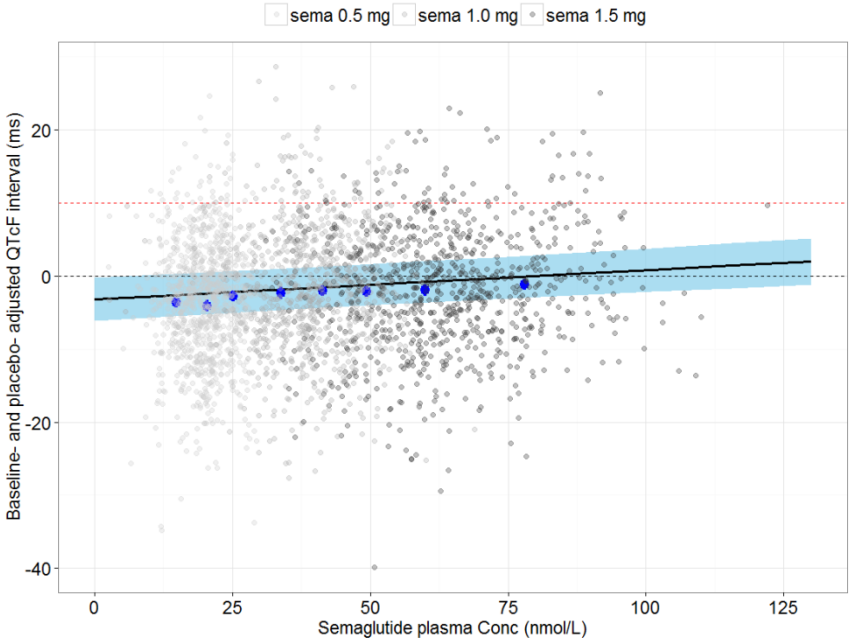
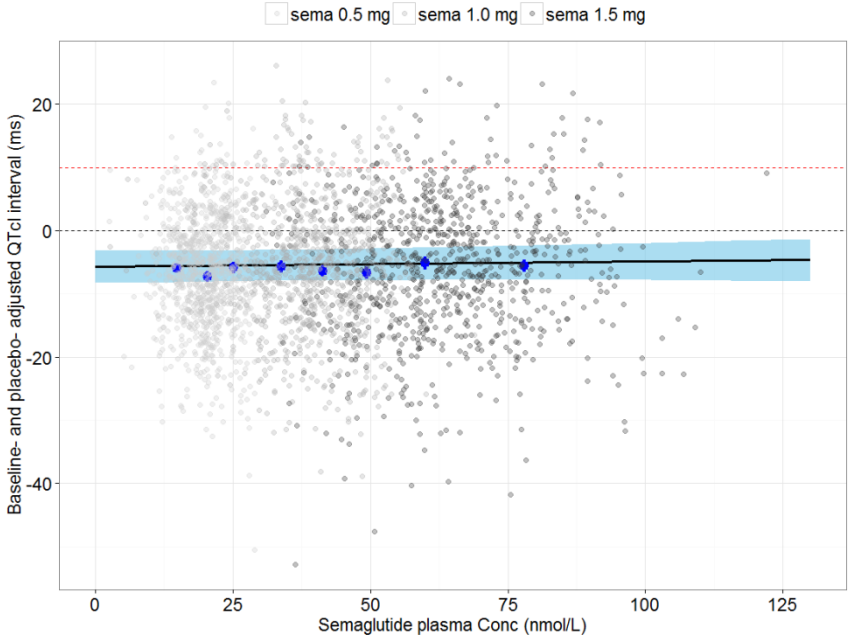
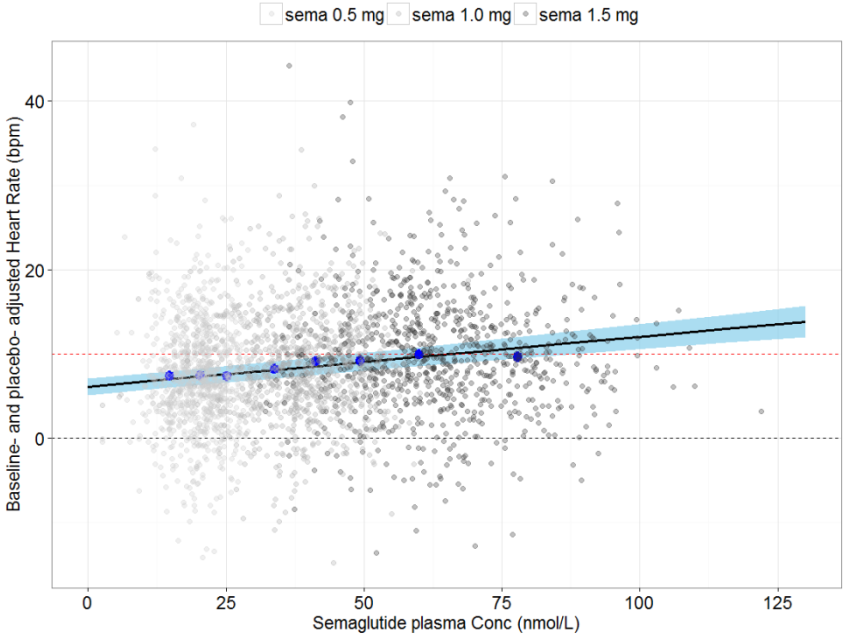


Figure 8: ΔΔQTcI vs. Semaglutide Concentrations



In addition, the relationship between baseline-adjusted heart rate (ΔHR) and semaglutide concentrations was also explored using linear mixed effect modeling procedure described above and visualized in
Figure 9. A significant relationship between ΔHR and semaglutide concentrations was observed (p-value<0.0001). The mean (90% CI) ΔΔHR increase at mean steady-state C_{max} of 74.19 nmol/L following supratherapeutic dosing regimen 1.5 mg once weekly is estimated to be 10.49 (9.29, 11.71) bpm.

Figure 9: ΔΔHR vs. Semaglutide Concentrations



5.4 CLINICAL ASSESSMENTS

5.4.1 Safety assessments

None of the events identified to be of clinical importance per the ICH E14 guidelines, i.e. syncope, seizure, significant ventricular arrhythmias or sudden cardiac death, occurred in this study.

5.4.2 ECG assessments

Overall ECG acquisition and interpretation in this study appears acceptable.

5.4.3 PR and QRS Interval

There was no clinically meaningful effect on PR and QRS intervals.

6 APPENDIX

6.1 HIGHLIGHTS OF CLINICAL PHARMACOLOGY

Therapeutic dose	**Type 2 diabetes indication** The proposed clinical doses are 0.5 mg and 1.0 mg once weekly (OW) administered by subcutaneous administration. The starting dose is 0.25 mg OW. After 4 weeks, the dose should be increased to 0.5 mg OW. After at least 4 weeks with a dose of 0.5 mg OW, the dose can be increased to 1.0 mg OW.
Maximum tolerated dose	For single dose administration in healthy male subjects, the maximum tolerated dose was 15 µg/kg body weight (~ mean 1.25 mg, range 1.10–1.40 mg). Higher doses of semaglutide are tolerated when stepwise dose-escalation is used.

Principal adverse events (AE)	Gastrointestinal AEs (nausea, diarrhoea, vomiting, constipation and dyspepsia) were the most frequently reported AEs during treatment with semaglutide and the most common AEs leading to discontinuation. The four weekly dose-escalation from 0.25 mg OW to 0.5 mg OW and 1.0 mg OW was introduced to mitigate gastrointestinal AEs. As shown by exposure-response analysis based on data from phase 3, the proportion of subjects reporting nausea and vomiting increased with exposure, whereas the proportion of subjects reporting diarrhoea or constipation appeared to be exposure independent. The exposure-response analysis indicated tolerance development for nausea and vomiting. No indication of tolerance development was seen for diarrhoea or constipation.	
Maximum dose tested	Single Dose	**Healthy subjects** The maximum single dose tested in healthy subjects was 20 µg/kg body weight (~ mean 1.68 mg, range 1.40–2.10 mg).
	Multiple Dose	**Healthy subjects** The maximum multiple dose tested was 1.5 mg OW. This dose level was well tolerated and was reached by four weekly dose-escalation; 0.25 mg semaglutide OW for four weeks, 0.5 mg OW for four weeks, 1.0 mg OW for four weeks followed by 1.5 mg OW for four weeks; a total of 16 weeks.
		Subjects with type 2 diabetes The maximum multiple dose tested was 1.6 mg OW (phase 2 dose finding study). The maximum dose of 1.6 mg was reached by weekly dose escalation; 0.4 mg semaglutide OW for one week, 0.8 mg OW for one week followed by 1.6 mg OW for 10 weeks; a total of 12 weeks.

<table>
<tr>
<td>Exposures Achieved at Maximum Tested Dose</td>
<td>Single Dose</td>
<td>Healthy subjects

Single dose exposure of semaglutide 20 µg/kg body weight (~ mean 1.68 mg, range 1.40– 2.10 mg):
<table>
<tr><td></td><td>Mean</td><td>CV%</td></tr>
<tr><td>AUC τ (nmol.h/L)</td><td>3331*)</td><td>10.9</td></tr>
<tr><td>Cmax (nmol/L)</td><td>25.7*)</td><td>17.2</td></tr>
</table>
Means are geometric means. N=6 for AUCτ. N=6 for Cmax

*) Luminescence oxygen channeling immunoassay (LOCI) was used in this first human dose trial. This assay was found to be influenced by a matrix effect and an assay based on LC-MS/MS was used in other trials reported in this document.
PK data derived from LOCI data should not be directly compared to LC-MS/MS data.</td>
</tr>
<tr>
<td></td>
<td>Multiple Dose</td>
<td>Healthy subjects

Steady state exposure at semaglutide 1.5 mg:
<table>
<tr><td></td><td>Mean</td><td>CV%</td></tr>
<tr><td>AUC τ (nmol.h/L)</td><td>9928</td><td>18.0</td></tr>
<tr><td>Cmax (nmol/L)</td><td>72.6</td><td>20.8</td></tr>
</table>
Means are geometric means. N=76. Cavg as calculated AUCτ/168 =59.1 nmol/L

Subjects with type 2 diabetes

In the phase 2 dose finding trial testing the dose of 1.6 mg, PK evaluation was based on sparse sampling and model based exposure estimates. Semaglutide concentrations were based on LOCI assay, and therefore the data are not comparable with those from other trials
Based on the population PK analysis of phase 3 data for the highest therapeutic dose of 1.0 mg, the 95% range of exposure (Cavg) was 18.8–46.9 nmol/L.</td>
</tr>
</table>

<table>
<tr>
<td>Range of linear PK</td>
<td>
Healthy subjects

Dose-proportionality of semaglutide was shown over the dose range of 0.25–1.5 mg, using steady state data at the 0.25, 0.5, 1.0 and 1.5 mg dose levels:
<table>
<tr><td></td><td>Estimated doubling constant</td><td>95 % CI</td></tr>
<tr><td>AUC_{0-168h}</td><td>2.02 *)</td><td>[2.00; 2.04]</td></tr>
<tr><td>AUC_{0-48h}</td><td>2.01</td><td>[1.99; 2.04]</td></tr>
<tr><td>C_{max}</td><td>2.00</td><td>[1.97; 2.03]</td></tr>
</table>
*) p=0.0474. In a sensitivity analysis, excluding 7 suspected non-compliant subjects, the increase in AUC_{0-168h} with increasing dose were consistent with dose proportionality: 2.01 [2.00; 2.03]$_{95\%\ CI,}$ p=0.0726

Subjects with type 2 diabetes

Based on population PK analysis, semaglutide exposure was consistent with dose-proportionality; the estimated, dose-normalised, exposure of 0.5 mg relative to 1.0 mg was 1.00 [0.98; 1.01]$_{90\%\ CI}$
</td>
</tr>
</table>

<table>
<tr>
<td>Accumula-tion at steady state</td>
<td>
The accumulation ratio for semaglutide was close to 2 in healthy Caucasian and Japanese subjects at both the 0.5 mg and 1.0 mg dose level:
<table>
<tr><td></td><td>$R_{acc,\ DC,\ sema\ 0\text{-}168\ h}$</td><td>95 % CI</td></tr>
<tr><td>Caucasian subjects; 0.5 mg OW (N=7)</td><td>2.30</td><td>[2.14 ; 2.48]</td></tr>
<tr><td>Caucasian subjects; 1.0 mg OW (N=6)</td><td>2.31</td><td>[2.14 ; 2.50]</td></tr>
<tr><td>Japanese subjects; 0.5 mg OW (N=8)</td><td>1.99</td><td>[1.87 ; 2.13]</td></tr>
<tr><td>Japanese subjects; 1.0 mg OW (N=8)</td><td>2.09</td><td>[1.95 ; 2.24]</td></tr>
</table>
$R_{acc,\ DC}$: dose corrected accumulation ratio (based on a first dose of 0.25 mg),
</td>
</tr>
</table>

<table>
<tr><td>Metabolites</td><td colspan="2">Following a single dose of [^{3}H] semaglutide, intact semaglutide was the primary component observed in plasma (83% of total exposure). Semaglutide was metabolized by proteolytic degradation of the peptide backbone and beta- oxidation of the fatty acid side-chain before excretion via urine and faeces. The largest metabolite in plasma and the two primary metabolites in urine were structurally identified, and they are all products of this metabolism. The intact linker was excreted via urine as part of the two primary urine metabolites .
In plasma, 6 metabolites were detected, each below 8% of the total exposure. In urine, 21 metabolites were detected, the two most abundant each accounting for 14% of the given dose (remaining metabolites each <2%). Approximately 3% of the dose was excreted as intact semaglutide via urine. In faeces, 7 minor metabolites were detected (0.1–1.5%). Metabolism is similar in humans and the non-clinical species.</td></tr>
<tr><td rowspan="2">Absorption</td><td>Absolute/ relative bio-availability</td><td>Absolute bioavailability (s.c. vs i.v.) was 89%; Ratio: 0.89 [0.83; 0.94]$_{95\% CI}$.

Bioavailability of semaglutide after s.c. administration in the thigh and upper arm relative to the abdomen was assessed by population PK analysis (subjects with type 2 diabetes):
<table>
<tr><td></td><td>Relative steady state exposure</td><td>90 % CI</td></tr>
<tr><td>Thigh/abdomen</td><td>0.97</td><td>[0.93; 1.00]</td></tr>
<tr><td>Upper arm /abdomen</td><td>0.93</td><td>[0.90; 0.96]</td></tr>
</table></td></tr>
<tr><td>T_{max}</td><td>Parent: The observed median t_{max} for semaglutide was 1–3 days (range 26–60 hours) and was similar across doses and populations.

Metabolites: NA, as no major metabolites were identified.</td></tr>
</table>

Distribution	Vd/F or Vd	**Healthy subjects**: Single i.v. administration (0.25 mg), mean V_z (CV): 6.2 L (22.1) Steady state (0.5 mg/1.0 mg), range of mean V_z/F across trials: 7.1 to 9.3 L **Subjects with type 2 diabetes**: Steady state (1.0 mg), range of mean V_z/F across trials: 11.2 L to 13.9 L Population PK analysis: 12.2 L $[12.1; 12.4]_{95\% CI}$
	% bound	Plasma protein binding of semaglutide was > 99%. Albumin was the major binding plasma protein.

Elimination	Route	Both urine and faeces were shown to be important routes of excretion of semaglutide related material in animals and humans. Approximately 3% of the dose was excreted as intact semaglutide via urine. Minor elimination was detected via expired air.
	Terminal $t_{½}$	Parent: $t_{½}$ was approximately 1 week: range across single and multiple dose trials, dose levels and populations was 143–183 hours. $t_{½}$ following s.c. and i.v. administrations in the same group of subjects was 143 and 137 hours, respectively. Metabolites: NA, as no major metabolites were identified

	CL/F or CL	**Healthy subjects** Steady state (0.5 mg/1.0 mg), across trials range of mean CL/F: 0.032-0.041 L/h **Subjects with type 2 diabetes** Steady state (1.0 mg), across trials range of mean CL/F: 0.051-0.052 L/h Population PK analysis: 0.0478 L/h $[0.0468–0.0488]_{95\% CI}$
Intrinsic Factors	Analysis of intrinsic factors effect on semaglutide exposure is based on population PK analysis using data from five phase 3a trials in subjects with type 2 diabetes. The population PK analysis estimates exposure ratios taking all covariates in the model into account. In addition, single dose trials assessed the effect of hepatic and renal impairment on semaglutide PK.	
	Age	Exposure relative to subjects with an age <65 years: • 65–74 years: 1.01 $[0.99;1.03]_{90\% CI}$ • >74 years: 1.04 $[1.00;1.08]_{90\% CI}$
	Sex	Exposure relative to females: • Males: 0.96 $[0.95;0.98]_{90\% CI}$
	Body weight	Exposure relative to a subject with a body weight of 85 kg: • 55 kg (5% percentile of data set): 1.40 $[1.38;1.42]_{90\% CI}$ • 127 kg (95% percentile of data set): 0.73 $[0.72;0.74]_{90\% CI}$
	Race	Exposure relative to White subjects: • Black or African American: 1.03 $[0.99;1.07]_{90\% CI}$ • Asian (including Japanese) subjects: 1.01 $[0.99; 1.03]_{90\% CI}$

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<table>
<tr>
<td>Intrinsic Factors</td>
<td>Hepatic & Renal Impair-ment</td>
<td>
Hepatic impairment
The effect of hepatic impairment on semaglutide exposure was evaluated following a single dose of 0.5 mg for mild, moderate and severe hepatic impairment (classified according to the Child Pugh system):
<table>
<tr><td></td><td>Mild vs normal</td><td>Moderate vs normal</td><td>Severe vs normal</td></tr>
<tr><td>$AUC_{0-\infty}$ [90% CI]</td><td>0.95 [0.77;1.16]</td><td>1.02 [0.93;1.12]</td><td>0.97 [0.84;1.12]</td></tr>
<tr><td>C_{max} [90% CI]</td><td>0.99 [0.80;1.23]</td><td>1.02 [0.88;1.18]</td><td>1.15 [0.89;1.48] *)</td></tr>
</table>
*) A sensitivity analysis excluding a single extreme PK value resulted in a C_{max} ratio (severe/normal) closer to 1 and with the 90% CI within the interval: 1.05 [0.88; 1.25].

Renal impairment
The effect of renal impairment on semaglutide exposure was evaluated following a single dose of 0.5 mg for mild, moderate, severe and ESRD renal impairment (classified using the Cockcroft & Gault formula):
<table>
<tr><td></td><td>Mild vs normal</td><td>Moderate vs normal</td><td>Severe vs normal</td><td>ESRD vs normal</td></tr>
<tr><td>$AUC_{0-\infty}$</td><td>0.994</td><td>1.074</td><td>1.135</td><td>1.096</td></tr>
<tr><td>[95% CI]</td><td>[0.849;1.163]</td><td>[0.912;1.265]</td><td>[0.974;1.322]</td><td>[0.937;1.283]</td></tr>
<tr><td>C_{max}</td><td>0.902</td><td>0.794</td><td>0.859</td><td>0.818</td></tr>
<tr><td>[90% CI]</td><td>[0.73;1.11]</td><td>[0.64;0.99]</td><td>[0.70;1.06]</td><td>[0.66;1.01]</td></tr>
</table>
ESRD: end-stage renal disease

No linear relationship between creatinine clearance and exposure ($AUC_{0-\infty}$) or C_{max} was found.

Based on population PK analysis using the modification of diet in renal disease (MDRD) equation for classification of renal impairment, the relative exposure to subjects with normal renal function was:

Mild: 1.06 $[1.04;1.07]_{90\% CI}$
Moderate: 1.05 $[1.00;1.09]_{90\% CI}$
Severe: 1.09 $[1.03;1.15]_{90\% CI}$

</td>
</tr>
</table>

Extrinsic Factors	Drug interac-tions	N/A (No trials evaluated the effect of other drugs on semaglutide exposure)
	Food Effects	N/A
Expected High Clinical Exposure Scenario		Based on the population PK analysis an estimated worst scenario/expected highest exposure in the clinical setting (when including all covariates tested) evaluated to be the of a non-Hispanic or Latino, Black female above the age 74 years, with a body weight of 40 kg with severe renal impairment, and dosed with 1.0 mg semaglutide in the The estimated average concentration in steady state for profile was 60.6 nmol/L (95% prediction interval: 47–78 nmol/L). Based on full profiles from the clinical pharmacology difference between C_{avg} and C_{max} is approximately 5 1.0 mg steady state. Adding the 5 nmol/L to the upper C_{avg} from the worst case scenario above, gives an of 83 nmol/L. In addition, a missed dose and mitigation of this by taking 5 days and return to normal dosing regimen 2 days later proposed recommendation), an increase of maximum of 14% can be expected. Adding up the components, a worst case scenario for concentration is approximately 95 nmol/L. In the QTc evaluation, semaglutide concentrations of up approximately 120 nmol/L was investigated, and no was seen between semaglutide concentrations and change in QTcI.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JANELL E CHEN
05/03/2017

QIANYU DANG
05/03/2017

YOUWEI N BI
05/03/2017

LARS JOHANNESEN
05/03/2017

MICHAEL Y LI
05/03/2017

CHRISTINE E GARNETT
05/03/2017

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]

Application Information		
NDA # 209637	N/A	Efficacy Supplement Category: ☐ New Indication (SE1) ☐ New Dosing Regimen (SE2) ☐ New Route Of Administration (SE3) ☐ Comparative Efficacy Claim (SE4) ☐ New Patient Population (SE5) ☐ Rx To OTC Switch (SE6) ☐ Accelerated Approval Confirmatory Study (SE7) ☐ Labeling Change With Clinical Data (SE8) ☐ Manufacturing Change With Clinical Data (SE9) ☐ Animal Rule Confirmatory Study (SE10)
Proprietary Name: Ozempic (proposed) Established/Proper Name: semaglutide injection Dosage Form: injection Strengths: 0.25 mg, 0.5 mg or 1 mg Route(s) of Administration: s.c. injection		
Applicant: Novo Nordisk, Inc. Agent for Applicant (if applicable): N/A		
Date of Application: 12/5/2016 Date of Receipt: 12/5/2016 Date clock started after Unacceptable for Filing (UN): N/A		
PDUFA/BsUFA Goal Date: 12/5/2017	Action Goal Date (if different):	
Filing Date: 02/03/2017	Date of Filing Meeting: 01/19/2017	
Chemical Classification (original NDAs only) : ☒ Type 1- New Molecular Entity (NME); NME and New Combination ☐ Type 2- New Active Ingredient; New Active Ingredient and New Dosage Form; New Active Ingredient and New Combination ☐ Type 3- New Dosage Form; New Dosage Form and New Combination ☐ Type 4- New Combination ☐ Type 5- New Formulation or New Manufacturer ☐ Type 7- Drug Already Marketed without Approved NDA ☐ Type 8- Partial Rx to OTC Switch ☐ Type 9-New Indication or Claim (will not be marketed as a separate NDA after approval) ☐ Type 10-New Indication or Claim (will be marketed as a separate NDA after approval)		
Proposed indication(s)/Proposed change(s): -as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (b) (4)		
Type of Original NDA: AND (if applicable) Type of NDA Supplement: ***If 505(b)(2)NDA/NDA Supplement: Draft the "505(b)(2) Assessment" review found at:*** *http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499.*		☒ 505(b)(1) ☐ 505(b)(2) ☐ 505(b)(1) ☐ 505(b)(2)

Type of BLA ***If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team***	☐ 351(a) ☐ 351(k)
Review Classification: ***The application will be a priority review if:*** • ***A complete response to a pediatric Written Request (WR) was included (a partial response to a WR that is sufficient to change the labeling should also be a priority review – check with DPMH)*** • ***The product is a Qualified Infectious Disease Product (QIDP)*** • ***A Tropical Disease Priority Review Voucher was submitted*** • ***A Pediatric Rare Disease Priority Review Voucher was submitted***	☒ Standard ☐ Priority ☐ Pediatric WR ☐ QIDP ☐ Tropical Disease Priority Review Voucher ☐ Pediatric Rare Disease Priority Review Voucher
Resubmission after withdrawal? ☐	Resubmission after refuse to file? ☐
Part 3 Combination Product? ☒ ***If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults***	☐ Convenience kit/Co-package ☒ Pre-filled drug delivery device/system (syringe, patch, etc.) ☐ Pre-filled biologic delivery device/system (syringe, patch, etc.) ☐ Device coated/impregnated/combined with drug ☐ Device coated/impregnated/combined with biologic ☐ Separate products requiring cross-labeling ☐ Drug/Biologic ☐ Possible combination based on cross-labeling of separate products ☐ Other (drug/device/biological product)
☐ Fast Track Designation ☐ Breakthrough Therapy Designation ***(set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager)*** ☐ Rolling Review ☐ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC Other:	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies (FDCA Section 505B) ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)
Collaborative Review Division (*if OTC product*):	
List referenced IND Number(s): 079754	

Goal Dates/Product Names/Classification Properties	**YES**	**NO**	**NA**	**Comment**
PDUFA/BsUFA and Action Goal dates correct in the electronic archive? ***If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.***	☒	☐		
Are the established/proper and applicant names correct in electronic archive? ***If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into electronic archive.***	☒	☐		

Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, orphan drug)? ***Check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at:*** *http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm* ***If no, ask the document room staff to make the appropriate entries.***	☒	☐	☐	
Application Integrity Policy	**YES**	**NO**	**NA**	**Comment**
Is the application affected by the Application Integrity Policy (AIP)? ***Check the AIP list at:*** *http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm*	☐	☒		
If yes, explain in comment column.				
If affected by AIP, has OC been notified of the submission? **If yes,** date notified:	☐	☐		
User Fees	**YES**	**NO**	**NA**	**Comment**
Is Form 3397 (User Fee Cover Sheet)/Form 3792 (Biosimilar User Fee Cover Sheet) included with authorized signature?	☒	☐		

User Fee Status ***If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period from receipt. Review stops. Contact the User Fee Staff. If appropriate, send UN letter.***	Payment for this application *(check daily email from UserFeeAR@fda.hhs.gov):* ☒ Paid ☐ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required
If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Contact the User Fee Staff. If appropriate, send UN letter.	Payment of other user fees: ☒ Not in arrears ☐ In arrears
User Fee Bundling Policy ***Refer to the guidance for industry, Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees at:*** *http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079320.pdf*	Has the user fee bundling policy been appropriately applied? ***If no, or you are not sure, consult the User Fee Staff.*** ☒ Yes ☐ No

505(b)(2) **(NDAs/NDA Efficacy Supplements only)**	**YES**	**NO**	**NA**	**Comment**
Is the application a 505(b)(2) NDA? *(Check the 356h form, cover letter, and annotated labeling).* **If yes**, answer the bulleted questions below:	☐	☒		
• Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?	☐	☐		

- Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? **[see 21 CFR 314.54(b)(1)].**

- Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug **[see 21 CFR 314.54(b)(2)]?**

If you answered yes to any of the above bulleted questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs for advice.

- Is there unexpired exclusivity on another listed drug product containing the same active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)?

Check the Electronic Orange Book at:
http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm

If yes, please list below:

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration

If there is unexpired, 5-year exclusivity remaining on another listed drug product containing the same active moiety, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity and GAIN exclusivity will extend both of the timeframes in this provision by 6 months and five years, respectively. 21 CFR 314.108(b)(2). Unexpired orphan or 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.

- If FDA has approved one or more pharmaceutically equivalent (PE) products in one or more NDAs before the submission date of the original 505(b)(2) application, did the applicant identify one such product as a listed drug (or an additional listed drug) relied upon and provide an appropriate patent certification or statement **[see 21 CFR 314.50(i)(1)(i)(C) and 314.54]**?

Check the Electronic Orange Book at:
http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm

If no, include template language in the 74-day letter.

Failure to identify a PE is an approvability issue but not a filing issue [see 21 CFR 314.125(b)(19)]

***Note: Pharmaceutical equivalents** are drug products in identical dosage forms and route(s) of administration that: **(1)** contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; **(2)** do not necessarily contain the same inactive ingredients; **and** **(3)** meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates.*

Exclusivity	YES	NO	NA	Comment
Does another product (same active moiety) have orphan exclusivity for the same indication? ***Check the Orphan Drug Designations and Approvals list at:*** *http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm*	☐	☒		
If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness **[see 21 CFR 316.3(b)(14)]**? ***If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy***	☐	☐	☒	
NDAs/NDA efficacy supplements only: Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? **If yes**, # years requested: ***Note:*** *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*	☐	☒	☐	
NDAs only: Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use?	☐	☒	☐	
If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? ***If yes, contact the Orange Book Staff (CDER-Orange Book Staff).***	☐	☐	☒	
BLAs only: Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act? ***If yes, notify Marlene Schultz-DePalo, CDER Purple Book Manager*** ***Note****: Exclusivity requests may be made for an original BLA submitted under Section 351(a) of the PHS Act (i.e., a biological reference product). A request may be located in Module 1.3.5.3 and/or other sections of the BLA and may be included in a supplement (or other correspondence) if exclusivity has not been previously requested in the original 351(a) BLA. An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*	☐	☐	☒	

Format and Content				
Do not check mixed submission if the only electronic component is the content of labeling (COL).	☐ All paper (except for COL) ☒ All electronic ☐ Mixed (paper/electronic) ☒ CTD ☐ Non-CTD ☐ Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?				
Overall Format/Content	**YES**	**NO**	**NA**	**Comment**
If electronic submission, does it follow the eCTD guidance?[1] **If not,** explain (e.g., waiver granted).	☒	☐	☐	
Index: Does the submission contain an accurate comprehensive index?	☒	☐		
Is the submission complete as required under 21 CFR 314.50 (*NDAs/NDA efficacy supplements*) or under 21 CFR 601.2 (*BLAs/BLA efficacy supplements*) including: ☒ legible ☒ English (or translated into English) ☒ pagination ☒ navigable hyperlinks (electronic submissions only) **If no**, explain.	☒	☐		
BLAs only: Companion application received if a shared or divided manufacturing arrangement? **If yes**, BLA #	☐	☐	☒	
Forms and Certifications				
***Electronic** forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, **paper** forms and certifications with hand-written signatures must be included.* ***Forms** include: user fee cover sheet (3397/3792), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); **Certifications** include: debarment certification, patent certification(s), field copy certification, and pediatric certification.*				
Application Form	**YES**	**NO**	**NA**	**Comment**
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)? ***If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].***	☒	☐		
Are all establishments and their registration numbers listed on the form/attached to the form?	☒	☐	☐	

[1] http://www fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm333969.pdf

Patent Information (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	☒	☐	☐	
Financial Disclosure	**YES**	**NO**	**NA**	**Comment**
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)? ***Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].*** ***Note:*** *Financial disclosure is required for bioequivalence studies that are the basis for approval.*	☒	☐		
Clinical Trials Database	**YES**	**NO**	**NA**	**Comment**
Is form FDA 3674 included with authorized signature? ***If yes, ensure that the application is also coded with the supporting document category, "Form 3674."*** ***If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant***	☒	☐		
Debarment Certification	**YES**	**NO**	**NA**	**Comment**
Is a correctly worded Debarment Certification included with authorized signature? ***Certification is not required for supplements if submitted in the original application; If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].*** ***Note:*** *Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge…"*	☒	☐	☐	
Field Copy Certification (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? ***Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)*** ***If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.***	☐	☐	☒	

Controlled Substance/Product with Abuse Potential	YES	NO	NA	Comment
For NMEs: Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? ***If yes,*** *date consult sent to the Controlled Substance Staff:* For non-NMEs: *Date of consult sent to Controlled Substance Staff*:	☐	☐	☒	
Pediatrics	**YES**	**NO**	**NA**	**Comment**
PREA Does the application trigger PREA? ***If yes, notify PeRC@fda.hhs.gov to schedule required PeRC meeting***[2] ***Note****: NDAs/BLAs/efficacy supplements for new active ingredients (including new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.*	☒	☐		
If the application triggers PREA, is there an agreed Initial Pediatric Study Plan (iPSP)? ***If no, may be an RTF issue - contact DPMH for advice.***	☒	☐	☐	
If required by the agreed iPSP, are the pediatric studies outlined in the agreed iPSP completed and included in the application? ***If no, may be an RTF issue - contact DPMH for advice.***	☐	☐	☒	
BPCA: Is this submission a complete response to a pediatric Written Request? ***If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required***[3]	☐	☒		

[2] http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/OfficeofNonprescriptionProducts/PediatricandMaternalHealthStaff/ucm027829.htm

[3] http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/OfficeofNonprescriptionProducts/PediatricandMaternalHealthStaff/ucm027837.htm

Proprietary Name	YES	NO	NA	Comment
Is a proposed proprietary name submitted? ***If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."***	☒	☐	☐	
REMS	**YES**	**NO**	**NA**	**Comment**
Is a REMS submitted? ***If yes, send consult to OSE/DRISK and notify OC/ OSI/DSC/PMSB via the CDER OSI RMP mailbox***	☒	☐	☐	
Prescription Labeling	☐ **Not applicable**			
Check all types of labeling submitted.	☒ Package Insert (Prescribing Information)(PI) ☐ Patient Package Insert (PPI) ☒ Instructions for Use (IFU) ☒ Medication Guide (MedGuide) ☒ Carton labeling ☒ Immediate container labels ☐ Diluent labeling ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is Electronic Content of Labeling (COL) submitted in SPL format? ***If no, request applicant to submit SPL before the filing date.***	☒	☐		
Is the PI submitted in Physician Labeling Rule (PLR) format?[4]	☒	☐		
If PI not submitted in PLR format, was a waiver or deferral requested before the application was received or in the submission? **If requested before application was submitted**, what is the status of the request? ***If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.***	☐	☐	☒	
For applications submitted on or after June 30, 2015: Is the PI submitted in Pregnancy and Lactation Labeling Rule (PLLR) format? Has a review of the available pregnancy, lactation, and females and males of reproductive potential data (if applicable) been included?	☒ ☒	☐ ☐	☐ ☐	
For applications submitted on or after June 30, 2015: If PI not submitted in PLLR format, was a waiver or deferral requested before the application was received or in the submission? **If requested before application was submitted**, what is the status of the request? ***If no waiver or deferral, request applicant to submit labeling in PLLR format before the filing date.***	☐	☐	☒	

[4] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/LabelingDevelopmentTeam/ucm025576 htm

Has all labeling [(PI, patient labeling (PPI, MedGuide, IFU), carton and immediate container labeling)] been consulted to OPDP?	☒	☐	☐	
Has PI and patient labeling (PPI, MedGuide, IFU) been consulted to OSE/DRISK? (*send WORD version if available*)	☒	☐	☐	
Has all labeling [PI, patient labeling (PPI, MedGuide, IFU) carton and immediate container labeling, PI, PPI been consulted/sent to OSE/DMEPA and appropriate CMC review office in OPQ (OBP or ONDP)?	☒	☐	☐	
OTC Labeling	☒ **Not Applicable**			
Check all types of labeling submitted.	☐ Outer carton label ☐ Immediate container label ☐ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is electronic content of labeling (COL) submitted? ***If no, request in 74-day letter.***	☐	☐		
Are annotated specifications submitted for all stock keeping units (SKUs)? ***If no, request in 74-day letter.***	☐	☐	☐	
If representative labeling is submitted, are all represented SKUs defined? ***If no, request in 74-day letter.***	☐	☐	☐	
All labeling/packaging sent to OSE/DMEPA?	☐	☐	☐	
Other Consults	**YES**	**NO**	**NA**	**Comment**
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) ***If yes, specify consult(s) and date(s) sent:*** ***QT study report to QT IRT 1/26/2017*** ***Clinical Inspections request sent 1/25/17*** ***DTOP – (Opth) request sent 1/26/2017*** ***Office of Biological Products (OBP) request sent 1/26/2017*** ***DPMH – pediatric and maternal health consult sent 12/13/2016***		☐	☐	
Meeting Minutes/SPAs	**YES**	**NO**	**NA**	**Comment**
End-of Phase 2 meeting(s)? **Date(s):** June 9, 2010	☒	☐		

Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? **Date(s):** August 2, 2016	☒	☐		
Any Special Protocol Assessments (SPAs)? **Date(s):** 11/20/2007	☒			SPA-1 and SPA-2 Carcinogenicity

ATTACHMENT

MEMO OF FILING MEETING

DATE: January 19, 2017

BACKGROUND: On December 5, 2016, Novo Nordisk submitted original NDA 209637 for semaglutide (s.c). Semaglutide injection is a long-acting glucagon-like peptide-1 (GLP-1) agonist. It is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus [redacted] (b) (4) [redacted] he sponsor in pursuing approval of semaglutide through the 505(b)(1) pathway. In addition, the application will be reviewed under the PDUFA V Program

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Martin White/Peter Franks	Y
	CPMS/TL:	Pam Lucarelli/Julie Van der Waag	Y
Cross-Discipline Team Leader (CDTL)	William Chong		Y
Division Director/Deputy	Jim Smith		Y
Office Director/Deputy	Cutis Rosenbraugh		N
Clinical	Reviewer:	Andreea Lungu	Y
	TL:	Bill Chong	Y
Social Scientist Review (*for OTC products*)	Reviewer:		
	TL:		
OTC Labeling Review (*for OTC products*)	Reviewer:		
	TL:		
Clinical Microbiology (*for antimicrobial products*)	Reviewer:		
	TL:		
Clinical Pharmacology	Reviewer:	Shalini Yapa	Y
	TL:	Manoj Khurana	Y
• Genomics	Reviewer:		
• Pharmacometrics	Reviewer:	Nitin Mehrotra	
Biostatistics	Reviewer:	Jiwei He	N

	TL:	Yun Wang	Y

Nonclinical (Pharmacology/Toxicology)	Reviewer:	Federica Basso	Y
	TL:	Ron Wange	Y
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Product Quality (CMC) Review Team:	ATL:	Su Tran	Y
	RBPM:	Anika Lalmansingh	Y
• Drug Substance	Reviewer:	Joseph Leginus	N
• Drug Product	Reviewer:	Muthu Ramaswamy	N
• Process	Reviewer:	Chaoyjing Ma	N
• Microbiology	Reviewer:	Elizabeth Bearr	N
• Facility	Reviewer:	N/A	
• Biopharmaceutics	Reviewer:	Vidya Pai	N
• Immunogenicity	Reviewer:		
• Labeling (BLAs only)	Reviewer:		
• Other (e.g., Branch Chiefs, EA Reviewer)			
OMP/OMPI/DMPP (MedGuide, PPI, IFU)	Reviewer:	Sharon Williams	N
	TL:	Shawna Hutchins	N
OMP/OPDP (PI, PPI, MedGuide, IFU, carton and immediate container labeling)	Reviewer:	Charuni Shah	N
	TL:		
OSE/DMEPA (proprietary name, carton/container labeling)	Reviewer:	Susan Rimmel	Y
	TL:	Hina Mehta	Y
OSE/DRISK (REMS)	Reviewer:	Till Olickal	Y
	TL:	Naomi Redd	Y
OC/OSI/DSC/PMSB (REMS)	Reviewer:		
	TL:		

Bioresearch Monitoring (OSI)	Reviewer:	Cynthia Kleppinger	Y
	TL:	Janice Pohlman	N
Controlled Substance Staff (CSS)	Reviewer:		
	TL:		
Other reviewers/disciplines			
CDRH	Reviewer:	Sarah Mollo	N
	TL:	Alan Stephens	N
DPMH	Reviewer:	Jane Liedtka	Y
	TL:	Miriam Dinatale	N
Other attendees	Monika Houston		Y

FILING MEETING DISCUSSION:

GENERAL • 505(b)(2) filing issues: o Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? o Did the applicant provide a scientific "bridge" demonstrating the relationship between the proposed product and the referenced product(s)/published literature? Describe the scientific bridge (e.g., information to demonstrate sufficient similarity between the proposed product and the listed drug(s) such as BA/BE studies or to justify reliance on information described in published literature):	☒ Not Applicable ☐ YES ☐ NO ☐ YES ☐ NO
• Per reviewers, are all parts in English or English translation? **If no**, explain:	☒ YES ☐ NO
• Electronic Submission comments **List comments**:	☐ Not Applicable ☒ No comments

CLINICAL **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☒ Review issues for 74-day letter
• Clinical study site(s) inspections(s) needed? **If no,** explain:	☒ YES ☐ NO
• Advisory Committee Meeting needed? **Comments**: ***If no, for an NME NDA or original BLA, include the reason. For example:*** ○ ***this drug/biologic is not the first in its class*** ○ ***the clinical study design was acceptable*** ○ ***the application did not raise significant safety or efficacy issues*** ○ ***the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease***	☐ YES Date if known: ☐ ☐ NO ☒ To be determined Reason:
• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? **Comments**:	☒ Not Applicable ☐ YES ☐ NO
CONTROLLED SUBSTANCE STAFF • Abuse Liability/Potential **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL MICROBIOLOGY **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

CLINICAL PHARMACOLOGY **Comments**: IRs sent to applicant	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical pharmacology study site(s) inspections(s) needed?	☐ YES ☒ NO
BIOSTATISTICS **Comments**: IRs sent to applicant	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) **Comments**: IRs sent to applicant	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
New Molecular Entity (NDAs only) • Is the product an NME?	 ☒ YES ☐ NO
Environmental Assessment • Categorical exclusion for environmental assessment (EA) requested? **If no**, was a complete EA submitted? **Comments**:	 ☒ YES ☐ NO ☐ YES ☐ NO
Facility Inspection • Establishment(s) ready for inspection? **Comments**:	☐ Not Applicable ☒ YES ☐ NO

Facility/Microbiology Review (BLAs only) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CMC Labeling Review (BLAs only) **Comments**:	☐ Review issues for 74-day letter
APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs) • Were there agreements made at the application's pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application? • If so, were the late submission components all submitted within 30 days?	☐ N/A ☒ YES ☐ NO ☒ YES ☐ NO
• What late submission components, if any, arrived after 30 days?	N/A
• Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components?	☒ YES ☐ NO
• Is a comprehensive and readily located list of all clinical sites included or referenced in the application?	☒ YES ☐ NO
• Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?	☒ YES ☐ NO

REGULATORY PROJECT MANAGEMENT
Signatory Authority: Mary Thanh Hai **Date of Mid-Cycle Meeting** (for NME NDAs/BLAs in "the Program" PDUFA V): May 10, 2017 **21st Century Review Milestones (see attached)** (listing review milestones in this document is optional): **Tentative Timelines** Receipt Date: December 5, 2016 Site Selection Meeting: TBD Filing meeting: January 19, 2017 Day 60 (filing date): February 3, 2017 74-day letter: February 17, 2017 Mid-Cycle Meeting: May 10, 2017 Mid-Cycle Communication Meeting: June 1, 2017 Labeling Planning Meeting: June 22, 2017 Complete Primary and Secondary Review: August 2, 2017 Pre-Late Cycle Meeting: ~August 2, 2017 Late Cycle Meeting with Applicant: August 30, 2017 Labeling Meetings: September 27, 2017, October 17, 2017 Wrap-up Meeting: October 10, 2017 Send labeling to OPDP and DMPP: October 20, 2017 CDTL Review: October 24, 2017 PeRC Meeting: November 1, 2017 Send labeling to Applicant: August 12, 2017 DD Review: November 14, 2017 OD Review and Sign-off: November 28, 2017 PDUFA goal date: December 5, 2017

REGULATORY CONCLUSIONS/DEFICIENCIES	
☐	The application is unsuitable for filing. Explain why:
☐	The application, on its face, appears to be suitable for filing. Review Issues: ☐ No review issues have been identified for the 74-day letter. ☒ Review issues have been identified for the 74-day letter. Review Classification: ☒ Standard Review ☐ Priority Review
ACTION ITEMS	
☒	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into the electronic archive (e.g., chemical classification, combination product

	classification, orphan drug).
☐	If RTF, notify everyone who already received a consult request, OSE PM, and RBPM
☐	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
☐	If priority review, notify applicant in writing by day 60 (see CST for choices)
☐	Send review issues/no review issues by day 74
☐	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
☐	Update the PDUFA V DARRTS page (for applications in the Program)
☐	Other

Annual review of template by OND ADRAs completed: April 2016

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

PETER D FRANKS
04/20/2017

REGULATORY PROJECT MANAGER
PHYSICIAN LABELING RULE (PLR) FORMAT REVIEW
OF THE PRESCRIBING INFORMATION

Complete for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Labeling Supplements

Application: NDA 209637

Application Type: New NDA

Drug Name(s)/Dosage Form(s): semaglutide injection

Applicant: Novo Nordisk

Receipt Date: 12/5/2016

Goal Date: 12/5/2017

1. Regulatory History and Applicant's Main Proposals

On December 5, 2016, Novo Nordisk submitted original NDA 209637 for semaglutide (s.c). Semaglutide injection is a long-acting glucagon-like peptide-1 (GLP-1) agonist. The applicant's proposed indications are listed below:

- as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus;
- (b) (4)

The applicant is pursuing approval of semaglutide through the 505(b)(1) pathway.

2. Review of the Prescribing Information

This review is based on the applicant's submitted Word format of the prescribing information (PI). The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements of Prescribing Information (SRPI)" checklist (see Section 4 of this review).

3. Conclusions/Recommendations

No SRPI format deficiencies were identified in the review of this PI.

4. Selected Requirements of Prescribing Information

The Selected Requirement of Prescribing Information (SRPI) is a 41-item, drop-down checklist of important format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and guidances.

Highlights

See Appendix for a sample tool illustrating Highlights format.

HIGHLIGHTS GENERAL FORMAT

YES 1. Highlights (HL) must be in a minimum of 8-point font and should be in two-column format, with ½ inch margins on all sides and between columns.

Comment:

YES 2. The length of HL must be one-half page or less unless a waiver has been granted in a previous submission. The HL Boxed Warning does not count against the one-half page requirement. Instructions to complete this item: If the length of the HL is one-half page or less, select "YES" in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page, select "NO" unless a waiver has been granted.

Comment: *HL longer than one-half page. Waiver submitted*

YES 3. A horizontal line must separate:

- HL from the Table of Contents (TOC), **and**
- TOC from the Full Prescribing Information (FPI).

Comment:

YES 4. All headings in HL (from Recent Major Changes to Use in Specific Populations) must be **bolded** and presented in the center of a horizontal line. (Each horizontal line should extend over the entire width of the column.) The HL headings (from Recent Major Changes to Use in Specific Populations) should be in UPPER CASE letters. See Appendix for HL format.

Comment:

YES 5. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between the product title and Initial U.S. Approval. See Appendix for HL format.

Comment:

YES 6. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.

Comment:

YES 7. Headings in HL must be presented in the following order:

Heading	Required/Optional
• **Highlights Heading**	Required

Selected Requirements of Prescribing Information

• **Highlights Limitation Statement**	Required
• **Product Title**	Required
• **Initial U.S. Approval**	Required
• **Boxed Warning**	Required if a BOXED WARNING is in the FPI
• **Recent Major Changes**	Required for only certain changes to PI*
• **Indications and Usage**	Required
• **Dosage and Administration**	Required
• **Dosage Forms and Strengths**	Required
• **Contraindications**	Required (if no contraindications must state "None.")
• **Warnings and Precautions**	Not required by regulation, but should be present
• **Adverse Reactions**	Required
• **Drug Interactions**	Optional
• **Use in Specific Populations**	Optional
• **Patient Counseling Information Statement**	Required
• **Revision Date**	Required

* RMC only applies to five labeling sections in the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS.

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

YES 8. At the beginning of HL, the following heading, **"HIGHLIGHTS OF PRESCRIBING INFORMATION"** must be **bolded** and should appear in all UPPER CASE letters.

Comment:

Highlights Limitation Statement

YES 9. The **bolded** HL Limitation Statement must include the following verbatim statement: "**These highlights do not include all the information needed to use (insert NAME OF DRUG PRODUCT) safely and effectively. See full prescribing information for (insert NAME OF DRUG PRODUCT).**" The name of drug product should appear in UPPER CASE letters.

Comment:

Product Title in Highlights

YES 10. Product title must be **bolded**.

Comment:

Initial U.S. Approval in Highlights

YES 11. Initial U.S. Approval must be **bolded**, and include the verbatim statement "**Initial U.S. Approval:**" followed by the **4-digit year**.

Comment:

Boxed Warning (BW) in Highlights

YES 12. All text in the BW must be **bolded**.

Comment:

YES 13. The BW must have a title in UPPER CASE, following the word "**WARNING**" and other words to identify the subject of the warning. Even if there is more than one warning, the term

"**WARNING**" and not "**WARNINGS**" should be used. For example: "**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**". If there is more than one warning in the BW title, the word "and" in lower case can separate the warnings. The BW title should be centered.

Comment:

YES 14. The BW must always have the verbatim statement "***See full prescribing information for complete boxed warning***." This statement must be placed immediately beneath the BW title, and should be centered and appear in *italics*.

Comment:

YES 15. The BW must be limited in length to 20 lines. (This includes white space but does not include the BW title and the statement "***See full prescribing information for complete boxed warning.***")

Comment:

Recent Major Changes (RMC) in Highlights

N/A 16. RMC pertains to only five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. Labeling sections for RMC must be listed in the same order in HL as they appear in the FPI.

Comment:

N/A 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(s) affected by the recent major change, together with each section's identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, "Warnings and Precautions, Acute Liver Failure (5.1) --- 8/2015."

Comment:

N/A 18. A changed section must be listed under the RMC heading for at least one year after the date of the labeling change and must be removed at the first printing subsequent to the one year period. (No listing should be one year older than the revision date.)

Comment:

Dosage Forms and Strengths in Highlights

YES 19. For a product that has more than one dosage form (e.g., capsules, tablets, injection), bulleted headings should be used.

Comment:

Contraindications in Highlights

YES 20. All contraindications listed in the FPI must also be listed in HL. If there is more than one contraindication, each contraindication should be bulleted. If no contraindications are known, must include the word "None."

Comment:

Selected Requirements of Prescribing Information

Adverse Reactions in Highlights

YES 21. For drug products other than vaccines, the verbatim **bolded** statement must be present: "**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer's U.S. phone number which should be a toll-free number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.**"

Comment:

Patient Counseling Information Statement in Highlights

YES 22. The Patient Counseling Information statement must include one of the following three **bolded** verbatim statements that is most applicable:

If a product **does not** have FDA-approved patient labeling:

- **See 17 for PATIENT COUNSELING INFORMATION**

If a product **has (or will have)** FDA-approved patient labeling:

- **See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling**
- **See 17 for PATIENT COUNSELING INFORMATION and Medication Guide**

Comment:

Revision Date in Highlights

YES 23. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., "**Revised: 8/2015** ").

Comment:

Contents: Table of Contents (TOC)

See Appendix for a sample tool illustrating Table of Contents format.

YES 24. The TOC should be in a two-column format.

Comment:

YES 25. The following heading must appear at the beginning of the TOC: **"FULL PRESCRIBING INFORMATION: CONTENTS."** This heading should be in all UPPER CASE letters and **bolded**.

Comment:

YES 26. The same title for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.

Comment:

YES 27. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.

Comment:

YES 28. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (for, of, to) and articles (a, an, the), or conjunctions (or, and)].

Comment:

YES 29. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.

Comment:

N/A 30. If a section or subsection required by regulation [21 CFR 201.56(d)(1)] is omitted from the FPI, the numbering in the TOC must not change. The heading "**FULL PRESCRIBING INFORMATION: CONTENTS***" must be followed by an asterisk and the following statement must appear at the end of the TOC: "*Sections or subsections omitted from the full prescribing information are not listed."

Comment:

Full Prescribing Information (FPI)

FULL PRESCRIBING INFORMATION: GENERAL FORMAT

YES 31. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. (Section and subsection headings should be in UPPER CASE and title case, respectively.) If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

BOXED WARNING
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Lactation (if not required to be in Pregnancy and Lactation Labeling Rule (PLLR) format, use "**Labor and Delivery**")
8.3 Females and Males of Reproductive Potential (if not required to be in PLLR format, use "**Nursing Mothers**")
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

YES 32. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, *"[see Warnings and Precautions (5.2)]."*

Comment:

Selected Requirements of Prescribing Information

N/A 33. For each RMC listed in HL, the corresponding new or modified text in the FPI must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

FPI Heading

YES 34. The following heading "**FULL PRESCRIBING INFORMATION"** must be **bolded,** must appear at the beginning of the FPI, and should be in UPPER CASE.

Comment:

BOXED WARNING Section in the FPI

YES 35. All text in the BW should be **bolded**.

Comment:

YES 36. The BW must have a title in UPPER CASE, following the word "**WARNING**" and other words to identify the subject of the warning. (Even if there is more than one warning, the term, "**WARNING**" and not "**WARNINGS**" should be used.) For example: "**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**". If there is more than one warning in the BW title, the word "and" in lower case can separate the warnings.

Comment:

CONTRAINDICATIONS Section in the FPI

N/A 37. If no Contraindications are known, this section must state "None."

Comment:

ADVERSE REACTIONS Section in the FPI

YES 38. When clinical trials adverse reactions data are included (typically in the "Clinical Trials Experience" subsection), the following verbatim statement (or appropriate modification) should precede the presentation of adverse reactions from clinical trials:

> "Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice."

Comment:

N/A 39. When postmarketing adverse reaction data are included (typically in the "Postmarketing Experience" subsection), the following verbatim statement (or appropriate modification) should precede the presentation of adverse reactions:

"The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure."

Comment:

Selected Requirements of Prescribing Information

PATIENT COUNSELING INFORMATION Section in the FPI

YES 40. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION). The reference statement should appear at the beginning of Section 17 and include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Instructions for Use, or Medication Guide). Recommended language for the reference statement should include one of the following five verbatim statements that is most applicable:

- Advise the patient to read the FDA-approved patient labeling (Patient Information).
- Advise the patient to read the FDA-approved patient labeling (Instructions for Use).
- Advise the patient to read the FDA-approved patient labeling (Patient Information and Instructions for Use).
- Advise the patient to read the FDA-approved patient labeling (Medication Guide).
- Advise the patient to read the FDA-approved patient labeling (Medication Guide and Instructions for Use).

Comment:

YES 41. FDA-approved patient labeling (e.g., Patient Information, Instructions for Use, or Medication Guide) must not be included as a subsection under Section 17 (PATIENT COUNSELING INFORMATION). All FDA-approved patient labeling must appear at the end of the PI upon approval.

Comment:

Appendix: Highlights and Table of Contents Format

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use PROPRIETARY NAME safely and effectively. See full prescribing information for PROPRIETARY NAME.

PROPRIETARY NAME (non-proprietary name) dosage form, route of administration, controlled substance symbol
Initial U.S. Approval: YYYY

WARNING: TITLE OF WARNING
See full prescribing information for complete boxed warning.

- **Text (4)**
- **Text (5.x)**

----------RECENT MAJOR CHANGES----------
Section Title, Subsection Title (x.x) M/201Y
Section Title, Subsection Title (x.x) M/201Y

----------INDICATIONS AND USAGE----------
PROPRIETARY NAME is a (insert FDA established pharmacologic class text phrase) indicated for … (1)

Limitations of Use: Text (1)

----------DOSAGE AND ADMINISTRATION----------
- Text (2.x)
- Text (2.x)

----------DOSAGE FORMS AND STRENGTHS----------
Dosage form(s): strength(s) (3)

----------CONTRAINDICATIONS----------
- Text (4)
- Text (4)

----------WARNINGS AND PRECAUTIONS----------
- Text (5.x)
- Text (5.x)

----------ADVERSE REACTIONS----------
Most common adverse reactions (incidence > x%) are text (6.x)

To report SUSPECTED ADVERSE REACTIONS, contact name of manufacturer at toll-free phone # or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------
- Text (7.x)
- Text (7.x)

----------USE IN SPECIFIC POPULATIONS----------
- Text (8.x)
- Text (8.x)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling OR and Medication Guide.

Revised: M/201Y

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MARTIN L WHITE
04/19/2017