

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

213182Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**



IND 114464

MEETING MINUTES

Novo Nordisk Inc.
Attention: Stephanie DeChiaro
Director, Regulatory Affairs
800 Scudders Mill Rd.
P.O. Box 846
Plainsboro, NJ 08536

Dear Ms. DeChiaro:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for semaglutide tablets.

We also refer to the meeting between representatives of your firm and the FDA on February 27, 2019. The purpose of the meeting was to discuss filing and formatting of the NDA for the cardiovascular indication proposed for oral semaglutide.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Peter Franks, Regulatory Project Manager at (240) 402-4197.

Sincerely,

{See appended electronic signature page}

Lisa B. Yanoff, M.D.
Director (Acting)
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: Pre-NDA

Meeting Date and Time: February 27, 2019; 12:00 PM – 1:00 PM EST
Meeting Location: White Oak Campus, Building 22, Room 1311

Application Number: IND 114464
Product Name: semaglutide tablets

Indications: as an adjunct to diet and exercise to improve glycemic control in adult patients with type 2 diabetes mellitus; to reduce the risk of major adverse cardiovascular events (cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke) in adults with type 2 diabetes mellitus and established cardiovascular disease (b) (4)

Applicant Name: Novo Nordisk, Inc.

Meeting Chair: Lisa Yanoff
Meeting Recorder: Peter Franks

FDA ATTENDEES

Division of Metabolism and Endocrinology Products

Lisa Yanoff, M.D., Director (Acting)

Andreea Lungu, M.D., Clinical Reviewer

Peter Franks, M.S., Regulatory Project Manager

Julie Van der Waag, MPH, Chief, Project Management Staff

Office of Biostatistics

Yun Wang, Ph.D., Statistical Team Lead

Yoonhee Kim, Ph.D., Mathematical Statistician

Office of Clinical Pharmacology

S.W. Johnny Lau, Ph.D., Clinical Pharmacology Reviewer

Office of Surveillance and Epidemiology

Till Olickal, PhD, PharmD, Risk Management Analyst, DRISK

Office of Scientific Investigations
Cynthia Kleppinger, M.D., Senior Medical Officer

SPONSOR ATTENDEES

| | |
|--------------------------|--|
| Jacob Bonde Jacobsen | Statistical Specialist, Biostatistics |
| Kamilla Kjær Frederiksen | Senior Regulatory Professional, HQ Regulatory Affairs |
| Mads Frederik Rasmussen | Corporate Project Vice President, Semaglutide Diabetes and Diabetes Outcomes |
| Mette Thomsen | International Medical Director, Medical and Science |
| Premlata Gunapu | Manager, US Regulatory Affairs |
| Robert Clark | Vice President, US Regulatory Affairs |
| Stephanie DeChiaro | Senior Director, US Regulatory Affairs |
| Trine Kruse | Director, Medical Writing |
| Vibeke Hatorp | Senior Director, HQ Regulatory Affairs |

1.0 BACKGROUND

Novo Nordisk has requested a Type B Pre-NDA meeting to discuss filing and formatting of the NDA for the cardiovascular indication proposed for oral semaglutide. Semaglutide is a long acting glucagon-like peptide-1 (GLP-1) analogue that is being developed as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus (T2DM). In addition, a cardiovascular indication to reduce the risk of major adverse cardiovascular events ^{(b) (4)} in adults with type 2 diabetes mellitus and established cardiovascular disease ^{(b) (4)} is being proposed under a separate NDA. The peptide backbone of semaglutide has an acylation in position 26 with a fatty-acid derivative, which binds to albumin and thereby stabilizes the peptide backbone in plasma and decreases the renal clearance of the compound. The IND for semaglutide tablets, co-formulated with sodium N-[8-(2-hydroxybenzoyl) amino] caprylate (SNAC), was submitted on September 26, 2013, for once-daily oral administration as an adjunct to diet and exercise to improve glycemic control in patients with T2DM. SNAC is an excipient that exerts an absorption enhancing function, which increases the bioavailability of orally administered semaglutide.

On September 22, 2014, FDA provided Type C written responses. The response included recommendations and feedback on the oral semaglutide Phase 3 program.

On March 27, 2015, FDA provided Type C written responses. The response included advice on the oral semaglutide development program in pediatric subjects aged 10 to less than 18 years.

On July 10, 2015, FDA provided Type B meeting minutes for the End-of-Phase 2 Meeting, which occurred on June 11, 2015. During this meeting, the Agency provided comments on chemistry, manufacturing and controls (CMC), preclinical, and clinical topics related to the initiation of the Phase 3 program.

Novo Nordisk initiated a Phase 3 clinical development program in 2016 that is currently ongoing. The program includes a cardiovascular safety study (PIONEER 6).

On March 24, 2017, FDA provided Type C written responses. The response included recommendations and feedback on the quality development of the drug product.

NDA 209637 for Ozempic (semaglutide) injection 0.5 mg and 1 mg was approved on December 5, 2017, for once-weekly (OW) subcutaneous (s.c.) administration, as adjunct to diet and exercise to improve glycemic control in adults with T2DM.

On April 23, 2018, FDA provided recommendations and feedback for an amendment dated March 23, 2018, which contained a cardiovascular “bridging” strategy involving cardiovascular data from both the semaglutide injection and the semaglutide tablet trials.

On December 28, 2018, FDA provided Type B meeting minutes for the Pre-NDA meeting for the diabetes indication, which occurred on November 27, 2018. During this meeting, FDA recommended that the sponsor submit a pre-NDA meeting request to discuss the cardiovascular indication, for which the sponsor indicated that they may submit a separate NDA. The sponsor plans to submit a supplement to NDA 209637 for Ozempic for the cardiovascular indication.

Semaglutide is also being investigated in a subcutaneous injection for T2DM under IND 079754.

(b) (4)

FDA sent Preliminary Comments to Novo Nordisk on February 25, 2019.

2. DISCUSSION

2.1. Clinical

Question 1: Does the Agency agree to the proposed outline of documents to be included in the oral semaglutide [cardiovascular] CV NDA?

FDA Response to Question 1: Your proposal to submit a summary of evidence for CV risk reduction, as well as cross-reference to the oral semaglutide for T2DM and Ozempic NDAs is generally acceptable. For ease of review, please provide links to the relevant sections of the individual study reports in the summary document.

Please also include the following documents and forms, in Module 1.3 (administrative information):

- Form 3542a (patent information), if applicable
- Form 3454/3455 (financial disclosure)
- Debarment certification

You should also include the electronic content of labeling in structured product labeling (SPL) format in Module 1.14.

Refer to our response to Question 4 below regarding the initial Pediatric Study Plan (iPSP).

Meeting Discussion: *No further discussion.*

Question 2: Does the Agency agree to how the planned datasets and listings are included in the two NDAs?

FDA Response to Question 2: For the CV indication NDA, you are proposing to provide pooled ADaM datasets with relevant data from the PIONEER and SUSTAIN programs. Clarify what is meant by relevant data. For example, do you plan to only include MACE data, other CV AEs, etc? For the CV NDA, we ask that you submit data sets of ADSL, ADEVNT and ADTTE for PIONEER 6 and SUSTAIN 6 for each trial separately.

For the T2DM NDA, you are proposing to submit two pooled trial databases in ADaM format, one database containing the clinical pharmacology trials, and one containing the Phase 2 and 3 trials including PIONEER 6, in addition to the individual study datasets. You also propose to include the BIMO and OSI datasets to the T2DM NDA only. This approach is acceptable.

Meeting Discussion: *Novo Nordisk stated that they plan to submit 3 pooled datasets with the CV indication NDA, which would include the totality of all data from all trials, including the SUSTAIN 6 CV data, the PIONEER 6 CV data, and all non-CV trials from both programs. The 3 pooled datasets include 1 pooled dataset for the SUSTAIN 6 and PIONEER 6 trials, 1 pooled dataset for the non-CV SUSTAIN studies, and 1 pooled dataset for the non-CV PIONEER studies. The pooled datasets will include flags and trial IDs. FDA stated that we would need time to event for MACE, MACE-free survival (all-cause death, non-fatal stroke, and non-fatal MI), CV death, all-cause death, all strokes, and all MI to be easily identified in the datasets. Novo Nordisk indicated that this would be possible with separate flags and/or categories. FDA inquired as to why Novo Nordisk was submitting the non-CV data with the CV indication NDA. Novo Nordisk stated that the low number of CV-related events (68), were being provided for context only and were not intended to be analyzed as part of a pooled analysis. FDA stated that Novo Nordisk could perform the analysis for MACE-free survival, and to provide this for both studies separately in the clinical study reports. FDA recommended a data walkthrough meeting to occur soon after the NDA is submitted.*

Post meeting Comment: *A data walkthrough meeting was scheduled for April 4, 2019.*

Question 3: Does the Agency agree that safety data from PIONEER 6 should be evaluated and presented in the ISS for T2D NDA?

FDA Response to Question 3: The safety data from PIONEER 6 is relevant to the general safety of the oral semaglutide product and should be included in the ISS for the T2DM NDA.

Meeting Discussion: *No further discussion.*

(b) (4)

2.2. Proposed Approach for PIONEER 6 Labeling

Question 6: Does the Agency have any preliminary feedback on the labeling approach for the T2D NDA?

FDA Response to Question 6: You propose to include the data from PIONEER 6 in Section 14 Clinical Studies section of the Prescribing Information (PI) for the T2DM NDA, similar to the currently approved Ozempic label. (b) (4)

While your proposal to include data from PIONEER 6 in Section 14 may be generally reasonable, we cannot provide any agreement on labeling prior to the NDA review.

(b) (4)

(b) (4)

Meeting Discussion: *No further discussion.*

Question 7: Does the Agency have any preliminary feedback on the labeling approach for the CV NDA?

FDA Response to Question 7:

(b) (4)

The information to be included in the product labeling will ultimately be a review issue, and we have insufficient information at this time to provide agreement or disagreement with your proposal.

(b) (4)

(b) (4)

. We recommend that you analyze SUSTAIN 6 and PIONEER 6 studies separately, and then use Bayesian shrinkage analysis (Henderson et al. 2016)¹

(b) (4)

Meeting Discussion:

(b) (4)

They also stated that they will look into the Bayesian shrinkage analysis as advised by FDA. No additional discussion occurred.

3.0 OTHER IMPORTANT MEETING INFORMATION

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an

¹ Henderson NC, Louis TA, Wang C, Varadhan R (2016). "Bayesian Analysis of Heterogeneous Treatment Effects for Patient-Centered Outcomes Research." Health Services and Outcomes Research Methodology, 16(4), 213–233. doi:10.1007/s10742-016-0159-3.

assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End-of-Phase-2 (EOP2) meeting. In the absence of an EOP2 meeting, refer to the draft guidance below. The iPSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The iPSP should be submitted in PDF and Word format. Failure to include an Agreed iPSP with a marketing application could result in a refuse to file action.

For additional guidance on the timing, content, and submission of the iPSP, including an iPSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf>. In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email Pedsdrugs@fda.hhs.gov. For further guidance on pediatric product development, please refer to: <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm>.

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 [CFR 201.56\(a\) and \(d\)](#) and [201.57](#) including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) and [Pregnancy and Lactation Labeling Final Rule](#) websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products.
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential.
- Regulations and related guidance documents.
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of important format items from labeling regulations and guidances.
- FDA’s established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

Pursuant to the PLLR, you should include the following information with your application to support the changes in the Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of labeling. The application should include a review and summary of the available published literature regarding the drug’s use in pregnant and lactating women and the effects of the drug on male and female fertility (include search parameters and a copy of each reference publication), a cumulative review and summary of relevant cases reported in your pharmacovigilance database (from the time of product development to present), a summary of drug utilization rates amongst females of reproductive potential (e.g., aged 15 to 44 years) calculated cumulatively since initial approval, and an interim report of an ongoing pregnancy registry or a final report on a closed pregnancy registry. If you believe the information is not applicable, provide justification. Otherwise, this information should be located in Module 1. Refer to the draft guidance for industry – *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format* (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425398.pdf>).

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

DISCUSSION OF SAFETY ANALYSIS STRATEGY FOR THE ISS

After initiation of all trials planned for the phase 3 program, you should consider requesting a Type C meeting to gain agreement on the safety analysis strategy for the Integrated Summary of Safety (ISS) and related data requirements. Topics of discussion at this meeting would include pooling

strategy (i.e., specific studies to be pooled and analytic methodology intended to manage between-study design differences, if applicable), specific queries including use of specific standardized MedDRA queries (SMQs), and other important analyses intended to support safety. The meeting should be held after you have drafted an analytic plan for the ISS, and prior to programming work for pooled or other safety analyses planned for inclusion in the ISS. This meeting, if held, would precede the Pre-NDA meeting. Note that this meeting is optional; the issues can instead be addressed at the pre-NDA meeting.

To optimize the output of this meeting, submit the following documents for review as part of the briefing package:

- Description of all trials to be included in the ISS. Please provide a tabular listing of clinical trials including appropriate details.
- ISS statistical analysis plan, including proposed pooling strategy, rationale for inclusion or exclusion of trials from the pooled population(s), and planned analytic strategies to manage differences in trial designs (e.g., in length, randomization ratio imbalances, study populations, etc.).
- For a phase 3 program that includes trial(s) with multiple periods (e.g., double-blind randomized period, long-term extension period, etc.), submit planned criteria for analyses across the program for determination of start / end of trial period (i.e., method of assignment of study events to a specific study period).
- Prioritized list of previously observed and anticipated safety issues to be evaluated, and planned analytic strategy including any SMQs, modifications to specific SMQs, or sponsor-created groupings of Preferred Terms. A rationale supporting any proposed modifications to an SMQ or sponsor-created groupings should be provided.

When requesting this meeting, clearly mark your submission “**DISCUSS SAFETY ANALYSIS STRATEGY FOR THE ISS**” in large font, bolded type at the beginning of the cover letter for the Type C meeting request.

MANUFACTURING FACILITIES

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided

in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

| Site Name | Site Address | Federal Establishment Indicator (FEI) or Registration Number (CFN) | Drug Master File Number (if applicable) | Manufacturing Step(s) or Type of Testing [Establishment function] |
|-----------|--------------|--|---|---|
| 1. | | | | |
| 2. | | | | |

Corresponding names and titles of onsite contact:

| Site Name | Site Address | Onsite Contact (Person, Title) | Phone and Fax number | Email address |
|-----------|--------------|--------------------------------|----------------------|---------------|
| 1. | | | | |
| 2. | | | | |

FDA has made a preliminary determination that the application for this product would not be reviewed as a new molecular entity (NME) and would not be subject to the Program under PDUFA VI. Please note that this is a preliminary determination, based on information available to FDA at this time, and will be re-evaluated at the time your application is submitted. This determination is based on our understanding of the active moiety (21 CFR 314.108(a)) and whether another marketing application containing the same active moiety is approved or marketed. Please also note that the NME determination for an application is distinct from and independent of the new chemical entity (NCE) determination and any related exclusivity determinations, which are made after approval of an NDA

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

The Office of Scientific Investigations (OSI) requests that the items described in the draft Guidance for Industry Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions (February 2018) and the associated Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA ORA investigators who conduct those inspections. This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

Please refer to the draft Guidance for Industry Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions (February 2018) and the associated Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications:

<https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332466.pdf>

<https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf>.

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

/s/

LISA B YANOFF
03/26/2019 07:29:25 AM