

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

213051Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

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 November 29, 2018. The purpose of the meeting was to discuss aspects of the oral semaglutide development program and the NDA submission.

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 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
Sponsor Slides

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: Pre-NDA

Meeting Date and Time: November 29, 2018; 11:00 AM – 12:00 PM EST
Meeting Location: White Oak Campus, Building 22, Room 1417

Application Number: IND 114464
Product Name: semaglutide tablets

Indication: Type 2 diabetes mellitus
Sponsor 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)
Mitra Rauschecker, M.D., Clinical Team Lead (Acting)
Andreea Lungu, M.D., Clinical Reviewer
Federica Basso, Ph.D., Nonclinical Team Lead (Acting)
Elena Braithwaite, Ph.D., Nonclinical Reviewer
Peter Franks, M.S., Regulatory Project Manager
Allison Bean, Student Intern

Office of Biostatistics

Yun Wang, Ph.D., Statistical Team Lead
Eugenio Andraca-Carrera, Ph.D., Statistical Team Lead
Yoonhee Kim, Ph.D., Mathematical Statistician
Ya-Hui (Catherine) Hsueh Ph.D., Mathematical Statistician

Office of Biotechnology Products

Daniela Verthelyi, M.D., Ph.D., Team Lead, Laboratory of Immunology
Mohanraj Manangeeswaran, Ph.D., Reviewer, Laboratory of Immunology

Office of Clinical Pharmacology

Manoj Khurana, Ph.D., Clinical Pharmacology Team Lead
Tao Liu, Ph.D., Clinical Pharmacology Reviewer

Office of Surveillance and Epidemiology

Nichelle Rashid, Safety Regulatory Project Management Team Lead (Acting)
Ariane Conrad, Pharm.D., Safety Evaluator, DMEPA
Terrolyn Thomas, MS, MBA; Senior Regulatory Project Manager

Office of Scientific Investigations

Cynthia Kleppinger, M.D., Senior Medical Officer

SPONSOR ATTENDEES

Anders Hvelplund, Executive Director, US Clinical Development and Outcomes Research
Anne Phillips, Senior Vice President, Clinical Medical and Regulatory Affairs
Birgitte Lysgaard-Jensen, Senior Regulatory Professional, HQ Regulatory Affairs
Jan Vanggaard Andersen, Nonclinical Project Director, Nonclinical Project Management
Jeppe Juul, Statistical Programming Specialist, Biostatistics
Jeppe Zacho, Senior Director, Medical and Science
Mads Frederik Rasmussen, Corporate Project VP, Semaglutide Diabetes & 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
Stephen Gough, Senior Vice President, Global Chief Medical Officer
Trine Saugstrup, Statistical Director, Biostatistics
Vibeke Hatorp, Senior Director, HQ Regulatory Affairs

1.0 BACKGROUND

Novo Nordisk has requested a Type B Pre-NDA meeting under IND 114464 to discuss aspects of the oral semaglutide development program and the requirements for NDA submission. 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). Semaglutide is also being investigated in a subcutaneous injection for T2DM under IND 079754. (b) (4)

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 tablet, 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 intends to increase the bioavailability of orally administered semaglutide.

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

On March 27, 2015, FDA provided Type C written responses. The responses 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 responses 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.

FDA sent Preliminary Comments to Novo Nordisk on November 27, 2018.

2. DISCUSSION

The sponsor’s questions are followed by our **bolded** response. Any meeting discussion is in *italicized* text. Any post-meeting comments are underlined.

2.1. Clinical

Question 1: Does the Agency agree to the proposed approach for presentation of the efficacy evaluations in the SCE?

FDA Response to Question 1:

You propose to present the full evaluation of efficacy in the Summary of Clinical Efficacy (SCE) trial-by-trial, with no pooling of data across trials, and that the SCE will serve as Integrated Summary of Effectiveness (ISE). Your proposed approach seems reasonable. We agree with the use of the treatment policy estimand as a primary estimand for presentations of study results and potential claims of superiority, and non-inferiority.

Discussion: *No further discussion.*

Question 2: Does the Agency agree to 05 November 2018 as the cut-off date for the NDA?

FDA Response to Question 2:

Your proposal to included blinded safety data from 3 trials (PIONEER 7 extension, and clinical pharmacology trials 4248, and 4427) as of the NDA cut-off date of

November 5, 2018, is acceptable. If safety issues are identified that require an assessment of unblinded data from these trials, unblinding may be requested. Additionally, for PIONEER 6, we recommend you include all adjudicated events in the primary analysis between the cut-off date and the trial termination visit.

Discussion: *The sponsor referred to slide 2 of their presentation. The sponsor clarified that subjects' last visits in PIONEER 6 occurred between July and September 2018. All events that occurred up to the last study visit were adjudicated and will be included in the clinical study report and the corresponding datasets in the NDA submission. The sponsor also mentioned that they underwent adjudications for all clinical events occurred between last subject last visit and database lock for PIONEER 6 and describe the cases in the clinical study report. The database lock for PIONEER 6 occurred in November 2018. FDA had no further comments.*

Question 3: Does the Agency agree with the proposal of waiving the submission of a 4-month safety update to the NDA for oral semaglutide?

FDA Response to Question 3:

No, we do not agree. You should submit the 4-month safety update with any available new data.

Discussion: *No further discussion.*

Question 4: Does the Agency agree to only include data from oral semaglutide clinical trials in the ISS?

FDA Response to Question 4:

Your proposal is acceptable.

Discussion: *No further discussion.*

Question 5: Does the Agency agree to the proposed pooling strategy to be used in the ISS?

FDA Response to Question 5:

You are proposing to evaluate safety based on the following pools: Phase 3a pool (PIONEER 1-5, and 7-10), placebo pool (PIONEER 1, 4, 5, 8, and 9), and placebo dose pool (where all three doses of semaglutide were evaluated, PIONEER 1, 8, and 9). You also propose to present data from the cardiovascular outcome trial (PIONEER 6) separately from the Phase 3 pool.

We agree that data from the cardiovascular outcomes trial can be presented separately. To facilitate the safety review, we ask that you present the following additional pools:

1. A pool of placebo-controlled studies (PIONEER 1, 4, 5, and 8)
2. A pool of the multi-national Phase 3 studies (PIONEER 1-5, and 7, 8)
3. A pool of the Japanese safety studies (PIONEER 9 and 10)

When presenting the safety findings, we request that you present the findings by individual dose of semaglutide, pooled semaglutide, compared to placebo, compared to active comparator, and compared to all comparators (as applicable).

Discussion: *As an alternative to the pooling strategy that FDA recommended, the sponsor proposed a revised pooling strategy with 3 pools, including a Phase 3a pool, a placebo pool, and a placebo-dose pool. The sponsor referred to slide 3 of their presentation. FDA agreed with this pooling strategy. FDA would like to have the ability to separate out the Japanese studies (PIONEER 9 and 10), and the sponsor stated that these studies would be flagged in datasets, and easily separated for analysis.*

Question 6: Does the Agency agree with the proposed strategy for presentation of the safety evaluation in the Integrated Summary of Safety?

FDA Response to Question 6:

You propose to assess safety in the ISS via an integrated approach based on the data collected across the oral semaglutide clinical program, based on the safety analysis set, and the on-treatment observation period (with the exception of death, and adverse events with potential long latency between onset and diagnosis, for which the in-trial observation period will be used). Safety data from clinical pharmacology trials will also be presented in the ISS in a pool separate from the Phase 3 studies (exposure, and AEs). Safety data from the dose finding study 3790 will be presented separately as it includes doses not studied in the Phase 3 program. The evaluation of cardiovascular safety will be based on the cardiovascular outcomes trial PIONEER 6.

Your proposed strategy for presenting safety appears generally adequate, with the exception of the proposed pools for the Phase 3 studies (see our response to Question 5 above).

At the time of the NDA submission, please submit a document listing the source of the data for each of the safety tables.

Discussion: *No further discussion.*

Question 7: Does the Agency agree to the above proposal [regarding immunogenicity assays]?

FDA Response to Question 7:

No, we do not agree. For the oral semaglutide program, you will need to submit a complete immunogenicity dataset from the oral semaglutide program that includes data

from screening, confirmatory and titering ADA assays, as well as a neutralizing assay. Although your screening assay is not isotype specific, you should provide data supporting that your assay would detect anti-semaglutide antibodies of IgA isotype, if present in the serum. If there is clinical evidence of hypersensitivity, an assessment of IgE antibodies using an assay that can detect clinically relevant levels of IgE may be required. Please submit the preferred terms used to evaluate for hypersensitivity in the clinical program with the NDA submission and clarify if these terms were pre-specified.

Regarding the neutralizing assay, submitting a cross-reference for the validation would be acceptable. We recommend that the immunogenicity part of the submission be arranged into distinct sections (1) Immunogenicity Risk Assessment, including a risk assessment for the novel excipients used in your product (2) Tiered Bioanalytical Strategy and Assay Validation Summaries, (3) Clinical Study Design and Detailed Immunogenicity Sampling Plans, (4) Clinical Immunogenicity Data Analysis, and (5) Conclusions and Risk Evaluation and Mitigation Strategies if needed (REMS).

Discussion: *The sponsor stated that they would implement the recommendations as set forth in the FDA preliminary comments document. The sponsor referenced a November 14, 2018, submission to the IND which includes validated methods for antibody assays. The sponsor is awaiting feedback from FDA on these methods, and plans to reanalyze samples once the feedback is received. The sponsor inquired on the timeframe to provide feedback, and FDA stated that the review would be provided as soon as possible, since this is needed prior to the NDA submission which is planned for March 2019.*

2.1. Statistics

Question 8: Does the Agency agree to the planned ADaM domains that will be included in the NDA?

FDA Response to Question 8:

Yes, we agree with your proposal to submit electronic data sets for all Phase 2, Phase 3, and clinical pharmacology studies.

Discussion: *No further discussion.*

Question 9: Does the Agency have any comments to the format of the sample datasets provided?

FDA Response to Question 9:

In addition to analysis results metadata in define-xml, please provide analysis programs with adequate annotations that are used for key efficacy analysis including pre-specified sensitivity analysis, as well as post-hoc analyses included in the planned clinical study report, if any. Provide a separate tabular listing (see below example) in pdf format to describe the key efficacy analysis you have done, the list should include

the output file name, analysis program name, the title of results with table/figure number, datasets utilized, and macros used. All macros inside the actual program for running should also be submitted.

Example of tabular listing:

Output file name	Program Name	Title/Description	Datasets Utilized	Macro's Used
Eff_output	Eff_anal1.sas	Primary Efficacy analysis in Table XX.X in the clinical study report	ADLB, ADSL	%macro1

Please clarify a definition of “period 30” in the Table 4 Core Variables from the submitted Analysis Data Reviewer’s Guide Trial ID NN9924-4233. Please clarify the meaning of “period 30” for each trial. Also, clarify the difference between variables named TRT30P and TRTP. We prefer the same core variable names (for example, core variable indicating treatment arm as TRTP or etc.) across ADaM domains and across trials used in the key efficacy analyses.

Discussion: *The sponsor referred to slide 5 of their presentation and the sponsor will clarify the definition of variable names in the analysis data reviewer’s guide. FDA had no further comments.*

Question 10: Does the Agency have any comment to the excerpts from the Reviewer’s Guide?

FDA Response to Question 10:

See response to Question 9.

Discussion: *No further discussion.*

2.2. Regulatory

Question 11: Does the Agency have any input to the approach outlined above [regarding use of a priority review voucher]?

FDA Response to Question 11:

We do not have any comments.

Discussion: *No further discussion. See below discussion on Cardiovascular Strategy, which includes reference to the priority review voucher.*

2.3. Additional Discussion Topics

The sponsor included two additional topics with their slide presentation to discuss, if time permitted, which were not included in the meeting package. These topics included the cardiovascular strategy for oral semaglutide (b) (4)

Cardiovascular Strategy

The sponsor stated at the meeting that they intend to include a CV indication with the oral semaglutide NDA. FDA encouraged the sponsor to request a Type C meeting, in teleconference format, to review the topline safety and MACE results of the CVOT study. FDA stated that this teleconference should occur prior to the submission of the NDA, which is planned for March 2019.

Post Meeting Comment: *The sponsor submitted a formal meeting request on December 11, 2018, to discuss the CVOT study. In lieu of a type C meeting, the sponsor and FDA held an informal teleconference on December 20, 2018, for the sponsor to present the topline safety and MACE results from the PIONEER-6 study. Based on the presentation at this teleconference and lack of clarity on the data that will be relied upon for the sought-after indication, 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.*

In addition to the CV indication, the sponsor stated that they intend to submit a priority review voucher for the oral semaglutide NDA, which would entail a 6-month review clock. FDA recommended that if they do intend to use the voucher, that they may submit any finalized study reports to the IND as soon as possible, prior to the NDA submission. These would include clinical study reports, nonclinical reports, and/or clinical pharmacology reports. The sponsor inquired on if FDA had a preferred format for clinical pharmacology data, and FDA agreed to provide an example table with this information as soon as possible. Additionally, FDA recommended that a data walkthrough meeting should occur shortly after the NDA is submitted.

(b) (4)

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 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>.

4.0 ATTACHMENTS AND HANDOUTS

Sponsor's slides presented at the meeting

6 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page

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
12/28/2018 11:06:45 AM



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 114464

MEETING MINUTES

Novo Nordisk, Inc.
Attention: Stephanie DeChiaro
Associate Director Regulatory Affairs
P.O. Box 846
800 Scudders Mill Road
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 tablet.

We also refer to the meeting between representatives of your firm and the FDA on June 11, 2015. The purpose of the meeting was to discuss chemistry, manufacturing and controls (CMC), preclinical, and clinical topics related to the initiation of the phase 3 program.

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, contact Martin White, M.S., Regulatory Project Manager, at (240) 402-6018.

Sincerely,

{See appended electronic signature page}

Jean-Marc Guettier, M.D.
Director
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: End of Phase 2

Meeting Date and Time: Thursday, June 11, 2015; 2:00 – 3:00 PM
Meeting Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1419
Silver Spring, MD 20903

Application Number: 114464
Product Name: semaglutide tablet
Indication: Type 2 diabetes mellitus
Sponsor/Applicant Name: Novo Nordisk, Inc.

Meeting Chair: Jean-Marc Guettier, M.D., Director
Meeting Recorder: Martin White, M.S. Regulatory Project Manager

FDA ATTENDEES

Division of Metabolism and Endocrinology Products

Jean-Marc Guettier, M.D.	Director
William Chong, M.D.	Clinical Team Leader
Andreea Lungu, M.D.	Clinical Reviewer
Stephanie Leuenroth-Quinn, Ph.D.	Nonclinical Team Leader
Indra Antonipillai, Ph.D.	Nonclinical Reviewer
Monika Houstoun, Pharm.D.	Associate Director of Labeling
Julie Van der Waag, M.P.H.	Chief, Project Management Staff
Martin White, M.S.	Regulatory Project Manager
Michael White, Ph.D.	Regulatory Project Manager

Office of Biostatistics, Division of Biometrics II

Gregory Levin, Ph.D.	Statistical Team Leader
Cynthia Liu, M.A.	Biometrics Reviewer

Office of Clinical Pharmacology, Division of Clinical Pharmacology II

Manoj Khurana, Ph.D.	Clinical Pharmacology Team Leader
S.W. Johnny Lau, Ph.D.	Clinical Pharmacology Reviewer

SPONSOR ATTENDEES

Dorte Waaben	Vice President, CMC Diabetes oral portfolio
--------------	---

Henriette Mersebach	Executive Director, Clinical Development and Research
Henrik Kim Nielsen	Corporate Vice President, GLP-1, Obesity & Diabetes Complications
Jan Vanggaard Andersen	Nonclinical Project Director
Lars Holm Damgaard	Principal Statistician, Biostatistics Semaglutide
Mads Frederik Rasmussen	Corporate Project Vice President, Semaglutide
Marie-Louise Hartoft-Nielsen	International Medical Director, Medical and Science, Semaglutide
Marie Lindegaard	Vice President, Medical and Science, Semaglutide
Michelle Thompson	Senior Director, US Regulatory Affairs
Peter Kristensen	Senior Vice President, Global Development
Robert Clark	Vice President, US Regulatory Affairs
Stephanie DeChiaro	Director, US Regulatory Affairs
Tine Aggerholm Bækdal	Clinical Pharmacology Specialist, Clinical Pharmacology Oral Delivery
Vibeke Hatorp	Director Oral GLP-1 & Early Diabetes Projects

1.0 BACKGROUND

Semaglutide (NNC0113-0217) is a long-acting glucagon-like peptide-1 (GLP-1) analogue. 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 tablet, 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 type 2 diabetes mellitus (T2DM). SNAC is an excipient that exerts an absorption enhancing function, which increases the bioavailability of orally administered semaglutide.

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

On March 27, 2015, the Agency 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.

Novo Nordisk plans to initiate the phase 3 clinical development program in 2016.

Novo Nordisk is also conducting a separate clinical development program to investigate subcutaneous (s.c.) administration of semaglutide (IND 079754).

The purpose of this meeting is to discuss chemistry, manufacturing, and controls (CMC), preclinical, and clinical topics related to the initiation of the phase 3 program.

FDA sent Preliminary Comments to Novo Nordisk on June 9, 2015.

2.0 DISCUSSION

2.1 CMC

Question 1: *Novo Nordisk considers that comparability between the drug substance used in phase 1 and 2 and the drug substance to be used in phase 3 has been demonstrated. Does the Agency agree that the presented comparability package is sufficient for initiation of phase 3 and for the NDA?*

FDA Response to Question 1: We agree that the analytical and physico-chemical data provided support the conclusion that phase 3 technical batches of semaglutide drug substance are comparable with semaglutide drug substance batches used for phase 1 and 2. Be advised that if any significant differences are observed in the stability profiles of the phase 3 batches compared to phase 1 and phase 2 clinical batches, additional non-clinical studies may be required to qualify any differences in the impurity/degradant profile.

Discussion: *No discussion occurred.*

2.2 Non-Clinical

Question 2: *Does the Agency agree that the animal-to-human exposure ratios provided are adequate for the intended clinical use of SNAC in oral semaglutide?*

FDA Response to Question 2: Yes we agree, provided that no unanticipated safety concerns arise.

Discussion: *No discussion occurred.*

Question 3: *Does the Agency agree that no additional in vitro or in vivo non-clinical studies are necessary to assess the clinical relevance of the mortality observed at high SNAC exposures in animals prior to initiation of clinical phase 3 or for the NDA?*

FDA Response to Question 3: Yes we agree, provided that no unanticipated safety concerns arise.

Additional Nonclinical Comment: There is a concern for the accumulation of SNAC metabolites in patients with renal impairment. Please submit any completed nonclinical studies to address the pharmacologic activity and toxicity of SNAC metabolites (e.g. drug-drug interaction, activity, potency, protein binding). Additional nonclinical studies may be required to address the biological activity of SNAC metabolites.

Discussion: *No discussion occurred.*

2.3 Clinical Pharmacology

Question 4: *Does the Agency agree that the proposed clinical pharmacology programme is adequate to support the NDA submission and proposed indication?*

FDA Response to Question 4: In general, the clinical pharmacology program of oral semaglutide tablets appears reasonable to support a future NDA submission. However, we have the following comments for the clinical pharmacology program of oral semaglutide tablets:

- a. If the clinically-tested formulation of the oral semaglutide tablets is different from the to-be-marketed formulation of the oral semaglutide tablets, you need to address the bioequivalence issue between these formulations before submission of NDA for the oral semaglutide tablets.
- b. Trial NN9924-4154 tested the effect of food on the pharmacokinetics of the 5 mg and 10 mg oral semaglutide tablets. The oral semaglutide tablet strengths for the planned phase 3 trials are 3 mg, 7 mg, and 14 mg. Address the issue that the highest strength of a drug product intended to be marketed should be tested in the food effect bioavailability trial per the Guidance for Industry “Food-Effect Bioavailability and Fed Bioequivalence Studies” (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070241.pdf>) for oral semaglutide tablets.
- c. Trial NN9924-4250 aims to study the potential interaction between oral semaglutide and transporters such as the Organic Anion Transporting Polypeptide 1B1 (OATP1B1) and the Breast Cancer Resistance Protein (BCRP) because the oral semaglutide absorption enhancer, SNAC, and its metabolites inhibit these transporters in vitro. Consider studying rosuvastatin instead of atorvastatin. The draft Guidance for Industry “Drug Interaction Studies – Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations” (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292362.pdf>) recommends rosuvastatin as a substrate of BCRP and OATP1B1, whereas the same guidance recommends atorvastatin as a substrate of OATP1B1.

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

Discussion: *No discussion occurred.*

Post-meeting Comment: *Since you are conducting the DDI studies in parallel to the phase 3 trials, we recommend you monitor the use of concomitant medications for adverse events in the phase 3 trials.*

Question 5: Does the Agency agree that the proposed phase 3a development programme for oral semaglutide is adequate to support the following indication?

TRADENAME (oral semaglutide) is an oral GLP-1 receptor agonist indicated to improve glycaemic control in adult patients with type 2 diabetes mellitus as an adjunct to diet and exercise.

FDA Response to Question 5: No we do not agree. We have concerns that the program as currently designed will not allow for a robust benefit-risk characterization of oral semaglutide for the following reasons:

- a. **Limited placebo-controlled data:** [REDACTED] (b) (4)
[REDACTED] We recommend that your program include additional placebo-controlled studies to adequately and robustly characterize benefits and risks of the novel agent. With regards to benefits and proposed non-inferiority margins for active-controlled trials please see Question 19. Placebo-controlled trials are ethical and provide the best characterization of effect-size. With regards to safety, while we recognize that you have an ongoing semaglutide program for a subcutaneous dosage form, this program cannot address risks associated with oral delivery (i.e., GI adverse events when added to drugs known to have GI side effects) or risks specifically attributable to SNAC. We recommend use of additional placebo-controlled trials in your program.
- b. **Background Medications:** We suggest that you evaluate the safety and efficacy of oral semaglutide on the background of specific and most commonly used oral agents (e.g., at least background of metformin, background of metformin + sulfonylurea, as these two classes of drugs still represent the most commonly used drugs in the US to our knowledge). We recommend against broad, loosely defined types of background antidiabetic agents [REDACTED] (b) (4). In light of your specific product's adverse event profile which includes nausea, vomiting, and potential for dehydration and renal dysfunction, we are interested in specific and robust characterization of safety issues (e.g., GI tolerability, volume depletion, acid base issues) when combining your proposed product with specific agents (e.g., metformin and SGLT-2 inhibitors). We recommend characterizing the risks associated with co-administration use in randomized, placebo-controlled trials, in individuals receiving maximally effective doses of the background therapy(ies) at baseline.
- c. **Timing of the Primary Outcome:** [REDACTED] (b) (4)
[REDACTED] We recommend that the primary efficacy endpoint be assessed at 26 weeks. Controlled extensions, (not voluntary, active or placebo depending on need) out to 52 weeks to characterize long-term efficacy and safety data should be carried out. This

approach will result in a lower proportion of missing data and a more reliable estimate of efficacy.

Discussion: *The sponsor presented revisions to the proposed phase 3 program and the following changes were discussed:*

- a. *Addition of a pre-approval cardiovascular outcomes trial to acquire a minimum of 122 MACE events to rule out an excess CV risk of 80%. The FDA felt this approach to be reasonable.*
- b. *The time-point to assess the primary efficacy endpoint for the phase 3 studies was amended to be at 26 weeks. This is consistent with the FDA recommendations from the preliminary comments.*
- c. *The sponsor proposed to more explicitly define the background medication and to include some common clinical scenarios as recommended by the FDA (e.g., in combination with metformin, metformin +SU), and use scenarios of specific concern (e.g., in combination with SGLT2 inhibitor). The FDA noted that no trial included insulin background as advised in the preliminary comments. The sponsor stated that this is planned for their future studies.*
- d. *To address the FDA concerns about insufficient placebo-controlled data, the sponsor proposed the addition of a placebo arm in planned study with liraglutide as active comparator. The Agency commented that, while this is an improvement compared to the initial proposal, the FDA believes that more placebo-controlled data is better. The FDA also advised the sponsor to include a placebo arm in the renal impairment study for better characterization of safety and effect size in this patient population.*

(b) (4)



The FDA cannot endorse this approach at this time and still advises that the addition of a placebo arm in the renal impairment study would be the best approach to evaluating this patient population.

The FDA asked whether the sponsor anticipates that all studies will be completed at the time of NDA filing. The sponsor informed the agency that they will present all completed data at the time of filing the NDA.

Post-meeting comments: *The sponsor submitted additional information, submitted June 25, 2015, following the meeting stating that the linagliptin arm will be replaced with*

placebo in the renal impairment trial and that the protocol for CVOT will be submitted in October 2015 for review by the Division. This approach is acceptable.

Question 6: Does the Agency agree that the proposed number of exposed subjects and the duration of exposure in the proposed phase 3a programme at the time of NDA filing are sufficient to support an NDA?

FDA Response to Question 6: You plan to have 2,994 patients randomized to treatment with your drug product with 1,612 exposed for 12 months and 833 exposed for 18 months. This seems reasonable, but we refer you to our response to question 5 regarding the need for placebo controlled data. In addition, it is not clear whether this exposure will provide sufficient data for the evaluation of potential cardiovascular (CV) risk associated with oral semaglutide. Please see our answer to question 23 regarding CV risk evaluation for further details.

Discussion: No discussion occurred.

Question 7: Does the Agency agree to the proposed inclusion/exclusion criteria and that the criteria will allow for inclusion of subjects that are representative of the T2DM population?

FDA Response to Question 7: While the proposed inclusion and exclusion criteria appear generally reasonable, we ask that the population enrolled in your phase 3 programs be representative of the US population with T2DM who could be prescribed the drug should it become available. Unless specific inclusion criteria are used to ensure that a sufficient number of elderly patients and patients with long-standing disease and with co-morbid disease, it is unlikely that sufficient patients from these important demographic and disease subgroups will be enrolled (i.e., not restricting age of entry is unlikely to be sufficient). You should pre-specify what percentage of patients will be above the age of 60 to reflect the target population in the US. In addition, in your criteria clarify the exact type of GI surgery which would constitute an exclusion criterion so that it is not subject to investigator interpretation.

We may have additional comments once full study protocols are submitted.

Discussion: No discussion occurred.

Question 8: Does the Agency agree to the selection of the 3 doses (3, 7, 14 mg) for the proposed phase 3a programme?

FDA Response to Question 8: The approach to basing oral semaglutide dose selection on matching the systemic exposure between oral and subcutaneous semaglutide dosage forms may be reasonable from an efficacy perspective. We note however, that data derived from oral administration for systemic semaglutide concentrations, efficacy, and safety are available from Trial NN9924-3790. We recommend that exposure and response analyses from this trial be carefully

considered to help further support your dose selection for the phase 3 development program.

The risk-benefit ratio for each selected dose will be a review issue.

Discussion: No discussion occurred.

Post-meeting comments: The sponsor submitted additional information following the meeting stating that the selection of doses for the proposed phase 3a program is based on thorough evaluation of dose-response and exposure- response modelling taking safety and tolerability into consideration. We recommend that you submit the exposure-response data resulting from your phase 2 dose-finding study to the FDA.

Question 9: Does the Agency agree to the proposed dose escalation regimen?

FDA Response to Question 9: Your proposed 4-week dose escalation intervals for the phase 3 trials seem reasonable.

Discussion: No discussion occurred.

Question 10: Does the Agency agree that the proposed trial to investigate flexible dose adjustment with oral semaglutide (NN9924-4257), which will, mimic clinical practice, will provide useful information to the prescriber and that the design will allow for inclusion into the label?

FDA Response to Question 10: We do not agree that the information obtained from your proposed flexible dose study will provide meaningful data to enhance your phase 3 development program, and we do not view this as a pivotal study.

It is premature to discuss labeling at this time.

Discussion: The sponsor inquired why the FDA does not consider the flexible dose study to be a pivotal study and clarified what they think is the benefit of having such a study in their development program (i.e., information on how many patients will end up using each dose level). The FDA clarified the expectations of what would be considered a pivotal study for approval of diabetes drugs (i.e., study as monotherapy, add on to metformin, metformin plus sulfonylureas, insulin, other backgrounds if there are specific concerns) and the flexible dose study does not fit in this category.

The FDA reiterated that it does not believe that the data derived from the flexible dose study would be useful in evaluation of safety and efficacy of oral semaglutide.

Question 11: Does the Agency agree that the proposed primary endpoint (proportion of subjects with HbA1c<7.0%) in the flexible dose adjustment trial is adequate to support the objective of the trial and to allow for the data to be included into the label?

FDA Response to Question 11: Please see our answer to question 10 above.

Discussion: No discussion occurred.

Question 12: Does the Agency agree that the proposed dose levels of background medication of oral anti-diabetic drugs in add-on clinical trials are appropriate to reflect the target population and support the use of oral semaglutide in this patient population?

FDA Response to Question 12: No we do not agree. (b) (4)

You should clearly define the background anti-diabetic therapy (ies) for each specific phase 3 study (see our response to Question 5 above). This will ensure better characterization of the benefit-risks of your drug product in common use settings. Generally, we ask that applicants evaluate, at minimum, the add-on to metformin, add-on to metformin and sulfonylurea, and add-on to insulin settings. In addition, because of the specific adverse event profile with SNAC/semaglutide (nausea, vomiting, potential for dehydration), we recommend that you also study semaglutide on a background of an SGLT2 inhibitor to further evaluate the potential risk for dehydration and renal impairment.

The proposal dose levels for background medications (i.e., ≥ 1500 mg of metformin, $\geq \frac{1}{2}$ maximal approved dose, or maximally tolerated dose) are acceptable.

Discussion: See discussion included under question 5.

Question 13: Does the Agency agree with the choice and selected dose levels of comparators in the proposed development programme for oral semaglutide?

FDA Response to Question 13: As discussed in our response to Question 5, we advise you to include additional placebo-controlled data in your phase 3 program.

Discussion: No discussion occurred.

Question 14: Does the Agency agree to the proposed rescue criteria for the phase 3a trials?

FDA Response to Question 14: Your proposed rescue criteria based on fasting glucose appear reasonable. We advise you to consider adding additional rescue criteria based on HbA1c.

Discussion: No discussion occurred.

Question 15: For subjects requiring initiation of rescue medication, (b) (4)
Does the Agency agree?

FDA Response to Question 15: [REDACTED] (b) (4)

[REDACTED]. Patient should be offered an appropriate rescue agent and continue to be followed until trial completion. This is more consistent with clinical practice, and this approach will ensure the trial blind will be maintained.

Discussion: No discussion occurred.

Question 16: Does the Agency agree that this is an appropriate primary estimand?

FDA Response to Question 16: No, we do not agree. [REDACTED] (b) (4)

[REDACTED] We recommend that the primary estimand is the intention-to-treat (ITT) estimand, i.e., the difference in HbA1c in all randomized patients at the landmark visit regardless of adherence to treatment or use of rescue therapy. To reliably evaluate the ITT estimand, the analysis should use all data from all randomized subjects, regardless of treatment adherence or rescue status. If you propose an alternative estimand, you should justify that it is meaningful for all patients and estimable with minimal assumptions.

Discussion: The sponsor agreed to use the ITT estimand as the primary estimand (i.e., collecting and using all data regardless of adherence to treatment or use of rescue therapy) for the comparisons against active control arms, but proposed [REDACTED] (b) (4)

[REDACTED] **FDA did not agree with this proposal,** [REDACTED] (b) (4)

[REDACTED] **FDA continued to** recommend the evaluation of the intention-to-treat estimand, i.e., the difference in HbA1c in all randomized patients regardless of adherence or use of rescue, but also indicated that it is open to more discussions on this matter when protocols are submitted for review.

Question 17: Does the Agency agree [REDACTED] (b) (4) is an appropriate primary analysis for estimating the primary estimand?

FDA Response to Question 17: No, we do not agree. See response to Question 16. The most appropriate analysis will depend on the choice of primary estimand. In addition, you should clearly state the assumptions about missing data in your primary analysis and justify that those assumptions are reasonable. Generally missing data may attenuate differences, thus making it easier to conclude non-inferiority when non-inferiority does not exist. An imputation under the non-inferiority null method should be considered for the primary non-inferiority analysis (see page 341 of Koch Stat Med. 27, 333-342, 2008).

Discussion: The FDA accepted the sponsor's proposal for missing data handling for active-controlled comparisons. The missing data handling was not discussed for placebo-

controlled comparisons because the FDA did not agree with the sponsor's proposed modification for the placebo arm. See discussion points under Question 16.

Question 18: Does the Agency agree that the sensitivity analyses pre-specified above and included in the phase 3a trials are appropriate for investigating the robustness of the confirmatory MMRM-based analysis conclusions for HbA1c and body weight?

FDA Response to Question 18: The second and third sensitivity analyses you have proposed appear reasonable, although additional analyses may be needed and additional details on the proposed analyses should be submitted in the statistical analysis plans for FDA review. In particular, for each sensitivity analysis, a description should be provided as to what limitation(s) of the data or assumption(s) of the primary analysis is/are being evaluated and how the sensitivity analysis achieves this. The most appropriate analysis in describing the treatment effect will be a review issue.

Discussion: No discussion occurred.

Question 19: Does the Agency agree to the chosen non-inferiority margins?

FDA Response to Question 19:

(b) (4)

his rationale is not adequate. Each non-inferiority margin should be chosen to ensure that semaglutide preserves an acceptable proportion of the effect of the active comparator, which should be estimated from all historical adequate and well-controlled trials that are relevant to the setting of the non-inferiority trial. See the FDA draft Guidance for Industry "Non-Inferiority Clinical Trials" (<http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm202140.pdf>) for additional discussion. Please provide sufficiently detailed justification with supporting data.

Discussion: No discussion occurred.

Question 20: Does the Agency agree that the statistical testing strategy based on Bretz et al 2009 for the confirmatory hypotheses related to HbA1c and body weight will be sufficient statistical evidence for supporting label claims and inclusion of significant p-values in the clinical studies section of the label?

FDA Response to Question 20:

(b) (4)

Whether to include significant p-values or not will be a labeling issue.

Discussion: *The sponsor stated that the closed testing procedure for Study NN9924-4234 has been changed to match the ones described in the meeting package for Study NN9924-4223 and NN9924-4224. The FDA agreed with this change.*

Question 21: *Does the Agency agree to the proposed safety monitoring for the phase 3a clinical programme?*

FDA Response to Question 21: *Your proposal to use an internal trial safety committee to perform ongoing safety monitoring is acceptable. Your proposal to use a blinded, external event adjudication committee for fatal events, cardiovascular events, pancreatitis, thyroid neoplasms, and other neoplasms is acceptable.*

We do have some additional comments on your safety monitoring. In light of the theoretical effect of SNAC on cellular respiration, we recommend that you also adjudicate all acidosis events as adverse events of special interest (AESI).

It appears that several individuals in your phase 2 study had CPK elevation. Please clarify this finding at the meeting.

Other AESIs that we recommend you adjudicate in your phase 3 program based on the adverse event profile of your product are: hypovolemia, renal dysfunction, liver events, and CPK elevations.

Discussion: *The sponsor provided a verbal description regarding the patients that experienced CPK elevations in the phase 2 trial. The FDA asked that case reports with causality assessment be submitted for all cases of rhabdomyolysis which the sponsor agreed to provide following the meeting. The sponsor also confirmed that CPK will be collected systematically throughout the phase 3 program. If CPK elevation >10XULN is observed, this will be collected as an adverse events of special interest (AESI) and narratives will be generated. The sponsor also confirmed that the elevated CPK value will be confirmed with a second measurement. Acidosis and renal impairment will be adjudicated AESIs per FDA request.*

The sponsor requested further clarification on why the FDA is concerned regarding the possibility of liver events and hypovolemia events with oral semaglutide. The FDA clarified that the semaglutide/SNAC concentration in the portal circulation is unknown and that the FDA is concerned that it could potentially affect cellular respiration at the liver. The sponsor stated that the inhibition of the electron transport chain occurred at much higher concentrations in animal models than would be expected with the 300 mg of SNAC that will be incorporated into the proposed drug product, however the FDA stated that there remains concern. The FDA also asked whether lactate levels had been measured during the phase 1 and phase 2 studies. The sponsor confirmed that lactate levels were not obtained in the phase 2 trial, and agreed to evaluate lactate levels in 1-2 studies in the phase 3 program. The FDA recommended that this be done in trials which include a background of metformin. With regard to hypovolemia, the FDA is concerned given the known GI effects of GLP-1 inhibitors that patients using oral semaglutide may develop

hypovolemia. This is further increased by concerns for the GI tolerability of SNAC and would be a particular concern when used in combination with an SGLT2 inhibitor. Capture of these events should include events of hypotension and syncope as these are concerning clinical consequences.

Question 22: Does the Agency agree to the proposed immunogenicity assessment strategy?

FDA Response to Question 22: We cannot provide comment on your proposed immunogenicity assessment strategy at this time. We will provide comments in a separate communication at a later time.

Discussion: No discussion occurred.

Post-meeting Comments: The proposed immunogenicity assessment plan appears adequate, however the adequacy of the methods used has not been evaluated. In addition, note the following:

- a. We have not reviewed your assays. We recommend you submit SOPs and the assay development and validation reports of the immunogenicity assay/s including cut point determination for the assay to the agency prior to submission of your NDA. Until assays have been validated you should bank sera under appropriate conditions and in sufficient quantities to allow for re-testing if deemed necessary after review of the assays.
- b. You state that the sensitivity of your screening assay is (b) (4), please note that levels of antibodies as low as 100ng/ml have been associated with changes in PK.
- c. You state that “ (b) (4) ” The meaning of this is unclear. Confirm that all positive samples will be tested for crossreactivity with endogenous GLP-1 and neutralizing capacity.
- d. You state that “ (b) (4) ”. Note that the half-life of IgE is short (~2 days). Sampling for IgE should be conducted accordingly.

Question 23: Does the Agency agree that the requirement to establish the CV safety, at the time of NDA submission, as stated in the February 2008 guidance for Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes¹⁰, can be sufficiently covered by the planned phase 3 studies of oral semaglutide (b) (4) ?

FDA Response to Question 23: We do not have sufficient information to agree to this approach at this time. (b) (4)

You state that “the collective non-clinical and clinical evidence on SNAC from Emisphere and Novo Nordisk has not identified safety signals related to CV disease.” This information will need to be submitted for our consideration.

We recommend that you design your phase 3 program such that you will have sufficient data to rule out the pre-market risk margin of 1.8 described in the Guidance for Industry “Diabetes Mellitus — Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes” (<http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm071627.pdf>). Depending on the totality of data at that point, we will discuss the need for post-market risk evaluation.

Discussion: See discussion to question 5.

Question 24: Does the Agency agree that proposed trial (assuming data are supportive) will provide sufficient safety and efficacy data to support the approval of oral semaglutide for T2DM patients with moderate or severe renal impairment?

FDA Response to Question 24: You propose to enroll 440 patients with an eGFR of 15 – 59 ml/min/1.73m² for 26 weeks. We recommend that you stratify the enrollment by renal function category to assure that you have adequate representation across the moderate and severe renal impairment categories (e.g., eGFR of 15 – 29 ml/min/1.73m², 30 – 44 ml/min/1.73m², and 45 – 59 ml/min/1.73m²). We note that, based on the study synopsis, you do not propose a dose reduction in patients with renal impairment. Please clarify concerns, if any, regarding potential accumulation of SNAC metabolites in patients with renal impairment. Clarify how you will evaluate and mitigate these concerns, if any. As discussed in our response to Question 5, we would favor placebo for the comparator.

Discussion: The design of the renal impairment study was discussed at the meeting, specifically the choice of comparator. The FDA advised that using placebo as a comparator in this setting would be more helpful in understanding the safety profile of the drug in this patient population, as well as the true effect size in patients with renal impairment. In addition, since the true effect of (b) (4) in this patient population is not known, it would be difficult to design the study with an appropriate non inferiority margin.

Post-meeting comment: The sponsor submitted additional information following the meeting stating that they will remove (b) (4) arm and add a placebo arm in the renal impairment study. In addition, the sponsor has proposed only to include subjects

with moderate renal impairment (eGFR 30-59 ml/min/1.73m²) in the NN9924-4234 trial and suggested that stratification by eGFR is no longer needed.

The FDA is in agreement with replacing the (b) (4) arm with placebo. However, we continue to recommend enrollment stratification by eGFR in order to assure that sufficient numbers of patients at the lower end of the eGFR category will be enrolled in the study. We suggest that you enroll approximately 50% of the patients with eGFR 30 – 44 ml/min/1.73m², and approximately 50% with eGFR 45 – 59 ml/min/1.73m².

Question 25: *Does the Agency agree that proposed approach for evaluating the potential for drug-disease interaction (assuming data are supportive) will provide sufficient safety data to support the approval of oral semaglutide in patients with T2DM and gastrointestinal tract comorbidities?*

FDA Response to Question 25: *Your proposed approach to analyze the effect of upper gastrointestinal tract comorbidities on the systemic exposure of semaglutide through population pharmacokinetics in the phase 3 trials for oral semaglutide appears technically reasonable. We encourage you to submit the trial protocol and population pharmacokinetic analysis plan for our review before collecting the data. However, we are concerned that this proposed approach may not yield useful information to truly inform the use of oral semaglutide in this setting. These analyses will be limited by the quality of the baseline information entered by investigators. Upper gastrointestinal tract comorbidities are common in T2DM patients, and we recommend you to conduct dedicated trials to study the effect of the most common upper gastrointestinal tract comorbidities on the exposure of semaglutide in T2DM patients in addition to your proposed approach.*

Discussion: *The sponsor proposed to add a dedicated trial to assess the effect of upper GI comorbidities such as chronic gastritis and GERD on the exposure of semaglutide in T2DM patients. The FDA inquired about including patients with diabetic gastroparesis in the proposed PK trial. However, the sponsor did not see it necessary because they believe that absorption will be limited by the ingestion of food 30 minutes after the semaglutide administration. Therefore, absorption will only occur for 30 minutes regardless of the speed of gastric emptying.*

The sponsor also asserted that they will be able to quantitate semaglutide concentration in plasma samples for the dose they have chosen in the proposed PK trial.

Post-meeting Comment: *While you state that food will limit the absorption of oral semaglutide, we have concerns that most patients in real life will be unable to adhere to the recommended time between drug administration and ingestion of food. Because of this, an evaluation of changes in drug absorption in patients with diabetic gastroparesis may be valuable for future recommendations of clinical use. We also note that among the factors which can impact absorption is volume of co-ingested water. We suggest that you consider how this may impact your proposed studies as well as efficacy and safety in real-world use.*

Additional FDA Comments

Clinical:

1. Clarify whether SNAC is expected to have any glucose lowering effect at the proposed dose for your clinical program.

Discussion: No discussion occurred.

Post-meeting comment: The sponsor submitted additional information following the meeting and clarified that the glucose lowering effect of SNAC observed in animal studies is considered secondary to complex I inhibition seen at very high plasma concentrations, and that similar high plasma concentrations are considered achievable following administration of oral semaglutide (300 mg SNAC per tablet). In a 10 weeks multiple dose trial, two arms were dosed with either placebo or SNAC-placebo containing 300 mg SNAC alone. In the groups of subjects with T2DM there was no difference in the fasting plasma glucose (FPG) level either during the trial or at end of treatment (day 69). The change from baseline to end of treatment for FPG was 0.73 and 0.30 mmol/L (13 and 5 mg/dL) for SNAC-placebo and placebo, respectively in subjects with T2DM.

This additional information will need to be considered by the Agency. Additional comments may follow.

2. Clarify whether you anticipate that albumin level will have an impact on SNAC toxicity.

Discussion: No discussion occurred.

Post-meeting comment: The following information was received from the sponsor following the meeting: The clinical variation in plasma albumin concentration is considered to be within 2-fold, even taken severe hepatic impaired subjects into consideration. This variation will not impact the SNAC toxicity, taken the minor (<2 fold) effect on C_{max} (free) and the large animal-to-human exposure ratios into consideration. The study investigating the PK and PD of oral semaglutide in patients with liver impairment is under reporting. A post hoc analysis, found that, when all other explanatory variables in the statistical model were kept equal, a 10% decrease in serum albumin would result in that the fraction unbound of SNAC would increase by 15%. Based on our non-clinical data and the large animal-to-human exposure ratio this will not impact SNAC toxicity in humans at the clinical doses.

This additional information will need to be considered by the Agency. Additional comments may follow.

3. We may have additional comments regarding the proposed thorough QT study after the EOP2 meeting.

Discussion: *No discussion occurred.*

Nonclinical:

4. If any significant differences in the stability profiles of phase 3 batches are observed in comparison to phase 1 and phase 2 clinical batches, additional nonclinical studies may be required to qualify any differences in the impurity/degradant profile.

Discussion: *No discussion occurred.*

5. In your briefing package it was stated that carcinogenicity studies demonstrated that SNAC was not carcinogenic to the transgenic rasH2 mouse or the Sprague-Dawley rat. Please indicate when you plan to submit these study reports.

For general toxicology, supporting nonclinical toxicokinetic and carcinogenicity studies we encourage sponsors to both use Standards for the Exchange of Nonclinical Data (SEND) for regulatory submissions and to submit sample or test data sets before implementation becomes required. Sponsors will be provided feedback on the suitability of these test data sets. Information about submitting a test submission can be found here:

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm174459.htm>

Discussion: *No discussion occurred.*

Statistical:

6. Considerable efforts should be made to minimize missing data in your phase 3 clinical trials. Measurements on HbA1c at key time-points should be taken for all study subjects regardless of adherence to therapy or to the study protocol. A sizable amount of missing data will impact our confidence in study findings because missing data can induce bias and because assumptions about missing data cannot be verified. In addition, the statistical behavior of missing data is unlikely to be the same as the observed data since missing data tends to be associated with changes in adherence to randomized therapy.

The protocols for your phase 3 clinical trials should describe the procedures that will be in place to prevent missing data. We recommend that: (1) the protocols and informed consent forms clearly differentiate treatment discontinuation from study withdrawal; (2) the only reasons for study withdrawal are patient withdrawal of consent to contribute additional outcome information and loss to follow-up; (3) site investigators are trained about the importance of retention and steps to prevent missing data; (4) the consent forms include a statement educating patients about the continued scientific importance of their data even if

they discontinue study treatment early; and (5) several approaches are implemented to retain patients who fail to actively maintain contact with the investigator (e.g., telephone calls to friends or family members, e-mails, offers for transportation to the clinic, etc.).

Discussion: No discussion occurred.

- 7. Please clarify what is meant by the statement that the independent variables will be “all nested within visit” in the primary analysis.**

Discussion: No discussion occurred.

3.0 PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an 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 (EOP2) meeting. In the absence of an End-of-Phase 2 meeting, refer to the draft guidance below. The PSP 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 PSP 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 PSP, including a PSP 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 pdit@fda.hhs.gov. For further guidance on pediatric product development, please refer to: <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm>.

4.0 DATA STANDARDS FOR STUDIES

CDER strongly encourages IND sponsors to consider the implementation and use of data standards for the submission of applications for investigational new drugs and product registration. Such implementation should occur as early as possible in the product development

lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. CDER has produced a web page that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers. The web page may be found at:

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm>

5.0 LABORATORY TEST UNITS FOR CLINICAL TRIALS

CDER strongly encourages IND sponsors to identify the laboratory test units that will be reported in clinical trials that support applications for investigational new drugs and product registration. Although Système International (SI) units may be the standard reporting mechanism globally, dual reporting of a reasonable subset of laboratory tests in U.S. conventional units and SI units might be necessary to minimize conversion needs during review. Identification of units to be used for laboratory tests in clinical trials and solicitation of input from the review divisions should occur as early as possible in the development process. For more information, please see [CDER/CBER Position on Use of SI Units for Lab Tests](http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/ucm372553.htm) (<http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/ucm372553.htm>).

6.0 OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

The Office of Scientific Investigations (OSI) requests that the following items 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 field investigators who conduct those inspections (Item I and II). 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.

The dataset that is requested in Item III below is for use in a clinical site selection model that is being piloted in CDER. Electronic submission of the site level dataset is voluntary and is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process.

This request also provides instructions for where OSI requested items should be placed within an eCTD submission (Attachment 1, Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format).

I. Request for general study related information and comprehensive clinical investigator information (if items are provided elsewhere in submission, describe location or provide link to requested information).

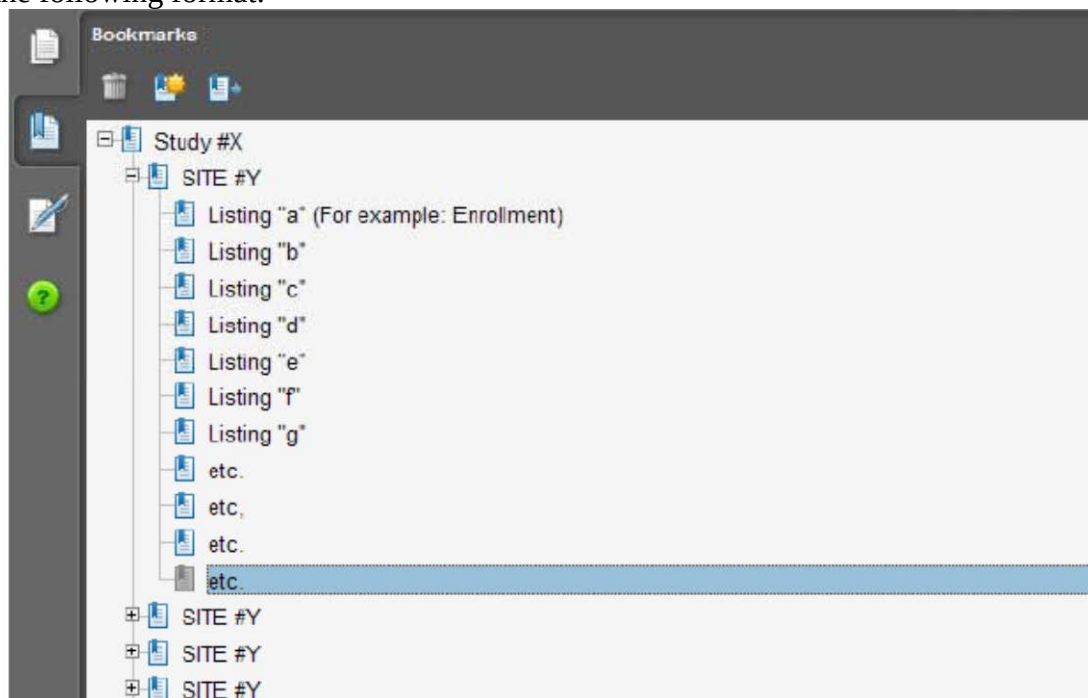
1. Please include the following information in a tabular format in the original NDA for each of the completed pivotal clinical trials:
 - a. Site number
 - b. Principal investigator

- c. Site Location: Address (e.g., Street, City, State, Country) and contact information (i.e., phone, fax, email)
 - d. Location of Principal Investigator: Address (e.g., Street, City, State, and Country) and contact information (i.e., phone, fax, email). If the Applicant is aware of changes to a clinical investigator's site address or contact information since the time of the clinical investigator's participation in the study, we request that this updated information also be provided.
2. Please include the following information in a tabular format, *by site*, in the original NDA for each of the completed pivotal clinical trials:
 - a. Number of subjects screened at each site
 - b. Number of subjects randomized at each site
 - c. Number of subjects treated who prematurely discontinued for each site by site
3. Please include the following information in a tabular format in the NDA for each of the completed pivotal clinical trials:
 - a. Location at which sponsor trial documentation is maintained (e.g., , monitoring plans and reports, training records, data management plans, drug accountability records, IND safety reports, or other sponsor records as described ICH E6, Section 8). This is the actual physical site(s) where documents are maintained and would be available for inspection
 - b. Name, address and contact information of all Contract Research Organization (CROs) used in the conduct of the clinical trials and brief statement of trial related functions transferred to them. If this information has been submitted in eCTD format previously (e.g., as an addendum to a Form FDA 1571, you may identify the location(s) and/or provide link(s) to information previously provided.
 - c. The location at which trial documentation and records generated by the CROs with respect to their roles and responsibilities in conduct of respective studies is maintained. As above, this is the actual physical site where documents would be available for inspection.
4. For each pivotal trial, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).
5. For each pivotal trial provide original protocol and all amendments ((or identify the location and/or provide a link if provided elsewhere in the submission).

II. Request for Subject Level Data Listings by Site

1. For each pivotal trial: Site-specific individual subject data listings (hereafter referred to as "line listings"). For each site, provide line listings for:
 - a. Listing for each subject consented/enrolled; for subjects who were not randomized to treatment and/or treated with study therapy, include reason not randomized and/or treated
 - b. Subject listing for treatment assignment (randomization)

- c. Listing of subjects that discontinued from study treatment and subjects that discontinued from the study completely (i.e., withdrew consent) with date and reason discontinued
 - d. Listing of per protocol subjects/ non-per protocol subjects and reason not per protocol
 - e. By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)
 - f. By subject listing, of AEs, SAEs, deaths and dates
 - g. By subject listing of protocol violations and/or deviations reported in the NDA, including a description of the deviation/violation
 - h. By subject listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint.
 - i. By subject listing of concomitant medications (as appropriate to the pivotal clinical trials)
 - j. By subject listing, of testing (e.g., laboratory, ECG) performed for safety monitoring
2. We request that one PDF file be created for each pivotal Phase 2 and Phase 3 study using the following format:



III. Request for Site Level Dataset:

OSI is piloting a risk based model for site selection. Voluntary electronic submission of site level datasets is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. If you wish to voluntarily provide a dataset, please refer to the draft “Guidance for Industry Providing Submissions in Electronic Format – Summary Level Clinical Site Data for CDER’s Inspection Planning” (available at the following link

<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf>) for the structure and format of this data set.

7.0 ISSUES REQUIRING FURTHER DISCUSSION

The agency will provide feedback on additional information submitted after the June 11, 2015 meeting. In addition, the agency may provide additional comments regarding the proposed thorough QT study.

8.0 ACTION ITEMS

Action Item/Description	Owner	Due Date
Novo Nordisk will provide case report form for patient with Rhabdomyolysis	Sponsor	TBD

9.0 ATTACHMENTS AND HANDOUTS

The attached slides were presented by Novo Nordisk at the meeting.

11 Page(s) have been Withheld in Full as B4 (CCI/TS) immediately following this page

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

/s/

JENNIFER R PIPPINS

07/10/2015

For Dr. Guettier