CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208583Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS
EXCLUSIVITY SUMMARY

NDA # 208583

Trade Name   Xultophy 100/3.6

Generic Name   insulin degludec and liraglutide injection

Applicant Name   Novo Nordisk, Inc.

Approval Date, If Known   11/21/16

PART I   IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

   a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?       YES ☒    NO ☐

   If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3, SE4, SE5, SE6, SE7, SE8 505(b)(1)

   b) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

       YES ☒    NO ☐

   If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

       N/A

   If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

       N/A
c) Did the applicant request exclusivity?  
   YES ❑  NO ☒

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?  
   N/A

d) Has pediatric exclusivity been granted for this Active Moiety?  
   YES ❑  NO ☒

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?  
   N/A

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?  
   YES ❑  NO ☒

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II  FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES  
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

   N/A  YES ❑  NO ☒

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).
2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES ☒ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #.(s).

NDA# 022341  Victoza (liraglutide) injection
NDA# 203314  Tresiba (insulin degludec injection)

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered “NO” for original approvals of new molecular entities.)
IF “YES,” GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the
answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES ☒ NO ☐

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES ☒ NO ☐

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

N/A

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES ☐ NO ☒

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES ☐ NO ☒

If yes, explain:

N/A

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?
If yes, explain:

N/A

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

NN9068-3951
NN9068-3912
NN9068-3952

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

NN9068-3951

NN9068-3912

NN9068-3952

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

N/A

b) For each investigation identified as "essential to the approval", does the investigation
duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

NN9068-3951  YES ☐  NO ✗

NN9068-3912  YES ☐  NO ✗

NN9068-3952  YES ☐  NO ✗

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

N/A

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

NN9068-3951
NN9068-3912
NN9068-3952

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

NN9068-3951  IND # 109121  YES ✗  NO ☐
Explain:

NN9068-3912  IND # 109121  YES ✗  NO ☐
(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

N/A

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES ☐ NO ☑

If yes, explain:

N/A

Name of person completing form: Marisa Petruccelli
Title: Regulatory Project Manager
Date: 11/18/16

Name of Office/Division Director signing form: Jean-Marc Guettier, M.D.
Title: Director, Division of Metabolism and Endocrinology Products

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MARISA PETRUCCELLI
11/22/2016

LISA B YANOFF
11/22/2016
# ACTION PACKAGE CHECKLIST

## APPLICATION INFORMATION

<table>
<thead>
<tr>
<th>NDA #</th>
<th>208583</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Proprietary Name:</strong></td>
<td>Xultophy 100/3.6</td>
</tr>
<tr>
<td><strong>Established/Proper Name:</strong></td>
<td>insulin degludec and liraglutide</td>
</tr>
<tr>
<td><strong>Dosage Form:</strong></td>
<td>injection</td>
</tr>
<tr>
<td><strong>Applicant:</strong></td>
<td>Novo Nordisk Inc.</td>
</tr>
<tr>
<td><strong>RPM:</strong></td>
<td>Marisa Petruccelli</td>
</tr>
<tr>
<td><strong>Division:</strong></td>
<td>Metabolism and Endocrinology Products</td>
</tr>
</tbody>
</table>

### NDA Application Type:
- ☒ 505(b)(1)
- ☐ 505(b)(2)

### Efficacy Supplement:
- ☐ 505(b)(1)
- ☐ 505(b)(2)

### BLA Application Type:
- ☐ 351(k)
- ☐ 351(a)

### For ALL 505(b)(2) applications, two months prior to EVERY action:
- Review the information in the 505(b)(2) Assessment and submit the draft to CDER OND IO for clearance.
- Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)
  - No changes
  - New patent/exclusivity (notify CDER OND IO)

### Note:
If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.

### Actions

- **Proposed action**
  - Action date: November 21, 2016
  - User Fee Goal Date is December 14, 2016

- **Previous actions (specify type and date for each action taken)**
  - None

### If accelerated approval or approval based on efficacy studies in animals, were promotional materials received?

Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see [link](http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf)). If not submitted, explain ______

### Application Characteristics

<table>
<thead>
<tr>
<th>AP</th>
<th>TA</th>
<th>CR</th>
</tr>
</thead>
<tbody>
<tr>
<td>☒</td>
<td>☐</td>
<td>☐</td>
</tr>
</tbody>
</table>

---

1 The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 2) lists the documents to be included in the Action Package.

2 For resubmissions, 505(b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).

3 Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA.
Review priority:  
- Standard
- Priority

Chemical classification (new NDAs only):  
Type 4 New Combination  
(Confirms the chemical classification at the time of approval)

- Fast Track
- Rolling Review
- Orphan drug designation
- Breakthrough Therapy designation

(Note: Set the submission property in DARTS and notify the CDER Breakthrough Therapy Program Manager.
Refer to the “RPM BT Checklist for Considerations after Designation Granted” for other required actions: CST SharePoint)

NDAs: Subpart H
- Accelerated approval (21 CFR 314.510)
- Restricted distribution (21 CFR 314.520)
- Approval based on animal studies

Subpart I
- Submitted in response to a PMR
- Submitted in response to a PMC
- Submitted in response to a Pediatric Written Request

BLAs: Subpart E
- Accelerated approval (21 CFR 601.41)
- Restricted distribution (21 CFR 601.42)
- Approval based on animal studies

REM:  
- MedGuide
- Communication Plan
- ETASU
- MedGuide w/o REMS
- REMS not required

Comments:

- BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (approvals only)
  - Yes
  - No
  - N/A

- Public communications (approvals only)
  - Office of Executive Programs (OEP) liaison has been notified of action
    - Yes
    - No

  - Indicate what types (if any) of information were issued

- Exclusivity
  - Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)?
    - No
    - Yes
    - N/A

- Patent Information (NDAs only)
  - Patent Information:
    - Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.
    - Verified
    - Not applicable because drug is an old antibiotic

CONTENTS OF ACTION PACKAGE

Officer/Employee List

- List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (approvals only)
  - Included

Documentation of consent/non-consent by officers/employees

- Included
### Action Letters

- Copies of all action letters *(including approval letter with final labeling)*
  - Action(s) and date(s): Approval 11/21/16

### Labeling

- **Package Insert** *(write submission/communication date at upper right of first page of PI)*
  - Most recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)*
    - Included
    - See attached approval letter
  - Original applicant-proposed labeling
    - Included
    - Submitted 9/14/16

- **Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling** *(write submission/communication date at upper right of first page of each piece)*
  - Most recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)*
    - Included
    - See attached approval letter
  - Original applicant-proposed labeling
    - Included
    - Submitted 9/14/16

- **Labels** *(full color carton and immediate-container labels)* *(write submission/communication date on upper right of first page of each submission)*
  - Most recent draft labeling
    - Included
    - See attached approval letter

- **Proprietary Name**
  - Acceptability/non-acceptability letter(s) *(indicate date(s))*
  - Review(s) *(indicate date(s))*
  - RPM: 11/02/2015
    - DMEPA: 11/02/2016, 9/28/16, 8/19/16, 7/13/16, 4/18/16
    - DMPP/PLT: ✗ 8/29/16
    - OPDP: ✗ 8/29/16
    - SEALD: None
    - CSS: None
    - Product Quality ✗ from 5/9/16
    - Integrated Quality Assessment Other: None
  - Updated name review: 9/20/16
  - Updated name conditionally acceptable: 9/22/16
  - Conditionally acceptable: 11/12/15
  - Review: 11/11/15

- **Labeling reviews** *(indicate dates of reviews)*

### Administrative / Regulatory Documents

- **RPM Filing Review***/Memo of Filing Meeting* *(indicate date of each review)*
  - 11-13-15

- **All NDA 505(b)(2) Actions** Date each action cleared by 505(b)(2) Clearance Committee
  - Not a (b)(2)

- **NDAs only: Exclusivity Summary** *(signed by Division Director)*
  - Included
| **Application Integrity Policy (AIP) Status and Related Documents**

[http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm](http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm) |
<table>
<thead>
<tr>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>• Applicant is on the AIP</td>
</tr>
<tr>
<td>• This application is on the AIP</td>
</tr>
<tr>
<td>o If yes, Center Director’s Exception for Review memo <em>(indicate date)</em></td>
</tr>
<tr>
<td>o If yes, OC clearance for approval <em>(indicate date of clearance communication)</em></td>
</tr>
<tr>
<td>• Not an AP action</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Pediatrics (approvals only)</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>• Date reviewed by PeRC  8/10/16</td>
</tr>
<tr>
<td>If PeRC review not necessary, explain:</td>
</tr>
</tbody>
</table>

| **Breakthrough Therapy Designation** | ☒ N/A |
| --- |
| • Breakthrough Therapy Designation Letter(s) (granted, denied, an/or rescinded) |  |
| • CDER Medical Policy Council Breakthrough Therapy Designation Determination Review Template(s) *(include only the completed template(s) and not the meeting minutes)* |  |
| • CDER Medical Policy Council Brief – Evaluating a Breakthrough Therapy Designation for Recission Template(s) *(include only the completed template(s) and not the meeting minutes)* *(completed CDER MPC templates can be found in DARRTS as clinical reviews or on the MPC SharePoint Site)* |  |

| **Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, Formal Dispute Resolution Request decisional letters, etc.) *(do not include OPDP letters regarding pre-launch promotional materials as these are non-disclosable; do not include previous action letters, as these are located elsewhere in package)*** | ☒ Included |

| **Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes)** | ☒ Included |

<table>
<thead>
<tr>
<th><strong>Minutes of Meetings</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>• If not the first review cycle, any end-of-review meeting <em>(indicate date of mtg)</em></td>
</tr>
<tr>
<td>• Pre-NDA/BLA meeting <em>(indicate date of mtg)</em></td>
</tr>
<tr>
<td>• EOP2 meeting <em>(indicate date of mtg)</em></td>
</tr>
<tr>
<td>• Mid-cycle Communication <em>(indicate date of mtg)</em></td>
</tr>
<tr>
<td>• Late-cycle Meeting <em>(indicate date of mtg)</em></td>
</tr>
<tr>
<td>• Other milestone meetings (e.g., EOP2a, CMC focused milestone meetings) <em>(indicate dates of mtgs)</em></td>
</tr>
</tbody>
</table>

---

4 Filing reviews for scientific disciplines are NOT required to be included in the action package.
Advisory Committee Meeting(s) | Summary Minutes included
--- | ---
Date(s) of Meeting(s) | 5/24/16 AC held

### Decisional and Summary Memos

Office Director Decisional Memo *(indicate date for each review)* | None | not an NME
Division Director Summary Review *(indicate date for each review)* | See CDTL Review
Cross-Discipline Team Leader Review *(indicate date for each review)* | 11/21/16
PMR/PMC Development Templates *(indicate total number)* | None

### Clinical

Clinical Reviews

- Clinical Team Leader Review(s) *(indicate date for each review)* | No separate review
- Clinical review(s) *(indicate date for each review)* | 11/21/16, 11/13/2015
- Social scientist review(s) *(if OTC drug)* *(indicate date for each review)* | None

Financial Disclosure reviews(s) or location/date if addressed in another review OR
If no financial disclosure information was required, check here □ and include a review/memo explaining why not *(indicate date of review/memo)*

Clinical reviews from immunology and other clinical areas/divisions/Centers *(indicate date of each review)*

Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)* | N/A

Risk Management

- REMS Documents and REMS Supporting Document *(indicate date(s) of submission(s))* | 11/15/16, 11/2/16, 9/30/16
- REMS Memo(s) and letter(s) *(indicate date(s))* | 11/21/16
- Risk management review(s) and recommendations *(including those by OSE and CSS)* *(indicate date of each review and indicate location/date if incorporated into another review)* | 11/21/16, 8/28/16, 7/14/16

OSI Clinical Inspection Review Summary(ies) *(include copies of OSI letters to investigators)* | 5/26/16

### Clinical Microbiology

- None
- Clinical Microbiology Team Leader Review(s) *(indicate date for each review)* | N/A
- Clinical Microbiology Review(s) *(indicate date for each review)* | N/A

### Biostatistics

- Statistical Division Director Review(s) *(indicate date for each review)* | No separate review
- Statistical Team Leader Review(s) *(indicate date for each review)* | No separate review
- Statistical Review(s) *(indicate date for each review)* | 6/15/16, 11/02/2015

Reference ID: 4030450
<table>
<thead>
<tr>
<th>Clinical Pharmacology</th>
<th>None</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical Pharmacology Division Director Review(s) <em>indicate date for each review</em></td>
<td>None</td>
</tr>
<tr>
<td>Clinical Pharmacology Team Leader Review(s) <em>indicate date for each review</em></td>
<td>None</td>
</tr>
<tr>
<td>Clinical Pharmacology review(s) <em>indicate date for each review</em></td>
<td>6/17/16, 11/06/2015</td>
</tr>
<tr>
<td>OSI Clinical Pharmacology Inspection Review Summary <em>include copies of OSI letters</em></td>
<td>8/2/16, 1/21/16, 12/22/15</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Nonclinical</th>
<th>None</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pharmacology/Toxicology Discipline Reviews</td>
<td></td>
</tr>
<tr>
<td>ADP/T Review(s) <em>indicate date for each review</em></td>
<td>None</td>
</tr>
<tr>
<td>Supervisory Review(s) <em>indicate date for each review</em></td>
<td>None</td>
</tr>
<tr>
<td>Pharm/tox review(s), including referenced IND reviews <em>indicate date for each review</em></td>
<td>5/12/16, 10/27/2015</td>
</tr>
<tr>
<td>Review(s) by other disciplines/divisions/Centers requested by P/T reviewer <em>indicate date for each review</em></td>
<td>None</td>
</tr>
<tr>
<td>Statistical review(s) of carcinogenicity studies <em>indicate date for each review</em></td>
<td>None</td>
</tr>
<tr>
<td>ECAC/CAC report/memo of meeting</td>
<td>None</td>
</tr>
<tr>
<td>OSI Nonclinical Inspection Review Summary <em>include copies of OSI letters</em></td>
<td>None requested</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Product Quality</th>
<th>None</th>
</tr>
</thead>
<tbody>
<tr>
<td>Product Quality Discipline Reviews</td>
<td></td>
</tr>
<tr>
<td>Tertiary review <em>indicate date for each review</em></td>
<td>None</td>
</tr>
<tr>
<td>Secondary review (e.g., Branch Chief) <em>indicate date for each review</em></td>
<td>None</td>
</tr>
<tr>
<td>Integrated Quality Assessment (contains the Executive Summary and the primary reviews from each product quality review discipline) <em>indicate date for each review</em></td>
<td>5/9/16</td>
</tr>
<tr>
<td>Reviews by other disciplines/divisions/Centers requested by product quality review team <em>indicate date of each review</em></td>
<td>CDRH Compliance 2/25/16</td>
</tr>
<tr>
<td>Environmental Assessment (check one) (original and supplemental applications)</td>
<td>5/9/16 on page 37 of Integrated Quality Assessment</td>
</tr>
<tr>
<td>Categorical Exclusion <em>indicate review date</em>(all original applications and all efficacy supplements that could increase the patient population)</td>
<td></td>
</tr>
<tr>
<td>Review &amp; FONSSI <em>indicate date of review</em></td>
<td></td>
</tr>
<tr>
<td>Review &amp; Environmental Impact Statement <em>indicate date of each review</em></td>
<td></td>
</tr>
<tr>
<td>Facilities Review/Inspection</td>
<td>Acceptable</td>
</tr>
<tr>
<td>Facilities inspections <em>action must be taken prior to the re-evaluation date</em> (only original applications and efficacy supplements that require a manufacturing facility inspection (e.g., new strength, manufacturing process, or manufacturing site change)</td>
<td></td>
</tr>
<tr>
<td>Acceptable Re-evaluation date:</td>
<td></td>
</tr>
<tr>
<td>Withhold recommendation</td>
<td></td>
</tr>
<tr>
<td>Not applicable</td>
<td></td>
</tr>
<tr>
<td>Day of Approval Activities</td>
<td>Status</td>
</tr>
<tr>
<td>-------------------------------------------------------------------------------------------</td>
<td>--------------</td>
</tr>
<tr>
<td>❖ For all 505(b)(2) applications:</td>
<td>No changes</td>
</tr>
<tr>
<td>• Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)</td>
<td>New patent/exclusivity (Notify CDER OND IO)</td>
</tr>
<tr>
<td>❖ Finalize 505(b)(2) assessment</td>
<td>Done</td>
</tr>
<tr>
<td>❖ For Breakthrough Therapy (BT) Designated drugs:</td>
<td>Done</td>
</tr>
<tr>
<td>• Notify the CDER BT Program Manager</td>
<td>Send email to CDER OND IO</td>
</tr>
<tr>
<td>❖ For products that need to be added to the flush list (generally opioids): Flush List</td>
<td>Done</td>
</tr>
<tr>
<td>• Notify the Division of Online Communications, Office of Communications</td>
<td></td>
</tr>
<tr>
<td>❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email</td>
<td>Done</td>
</tr>
<tr>
<td>❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter</td>
<td>Done</td>
</tr>
<tr>
<td>❖ Ensure that proprietary name, if any, and established name are listed in the Application Product Names section of DARRTS, and that the proprietary name is identified as the “preferred” name</td>
<td>Done</td>
</tr>
<tr>
<td>❖ Ensure Pediatric Record is accurate</td>
<td>Done</td>
</tr>
<tr>
<td>❖ Send approval email within one business day to CDER-APPROVALS</td>
<td>Done</td>
</tr>
</tbody>
</table>
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MARISA PETRUCCELLI
12/19/2016
Good morning,

I have a request regarding the Xultophy REMS: please update the name of the REMS program to “Xultophy 100/3.6 REMS: Risk Evaluation and Mitigation Strategy” on the first slide on the Xultophy 100/3.6 REMS presentation. All other changes to the REMS materials are acceptable. Please make this update and resubmit all REMS materials to the NDA.

Please let me know if there are any questions.

Thank you,

Marisa

---

Marisa Petruccelli
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
Office of Drug Evaluation II
U.S. Food and Drug Administration
Tel: 240-402-6147
Marisa.Petruccelli@fda.hhs.gov

U.S. FOOD & DRUG ADMINISTRATION

Reference ID: 4006929
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MARISA PETRUCCELLI
11/01/2016
NDA 208583

Novo Nordisk Inc.
800 Scudders Mill Road
Plainsboro, NJ 08536

ATTENTION: Rick Spring
Associate Director, Regulatory Affairs

Dear Mr. Spring:

Please refer to your New Drug Application (NDA) dated September 14, 2015, received September 14, 2015, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Insulin Degludec and Liraglutide Injection, 100 units insulin degludec and 3.6 mg liraglutide per mL.

We also refer to your September 6, 2016, correspondence, received September 6, 2016, requesting review of your proposed proprietary name, Xultophy 100/3.6.

We have completed our review of the proposed proprietary name, Xultophy 100/3.6 and have concluded that it is conditionally acceptable.

If any of the proposed product characteristics as stated in your above submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review. Additionally, if your application receives a complete response, a new request for name review for your proposed name should be submitted when you respond to the application deficiencies.

If you require information on submitting requests for proprietary name review or PDUFA performance goals associated with proprietary name reviews, we refer you to the following:

- Guidance for Industry Contents of a Complete Submission for the Evaluation of Proprietary Names 
- PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2013 through 2017, 
  (http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM270412.pdf)
If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Terrolyn Thomas, MS, MBA, Senior Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at 240-402-3981. For any other information regarding this application, contact Marisa Petruccelli, Regulatory Project Manager in the Office of New Drugs, at 240-402-6147.

Sincerely,

See appended electronic signature page

Todd Bridges, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

LUBNA A MERCHANT on behalf of TODD D BRIDGES
09/22/2016
MEMORANDUM OF TELECONFERENCE

Teleconference Date: September 1, 2016

Application Number: NDA 208583
Product Name: Xultophy (insulin degludec and liraglutide) injection
Sponsor/Applicant Name: Novo Nordisk, Inc.

Subject: Update on review timeline

FDA Participants
Marisa Petruccelli, DMEP
Tania Condarco, MD, DMEP
Lisa Yanoff, MD, DMEP

Applicant Participants
Anne Phillips - SVP, Clinical Development, Medical Affairs, Regulatory Affairs
Michelle Thompson – Senior Director, Regulatory Affairs
Marianne Bork Samuelsen - RA Director
Finn Møllgaard - Regulatory Corporate Vice President
Christian Foged - Project Vice President
Martin Holst Lange - Corporate Project Vice President
Todd Hobbs - Vice President, Chief Medical Officer North America
Rick Spring - Associate Director, Regulatory Affairs
Aditi Bhobe - Associate Manager, Regulatory Affairs
Irene Langebakke, International Medical Director

1.0 BACKGROUND:

FDA arranged a teleconference to explain that a clock extension would be applied to the NDA 208583 review timeline citing the August 24, 2016 submission as a major amendment.

2.0 DISCUSSION:

FDA explained that the pen dial redesign proposal included in the August 24, 2016, submission would require review and discussion across multiple divisions and that not enough time remains in this review cycle to allow for that. FDA also explained that more time was needed to consider the proprietary name and possible modifiers or alternatives that would express that there are two components to this product. FDA welcomed Novo Nordisk to consider possible alternatives, evaluate them, and share their findings with FDA, but clarified that this was not required, as FDA will be determining its own preference concurrently.

FDA also added that more time will be needed to finalize labeling, because it will depend on the pen dial redesign and proprietary name decisions.
3.0 ACTION ITEMS:
FDA will issue a formal major amendment extension letter.
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MARISA PETRUCCELLI
09/07/2016
Good afternoon,

After further internal discussion, we have determined that a numerical modifier is FDA’s preferred approach for the proprietary name for your product. We recommend the following: Xultophy 100/3.6

We request that you submit a new request for proprietary name for our review, or that you submit an alternative approach and explain why you do not agree with our recommendation.

Please let me know if you have any questions.

Thank you,

Marisa Petruccelli
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Phone: 240-402-6147
Fax: 301-796-9712
marisa.petruccelli@fda.hhs.gov
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MARISA PETRUCCELLI
09/02/2016
NDA 208583

Novo Nordisk Inc.
Attention: Robert B. Clark
Vice President, Regulatory Affairs
800 Scudders Mill Road
Plainsboro, NJ 08536

Dear Mr. Clark:

Please refer to your New Drug Application (NDA) dated September 12, 2015, received September 14, 2015, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for insulin degludec and liraglutide injection.

On August 24, 2016, we received your major amendment to this application. Therefore, we are extending the goal date by three months to provide time for a full review of the submission. The extended user fee goal date is December 14, 2016.

In addition, we are establishing a new timeline for communicating labeling changes and/or postmarketing requirements/commitments in accordance with “PDUFA REAUTHORIZATION PERFORMANCE GOALS AND PROCEDURES – FISCAL YEARS 2013 THROUGH 2017.” If major deficiencies are not identified during our review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by November 14, 2016.

If you have any questions, call Marisa Petruccelli, Regulatory Project Manager, at (240) 402-6147.

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

Reference ID: 3981336
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JEAN-MARC P GUETTIER
09/02/2016
Good morning,

Please refer to your August 25, 2016, REMS submission to NDA 208583. Following are comments regarding the Xultophy REMS Document, REMS materials and REMS Supporting Document:

Line numbering must be removed from the final version of the REMS Document. The Agency will fill in the date of approval in the final approved version of the REMS. In addition, line numbering must be removed from the final version of all the REMS materials (letters, factsheet, and REMS Supporting Document). Please submit final, clean versions of all REMS materials.

Thank you,
Marisa

Marisa Petruccelli
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Phone: 240-402-6147
Fax: 301-796-9712
marisa.petruccelli@fda.hhs.gov
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MARISA PETRUCCCELLI
08/29/2016
Hi Rick,

Because the statement has been deleted from the current version of the draft label, this statement should also be deleted from all REMS documents to maintain consistency with the label.

Thank you,
Marisa

From: RSPR (Rick Spring) [mailto:rspr@novonordisk.com]
Sent: Tuesday, August 23, 2016 2:24 PM
To: Petrucci, Marisa
Subject: RE: NDA 208583 Xultophy REMS and updated PI - Follow up question

Marisa,

I wanted to check with you on the one statement. Please see chronology below.

Chronology:

**June 17, 2016** – FDA Comment received of the PI -

*FDA Comment: This statement is not acceptable. The IDegLira program had an abbreviated safety program because it is a combination of two already approved drugs. The Xultophy label must include all important safety information for both liraglutide and insulin degludec.*

- **July 6, 2016** – NN submitted an updated PI agreeing to FDA’s comment above and deleted the text

**July 19, 2016** (General Advice Letter) – FDA recommended deletion of the statement

- **July 29, 2016** – NN Submitted updated REMS materials wherein the statement was deleted from ALL the REMS materials which included it, to align with the updated PI as well as the General Advice Letter dated July 19, 2016
August 23, 2016 – Received comments from the FDA for the REMS material to re-insert the statement except wherein the Agency has requested that we delete it.

- To doublecheck before implementing, should we re-insert the statement and delete it everywhere.

OK should we delete the statement.

If you have any questions, please let me know. Thank you.

Rick

From: Petruccelli, Marisa [mailto:Marisa.Petruccelli@fda.hhs.gov]
Sent: Tuesday, August 23, 2016 10:17 AM
To: RSPR (Rick Spring)
Subject: FW: NDA 208583 Xultophy REMS and updated PI

Rick,

Attached and below are draft comments for review during our tcon:

Draft FDA’s Comments to NN:

1. **PI** – no changes required for the PI.
2. **REMS Document**: FDA concurs with the changes you proposed on the REMS Document and REMS Supporting Document included in your submission received by the Agency on May 6, 2016.
   - REMS Supporting Document – FDA accepts the revisions submitted on May 6, 2016. Additional changes to the REMS Supporting Document as per #3 and #4 below.

3. **REMS Supporting Document**: Revise REMS Supporting Document to reflect requested changes to the REMS message map for healthcare providers (see Table 1 below) and REMS materials.
   - REMS Supporting Document
     - Replace the REMS Message Map in the REMS Supporting Document with Table 1 included in FDA’s comments from July 19, 2016.
     - See comments in REMS Supporting document.
   - REMS Assessment Plan – revise as in FDA’s comments from July 19, 2016.

4. **REMS materials**:
   - REMS Letter for Healthcare Providers – see attached documents in track changes
5. REMS Assessment Surveys
   - Survey questions should focus on the messages included in the REMS Message Map.
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MARISA PETRUCELLI
08/24/2016
MEMORANDUM OF TELECONFERENCE

Teleconference Date: August 23, 2016

Application Number: NDA 208583
Product Name: Xultophy (insulin degludec and liraglutide) injection
Sponsor/Applicant Name: Novo Nordisk, Inc.

Subject: Teleconference to clarify FDA REMS comments

FDA Participants
Marisa Petruccelli, DMEP
Elisabeth Hanan, DMEP
Cynthia LaCivita, DRISK
Amarilys Vega, DRISK
Mei-Yean Chen, DRISK

Sponsor/Applicant Participants
Rick Spring, Regulatory Affairs
Michelle Thompson, Regulatory Affairs
Bob Clarke, Regulatory Affairs

1.0 BACKGROUND:

FDA provided comments on the NDA 208583 REMS on July 19, 2016, and Novo Nordisk responded by submitting updated REMS materials on July 29, 2016. In response to this update, FDA provided additional comments on August 17, 2016. Novo Nordisk saw discrepancies between the July 19 and August 17 comments and this teleconference was scheduled to provide clarification.

2.0 DISCUSSION:

FDA reiterated that the comments and revisions to the REMS materials are not intended to change the Prescribing Information (PI). FDA explained that the REMS message map is intended to highlight key messages of the REMS. The message map was revised to remove some messages that are not necessary to test in the REMS assessment; however, these messages are to be kept elsewhere in the materials for context.

During the teleconference, FDA sent a response email to Novo Nordisk along with draft comments on the REMS materials (attached below). During the teleconference FDA walked through the draft comments with Novo Nordisk and clarified any questions.

3.0 ACTION ITEMS:
Novo Nordisk agreed to resubmit a clean and track changes version of the materials on or before August 26, 2016.

Reference ID: 3976048
From: Petruccelli, Marisa
To: "RSPR (Rick Spring)"
Subject: FW: NDA 208583 Xultophy REMS and updated PI
Date: Tuesday, August 23, 2016 10:17:00 AM
Attachments: REMS Slides (tracked)FDARevised 8 23 2016.pdf
   remsfactsheet-tracked FDARevised 8 23 2016.docx
   rems-letter-hcp-trackedFDA Revised 8 23 2016.doc
   rems-letter-prof-soc-trackedFDARevised 8 23 2016.doc
   rems-website-tracked FDARevised 8 23 2016.docx
   proposed-rems-support-trackedFDARevised 8 23 2016.doc

Rick,

Attached and below are draft comments for review during our tcon:

Draft FDA’s Comments to NN:

1. **PI** – no changes required for the PI.
2. **REMS Document**: FDA concurs with the changes you proposed on the REMS Document and REMS Supporting Document included in your submission received by the Agency on May 6, 2016.
   - REMS Supporting Document – FDA accepts the revisions submitted on May 6, 2016. Additional changes to the REMS Supporting Document as per #3 and #4 below.

3. **REMS Supporting Document**: Revise REMS Supporting Document to reflect requested changes to the REMS message map for healthcare providers (see Table 1 below) and REMS materials.
   - REMS Supporting Document
     - Replace the REMS Message Map in the REMS Supporting Document with Table 1 included in FDA’s comments from July 19, 2016.
     - See comments in REMS Supporting document.
   - REMS Assessment Plan – revise as in FDA’s comments from July 19, 2016.

4. **REMS materials**:
   - REMS Letter for Healthcare Providers – see attached documents in track changes
   - REMS Letter for Professional Societies – see attached documents in track changes
   - REMS Factsheet – see attached documents in track changes
   - REMS Slides – see attached documents in track changes
   - REMS Website – see attached documents in track changes

5. **REMS Assessment Surveys**
   - Survey questions should focus on the messages included in the REMS Message Map.

30 Page(s) has 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/

MARISA PETRUCCELLI
08/23/2016
Good morning,

We have reviewed your August 16, 2016, response to the inquiry below. In light of the revised indication, the recommended starting dose should be 16 units. It would be acceptable to redesign the Pen to display units starting at 10 so that clinical discretion can be used in the case of illness or other conditions necessitating a dose reduction.

Please confirm receipt of this email and let me know if you have any questions.

Thank you,

Marisa

Marisa Petruccelli
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Phone: 240-402-6147
Fax: 301-796-9712
marisa.petruccelli@fda.hhs.gov
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MARISA PETRUCCELLI
08/18/2016
Good afternoon,

We have a request regarding NDA 208583: 
We would recommend that the pen dial be revised

Ideally, your dial could be configured in a way that would mechanically provide for administration of volumes necessary to prime the pen. We would be interested in understanding the feasibility of these design approaches.

Please confirm receipt of this request and provide a timeframe for response.

Thank you,
Marisa

Marisa Petruccelli
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Phone: 240-402-6147
Fax: 301-796-9712
marisa.petruccelli@fda.hhs.gov
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MARISA PETRUCCELLI
08/10/2016
Good morning,

Please refer to your July 29, 2016, submission containing updated REMS materials and a revised PI for NDA 208583.

In your submission, you asked for clarification on the Agency’s rationale for the deletion of the ‘human relevance of liraglutide-induced rodent thyroid C-cell tumors’ text. We have reviewed your question, and have determined that the following text, “It is unknown whether XULTOPHY* thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans, as human relevance of liraglutide-induced rodent thyroid C-cell tumors determined.” should be kept as it aligns with labeling, particularly in the boxed warning.

Please update the materials you provided in your July 29 submission to account for this change.

Please let me know if you have any questions.

Thank you,

Marisa

Marisa Petruccelli
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Phone: 240-402-6147
Fax: 301-796-9712
marisa.petruccelli@fda.hhs.gov

Reference ID: 3969742
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MARISA PETRUCCELLI
08/09/2016
Good morning,

We have reviewed the document entitled: “Novo Nordisk Response to FDA information Request dated 14 June 2016, PLLR Compliance, Pharmacovigilance Database Information for Liraglutide” that was submitted to NDA 208583, insulin degludec/liraglutide on June 28, 2016, and have some clarifying questions. Please address the following issues by COB Monday August 8, 2016:

- The descriptions of the fetal defects do not match those noted in Table 1. Identify each defect described and its corresponding notation in Table 1. Also, for each fetal defect noted in Table 1, identify its description. The descriptions and fetal defects tabulated do not match.
- Both Trisomy 21 and cytogenetic abnormalities are described in the IR response. Please assure that each genetic abnormality is described and that Trisomy 21 is not counted twice.

Please confirm receipt of this request and let me know if there are any questions.

Thank you,
Marisa

Marisa Petruccelli
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Phone:  240-402-6147
Fax:  301-796-9712
marisa.petruccelli@fda.hhs.gov
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MARISA PETRUCCELLI
08/03/2016
Hi Rick,

To clarify, the approach that we are suggesting for studies 3951 and 3912 assumes that patients who withdraw from the experimental arm were on the control (rather than the experimental) treatment from baseline. Assuming that patients who stop taking IDegLira will lose any benefit that may have been observed, and thus will have 6-month HbA1c measurements consistent to those in the control group with similar baseline HbA1c. Therefore, we would like an approach involving multiple imputations based on a model for 6-month HbA1c from control group data with baseline HbA1c as a covariate and where the intermediate measurements of HbA1c are ignored.

Please let me know if you have any additional questions.

Thank you,

Marisa

From: RSPR (Rick Spring) [mailto:rspr@novonordisk.com]
Sent: Monday, August 01, 2016 12:27 PM
To: Petruccelli, Marisa
Subject: RE: NDA 208583 Follow-up comments/request - Novo Nordisk Confirmation (Clarifying Question to Statistics Information Request)

Marisa,

Hi! Per my voicemail, Novo Nordisk has a clarifying question regarding the Statistical Information Request received on July 29th.

- Could the Agency confirm that the “jump-to-control” method referred to in the FDA follow-up comments would correspond to the “copy reference” method in the NDA?

As discussed previously in February with the Agency, Novo Nordisk would like to again note that the method referenced as “copy reference” in the NDA (2.7.3 Appendix 6.2) corresponds to the “jump-to-reference” method described by Carpenter\(^1\) except that it does not take into account the subjects differentness in observed outcome relative to the subjects own treatment group. The “copy reference” method referred to in the NDA is a pattern mixture model based on a sequential regression methodology as described in O'Kelly et al.\(^2\) mimicking an intention-to-treat scenario where withdrawn IDegLira patients were assumed to have been treated with the comparator treatment throughout the trial. This method’s assumption was that the treatment effect of IDegLira ceased immediately after trial withdrawal. To simulate the immediate cessation of treatment effect after withdrawal, patients in the IDegLira arm were assumed to have the same mean response as the patients treated with the comparator throughout the trial. Patients who withdrew from the comparator group were assumed to have remained on their assigned treatment during the entire treatment period.

Therefore, Novo Nordisk would like to be clear that the Agency is requesting for studies B (3951) and D (3912) (as identified in the product label) the results from Novo Nordisk’s “copy reference” analysis in the NDA in place of the “jump to reference” analyses of the NDA that appear in the PI submitted on July 6, 2016.

Reference ID: 3967014
If you have any further questions or would like to discuss briefly with our statisticians, please let me know. You can also reach my on my cell (609-987-5046) if I’m not in my office (609-987-5046). Thank you.

Rick


2: Clinical Trials with Missing Data – A guide for practitioners. Michael O’Kelly and Bohdana Ratich. Wiley

From: RSPR (Rick Spring)
Sent: Friday, July 29, 2016 3:50 PM
To: Petruccelli, Marisa
Subject: RE: NDA 208583 Follow-up comments/request - Novo Nordisk Confirmation

Marisa,

Hi! I confirm receipt of the email. I’ll let you know if the team has any questions. Have a great weekend! Thank you.

Rick

From: Petruccelli, Marisa [mailto:Marisa.Petruccelli@fda.hhs.gov]
Sent: Friday, July 29, 2016 3:31 PM
To: RSPR (Rick Spring)
Subject: NDA 208583 Follow-up comments/request

Good afternoon,

Please refer to the updated PI and labeling history submitted to NDA 208583 on July 6, 2016.

In reference to your statement in 1.1.6 of the labeling history, “Specifically, withdrawn IDegLira subjects are assumed to have the same conditional mean as the comparator arm conditional on the previous levels of the endpoint and other covariates,” we have the following comments:

Frequently for products that affect blood glucose, the effect is seen by 3 months with further product use maintaining that effect. Therefore, regardless of which treatment arm is solely used for a model, the conditional mean for 6 months will be approximately the 3-month value.

Also, if discontinuing IDegLira means that subjects will be given one product as a substitute for IDegLira, there may be a washout of some or all of the IDegLira effect. We believe that this should be considered when addressing missing data and that it is not considered by your proposed reference-based analysis. For studies B (3951) and D (3912) (as identified in the product label), we want to include in the product label the results from the “jump-to-control” analysis. We are recommending this approach for those studies because we think that it is very plausible that subjects, who discontinue IDegLira in those settings, will get to the control therapy.

Reference ID: 3967014
For the studies A (3697), C (3851), and E (3952) (as identified in the product label), we want results from a “return to baseline” analysis included in the product label. The “return to baseline” analysis would have the 6-month HbA1c measurement equal to the baseline value plus an error (the error standard deviation could equal the residual standard deviation from your primary analysis).

For the percentage of patients achieving $\text{HbA}_{1c} < 7\%$ (or $\leq 6.5\%$), these should be percentage known to have achieved $\text{HbA}_{1c} < 7\%$ (or $\leq 6.5\%$). Subjects with missing data for this endpoint should be included in the denominator, but not the numerator.

To improve reproducibility of your findings, please provide all SAS codes that were used to produce your results. All codes should have clarifying comments.

Please confirm receipt of these comments and provide a response within one week, if possible.

Thank you,
Marisa

**Marisa Petruccelli**
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Phone: 240-402-6147
Fax: 301-796-9712
marisa.petruccelli@fda.hhs.gov
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MARISA PETRUCCELLI
08/02/2016
Good afternoon,

Please refer to the updated PI and labeling history submitted to NDA 208583 on July 6, 2016.

In reference to your statement in 1.1.6 of the labeling history, “Specifically, withdrawn IDegLira subjects are assumed to have the same conditional mean as the comparator arm conditional on the previous levels of the endpoint and other covariates,” we have the following comments:

Frequently for products that affect blood glucose, the effect is seen by 3 months with further product use maintaining that effect. Therefore, regardless of which treatment arm is solely used for a model, the conditional mean for 6 months will be approximately the 3-month value.

Also, if discontinuing IDegLira means that subjects will be given one product as a substitute for IDegLira, there may be a washout of some or all of the IDegLira effect. We believe that this should be considered when addressing missing data and that it is not considered by your proposed reference-based analysis. For studies B (3951) and D (3912) (as identified in the product label), we want to include in the product label the results from the “jump-to-control” analysis. We are recommending this approach for those studies because we think that it is very plausible that subjects, who discontinue IDegLira in those settings, will get to the control therapy.

For the studies A (3697), C (3851), and E (3952) (as identified in the product label), we want results from a “return to baseline” analysis included in the product label. The “return to baseline” analysis would have the 6-month HbA1c measurement equal to the baseline value plus an error (the error standard deviation could equal the residual standard deviation from your primary analysis).

For the percentage of patients achieving HbA1c < 7% (or ≤ 6.5%), these should be percentage known to have achieved HbA1c < 7% (or ≤ 6.5%). Subjects with missing data for this endpoint should be included in the denominator, but not the numerator.

To improve reproducibility of your findings, please provide all SAS codes that were used to produce your results. All codes should have clarifying comments.

Please confirm receipt of these comments and provide a response within one week, if possible.

Thank you,

Marisa

Marisa Petruccelli
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MARISA PETRUCCELLI
07/29/2016
Good morning,

In follow up to our phone conversation earlier this week in which you asked for clarification on our July 19 REMS comments for NDA 208583: You are correct in your assessment that the requested changes will result in differences between the Xultophy REMS as compared to the Victoza and Saxenda REMS. The next REMS modifications to the Saxenda and Victoza REMS should include changes to bring them into alignment with Xultophy.

Thank you,
Marisa

Marisa Petruccelli
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Phone: 240-402-6147
Fax: 301-796-9712
marisa.petruccelli@fda.hhs.gov
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MARISA PETRUCCELLI
07/22/2016
Pediatric Research Equity Act (PREA) Waiver Request, Deferral Request/Pediatric Plan and Assessment Template(s)

**BACKGROUND**

Please check all that apply: 
- [x] Full Waiver 
- [ ] Partial Waiver 
- [ ] Pediatric Assessment 
- [ ] Deferral/Pediatric Plan

<table>
<thead>
<tr>
<th>NDA#</th>
<th>NDA 208583</th>
</tr>
</thead>
</table>

**PRODUCT PROPRIETARY NAME:** Xultophy  
**ESTABLISHED/Generic NAME:** insulin degludec and liraglutide

**APPLICANT/SPONSOR:** Novo Nordisk, Inc.

**PREVIOUSLY APPROVED INDICATION/S:**
This product is a new combination

**PROPOSED INDICATION/S:**
adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus

<table>
<thead>
<tr>
<th>NDA STAMP DATE</th>
<th>9/14/15</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>PDUFA GOAL DATE</th>
<th>9/14/16</th>
</tr>
</thead>
</table>

**SUPPLEMENT TYPE:** N/A

**SUPPLEMENT NUMBER:** N/A

*Does this application provide for (If yes, please check all categories that apply and proceed to the next question):*

- [x] NEW active ingredient(s) (includes new combination);  
- [ ] indication(s);  
- [ ] dosage form;  
- [ ] dosing regimen;  
- [ ] route of administration?
Did the sponsor submit an Agreed iPSP? Yes ☒ No ☐

Did FDA confirm its agreement to the sponsor’s Agreed iPSP? Yes ☒ No ☐

Has the sponsor submitted a Proposed Pediatric Study Request (PPSR) or does the Division believe there is an additional public health benefit to issuing a Written Request for this product, even if the plan is to grant a waiver for this indication? (Please note, Written Requests may include approved and unapproved indications and may apply to the entire moiety, not just this product.)

Yes ☐ No ☒

Is this application in response to a PREA (Postmarketing Requirement) PMR? Yes ☐ No ☒

If Yes, PMR # _________ NDA # _________

Does the division agree that this is a complete response to the PMR? Yes ☐ No ☒

If Yes, to either question Please complete the Pediatric Assessment Template.

If No, complete all appropriate portions of the template, including the assessment template if the division believes this application constitutes an assessment for any particular age group.
WAIVER REQUEST

Please attach:

☐ Draft Labeling (If Waiving for Safety and/or Efficacy) from the sponsor unless the Division plans to change.
If changing the sponsor’s proposed language, include the appropriate language under Question 4 in this form.
☒ Pediatric Record

1. Pediatric age group(s) to be waived.
   0-17

2. Reason(s) for waiving pediatric assessment requirements (Choose one. If there are different reasons for different age groups or indications, please choose the appropriate reason for each age group or indication. This section should reflect the Division’s thinking.)

☒ Studies are impossible or highly impractical (e.g. the number of pediatric patients is so small or is geographically dispersed). (Please note that in the DARRTS record, this reason is captured as “Not Feasible.”) If applicable, chose from the adult-related conditions on the next page.

☐ The product would be ineffective and/or unsafe in one or more of the pediatric group(s) for which a waiver is being requested. Note: If this is the reason the studies are being waived, this information MUST be included in the pediatric use section of labeling. Please provide the draft language you intend to include in the label. The language must be included in section 8.4 and describe the safety or efficacy concerns in detail.

☒ The product fails to represent a meaningful therapeutic benefit over existing therapies for pediatric patients and is unlikely to be used in a substantial number of all pediatric age groups or the pediatric age group(s) for which a waiver is being requested.

☐ Reasonable attempts to produce a pediatric formulation for one or more of the pediatric age group(s) for which the waiver is being requested have failed. (Provide documentation from Sponsor) Note: Sponsor must provide data to support this claim for review by the Division, and this data will be publicly posted. (This reason is for Partial Waivers Only)
3 Provide justification for Waiver:

The necessary studies in pediatric patients, ages 0-10 years of age are impossible or highly impracticable because there are too few children with type 2 diabetes in this age group. Partial waivers are typically granted for drugs to treat type 2 diabetes in this age group.

Metformin is the recommended first line therapy for type 2 diabetes in the pediatric population. For patients aged 10-17 years of age, the therapeutic benefit from an injection of a fixed combination of a basal insulin/GLP-1 product as add on to monotherapy with metformin (i.e. three-drug regimen) is undefined with no foreseeable therapeutic benefit over the use of the individual components. In the Agency’s experience with other combination drug products, i.e. anti-hypertensives, the pediatric population is unlikely to use these products.
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MARISA PETRUCCELLI
07/19/2016
Good afternoon,

We have some preliminary questions regarding your labeling comprehension study results (document entitled Labeling Comprehension Test Prescribing Information Final Report) submitted to NDA 208583 on June 3, 2016.

- We noted that Appendix B includes subjective feedback provided by the participants that provided incorrect responses. These comments appear to be excerpts of their feedback instead of the verbatim statements provided by these participants. In addition, the comments submitted did not clearly demonstrate that study participants were able to communicate dosing information without indicating a term of measure (e.g., units). We request that you provide the verbatim responses and specific subjective data for our review of whether participants were able to communicate dosing information.

- In addition, we noted that participants were instructed to write their dosing recommendations on cards for the assigned case scenarios. The results submitted did not indicate the specific responses provided by study participants so that we are able to determine if the prescriber participants communicated dosing information without indicating a term of measure (e.g., units). We request that you provide the written responses provided by all study participants for Task 1, 3, and 6 (i.e., tasks requiring participants to determine initiation doses).

We request that you respond to this information request no later than close of business on **Wednesday, July 6, 2016**. Please let us know if you will not be able to meet this deadline.

Thank you in advance,

**Marisa Petruccelli**
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Phone: 240-402-6147
Fax: 301-796-9712
marisa.petruccelli@fda.hhs.gov
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MARISA PETRUCCELLI
06/29/2016
Hi Rick,

Attached is a draft of the IDegLira PI containing some preliminary FDA comments. We have not fully reviewed all sections of the PI yet, and will have further comments to make throughout the PI as negotiations continue. We are hoping you can have a response in 2-3 weeks. Once you and your team have looked over our edits, please let me know what you think a feasible timeframe for response will be.

Please confirm receipt of this email and let me know if there are any questions.

Thank you,

Marisa Petruccelli
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Phone: 240-402-6147
Fax: 301-796-9712
marisa.petruccelli@fda.hhs.gov

Reference ID: 3947574
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MARISA PETRUCELLI
06/17/2016
Good afternoon,

I have a follow-up information request regarding PLLR compliance for NDA 208583. Together with submission of the proposed labeling for PLLR compliance, you should have provided a cumulative review and summary of cases from your pharmacovigilance database regarding liraglutide use in pregnant and lactating women and any reports of infertility in females or males of reproductive potential. Please provide the required pregnancy, lactation and infertility pharmacovigilance data for liraglutide.

Please confirm receipt of this request and provide the requested data within two weeks.

Please let me know if you have any clarifying questions.

Thank you,
Marisa

Marisa Petruccelli
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Phone: 240-402-6147
Fax: 301-796-9712
marisa.petruccelli@fda.hhs.gov
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MARISA PETRUCCELLI
06/14/2016
Good afternoon,

We have the following comments on your proposed Carton and Container labeling submitted for NDA 208583. Please note, we are still reviewing the labeling and will have further comments.

Carton Labeling
1. (b)(4) should be deleted.
2. (b)(4) should be revised to “100 units/mL”.
3. On the primary display panel, consider adding line spaces between the proprietary name, established name, “For Single Patient Use Only” warning, and concentration statement since this information appears cluttered on the label. Since there is a large amount blank space available, this modification should improve readability.
4. Revise the statement (b)(4) to “See prescribing information” for improved clarity.
5. Revise the statement (b)(4) to “Must be refrigerated”.
6. Include the statements “Date of first opening ___/___/____. Discard unused portion 21 days after first opening.” Since there will be multiple pens in each carton, we recommend including space for users to make note of the date for each pen in the box.

Professional Sample Label and Labeling
1. Increase the size and prominence of the “Sample. Not for Resale” statement on the drug sample’s label and the “Sample” statement on the drug sample container’s labeling so that it is clear that these are drug samples, per 21CFR 203.38(c).

Please let me know if you have any questions.

Thank you,
Marisa

Marisa Petruccelli
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Phone: 240-402-6147
Fax: 301-796-9712
marisa.petruccelli@fda.hhs.gov
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MARISA PETRUCCELLI
05/25/2016
Dear Mr. Spring:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for insulin degludec and liraglutide injection.

We also refer to your email dated May 12, 2016, concerning Novo Nordisk comments on FDA Briefing Material for the May 24, 2016, meeting of the Endocrinologic and Metabolic Drugs Advisory Committee for NDA 208583 insulin degludec and liraglutide injection.

Thank you for citing sections in the FDA briefing materials that needed corrections or clarification. Below please find our response to your comments. Note that we will not issue written errata. Corrections will be included in FDA presentations where indicated.

Specific Novo Nordisk comments are listed below. FDA responses are in bold font.

1. Page 9, first paragraph: “...in many trials the dose in the insulin arm was capped...” The dose was only capped in one trial (3912).

   **FDA response:** We agree and will make this point clear in the FDA presentations.

2. Page 18, section 1.2, last sentence, “Three other trials, a factorial study with three arms comparing IDegLira to each of the individual components, a placebo controlled trial, and an active comparator trial against insulin glargine were also submitted.” The phase 3 program is summarized incorrectly by erroneously counting the ‘factorial study with three arms’ (i.e., 3697) among the ‘three other trials’.

   **FDA Response:** The FDA presentations do not categorize the trials into pivotal and ‘other’. Therefore, your concern will be addressed through the FDA presentations.

3. Page 18, 2nd paragraph, last 5 sentences. The text is confusing as to which trials were ‘regulatory’ and addressing the combination drug rule. For this text, it seems as if it’s 3912 and 3851, which is not the case – and 3967 (the regulatory trial) is referred to as one of the 3 other trials.
FDA Response: While we do not entirely agree that this language is confusing, we agree that 3697 would be designed to question about contribution to claimed effect of insulin degludec. We will make this point clear in the FDA presentations.

4. Page 46, Section 5.3.1: “Four of the 5 deaths were due to cardiovascular causes (with 3 of these deaths adjudicated as CV death, see Table 21 in Appendix).” The FDA states 4 of the 5 deaths are due to CV causes, whereas the Novo Nordisk Briefing Book presents the preferred terms and Table 7-7 showing that the EAC adjudicated only 3 cases as CV deaths.

FDA Response: In the briefing book we included non-treatment emergent trial deaths and treatment emergent trial deaths. Our presentation will include only treatment emergent deaths for a total of 4. We do not believe that any discrepancy in this regard will substantially affect the meeting and do not plan to issue an erratum.

5. Page 46, General safety results, section on Deaths, last sentence should read IGlar instead of IDeg.

FDA Response: The table of deaths shown in the presentation will be corrected.

6. Page 67, Section 8.3 Pancreatitis or suspicion of pancreatitis states, “Of the five events reported as ‘pancreatitis’ by the investigator, that were sent for adjudication, only 2 events were adjudicated as acute pancreatitis (1 event for liraglutide and 1 event for IDeg).” Liraglutide should have 2 events as in the Novo Nordisk Briefing Book, Page 106, for a total of 3 events (2 liraglutide and 1 IDeg).

FDA Response: The information in the briefing book is based on page 200 of the ISS which reads: “Of the 5 events sent for adjudication, 2 events were confirmed (1 treatment-emergent event in the liraglutide group and 1 event reported 66 days after last dose of IDeg) and classified as acute pancreatitis (see details in Table 2–38). Three (3) events reported as pancreatitis were not confirmed by the EAC (Table 2–38).”

This information is also consistent with figure 2-12 titled “Adjudication of event reported as pancreatitis by the investigator – safety analysis set.”

7. Page 67, Section 8.3 Pancreatitis or suspicion of pancreatitis states, “Adverse event reports of ‘lipase increased’ or ‘amylase increase’ were also examined. However, these were not adjudicated.” These events were adjudicated.

FDA Response: Per table 2-15 in the ISS, in all phase 3 trials except for trial 3952, amylase and lipase >3X ULN were considered MESIs (see below).
However this table is unclear if the “Adjudicated” also applied to all trials, or just the ones that also had a “MESI classification.”

When looking at the specific CSR of trial 3952, table 9-4 (page 61) does not list amylase and lipase as items that were adjudicated. Furthermore, in section 12.5.4.5 titled “Elevated lipase and amylase” (page 148 of CSR for trial 3952), there is again no mention that amylase or lipase were adjudicated. Therefore, these tables/sections do not clearly communicate that these events were also adjudicated for this trial.

Nevertheless, we are not planning to discuss the adjudication of amylase and lipase increases at the meeting, and we do not believe that clarifying this point will meaningfully change the outcome of the meeting. We do not plan to issue an erratum for this point.

8. Page 114, Figure 4 (c-peptide during meal test), the color codes are missing. The color codes should be the same as those used in Figure 3 (i.e., IDegLira in green and IDeg in red), and when doing so, the FDA presented curves are not correct, as the lowest curve should be insulin degludec.

FDA Response: We agree. This occurred during pdf conversion of the document and was unintentional. FDA’s backup slides will include a corrected figure. We do not believe that this error will substantially affect the meeting, and we do not plan to issue an erratum for this issue.

The FDA considers this to be its final position on the FDA briefing materials for NDA 208583 insulin degludec and liraglutide injection.

If you have any questions, call Marisa Petruccelli, Regulatory Project Manager, at (240) 402-6147.
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
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JEAN-MARC P GUETTIER
05/20/2016
Good afternoon,

We acknowledge your May 12, 2016, comments on FDA Briefing Material for the May 24, 2016, meeting of the Endocrinologic and Metabolic Drugs Advisory Committee for NDA 208583 insulin degludec and liraglutide injection. We will not issue written Errata; your comments will be addressed during FDA presentations. A more detailed response to each of your comments will follow in a letter shortly.

Please let me know if there are any questions.

Thank you,
Marisa

-----Original Message-----
From: RSPR (Rick Spring) [mailto:rspr@novonordisk.com]
Sent: Thursday, May 12, 2016 12:44 PM
To: Bonner, LaToya
Cc: Ngo, Diem-Kieu (CDR,USPHS); Petruccelli, Marisa; TDOU (Tin Ming Douglas)
Subject: RE: Upcoming Endocrinologic and Metabolic Drugs Advisory Committee (EMDAC) Meeting - May 24, 2016: NN Corrections to the FDA Briefing Document

LaToya,

Hi! Please find attached some comments we had to the FDA's Briefing Document that we mentioned at the Late Cycle Meeting on May 9, 2016. If you have any questions, please let me know. Thank you.

Rick

6 Page(s) has 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/

MARISA PETRUCCELLI
05/19/2016
Good morning,

I have an information request regarding NDA 208583. Please confirm receipt of this request and provide a response by COB Monday, May 16.

1. Your protocol states that titration occurred twice a week for patients taking lDegLira or lDeg over the 26 week treatment period. Since investigators were required to record these doses at each visit (visits occurred once weekly), it is unclear why the datasets only have non-imputed data for 8 visits (as shown in table 1) [source dataset snfdo studyid NN9068-3697].

Table 1

<table>
<thead>
<tr>
<th>Obs</th>
<th>SUBJID</th>
<th>STUDYID</th>
<th>TOPIC_CD</th>
<th>VISID</th>
<th>TIMINGC</th>
<th>FVSTDU</th>
<th>LOCF</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>101007</td>
<td>NN9068-3697</td>
<td>INSULIN_DOSE_DAILY_ACT_U</td>
<td>30</td>
<td>1 Weeks</td>
<td>12.6667</td>
<td>N</td>
</tr>
<tr>
<td>2</td>
<td>101007</td>
<td>NN9068-3697</td>
<td>INSULIN_DOSE_DAILY_ACT_U</td>
<td>40</td>
<td>2 Weeks</td>
<td>18.0000</td>
<td>N</td>
</tr>
<tr>
<td>3</td>
<td>101007</td>
<td>NN9068-3697</td>
<td>INSULIN_DOSE_DAILY_ACT_U</td>
<td>60</td>
<td>4 Weeks</td>
<td>24.0000</td>
<td>N</td>
</tr>
<tr>
<td>4</td>
<td>101007</td>
<td>NN9068-3697</td>
<td>INSULIN_DOSE_DAILY_ACT_U</td>
<td>100</td>
<td>8 Weeks</td>
<td>32.0000</td>
<td>N</td>
</tr>
<tr>
<td>5</td>
<td>101007</td>
<td>NN9068-3697</td>
<td>INSULIN_DOSE_DAILY_ACT_U</td>
<td>140</td>
<td>12 Weeks</td>
<td>40.0000</td>
<td>N</td>
</tr>
<tr>
<td>6</td>
<td>101007</td>
<td>NN9068-3697</td>
<td>INSULIN_DOSE_DAILY_ACT_U</td>
<td>180</td>
<td>16 Weeks</td>
<td>40.0000</td>
<td>N</td>
</tr>
<tr>
<td>7</td>
<td>101007</td>
<td>NN9068-3697</td>
<td>INSULIN_DOSE_DAILY_ACT_U</td>
<td>220</td>
<td>20 Weeks</td>
<td>46.0000</td>
<td>N</td>
</tr>
<tr>
<td>8</td>
<td>101007</td>
<td>NN9068-3697</td>
<td>INSULIN_DOSE_DAILY_ACT_U</td>
<td>280</td>
<td>26 Weeks</td>
<td>48.0000</td>
<td>N</td>
</tr>
</tbody>
</table>

2. Also explain why the values in table 1 are different for the same time periods from the extension data shown in table 2 [source dataset snfdo studyid NN9068-3697]

Table 2

<table>
<thead>
<tr>
<th>Obs</th>
<th>SUBJID</th>
<th>STUDYID</th>
<th>TOPIC_CD</th>
<th>VISID</th>
<th>TIMINGC</th>
<th>FVSTDU</th>
<th>LOCF</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>101007</td>
<td>NN9068-3697-main-ext</td>
<td>INSULIN_DOSE_DAILY_ACT_U</td>
<td>30</td>
<td>1 Weeks</td>
<td>12.6667</td>
<td>N</td>
</tr>
<tr>
<td>2</td>
<td>101007</td>
<td>NN9068-3697-main-ext</td>
<td>INSULIN_DOSE_DAILY_ACT_U</td>
<td>40</td>
<td>2 Weeks</td>
<td>18.0000</td>
<td>N</td>
</tr>
<tr>
<td>3</td>
<td>101007</td>
<td>NN9068-3697-main-ext</td>
<td>INSULIN_DOSE_DAILY_ACT_U</td>
<td>50</td>
<td>3 Weeks</td>
<td>18.0000</td>
<td>Y</td>
</tr>
<tr>
<td>4</td>
<td>101007</td>
<td>NN9068-3697-main-ext</td>
<td>INSULIN_DOSE_DAILY_ACT_U</td>
<td>60</td>
<td>4 Weeks</td>
<td>24.0000</td>
<td>N</td>
</tr>
<tr>
<td>5</td>
<td>101007</td>
<td>NN9068-3697-main-ext</td>
<td>INSULIN_DOSE_DAILY_ACT_U</td>
<td>70</td>
<td>5 Weeks</td>
<td>24.0000</td>
<td>Y</td>
</tr>
<tr>
<td>6</td>
<td>101007</td>
<td>NN9068-3697-main-ext</td>
<td>INSULIN_DOSE_DAILY_ACT_U</td>
<td>80</td>
<td>6 Weeks</td>
<td>24.0000</td>
<td>Y</td>
</tr>
<tr>
<td>7</td>
<td>101007</td>
<td>NN9068-3697-main-ext</td>
<td>INSULIN_DOSE_DAILY_ACT_U</td>
<td>90</td>
<td>7 Weeks</td>
<td>24.0000</td>
<td>Y</td>
</tr>
<tr>
<td>8</td>
<td>101007</td>
<td>NN9068-3697-main-ext</td>
<td>INSULIN_DOSE_DAILY_ACT_U</td>
<td>100</td>
<td>8 Weeks</td>
<td>32.0000</td>
<td>N</td>
</tr>
<tr>
<td>9</td>
<td>101007</td>
<td>NN9068-3697-main-ext</td>
<td>INSULIN_DOSE_DAILY_ACT_U</td>
<td>110</td>
<td>9 Weeks</td>
<td>32.0000</td>
<td>Y</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>101007</td>
<td>NN9068-3697-main-ext</td>
<td>INSULIN_DOSE_DAILY_ACT_U</td>
<td>120</td>
<td>10 Weeks</td>
<td>32.0000</td>
<td>Y</td>
</tr>
<tr>
<td>11</td>
<td>101007</td>
<td>NN9068-3697-main-ext</td>
<td>INSULIN_DOSE_DAILY_ACT_U</td>
<td>130</td>
<td>11 Weeks</td>
<td>32.0000</td>
<td>Y</td>
</tr>
<tr>
<td>12</td>
<td>101007</td>
<td>NN9068-3697-main-ext</td>
<td>INSULIN_DOSE_DAILY_ACT_U</td>
<td>140</td>
<td>12 Weeks</td>
<td>40.0000</td>
<td>N</td>
</tr>
<tr>
<td>13</td>
<td>101007</td>
<td>NN9068-3697-main-ext</td>
<td>INSULIN_DOSE_DAILY_ACT_U</td>
<td>150</td>
<td>13 Weeks</td>
<td>40.0000</td>
<td>Y</td>
</tr>
<tr>
<td>14</td>
<td>101007</td>
<td>NN9068-3697-main-ext</td>
<td>INSULIN_DOSE_DAILY_ACT_U</td>
<td>160</td>
<td>14 Weeks</td>
<td>40.0000</td>
<td>Y</td>
</tr>
<tr>
<td>15</td>
<td>101007</td>
<td>NN9068-3697-main-ext</td>
<td>INSULIN_DOSE_DAILY_ACT_U</td>
<td>170</td>
<td>15 Weeks</td>
<td>40.0000</td>
<td>Y</td>
</tr>
<tr>
<td>16</td>
<td>101007</td>
<td>NN9068-3697-main-ext</td>
<td>INSULIN_DOSE_DAILY_ACT_U</td>
<td>180</td>
<td>16 Weeks</td>
<td>40.0000</td>
<td>N</td>
</tr>
<tr>
<td>17</td>
<td>101007</td>
<td>NN9068-3697-main-ext</td>
<td>INSULIN_DOSE_DAILY_ACT_U</td>
<td>190</td>
<td>17 Weeks</td>
<td>40.0000</td>
<td>Y</td>
</tr>
<tr>
<td>18</td>
<td>101007</td>
<td>NN9068-3697-main-ext</td>
<td>INSULIN_DOSE_DAILY_ACT_U</td>
<td>200</td>
<td>18 Weeks</td>
<td>40.0000</td>
<td>Y</td>
</tr>
<tr>
<td>19</td>
<td>101007</td>
<td>NN9068-3697-main-ext</td>
<td>INSULIN_DOSE_DAILY_ACT_U</td>
<td>210</td>
<td>19 Weeks</td>
<td>40.0000</td>
<td>Y</td>
</tr>
<tr>
<td>20</td>
<td>101007</td>
<td>NN9068-3697-main-ext</td>
<td>INSULIN_DOSE_DAILY_ACT_U</td>
<td>220</td>
<td>20 Weeks</td>
<td>46.0000</td>
<td>N</td>
</tr>
<tr>
<td>21</td>
<td>101007</td>
<td>NN9068-3697-main-ext</td>
<td>INSULIN_DOSE_DAILY_ACT_U</td>
<td>230</td>
<td>21 Weeks</td>
<td>46.0000</td>
<td>Y</td>
</tr>
<tr>
<td>22</td>
<td>101007</td>
<td>NN9068-3697-main-ext</td>
<td>INSULIN_DOSE_DAILY_ACT_U</td>
<td>240</td>
<td>22 Weeks</td>
<td>46.0000</td>
<td>Y</td>
</tr>
<tr>
<td>23</td>
<td>101007</td>
<td>NN9068-3697-main-ext</td>
<td>INSULIN_DOSE_DAILY_ACT_U</td>
<td>250</td>
<td>23 Weeks</td>
<td>46.0000</td>
<td>Y</td>
</tr>
<tr>
<td>24</td>
<td>101007</td>
<td>NN9068-3697-main-ext</td>
<td>INSULIN_DOSE_DAILY_ACT_U</td>
<td>260</td>
<td>24 Weeks</td>
<td>46.0000</td>
<td>Y</td>
</tr>
<tr>
<td>25</td>
<td>101007</td>
<td>NN9068-3697-main-ext</td>
<td>INSULIN_DOSE_DAILY_ACT_U</td>
<td>270</td>
<td>25 Weeks</td>
<td>46.0000</td>
<td>Y</td>
</tr>
<tr>
<td>26</td>
<td>101007</td>
<td>NN9068-3697-main-ext</td>
<td>INSULIN_DOSE_DAILY_ACT_U</td>
<td>280</td>
<td>26 Weeks</td>
<td>48.0000</td>
<td>N</td>
</tr>
</tbody>
</table>

Please let me know if there are any questions.

Thank you,

**Marisa Petruccelli**

Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Phone: 240-402-6147
Fax: 301-796-9712
marisa.petruccelli@fda.hhs.gov
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MARISA PETRUCCELLI
05/13/2016
Good morning,

I have an information request for NDA 208583. Please confirm receipt of this request and provide a response by COB Thursday, May 12.

Please provide an MMRM, jump to reference, jump to control, and tipping point analysis (all similar to what was done for the primary analysis) for the 52 week HbA1c data from trial 3697.

Thank you,
Marisa

Marisa Petruccelli
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Phone: 240-402-6147
Fax: 301-796-9712
marisa.petruccelli@fda.hhs.gov
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

----------------------------------------------------
MARISA PETRUCCELLI
05/11/2016
Good afternoon,

FDA revised the proposed Xultophy REMS Document (attached) to align with the Saxenda REMS document and to reflect FDA’s current thinking about the description of relevant elements of the communication plan. Please revise the REMS Supporting Document to reflect modifications to the REMS Document and REMS materials.

Please confirm receipt of this request and provide a response within two weeks.

Thank you,

Marisa

Marisa Petruccelli
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Phone: 240-402-6147
Fax: 301-796-9712
marisa.petruccelli@fda.hhs.gov
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MARISA PETRUCCELLI
05/11/2016
Good afternoon Anika: we will adjust the master batch record to correct the inaccuracy. Rick Spring from my team will be in touch.

Best regards,

Bob Clark

Robert Clark

On May 9, 2016, at 12:49 PM, Lalmansingh, Anika <Anika.Lalmansingh@fda.hhs.gov> wrote:

Information Request – CMC

NDA 208583

Good afternoon Bob,

Please fix your master batch records to accurately reflect the molar quantity of insulin degludec drug substance used in your formulation. We note a discrepancy between what is provided in your batch formula versus master batch records.

A confirmation email as soon as possible that the discrepancy will be corrected is sufficient.

Kind Regards.

-Anika

Anika Lalmansingh, PhD
Regulatory Business Process Manager, Office of Program and Regulatory Operations (OPRO)
Office of Pharmaceutical Quality/CDER/FDA
10903 New Hampshire Ave, Bldg #75 Room 4631, Silver Spring, MD 20993-0002
(240) 402-0356 • anika.lalmansingh@fda.hhs.gov

This e-mail message is intended for the exclusive use of the recipient(s) named above. It may contain information that is protected, privileged, or confidential, and it should not be disseminated, distributed, or copied to persons not authorized to receive such information. If you are not the intended recipient, any dissemination, distribution or copying is strictly prohibited. If you think you have received this e-mail message in error, please e-mail the sender immediately anika.lalmansingh@fda.hhs.gov.
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ANIKA A LALMANSINGH
05/09/2016
Good afternoon,

I have an information request (IR) for NDA 208583. Please confirm receipt of this request and provide a response within one week.

Please clarify the titration goals for trial 3952. Your briefing package states that the titration goals for this program were 72-90 mg/dL, while your November 30, 2015, response (attached) to our November 18 IR states on page 17 that the goal was 71-90 mg/dL (see below):

![Titration Goals Chart]

Thank you,
Marisa

**Marisa Petruccelli**
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Phone: 240-402-6147
Fax: 301-796-9712
marisa.petruccelli@fda.hhs.gov
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MARISA PETRUCELLI
05/03/2016
Good morning,

I have an information request on behalf of CDRH regarding the pen injector for NDA 208583:

The dial, dose button, and the cartridge holder are made with (b)(4) You state within the Biological Evaluation of PDS290 that cytotoxicity testing is sufficient to evaluate these components because “epidermal inflammation caused by cytotoxicity is a prerequisite in the sensitization pathway”; therefore, a negative cytotoxicity result means the components will not cause sensitization and irritation reactions. This rationale does not address the fact that non cytotoxic chemicals can be irritating or sensitizing. Therefore, a negative cytotoxicity test result is not sufficient to demonstrate the device is non-sensitizing and non-irritating. To address the (b)(4) you also provided a table that lists the chemical composition for the “potential leachables” from the masterbatch; however, this table does not address the potential impurities (b)(4) Please provide biocompatibility tests on the final finished dial, dose button, and cartridge holder for cytotoxicity, sensitization and irritation. Alternatively, you may provide a scientific justification (b)(4)

Please confirm receipt of this request and provide a response within one week, by 4/28/2016.

Thank you,

Marisa Petruccelli
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Phone: 240-402-6147
Fax: 301-796-9712
marisa.petruccelli@fda.hhs.gov
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MARISA PETRUCCELLI
04/21/2016
GENERAL ADVICE

Novo Nordisk Inc.
Attention: Rick Spring
Associate Director, Regulatory Affairs
800 Scudders Mill Road
Plainsboro, NJ 08536

Dear Mr. Spring:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for insulin degludec and liraglutide [rDNA origin] injection.

We also refer to your March 14, 2016, submission, containing a labeling comprehension study protocol.

We have reviewed the referenced material and have the following recommendations regarding the material provided and moderator script. You do not need to submit the revised protocol for review provided that you agree with the following recommendations.

a. We recommend that you provide the entire Prescribing Information (PI) instead of only supplying the Dosage and Administration Section to simulate real use of the PI and that you do not specifically direct participants to read the Dosing and Administration Section during the case-based scenarios. For example, you state “Use the Dosage and Administration section of the Physician Insert to determine a starting dose of Xultophy…” for Task 1 and “Explain in your own words how to titrate… based on Dosage and Administration Section of Physician Insert” for Task 8. Providing participants with only Dosage and Administration Section of the PI and directing participants to read it to prescribe the correct dose of the product does not mimic actual use and may not inform the review of the product in terms of whether prescribers can find and comprehend the information in the labeling.

b. We recommend you do not direct participants to read Table 1 in Dosage and Administration Section to help determine the amount of active ingredients in specific doses of the product. For example, you state “Use Table 1 in Dosage and Administration Section of the Physician Insert to determine the number of units of insulin Degludec and milligrams of Liraglutide in Xultophy dose of 10” in Task 2. In actual use, prescribers would have to find this information in the PI by themselves. Therefore, we encourage you to revise the scenarios to delete these types of directives.
c. We recommend that you do not direct participants to read the PI. The PI should be available for use at the physician’s discretion. Also, make sure to collect data regarding the number of participants that refer to the PI and those that do not use the PI for dosing instructions. In addition, collect the number of correct and incorrect responses during the tasks and separate those data based on participant use of the PI to facilitate comparison of prescribing performance.

d. We recommend that you add a use scenario to assess the prescribers’ comprehension regarding the dose limitation of this product and identify when the product is not appropriate for patients that need higher doses of basal insulin. For example, include a patient scenario where the patient is currently taking 80 units of insulin degludec daily and ask participants to initiate Xultophy.

e. Please ensure that participants complete each test scenario.

f. Provide any subjective feedback provided by participants regarding the tasks.

If you have any questions, call Marisa Petruccelli, Regulatory Project Manager, at (240) 402-6147.

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

/s/

JEAN-MARC P GUETTIER
04/20/2016
Good afternoon,

I have an information request regarding NDA 208583. In your analysis for study 3697, you are including a variable indicating participation in the sub-study. Please clarify why you planned to include the variable sub-study in the HbA1c analysis model for study 3697.

Please confirm receipt of this request and provide a response by Friday, April 1, if possible.

Thank you,
Marisa

Marisa Petruccelli
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Phone: 240-402-6147
Fax: 301-796-9712
marisa.petruccelli@fda.hhs.gov
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MARISA PETRUCCELLI
03/30/2016
Good morning,

I have an information request regarding NDA 208583. In the CSR of study 369, page 92 you state that:

“The results presented reflect the data available in the clinical database as of 15 Jan 2013. The database was re-opened after DBL in order to:

· re-categorise or re-calculate PK samples that were identified as ambient (37 samples) or analysed using a non-valid calibration curve (470 samples), respectively (4Feb 2013)”

Please clarify if these samples included samples in the meal test portion of the sub-study.

Please confirm receipt of this request and provide a response within 7 days.

Thank you,

Marisa

Marisa Petruccelli
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Phone: 240-402-6147
Fax: 301-796-9712
marisa.petruccelli@fda.hhs.gov
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MARISA PETRUCCELLI
03/24/2016
Good morning,

I have an additional information request today for NDA 208583 IdegLira. For trials 3951 and 3851, fill in table 1 below with the proportion of patients for each trial that reached titration goal (based on SMPG target) at each visit.

<table>
<thead>
<tr>
<th></th>
<th>Trial 3851</th>
<th>Trial 3951</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>IDegLira</td>
<td>GLP-1 RA</td>
</tr>
<tr>
<td>Week 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Etc...</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Please confirm receipt of this request and provide a response within 7 days.

Thank you,

Marisa

Marisa Petruccelli
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Phone: 240-402-6147
Fax: 301-796-9712
marisa.petruccelli@fda.hhs.gov
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MARISA PETRUCCELLI
03/24/2016
Hi Rick,

We request that you submit a total of ten (10) additional sample pen devices for insulin degludec/liraglutide NDA 208583 to aid in our review process. We request that you submit this information to us no later than close of business on Friday, April 8, 2016.

Please confirm receipt of this request and let me know if this will be feasible.

Thank you,

Marisa

Marisa Petruccelli
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Phone: 240-402-6147
Fax: 301-796-9712
marisa.petruccelli@fda.hhs.gov
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MARISA PETRUCCELLI
03/23/2016
NDA 208583

Novo Nordisk Inc.
Attention: Robert B. Clark
Vice President, Regulatory Affairs
800 Scudders Mill Road
Plainsboro, NJ 08536

Dear Mr. Clark:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for insulin degludec and liraglutide [rDNA origin] injection.

We also refer to the teleconference between representatives of your firm and the FDA on February 18, 2016. The purpose of the teleconference was to provide you an update on the status of the review of your application.

A record of the teleconference is enclosed for your information.

If you have any questions, call Marisa Petruccelli, Regulatory Project Manager at (240) 402-6147.

Sincerely,

{See appended electronic signature page}

Lisa Yanoff, M.D.
Clinical Team Leader
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure:
Mid-Cycle Communication
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MID-CYCLE COMMUNICATION

Meeting Date and Time: February 18, 2016, 2:30pm

Application Number: NDA 208583
Product Name: insulin degludec and liraglutide [rDNA origin] injection
Indication: adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus
Applicant Name: Novo Nordisk Inc.

Meeting Chair: Jean-Marc Guettier, M.D.
Meeting Recorder: Marisa Petruccelli

FDA ATTENDEES
Jean-Marc Guettier, M.D., Division Director
Lisa Yanoff, M.D., Clinical Team Leader
Tania Condarco, M.D., Clinical Reviewer
Julie Van der Waag, MPH, Chief, Project Management Staff
Marisa Petruccelli, Project Manager
Mark Rothmann, PhD, Biometrics Team Leader
Anna Ketterman, Dipl. Math, MA, Biometrics Reviewer
Sapana Patel, PharmD, Pharmacist, General Hospital Devices Branch, CDRH
Amarilyys Vega, MD, MPH, Medical Officer, DRISK
Ariane Conrad, PharmD, BCACP, CDE, FASCP, Safety Evaluator, DMEPA
Yelena Maslov, PharmD., Team Leader, DMEPA
Elizabeth Godwin, MSHS, CCRP, Project Manager

EASTERN RESEARCH GROUP ATTENDEES
Peggah Khorrami, Independent Assessor, Eastern Research Group

APPLICANT ATTENDEES
Bob Clark – Vice President – Regulatory Affairs
Marianne Bork Samuelsen – RA Director
Finn Møllgaard – Regulatory Corporate Vice President
Christian Foged - Project Vice President
Martin Holst Lange - Corporate Project Vice President
Stephen Charles Langford Gough - Senior Principal Clinical Scientist
Pernille Poulsen – Medical and Science Director
Ole Kim Eskerod – Medical and science Vice President
Irene Hedelund Langbakk - International Medical Director
Lucine M. Lehmam - International Medical Director

Reference ID: 3902190
1.0 INTRODUCTION

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may or may not be able to consider your response before we take an action on your application during this review cycle.

2.0 SIGNIFICANT ISSUES

In the course of our review we identified multiple anomalies in data for the main efficacy endpoint (HbA1c).

Please note that this is not an exhaustive list of all data anomalies. We identified similar issues with all efficacy datasets. The examples below from study 3697 are used to illustrate specific issues:
1. In this example, visits were repeated and were recorded out of chronological order.

<table>
<thead>
<tr>
<th>SUBJID</th>
<th>VISID</th>
<th>TIMINGC</th>
<th>TARMLB</th>
<th>FVSTDU</th>
<th>TRLDAY</th>
<th>DELETEFL</th>
<th>S_COMMNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>202016</td>
<td>10</td>
<td>-2 WEEKS</td>
<td>IDEGLIRA</td>
<td>8.7</td>
<td>-13</td>
<td></td>
<td></td>
</tr>
<tr>
<td>202016</td>
<td>20</td>
<td>0 WEEKS</td>
<td>IDEGLIRA</td>
<td>8.6</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>202016</td>
<td>60</td>
<td>4 WEEKS</td>
<td>IDEGLIRA</td>
<td>9.4</td>
<td>39</td>
<td></td>
<td></td>
</tr>
<tr>
<td>202016</td>
<td>100</td>
<td>8 WEEKS</td>
<td>IDEGLIRA</td>
<td>9.5</td>
<td>66</td>
<td></td>
<td></td>
</tr>
<tr>
<td>202016</td>
<td>140</td>
<td>12 WEEKS</td>
<td>IDEGLIRA</td>
<td>9.5</td>
<td>95</td>
<td>Y</td>
<td>DELETED, SPECIMEN BEYOND STABILITY</td>
</tr>
<tr>
<td>202016</td>
<td>140</td>
<td>12 WEEKS</td>
<td>IDEGLIRA</td>
<td>7.3</td>
<td>166</td>
<td></td>
<td></td>
</tr>
<tr>
<td>202016</td>
<td>180</td>
<td>16 WEEKS</td>
<td>IDEGLIRA</td>
<td>8.1</td>
<td>123</td>
<td>Y</td>
<td></td>
</tr>
<tr>
<td>202016</td>
<td>180</td>
<td>16 WEEKS</td>
<td>IDEGLIRA</td>
<td>7.6</td>
<td>144</td>
<td></td>
<td></td>
</tr>
<tr>
<td>202016</td>
<td>220</td>
<td>20 WEEKS</td>
<td>IDEGLIRA</td>
<td>7.5</td>
<td>152</td>
<td></td>
<td></td>
</tr>
<tr>
<td>202016</td>
<td>280</td>
<td>26 WEEKS</td>
<td>IDEGLIRA</td>
<td>7.5</td>
<td>193</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The next example is used to illustrate two issues that we have seen in the data:

2. 
   a. In this example, multiple visits were taken on the same day and recorded as visits several weeks apart.
   b. This example also shows existing data points with the claim that data were not available.

<table>
<thead>
<tr>
<th>SUBJID</th>
<th>VISID</th>
<th>TIMINGC</th>
<th>TARMLB</th>
<th>FVSTDU</th>
<th>TRLDAY</th>
<th>DELETEFL</th>
<th>S_COMMNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>262002</td>
<td>10</td>
<td>-2 WEEKS</td>
<td>IDEG</td>
<td>9.5</td>
<td>-14</td>
<td></td>
<td>SELECTED TESTS DELETED - NO SPECIMEN RECEIVED</td>
</tr>
<tr>
<td>262002</td>
<td>20</td>
<td>0 WEEKS</td>
<td>IDEG</td>
<td>9.5</td>
<td>-14</td>
<td></td>
<td>SELECTED TESTS DELETED - NO SPECIMEN RECEIVED</td>
</tr>
<tr>
<td>262002</td>
<td>60</td>
<td>4 WEEKS</td>
<td>IDEG</td>
<td>8.9</td>
<td>28</td>
<td></td>
<td></td>
</tr>
<tr>
<td>262002</td>
<td>100</td>
<td>8 WEEKS</td>
<td>IDEG</td>
<td>7.9</td>
<td>56</td>
<td></td>
<td></td>
</tr>
<tr>
<td>262002</td>
<td>140</td>
<td>12 WEEKS</td>
<td>IDEG</td>
<td>7.5</td>
<td>84</td>
<td>Y</td>
<td>SELECTED TESTS DELETED - NO SPECIMEN RECEIVED</td>
</tr>
</tbody>
</table>
Meeting Discussion:
The applicant provided slides, attached below, in response to this issue. The applicant confirmed it will provide a data handling standards document, which will explain the data anomalies and demonstrate that they were handled in a prospective manner. The applicant also agreed to provide updated pooled datasets (and corresponding define.pdf) with an additional table column explaining the reason for values not used (deletion flag=Y) and the reason in case of anomalies.

The applicant indicated that the anomalies were already present when it received the data and suggested that the anomalies affect less than one percent of patient data. In its response to the Statistics information request (see below), the applicant will further explain the magnitude of anomalies in the data sets so FDA can better understand the extent of the problem.

3.0 INFORMATION REQUESTS

Statistics

Please refer to the review issue explained above. For each study, you should examine the appropriate datasets for such data anomalies. You should make corrections as appropriate and
provide in the respective dataset an explanation for the changes. You should send us new corrected datasets with updated define files.

In the Information Request (IR) dated December 14, 2015, we asked you to clarify multiple data exclusions. As was indicated in the IR, the clarifications for most of the exclusions were not provided in the dataset. Your response to the IR, received on December 21, 2015, provided only a summary of causes; no specific clarifications for each excluded observation were given. You should provide the requested additional information.

Please provide all responses within two weeks. Please let us know if more time will be needed.

Meeting Discussion:
The applicant agreed to provide the data handling standards document within a few days, and updated pooled data sets within three weeks. The response to the information request will also include a discussion of the magnitude of the data anomalies.

Device

You state that all PDS290 IDegLira pen-injector device components which come into direct or indirect contact with users consist of [__] We are unable to locate test reports for cytotoxicity, sensitization, and irritation within the NDA for the proposed device constituent of your combination product. Please submit the test reports as an amendment to the NDA or submit a letter of authorization from the device manufacturer and location within the DMF of the requested test reports within one week.

4.0 MAJOR SAFETY CONCERNS/RISK MANAGEMENT

Upon review of your human factor study results submitted on September 14, 2015, we noted that you included all users (including prescribers) to determine their ability to appropriately use the pen injector device. You have not provided data to determine if prescribers were able to appropriately prescribe and dose this medication, make dose titrations, and convert patients to this medication from other therapies. Considering that this is a novel multi-ingredient product that combines insulin with a GLP-1 agonist, we do not have sufficient data to conclude that prescribers would be able to safely prescribe this product, and the study results provided do not adequately address this concern. If you have completed any formative or summative studies to address this concern, please submit this information to the NDA. If no studies have been completed, please provide a response on how you plan to address these concerns.

Meeting Discussion:
FDA discussed the need to ensure that prescribers would be able to safely prescribe and make therapy adjustments for this product based on information provided in the Dosing and Administration section of the package insert (PI). FDA recommended a prescriber labeling comprehension study to inform whether the dosing instructions in the Dosing and Administration section of the proposed PI are adequate. The applicant agreed to submit a proposed protocol to FDA for review prior to study initiation.
5.0 RISK MANAGEMENT

We intend to make revisions to your proposed REMS to align it with the recent Saxenda REMS modification approved on February 1, 2016. We will follow up with you regarding these revisions.

Meeting Discussion: The applicant stated that it had no questions regarding this issue.

6.0 ADVISORY COMMITTEE MEETING

The purpose of this AC is to discuss the potential risks and benefits of starting two anti-diabetic agents simultaneously, and to discuss the population for which this approach would be best suited.

Our tentative date for the AC meeting is May 25, 2016.

We have tentative plans for a 90-minute sponsor presentation.

Meeting Discussion: The applicant inquired whether there was any further specific information that FDA could convey at this time. FDA stated that it had nothing additional to convey at this time. Further communication between the applicant and FDA, as needed, would occur closer to the meeting date.

7.0 LATE-CYCLE MEETING /OTHER PROJECTED MILESTONES

- Tentative LCM date: May 9, 2016
- Labeling to Applicant: July 18, 2016

2 Page(s) has 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/

LISA B YANOFF
03/15/2016
Good morning, Rick,

As discussed during our February 29, 2016 teleconference to discuss issues with statistics for NDA 208583, we are providing the analyses and corresponding codes we ran on study 3697.

I will follow up at a later date with the error message we received from SAS 9.3, also discussed during the 2-29 teleconference.

Please let me know if there are any questions.

Thank you,
Marisa

Marisa Petruccelli
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Phone: 240-402-6147
Fax: 301-796-9712
marisa.petruccelli@fda.hhs.gov
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MARISA PETRUCCELLI
03/14/2016
MEMORANDUM OF TELECONFERENCE

Teleconference Date: February 29, 2016

Application Number: 208583
Product Name: insulin degludec and liraglutide
Sponsor/Applicant Name: Novo Nordisk, Inc.

Subject: Informal Teleconference to Discuss SAS and Coding Issues

FDA Participants
Tania Condarco, M.D., Clinical Reviewer
Julie Van der Waag, MPH, Chief, Project Management Staff
Marisa Petruccelli, Project Manager
Mark Rothmann, PhD, Biometrics Team Leader
Anna Kettermann, Dipl. Math, MA, Biometrics Reviewer
Paul Schuette, PhD, Scientific Computing Coordinator

Sponsor/Applicant Participants
Martin Holst Lange - Corporate Project Vice President
Robin Evers - Senior Vice President Regulatory Affairs
Bob Clark – Vice President, Regulatory Affairs
Pernille Poulsen - Director, Medical & Science
Anne Bording Jensen - Senior Vice President, Clinical Operations Management
Kamilla Begtrup - Principal Statistician, Biostatistics
Trine Julie Abrahamsen - Senior Statistician, Biostatistics
Tina Christiansen - Vice President, Biostatistics
Michael N. Frederiksen - Programming Specialist, Biostatistics
Birgitte Lysgaard-Jensen - Senior Regulatory Professional
Sascha Eichendorff - Regulatory Professional
Peter Falck Christens - Manager, Biostatistics
Paul Gilbert Drake - Medical Writing Specialist
Marianne Bork Samuelsen – Director, Regulatory Affairs
Christian Foged - Project Vice President
Nina Liang - Associate Director, Regulatory Affairs
Rick Spring – Associated Director, Regulatory Affairs
Aditi Bhobe - Associate Manager, Regulatory Affairs
Tin Ming Douglas - Specialist, Regulatory Affairs

1.0 BACKGROUND:

This teleconference is to discuss issues raised during the review of NDA 208583.

2.0 DISCUSSION:

Version: 03/05/2015

Reference ID: 3900999
Prior to the teleconference, FDA provided Novo Nordisk with the following tentative agenda:

1. Introductions
2. Introductory Remarks by Dr. Rothmann
3. Excerpt of error message
4. FDA would like a general idea of what was done by each piece of the program
5. FDA is requesting separate programs for each analysis so that we can run them separately and clarity on the define file.
6. Analyses performed by FDA and FDA’s codes
7. Good computing practices (related to future submissions)

The teleconference began with a clarification that FDA does not regulate computing.

*Excerpt of SAS 9.4 Error Message*

Novo Nordisk walked through an error message created in SAS 9.4 that FDA had provided before the call (attached below). Novo Nordisk explained that they were able to reproduce the error message in SAS 9.4, but that SAS 9.3 was able to run without creating an error. FDA explained that it was not able to run the code in SAS 9.3 without receiving an error message. FDA will provide this error message to Novo Nordisk as an example.

Novo Nordisk explained that by excluding the subject from Singapore before trying to impute, they were able to run the code in SAS 9.4 without error. Novo Nordisk explained that some code was added to be able to handle that subject in SAS 9.4; this code will be provided to FDA, and was shown during the call.

*Walk through of macro sensitivity program*

Novo Nordisk walked through each section of the ‘macro Sensitivity.pdf’ provided by FDA prior to the call. The program corresponds to Table 52: Change in HbA1c (%) at end of trial – trial 3697 - sensitivity analysis – full analysis set in Appendix 6.3 of Module 2.7.3.

Novo Nordisk confirmed that analysis utilizing Mixed-Effect Model with Repeated Measures (MMRM) did not include LOCF values.
Novo Nordisk explained that in the Copy to Reference approach, imputation was done sequentially starting at the first post-baseline visit.
Novo Nordisk noted that Appendix 6.2 of Module 2.7.3 describes how the multiple imputation analyses were done and will send this information to FDA.

*Separate Macro Programs*

Novo Nordisk has proposed to provide separate programs for each analysis so that macros can be run separately in SAS 9.4. This will include separate programs for MMRM, jump to reference, and tipping point analyses. FDA requested that memory requirements for each program be included so we can determine if our machines are powerful enough to run the codes. Novo Nordisk will provide this by March 7.

*Missing Data*
Dr. Rothmann added that internal discussions on a new missing data policy are ongoing and that Novo Nordisk will be updated accordingly. Based on the new policy, FDA may request additional analyses.

**Good Computing Practices**
FDA provided some general guidance on good computing practices and referenced PhUSE: Pharmaceutical Users Exchange, which is an interest group for good programming practices. FDA explained that one challenge during the current NDA review is inferring the function of individual steps of the macros, and explained that additional documentation outside of the macro to describe its flow, especially for macros as complex as this one, would be very helpful. FDA also suggested that a walk-through such as the one done today be done earlier in the process, at a pre-NDA meeting, or at a technical walk-through meeting scheduled shortly after NDA submission.

### 3.0 ACTION ITEMS:

**For FDA**

- FDA explained that it was not able to run the code in SAS 9.3 without receiving analysis results. FDA will provide this error message to Novo Nordisk as an example.
- FDA will provide its analyses and codes to Novo Nordisk.
- After reviewing the program code in more detail, FDA will send Novo Nordisk any clarifying questions.

**For Novo Nordisk**

- Novo Nordisk explained that some code was added to be able to handle the Singapore subject in SAS 9.4; this code will be provided to FDA.
- Novo Nordisk noted that Appendix 6.2 of Module 2.7.3 describes the multiple imputation analyses and will send this information to FDA.
- Novo Nordisk will provide separate macros for each analysis, including memory requirements, by March 7.
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MARISA PETRUCELLI
03/11/2016
Good afternoon,

I have an information request for NDA 208583 IDegLira. Please confirm receipt of this request and provide a response within two weeks.
Conduct dose response analysis for liraglutide (preferably using the Phase 2 trials 1310 and 1571) and submit the results of your analysis along with model code and input data files. We are aware of the dose-response analysis that you conducted using trial 1310 data in liraglutide NDA 022341. However, this analysis had limitations of identifying the ED50 to be higher than the maximum dose tested in the trial (0.75 mg).

Please let me know if you have any questions.

Thank you,
Marisa

**Marisa Petruccelli**
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Phone: 240-402-6147
Fax: 301-796-9712
marisa.petruccelli@fda.hhs.gov
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MARISA PETRUCCELLI
03/08/2016
Good afternoon,

I have the following information request regarding NDA 208583 IDegLira. Please confirm receipt and provide a response within 7 days from today.

1. In the ISS, section 1.1.1.5, section titled “origin of safety data,” you note 2 separate databases: a “clinical database” and a “safety database.” Please define each database, and describe what are the differences between them. Also clarify how these differ from the Safety analysis set (SAS) and the full analysis set (FAS).
2. Indicate which of the above listed groups (in #1) is used for the presentation of data in section 5.3.5.3 of the ISS (i.e., for table 2-11 [page 126], which of the above describes the population examined.)
3. Provide adjusted rates (using the methodology described in appendix 7.16 of the ISS) of ISS table 83 titled “83: Cardiac arrhythmia events (predefined MedDRA search) by SOC, HLG, and PT - treatment-emergent - completed phase 3 trials” (page 1825).
4. Provide narrative for patient 408009 reported as having prolonged QTc.

Please let me know if there are any questions.

Thank you,
Marisa

**Marisa Petruccelli**
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Phone: 240-402-6147
Fax: 301-796-9712
marisa.petruccelli@fda.hhs.gov
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MARISA PETRUCCELLI
03/04/2016
Good afternoon,

I have an information request regarding NDA 208583. Please clarify what (if any) were the differences in the EAC charters across phase 3 programs. Please confirm receipt of this request and provide a response within 7 days.

Please let me know if there are any questions.

Thank you,

Marisa Petruccelli  
Regulatory Project Manager  
Division of Metabolism and Endocrinology Products  
Center for Drug Evaluation and Research  
U.S. Food and Drug Administration  
Phone: 240-402-6147  
Fax: 301-796-9712  
marisa.petruccelli@fda.hhs.gov
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MARISA PETRUCCELLI
03/01/2016
Good morning,

I have an additional information request for NDA 208583. Please confirm receipt and provide a response by close of business this Friday, February 26.

For Figure 2-8 in the ISS, clarify what “PTQ search” (highlighted below) refers to for each of the following:

- Cardiovascular events
- Pancreatitis or suspicion of pancreatitis including elevated lipase/amylose
- Neoplasms
- Thyroid disease (including elevated calcitonin)

---

a. The Novo Nordisk Event Adjudication Group (NN-EAG); events identified by pre-defined PTQ search
b. Based on review by medically qualified personnel, referral of these events for adjudication was considered inappropriate
Please let me know if you have any questions.

Thank you,
Marisa

Marisa Petruccelli
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Phone:  240-402-6147
Fax:  301-796-9712
marisa.petruccelli@fda.hhs.gov
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MARISA PETRUCCELLI
02/24/2016
Good afternoon,

I have an additional information request for NDA 208583 IDegLira from CDRH. Please confirm receipt of this IR and provide a response to the NDA by March 1, 2016.

1. You have completed dose accuracy verification per ISO 11608-1:2012, and the results appear to comply. However, Gage R&R verification has not been provided to demonstrate the accuracy and precision of the test. Per ISO 11608-1:2012 “The repeatability and reproducibility (Gauge R&R) of the test apparatus shall be no greater than 20% of the allowed tolerance range for any given measurement.” You should provide Gage R&R testing results that demonstrate the provided test protocol for dose accuracy is adequate.

2. You have provided a list of device specifications (Table 1: Functional design Requirements as Verification Activities). The list is comprehensive and references various analysis and laboratory verification tests; however, the test reports could not be located. Please provide the full test report or the locations of the test reports within the submission. Please also provide a traceability matrix that identifies all device features and functions, the associated requirements, and the supporting verification/validation documents (e.g. spring specifications, connection features etc.). Additional functional requirements may be needed based on the device functions.

Additional comments:

It appears in Table 7 that 60 samples were tested at one (1) unit increments you should provide the related protocol to clarify the procedure and results (Summary Report of Qualification Testing). We recommend you note if the needle was replaced in between each application.

In Table 4 shown below it is noted that the lower limit for a dosage is μL. Please justify the clinical acceptability of this requirement.
Please let me know if you have any questions.

Thank you,

**Marisa Petruccelli**
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Phone: 240-402-6147
Fax: 301-796-9712
[marisa.petruccelli@fda.hhs.gov](mailto:marisa.petruccelli@fda.hhs.gov)
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MARISA PETRUCCELLI
02/23/2016
Good morning,

I have an additional information request for NDA 208583.

We have identified some preliminary issues with your human factors study results (reference # DV0262-UT94-2014) submitted on September 14, 2015, for insulin degludec/liraglutide (NDA 208583):

- We have noted that the data you have provided is organized based on the perceived error severity instead of the specific use errors noted in the study. In order to fully understand and evaluate the results of your HF Study, we request that you provide a summary table that describes: (1) study tasks, (2) associated use errors noted with each task during the study, (3) the number of participants committing the error, (4) the specific user group for each participant, (5) the user’s subjective feedback for each error, (6) root cause of each use error, and (7) mitigation strategies for addressing each of these errors.
- In addition, we noted that several study participants did not depress the dose button for a recommended count of 6. We request that you submit data to clarify the minimum length of time that the button must be pressed in order to deliver the full dose of medication from the pen injector. We also request that you submit data indicating the length of time that the study participants failing this task did press the dose button.

We request that you submit this information to us by close of business on **Friday, February 26, 2016**. Please let us know if you will not be able to meet this deadline or if you have any questions.

Thank you,

Marisa

**Marisa Petruccelli**

Regulatory Project Manager

Division of Metabolism and Endocrinology Products

Center for Drug Evaluation and Research

U.S. Food and Drug Administration

Phone: 240-402-6147

Fax: 301-796-9712

marisa.petrucelli@fda.hhs.gov
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MARISA PETRUCCELLI
02/18/2016
Good morning, Rick,

Attached I have the agenda for the NDA 208583 Mid-Cycle Communication scheduled for this Thursday, February 18. As I mentioned previously, we would like to change the teleconference start time from 2:00pm ET to 2:30pm due to a scheduling conflict on our end. I have booked an hour for us, but we may not necessarily need to use that full time.

I have included a list of tentative FDA attendees in the agenda. Please let me know today tentative Novo Nordisk attendees, as well as a call-in number.

Please let me know if there are any questions.

Thank you,

Marisa

Marisa Petruccelli
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Phone: 240-402-6147
Fax: 301-796-9712
marisa.petruccelli@fda.hhs.gov
1. **Introductions**

**Tentative FDA Attendees**

Jean-Marc Guettier, M.D., Division Director  
Lisa Yanoff, M.D., Clinical Team Leader  
Tania Condarco, M.D., Clinical Reviewer  
Julie Van der Waag, MPH, Chief, Project Management Staff  
Marisa Petruccelli, Project Manager  
Mark Rothmann, PhD, Biometrics Team Leader  
Anna Kettermann, Dipl. Math, MA, Biometrics Reviewer  
Sapana Patel, PharmD, Pharmacist, General Hospital Devices Branch, CDRH  
CDR Alan Stevens, Acting Chief, General Hospital Devices Branch, CDRH  
Amarilys Vega, MD, MPH, Medical Officer, DRISK  
Naomi Redd, PharmD, Team Leader, DRISK  
Ariane Conrad, PharmD, BCACP, CDE, FASCP, Safety Evaluator, DMEPA  
Yelena Maslov, Pharm.D., Team Leader, DMEPA  
LaToya Bonner, Pharm.D., NCPS, Designated Federal Official, DACCM

**Eastern Research Group**

2. **Introductory Comments**

We are providing these comments to you before we complete our review of the entire application to give you **preliminary** notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may or may not be able to consider your response before we take an action on your application during this review cycle.

3. **Significant Review Issues**

**Statistics**

In the course of our review we identified multiple anomalies in data for the main efficacy endpoint (HbA1c).

Please note that this is *not an exhaustive list* of all data anomalies. We identified similar issues with all efficacy datasets. The examples below from study 3697 are used to illustrate specific issues:

1. In this example, visits were repeated and were recorded out of chronological order.
The next example is used to illustrate two issues that we have seen in the data:

2. In this example, multiple visits were taken on the same day and recorded as visits several weeks apart.
   b. This example also shows existing data points with the claim that data were not available.
3. In this example, the subject had multiple retesting:

<table>
<thead>
<tr>
<th>SUBJID</th>
<th>VISID</th>
<th>TIMINGC</th>
<th>TARMLB</th>
<th>FVSTDU</th>
<th>TRLDAY</th>
<th>DELETEFL</th>
<th>S_COMMNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>942045</td>
<td>10</td>
<td>-2 Weeks</td>
<td>IDegLira</td>
<td>8.6</td>
<td>-8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>942045</td>
<td>20</td>
<td>0 Weeks</td>
<td>IDegLira</td>
<td>8.6</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>942045</td>
<td>60</td>
<td>4 Weeks</td>
<td>IDegLira</td>
<td>9.0</td>
<td>28</td>
<td></td>
<td></td>
</tr>
<tr>
<td>942045</td>
<td>100</td>
<td>8 Weeks</td>
<td>IDegLira</td>
<td>8.8</td>
<td>57</td>
<td></td>
<td></td>
</tr>
<tr>
<td>942045</td>
<td>140</td>
<td>12 Weeks</td>
<td>IDegLira</td>
<td>8.5</td>
<td>85</td>
<td>Y</td>
<td></td>
</tr>
<tr>
<td>942045</td>
<td>140</td>
<td>12 Weeks</td>
<td>IDegLira</td>
<td>9.1</td>
<td>95</td>
<td>Y</td>
<td></td>
</tr>
<tr>
<td>942045</td>
<td>140</td>
<td>12 Weeks</td>
<td>IDegLira</td>
<td>9.2</td>
<td>97</td>
<td></td>
<td></td>
</tr>
<tr>
<td>942045</td>
<td>180</td>
<td>16 Weeks</td>
<td>IDegLira</td>
<td>8.9</td>
<td>114</td>
<td></td>
<td></td>
</tr>
<tr>
<td>942045</td>
<td>220</td>
<td>20 Weeks</td>
<td>IDegLira</td>
<td>8.3</td>
<td>141</td>
<td></td>
<td></td>
</tr>
<tr>
<td>942045</td>
<td>280</td>
<td>26 Weeks</td>
<td>IDegLira</td>
<td>8.7</td>
<td>180</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

4. Information Requests

Statistics

Please refer to the review issue explained above. For each study, you should examine the appropriate datasets for such data anomalies. You should make corrections as appropriate and provide in the respective dataset an explanation for the changes. You should send us new corrected datasets with updated define files.

In the Information Request (IR) dated December 14, 2015, we asked you to clarify multiple data exclusions. As was indicated in the IR, the clarifications for most of the exclusions were not provided in the dataset. Your response to the IR, received on December 21, 2015, provided only a summary of causes; no specific clarifications for each excluded observation were given. You should provide the requested additional information.

Please provide all responses within two weeks. Please let us know if more time will be needed.

Device

You state that all PDS290 IDegLira pen-injector device components which come into direct or indirect contact with users consist of [cytotoxicity, sensitization, and irritation within the NDA for the proposed device constituent of your combination product. Please submit the test reports as an amendment to the NDA or submit a letter of authorization from the device manufacturer and location within the DMF of the requested test reports within one week.](b)(4)
5. **Major Safety Concerns**

Upon review of your human factor study results submitted on September 14, 2015, we noted that you included all users (including prescribers) to determine their ability to appropriately use the pen injector device. You have not provided data to determine if prescribers were able to appropriately prescribe and dose this medication, make dose titrations, and convert patients to this medication from other therapies. Considering that this is a novel multi-ingredient product that combines insulin with a GLP-1 agonist, we do not have sufficient data to conclude that prescribers would be able to safely prescribe this product, and the study results provided do not adequately address this concern. If you have completed any formative or summative studies to address this concern, please submit this information to the NDA. If no studies have been completed, please provide a response on how you plan to address these concerns.

6. **Risk Management Update**

We intend to make revisions to your proposed REMS to align it with the recent Saxenda REMS modification approved on February 1, 2016. We will follow up with you regarding these revisions.

7. **Advisory Committee (AC) Meeting Plans**

- The purpose of this AC is to discuss the potential risks and benefits of starting two anti-diabetic agents simultaneously, and to discuss the population for which this approach would be best suited.

- Our tentative date for the AC meeting is May 25, 2016.

- We have tentative plans for a 90-minute sponsor presentation.

8. **Proposed Date and Format for Late-Cycle Meeting/Other Projected Milestones**

- Tentative LCM date: May 9, 2016

- Labeling to Applicant: May 26, 2016

Meeting minutes of this teleconference will be provided to you within 30 days of the teleconference (by March 19, 2016).
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MARISA PETRUCELLI
02/16/2016
Good morning,

I have an additional information request for NDA 208583. Please confirm receipt of this request and provide a response within one week.

Please clarify, for each trial, what instructions were given to patients for measurements of SMPG for IDegLira and for comparator. The 3697 protocol mentions that the daily SMPG values are recorded for IDegLira and degludec, while only the SMPG measures for 3 days prior to site visit are recorded for liraglutide; thus it is unclear if patients were instructed to perform daily SMPGs. If these instructions differed between treatment arms, please explain why.

Thank you,
Marisa

Marisa Petruccelli
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Phone: 240-402-6147
Fax: 301-796-9712
marisa.petruccelli@fda.hhs.gov
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MARISA PETRUCCELLI
01/14/2016
Good afternoon,

I have another information request regarding NDA 208583. Please confirm receipt and provide a response within one week.

1. For all the insulin comparator phase 3 trials, fill in table 1 below with the proportion of patients for each trial that reached titration goal (based on FPG target) at each visit.

Table 1. proportion of patients who reached FPG titration target at each visit.

<table>
<thead>
<tr>
<th>Visit</th>
<th>3697 IDegLira: N (%)</th>
<th>IDeg : N (%)</th>
<th>3697-ext IDegLira: N (%)</th>
<th>IDeg : N (%)</th>
<th>3912 IDegLira: N (%)</th>
<th>IDeg : N (%)</th>
<th>3952 IDegLira: N (%)</th>
<th>IGIAR: N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visit 1 (week...)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Visit 2 (week...)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Visit 3 (week ...)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Etc...</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

2. For patients in phase 3 trials who received ≤ 32 units and >32 units of comparator insulin fill in Table 2 (FAS, LOCF)

Table 2

<table>
<thead>
<tr>
<th>Study</th>
<th>FOR SUBSET OF PATIENTS≤32 UNITS</th>
<th>FOR SUBSET OF PATIENTS&gt;32 UNITS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Change in HbA1c</td>
<td>Mean baseline HbA1c</td>
</tr>
<tr>
<td>3697  (26 wks)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3697–ext (52 wks)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3912  (26 wks)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3952  (26 wks)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Reference ID: 3871116
3. Based on the results of the phase 3 trials, justify if there is any benefit of using IDegLira at doses less than 32 dose steps (where the liraglutide component is less than the approved 1.2 mg), vs. using comparator alone.

Please let me know if you have any questions.

Thank you,

**Marisa Petruccelli**  
Regulatory Project Manager  
Division of Metabolism and Endocrinology Products  
Center for Drug Evaluation and Research  
U.S. Food and Drug Administration  
Phone: 240-402-6147  
Fax: 301-796-9712  
marisa.petruccelli@fda.hhs.gov
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MARISA PETRUCCELLI
01/08/2016
Good afternoon,

Please see the below information request for NDA 208583. Please provided a response within one week.

1. Fill in Table 1 with information regarding IDegLira in each phase 3 trial.

   **Table 1: Patients randomized to IDegLira who met glycemic withdrawal criteria or were withdrawn due to requiring >50 dose steps.**

<table>
<thead>
<tr>
<th>Trial</th>
<th>Patients meeting glycemic withdrawal criteria *</th>
<th>Patients who were withdrawn or withdrew because they required &gt;50 dose steps</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N (%)</td>
<td>Week at which criteria was met: Average (range) wks</td>
</tr>
<tr>
<td>3697</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3697-ext</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3912</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3851</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3951</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3952</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

   *glycemic withdrawal criteria were the same in all phase 3 trials:
   - If the fasting SMPG values taken on three consecutive days or if any of the FPG samples analyzed by the central laboratory exceeded 1:
     - Baseline- week 6: >270 mg/dL
     - Week 7- week 12: > 240 mg/dL
     - Week 13-week 26 (to week 52 in trial 3697): > 200 mg/dl

2. For patients in Table 1, **for each study**, please provide demographic characteristics as per FDA information request sent on 12.23.15.

Please let me know if you have any questions.

Thank you,

Marisa

Marisa Petruccelli
Regulatory Project Manager

Reference ID: 3866578
The subject was to be called for an unscheduled visit as soon as possible. A confirmatory FPG was to be obtained and analysed by the central laboratory. If this FPG exceeded the above described values, and no treatable intercurrent cause for the hyperglycaemia was diagnosed, the subject was to be withdrawn.
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MARISA PETRUCCELLI
12/29/2015
Good morning,

I have an additional information request for NDA 208583:

For the patients identified in the information request response you submitted on December 10, 2015, who reached a dose of \(<32\) units, fill in the following table:

<table>
<thead>
<tr>
<th>Study</th>
<th>Change in HbA1c</th>
<th>N Mean Baseline A1c(SD)</th>
<th>End of trial A1c (SD)</th>
<th>Absolute change</th>
</tr>
</thead>
<tbody>
<tr>
<td>3697 (26 wks)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3697 – ext (52 wks)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3912 (26 wks)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3851 (26 wks)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3951 (26 wks)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3952 (26 wks)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

For the patients identified in the information request response you submitted December 10, 2015, who reached a dose of \(>32\) units, fill in the following table:

<table>
<thead>
<tr>
<th>Study</th>
<th>Change in HbA1c</th>
<th>N Mean Baseline A1c(SD)</th>
<th>End of trial A1c (SD)</th>
<th>Absolute change</th>
</tr>
</thead>
<tbody>
<tr>
<td>3697 (26 wks)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3697 – ext (52 wks)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Reference ID: 3865737
Please let me know if you have any questions. I will be back in the office on December 28.

Thank you,
Marisa

**Marisa Petruccelli**
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Phone: 240-402-6147
Fax: 301-796-9712
marisa.petruccelli@fda.hhs.gov
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MARISA PETRUCCELLI
12/24/2015
Good morning,

I have an additional information request for NDA 208583. Please provide a response within one week.

1. For the patients identified in the information request you submitted on December 10, 2015, regarding the end of trial dose of IDegLira across the phase 3 programs, provide pooled (for 3697, 3912, 3851, 3951, 3952) demographic characteristics of patients taking <= 32 dose steps of IDegLira and for patients taking >32 dose steps of IDegLira (fill in Table 1).

Table 1:

<table>
<thead>
<tr>
<th></th>
<th>IdegLira ( N= ) taking &lt;=32 dose steps N(%) or mean SD</th>
<th>IdegLira ( N= ) taking &gt;32 dose steps</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean age (years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age&gt;65 years of age; n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age&gt;75 years of age n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Male</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Body weight (Kg)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>BMI (kg/m^2)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Ethnicity</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hispanic or Latino</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Race</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black or African American</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td></td>
<td></td>
</tr>
<tr>
<td>American Indian or Alaska Native</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Duration of Diabetes (years)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>HbA1c (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>FPG (mg/dL)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Diabetes complications e (based on data from diabetes complications form)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any complication d</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetic neuropathy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetic retinopathy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetic nephropathy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Macroangiopathy</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Other commonly reported concomitant illnesses (i.e. reported in &gt;10% of patients)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Obesity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Osteoarthritis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depression</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Menopause</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastroesophageal reflux disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Pretrial anti-diabetic regimen</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3697 (main and Ext)</td>
<td>1 OAD</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2 OADs</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt;2 OADs</td>
<td></td>
</tr>
</tbody>
</table>

Reference ID: 3865001
<table>
<thead>
<tr>
<th>Oral antidiabetic drug class</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Biguanide n(%)</td>
<td>Metformin n (%)</td>
<td>Glinide n (%)</td>
<td>Repaglinide n (%)</td>
</tr>
<tr>
<td></td>
<td>Mean (SD) daily dosing in mg</td>
<td>Mean (SD) daily dosing in mg</td>
<td>Mean (SD) daily dosing in mg</td>
<td>Mean (SD) daily dosing in mg</td>
</tr>
<tr>
<td>Sulfonylurea n(%)</td>
<td>Glibenclamide n (%)</td>
<td>Gliclazide n (%)</td>
<td>Glimepiride n (%)</td>
<td>Glipizide n (%)</td>
</tr>
<tr>
<td></td>
<td>Mean (SD) daily dosing in mg</td>
<td>Mean (SD) daily dosing in mg</td>
<td>Mean (SD) daily dosing in mg</td>
<td>Mean (SD) daily dosing in mg</td>
</tr>
<tr>
<td></td>
<td>Thiazolidinedione n(%)</td>
<td>Pioglitazone n (%)</td>
<td>Mean (SD) daily dosing in mg</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Insulin used at baseline f</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Insulin glargine n (%)</td>
<td>Mean (SD) daily dosing in units</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Insulin detemir n (%)</td>
<td>Mean (SD) daily dosing in units</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Insulin neutral protamine Hagedorn n (%)</td>
<td>Mean (SD) daily dosing in units</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Biosynthetic human insulin (BHI) n (%)</td>
<td>Mean (SD) daily dosing in units</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Human insulin (HI) n (%)</td>
<td>Mean (SD) daily dosing in units</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Insulin aspart (Iasp) n (%)</td>
<td>Mean (SD) daily dosing in units</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean eGFR (mL/min/1.73 m2)</td>
<td>Mean eGFR</td>
<td>Mean eGFR &lt;60 mL/min/1.73 m2</td>
<td>% of patients with eGFR &lt;60 mL/min/1.73 m2</td>
<td>% of patients with eGFR &lt;30 mL/min/1.73 m2</td>
</tr>
</tbody>
</table>
2. Also, for each trial, for patients taking <= 32 dose steps of IDegLira, and for those taking >32 dose steps of IDegLira provide demographic characteristics (as in table 1).
3. For each trial for patients taking <= 32 dose steps of IDegLira, and for those taking >32 dose steps of IDegLira describe if there were any differences in disposition and withdrawal.
4. For the overall phase 3 program of IDegLira, provide the Mean eGFR (mL/min/1.73 m²) for IDegLira and for comparator.
5. For each phase 3 trial clarify the overall percentage of patients that an eGFR <60 mL/min/1.73m²
   a. Provide the n (%) for IDegLira and comparator.
6. For each phase 3 trial, clarify the percentage of patients who were >65 years of age and those who were >75 years of age.
   a. Provide the n (%) for IDegLira and comparator.
7. **Over titration of IDegLira:**
   a. In the CSR of trial 3697 (page 124-125) you state that “27 patients were titrated above the max dose of 50 dose steps of IDegLira due to misunderstanding of the titration algorithm.” For the patients identified, clarify if this overtitration resulted in AEs. Also, clarify why there were the problems with titration and what was done to clarify the titration algorithm. Also explain if the investigator’s explanation of the titration algorithm to these patients was sufficient to correct the overtitration error, if not, explain why.
   i. In a table, provide Unique subject IDs of these patients and the trial day where the error started, the highest dose received, and the day the error was corrected, the location of these patients (i.e. US), the reporting of AE (and what the AE was).
   b. For each of the remaining phase 3 trials (3912, 3851, 3951, 3952) provide the same explanation for patients who were overtitrated (i.e. received more than 50 dose steps) on IDegLira at any point during the trial
8. Fill in Table 2 below.

### Table 2: Statistical analyses of confirmatory secondary endpoints- adjusted for multiplicity- after 26 weeks of treatment - FAS

<table>
<thead>
<tr>
<th>Study (stats analysis)</th>
<th>Treatment group</th>
<th>FAS</th>
<th>n baseline</th>
<th>Baseline estimate (SD)</th>
<th>n EOT</th>
<th>EOT estimate (SD)</th>
<th>LS Mean change in estimate (SE)</th>
<th>Treatment difference (95% confidence interval)</th>
<th>P- Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>body weight change (Kg)</strong></td>
<td>3697 (26 wks)</td>
<td>IDegLira Degludec Liraglutide</td>
<td></td>
<td>-2.22 2.44</td>
<td></td>
<td>[-2.64; -1.80]#</td>
<td></td>
<td>[2.02; 2.86]~</td>
<td></td>
</tr>
<tr>
<td>3912 (26 wks)</td>
<td>IDegLira Degludec Liraglutide</td>
<td></td>
<td>0.68 7.61</td>
<td></td>
<td>[0.53; 0.87]#</td>
<td></td>
<td>[5.17;11.21]~</td>
<td></td>
<td>0.0023 &lt;0.0001</td>
</tr>
<tr>
<td><strong>Number of confirmed hypoglycemic episodes</strong></td>
<td>3697 (26 wks)</td>
<td>IDegLira Degludec Liraglutide</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.0023 &lt;0.0001</td>
</tr>
<tr>
<td>3912 (26 wks)</td>
<td>IDegLira Degludec Liraglutide</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>postprandial glucose increment AUC (0-4 hours)</strong></td>
<td>3697 (26 wks)</td>
<td>IDegLira Degludec Liraglutide</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.0023 0.70</td>
</tr>
</tbody>
</table>

Reference ID: 3865001
Data are based on trials NN9068-3697, NN9068-3912. ⑧ IDegLira versus IDeg; ⑨ IDegLira versus Liraglutide
N: number of subjects; SD: standard deviation; wks: weeks. EOT: End of trial: last visit before follow-up visit. Missing data are imputed using last observation carried forward. CI confidence intervals; ANOVA with treatment, region/country, relevant stratification factors as fixed effects and baseline response as covariate.
Source, 2.7.3 Summary of clinical efficacy, table 11-2; page 140;

9. Fill in Table 3 below: Data sets analysed- phase 3 trials

<table>
<thead>
<tr>
<th>STUDY</th>
<th>IDEGLIRA</th>
<th>COMPARATOR (S)</th>
<th>TOTAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>3697</td>
<td>N (%)</td>
<td>IDEg N (%)</td>
<td>Liraglutide N (%)</td>
</tr>
<tr>
<td>Randomized</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FAS</td>
<td>834 (100%)</td>
<td>414 (100%)</td>
<td>415 (100%)</td>
</tr>
<tr>
<td>PP</td>
<td>833 (99.9%)</td>
<td>413 (99.8%)</td>
<td>414 (99.8%)</td>
</tr>
<tr>
<td>SAS</td>
<td>755 (90.5%)</td>
<td>374 (90.3%)</td>
<td>362 (87.2%)</td>
</tr>
<tr>
<td>CAS</td>
<td>825 (98.9%)</td>
<td>412 (99.5%)</td>
<td>412 (99.3%)</td>
</tr>
<tr>
<td></td>
<td>736 (88.2%)</td>
<td>366 (88.4%)</td>
<td>342 (82.4%)</td>
</tr>
<tr>
<td>3912</td>
<td>IDEg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3851</td>
<td>Liraglutide</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3951</td>
<td>Placebo</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3952</td>
<td>IGlargine</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Please let me know if you have any questions.

Thank you,
Marisa

Marisa Petruccelli
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Phone: 240-402-6147
Fax: 301-796-9712
marisa.petruccelli@fda.hhs.gov
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MARISA PETRUCCELLI
12/23/2015
Good afternoon,

I have below an additional information request for NDA 208583. Please provide a response within one week:

For the phase 3 completed trials, fill in the following table with the respective baseline and end of trial (EOT) doses for the monocomponents of I DegLira and comparators. For trial 3697 please complete EOT at 26 and 52 weeks.

<table>
<thead>
<tr>
<th></th>
<th>3697 (26 wks)</th>
<th>3697 (52 wks)</th>
<th>3912(26 wks)</th>
<th>3851(26 wks)</th>
<th>3951(26 wks)</th>
<th>3952(26 wks)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Starting dose</strong></td>
<td><strong>Mean (SD)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>I DegLira</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>833</td>
<td>833</td>
<td>833</td>
<td>833</td>
<td>833</td>
<td>833</td>
</tr>
<tr>
<td>n</td>
<td>809</td>
<td>809</td>
<td>809</td>
<td>809</td>
<td>809</td>
<td>809</td>
</tr>
<tr>
<td>I Deg (U)</td>
<td>11.8 (1.4)</td>
<td>11.8 (1.4)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lira glutide</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mg</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Comparator</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liraglutide (mg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exenatide (mcg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo (mg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glargine (U)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dose at 26 weeks</td>
<td><strong>Mean (SD)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>I DegLira</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>833</td>
<td>833</td>
<td>833</td>
<td>833</td>
<td>833</td>
<td>833</td>
</tr>
<tr>
<td>n</td>
<td>816</td>
<td>816</td>
<td>816</td>
<td>816</td>
<td>816</td>
<td>816</td>
</tr>
<tr>
<td>I Deg (U)</td>
<td>38.1 (13)</td>
<td>38.1 (13)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lira glutide</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mg</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Comparator</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liraglutide (mg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Reference ID: 3861155
<table>
<thead>
<tr>
<th>Exenatide (mcg)</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>N (FAS)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo (mg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N (FAS)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glargine (U)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Dose at 52 weeks Mean (SD)**

<table>
<thead>
<tr>
<th>IDegLira : N (FAS)</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>IDeg (U)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liraglutide (mg)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Comparator**

<table>
<thead>
<tr>
<th>N (FAS)</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>IDeg (U)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>N (FAS)</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>IDeg (U)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liraglutide (mg)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Actual daily insulin dose (U) at end of trial**

<table>
<thead>
<tr>
<th>Treatment difference: IDegLira – Basal insulin</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Estimate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>95% CI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P value</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- -14.90 \[-23.38\] \[-25.52\]
- 17.14 \[-26.44; -20.31\] \[-28.90; -22.05\]
- <0.0001 \[<0.0001\] \[<0.0001\]

* Dose of IDeg in this trial was capped at 50 units

Source: Summary of Clinical Efficacy, Table 3-18, 3-19, pages 99-100

Please let me know if there are any questions.

Thank you,
Marisa

**Marisa Petruccelli**
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Phone: 240-402-6147
Fax: 301-796-9712
marisa.petruccelli@fda.hhs.gov
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MARISA PETRUCCELLI
12/15/2015
Good morning,

We have the following additional information requests regarding NDA 208583. Please provide a response within one week.

1. Your analysis dataset containing HbA1c measurements indicates that some of the HbA1c values were excluded from the analysis. Specifically, study 3697 dataset identifies 687 HbA1c observations with non-missing variable S_COMMNT (SRC comment). Of those 687 subjects, only 53 observations had a missing HbA1c value. At the same time 120 observations were excluded from your analysis. Please clarify how the excluded observations were selected.

2. For your phase 3 trials (3697, 3912, 3951, 3952, 3851), please fill in the following baseline characteristics table.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Randomization</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>IDegLira (N=X)</td>
</tr>
<tr>
<td></td>
<td>N(%) or mean SD</td>
</tr>
<tr>
<td></td>
<td>Comparator (N=X)</td>
</tr>
<tr>
<td></td>
<td>N(%) or mean SD</td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td></td>
</tr>
<tr>
<td>Body weight (Kg)</td>
<td></td>
</tr>
<tr>
<td>BMI (kg/m^2)</td>
<td></td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
</tr>
<tr>
<td>Hispanic or Latino</td>
<td></td>
</tr>
<tr>
<td>Not Hispanic or Latino</td>
<td></td>
</tr>
<tr>
<td>Race</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td></td>
</tr>
<tr>
<td>Black or African American</td>
<td></td>
</tr>
<tr>
<td>Asian Indian</td>
<td></td>
</tr>
<tr>
<td>Asian non-Indian</td>
<td></td>
</tr>
<tr>
<td>American Indian or Alaska Native</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td></td>
</tr>
<tr>
<td>Duration of Diabetes (years)</td>
<td></td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td></td>
</tr>
<tr>
<td>FPG (mg/dL)</td>
<td></td>
</tr>
<tr>
<td>Diabetes complications</td>
<td></td>
</tr>
<tr>
<td>All</td>
<td></td>
</tr>
<tr>
<td>Cardiovascular</td>
<td></td>
</tr>
<tr>
<td>Dermal</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td></td>
</tr>
</tbody>
</table>

Reference ID: 3859925
<table>
<thead>
<tr>
<th>Neurological</th>
<th>Ophthalmic</th>
<th>Renal</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Other (include as footnote what “other refers to)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Other commonly reported concomitant illnesses (i.e. reported in &gt;10% of patients)</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
</tr>
<tr>
<td>Obesity</td>
</tr>
</tbody>
</table>

**Pretrial anti-diabetic regimen**

<table>
<thead>
<tr>
<th>1 OAD</th>
<th>2 OADs</th>
<th>&gt;2 OADs</th>
</tr>
</thead>
<tbody>
<tr>
<td>3697</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3912</td>
<td>Basal insulin+:</td>
<td>1 OAD</td>
</tr>
<tr>
<td></td>
<td>&gt;2 OADs</td>
<td>Total insulin dose (u/kg):</td>
</tr>
<tr>
<td>3851</td>
<td>GLP-1+:</td>
<td>1 OAD</td>
</tr>
<tr>
<td></td>
<td>&gt;2 OADs</td>
<td>Total insulin dose (U):</td>
</tr>
<tr>
<td>3951</td>
<td>1 OAD</td>
<td>2 OADs</td>
</tr>
<tr>
<td></td>
<td>&gt;2 OADs</td>
<td></td>
</tr>
<tr>
<td>3952</td>
<td>Basal insulin+:</td>
<td>1 OAD</td>
</tr>
<tr>
<td></td>
<td>&gt;2 OADs</td>
<td>Total insulin dose (u/kg):</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Total insulin dose (U):</td>
</tr>
</tbody>
</table>

**Oral antidiabetic drug class**

<table>
<thead>
<tr>
<th>Biguanide n(%)</th>
<th>Metformin n (%)</th>
<th>Mean (SD) daily dosing in mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glinide n (%)</td>
<td>Fill in as done for the biguanide category</td>
<td></td>
</tr>
<tr>
<td>above</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-------</td>
<td>---</td>
<td>---</td>
</tr>
</tbody>
</table>
| **Sulfonylurea n(%)**  
*Fill in as done for the biguanide category above* |  |  |
| **Thiazolidinedione n(%)**  
*Fill in as done for the biguanide category above* |  |  |
| **Sponsor, fill in other antidiabetic drug classes that were seen in the phase 3 trials as above** |  |  |
| **Insulin used at baseline** |  |  |
| Insulin Glargine |  |  |
| Insulin Detemir |  |  |
| Insulin Neutral Protamine Hagedorn |  |  |
| *Sponsor, list other categories as pertinent* |  |  |
| **Mean eGFR (mL/min/1.73 m2)** |  |  |
| % of patients with eGFR <60 mL/min/1.73 m2 |  |  |
| % of patients with eGFR <30 mL/min/1.73 m2 |  |  |

Please let me know if you have any questions.

Thank you,

**Marisa Petruccelli**  
Regulatory Project Manager  
Division of Metabolism and Endocrinology Products  
Center for Drug Evaluation and Research  
U.S. Food and Drug Administration  
Phone: 240-402-6147  
Fax: 301-796-9712  
marisa.petruccelli@fda.hhs.gov
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MARISA PETRUCCELLI
12/14/2015
Good afternoon,

I have the following information request for NDA 208583. Please confirm receipt and provide a response within one week.

**Question 1:**
Clarify the following financial disclosure information.

In your “financial Disclosure Summary of US trial and non-US trials” for trial 3851 you list that there are 13 US investigators with disclosable interests, however in “Table of financial disclosures, form 3455” for this study you only list 11 investigators. Clarify this discrepancy.

Also, fill in the highlighted cells in the table below:

<table>
<thead>
<tr>
<th>Site No.</th>
<th>Name of Investigator</th>
<th>Trial Site Role (Principal or Sub-Investigator)</th>
<th>No. of Subjects Entered Treatment (Randomized subjects)</th>
<th>Certification and/or Disclosure for each Investigator* (Yes/No)</th>
<th>Disclosable Information ** (Yes/No)</th>
<th>Disclosable Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>(0) (0)</td>
<td>Principal Investigator</td>
<td>Yes</td>
<td>Yes</td>
<td>$209,880</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(0) (0)</td>
<td>Principal Investigator</td>
<td>Yes</td>
<td>Yes</td>
<td>$109,100</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(0) (0)</td>
<td>Principal Investigator</td>
<td>Yes</td>
<td>Yes</td>
<td>$155,380</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(0) (0)</td>
<td>Principal Investigator</td>
<td>Yes</td>
<td>Yes</td>
<td>$44,780</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(0) (0)</td>
<td>Principal Investigator</td>
<td>Yes</td>
<td>Yes</td>
<td>$66,850</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(0) (0)</td>
<td>Principal Investigator</td>
<td>Yes</td>
<td>Yes</td>
<td>$62,410</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(0) (0)</td>
<td>Principal Investigator</td>
<td>Yes</td>
<td>Yes</td>
<td>$28,960</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(0) (0)</td>
<td>Principal Investigator</td>
<td>Yes</td>
<td>Yes</td>
<td>$73,660</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(0) (0)</td>
<td>Principal Investigator</td>
<td>Yes</td>
<td>Yes</td>
<td>$125,520</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(0) (0)</td>
<td>Principal Investigator</td>
<td>Yes</td>
<td>Yes</td>
<td>$119,120</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(0) (0)</td>
<td>Principal Investigator</td>
<td>Yes</td>
<td>Yes</td>
<td>$45,400</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(0) (0)</td>
<td>Principal Investigator</td>
<td>Yes</td>
<td>Yes</td>
<td>$170,760</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Reference ID: 3858137
For trial 3951 in your “financial Disclosure Summary of US trial and non-US trials” you list that there are 6 US investigators with disclosable interests, however in “Table of financial disclosures, form 3455” for this study you only list 5 investigators. Clarify this discrepancy.

Also fill in the highlighted cells in the table below:

<table>
<thead>
<tr>
<th>Site No.</th>
<th>Name of Investigator</th>
<th>Trial Site Role (Principal or Sub-investigator)</th>
<th>No. of Subjects Entered Treatment (Randomized subjects)</th>
<th>Certification and/or Disclosure for each Investigator* (Yes/No)</th>
<th>Disclosable Information** (Yes/No)</th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Principal Investigator</td>
<td>(b)(6)</td>
<td>(b)(6)</td>
<td>Yes</td>
<td>Yes</td>
<td>$193,080</td>
</tr>
<tr>
<td></td>
<td>Principal Investigator</td>
<td>Yes</td>
<td>Yes</td>
<td></td>
<td>Yes</td>
<td>$55,810</td>
</tr>
<tr>
<td></td>
<td>Principal Investigator</td>
<td>Yes</td>
<td>Yes</td>
<td></td>
<td>Yes</td>
<td>$66,250</td>
</tr>
<tr>
<td></td>
<td>Principal Investigator</td>
<td>Yes</td>
<td>Yes</td>
<td></td>
<td>Yes</td>
<td>$67,600</td>
</tr>
<tr>
<td></td>
<td>Principal Investigator</td>
<td>Yes</td>
<td>Yes</td>
<td></td>
<td>Yes</td>
<td>$128,100</td>
</tr>
<tr>
<td></td>
<td>Principal Investigator</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>$45,400</td>
</tr>
</tbody>
</table>

For trials 3951 and 3851, clarify if the investigator: Bode Bruce is the same (at sites 109 [trial 3851], and site 802 [trial 3951]). If the investigator is the same in both trials, clarify why the disclosable information is different in the two trials.

**Question 2**: compare and contrast the methods used for the sensitivity analysis in the phase 3 trials and fill out the table below with this information.

**Table 1- sensitivity analyses used in phase 3 trials**

| Pivotal trials 3697 and 3912 | 3851, 3951, 3952 |

Please contact me with any questions.
Thank you,

Marisa Petruccelli  
Regulatory Project Manager  
Division of Metabolism and Endocrinology Products  
Center for Drug Evaluation and Research  
U.S. Food and Drug Administration  
Phone: 240-402-6147  
Fax: 301-796-9712  
marisa.petruccelli@fda.hhs.gov
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MARISA PETRUCCELLI
12/09/2015
Good afternoon,

Please see the below information request regarding NDA 208583. Please provide a response within one week.

1. Complete Table 1 with the number of subjects ([n] and %) taking the following doses of IDegLira at the end of the trial (26 weeks). For trial 3697 (in addition to the 26 week data), also provide the same information for participants at the end of 12 months.

<table>
<thead>
<tr>
<th>Trial</th>
<th>≤ 16</th>
<th>17 to ≤ 32</th>
<th>33 to 50 Inclusively</th>
<th>&gt;50</th>
</tr>
</thead>
<tbody>
<tr>
<td>3697 (26 week)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3697 (52 week)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3912</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3851</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3951</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3952</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

16 dose steps = 0.58 mg of liraglutide
33 dose steps = 1.19 mg of liraglutide
50 dose steps = 1.8 mg of liraglutide

2. For each trial, for patients taking fewer than 32 dose steps or greater than 50 dose steps, provide a summary of hypoglycemia and body weight change from baseline. For trials 3912 and 3952, which enrolled patients on basal insulin at baseline provide a summary of the change in basal insulin dose from baseline. Please also provide patient level information regarding titration of IDegLira including reason for achieved dose, i.e. reached titration goal, dose limiting adverse reaction, non-adherence, etc. For patients using more than 50 dose steps provide explanation for the overdose.

3. For each trial, for patients taking >50 dose steps, fill in Table 2.

Table 2- Adverse events and/or laboratory abnormalities reported for patients taking >50 dose steps of IDegLira

<table>
<thead>
<tr>
<th>Patient ID</th>
<th>Adverse event</th>
</tr>
</thead>
</table>

Reference ID: 3855445
<table>
<thead>
<tr>
<th>Trial</th>
<th>Patient ID</th>
<th>Dose of IdegLira</th>
<th>Dose of the liraglutide component</th>
<th>I.e. Pancreatitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>3697</td>
<td>XXXX</td>
<td>51 dose steps</td>
<td>XXX mg</td>
<td></td>
</tr>
<tr>
<td>3912</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3851</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3951</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3952</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Please let me know if there are any questions.

Thank you,

**Marisa Petruccelli**
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Phone: 240-402-6147
Fax: 301-796-9712
marisa.petruccelli@fda.hhs.gov
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MARISA PETRUCCELLI
12/03/2015
NDA 208583

FILING COMMUNICATION –
NO FILING REVIEW ISSUES IDENTIFIED

Novo Nordisk Inc.
Attention: Robert B. Clark
Vice President, Regulatory Affairs
800 Scudders Mill Road
Plainsboro, NJ 08536

Dear Mr. Clark:

Please refer to your New Drug Application (NDA) dated September 12, 2015, received September 14, 2015, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for insulin degludec and liraglutide [rDNA origin] injection.

We also refer to your amendments dated September 22, and October 22 and 28, 2015.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is Standard. Therefore, the user fee goal date is September 14, 2016. This application is also subject to the provisions of “the Program” under the Prescription Drug User Fee Act (PDUFA) V (refer to http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm272170.htm.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by May 26, 2016.

In addition, the planned date for our internal mid-cycle review meeting is February 10, 2016. We are currently planning to hold an advisory committee meeting to discuss this application.

At this time, we are notifying you that, we have not identified any potential review issues. Please note that our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

Reference ID: 3852671
We request that you submit the following information within 30 calendar days:

Statistics

1. The MMRM models specified in the documentation and SAS codes provided by the applicant did not function properly. It does not seem that these were the codes and datasets that were used to produce the results. Please clarify. If these are not the codes and datasets used to produce the results, please provide the codes that would reproduce your findings. Please include comments and clarifications in the codes.

2. Please clarify whether patients were measured for HbA1c post-rescue and also if those data were included in the submitted datasets.

Chemistry, Manufacturing, and Controls

3. It is acknowledged that the manufacturing site is Bagsvaerd, Denmark and that a Letter of Authorization (LoA) is provided for Drug Master File (DMF) 21494, which contains validation information for this site.

4. Regarding the validation of the bacterial endotoxins and sterility analytical procedures to be used during testing of the drug product, method suitability under actual conditions of use is requested; therefore, provide the results for the bacterial endotoxins and sterility test method verification for each site which will be performing release and/or stability testing for the drug product. Clearly identify the site in each verification report summary. If applicable, provide a reference to the location of the information in a DMF.

5. Regarding the comparability protocols—“Additional Drug Product Manufacturing Site” and “Additional Manufacturing Site for Assembly of PDS290 IDegLira pen-injector” found in 3.2.R, revise the protocols to clearly identify the proposed manufacturing site(s) for the drug product and auto-injector, and their respective operations noting any differences in the manufacturing process/equipment. Note that acceptability of your comparability protocols does not guarantee a CBE-30 filing category of your future supplement(s) as the current status of each facility will be evaluated upon our receipt of the supplement(s) and a final filing category will be determined at that time.

Device

The following questions relate to the device constituent parts of the combination product pen injector:
6. Section 3.2.P.7 of your submission contains use-related risk management documentation related to the use of the device. We are unable to locate design and manufacturing risk management documentation within the submission. We expect that you will present complete risk analysis information for the final-finished combination product. Please provide risk management documentation associated with the design and manufacturing processes of the combination product. This documentation should detail all relevant product risks, describe mitigations implemented to reduce those risks, and should provide rationale for any residual risks are considered as acceptable.

7. Section 3.2.P.7 of your submission contains a document titled, “PDS290 IDegLira pen-injector: Essential device performance and safety requirements”. This document appears to relate essential performance of the combination product to conformance to ISO 11608-1:2012. While ISO 11608-1:2012 is a useful and important design standard for needle based injection systems, it is not a substitution for a complete set of design requirements and verification activities for individual needle based injection systems. Please provide a complete list of functional design requirements and corresponding verification activities for the subject pen injector. Additional functional requirements may include, but will not necessarily be limited to:
   a. Forces required to manipulate the dose dial
   b. Forces required to activate the device
   c. Forces required to separate injector components
   d. Presence and accuracy of visual indicators/feedback
   e. Ability to reliably connect to disposable needle devices
   f. Presence and accuracy of audible indicators/feedback
   g. Biocompatible materials of construction

8. Section 3.2.P.7 of your submission contains a document titled, “PDS290 IDegLira pen-injector: Essential device performance and safety requirements”. This document includes a section titled, “release testing”. Based on information contained within this section, it appears that your batch release criteria includes an assessment of only dose accuracy, and specifically, an assessment of dose accuracy at the maximum dose condition. Please provide justification for this determination. Within your response, specifically discuss the acceptability of batch release testing which i) only challenges one aspect of device performance (dose accuracy) and; does not challenge the device to the worst case dose accuracy condition (lowest settable dose).

9. Section 3.2.P.7 of your submission contains a document titled, “Summary report of qualification testing”. This document appears to be a summary of verification testing completed on the pen injector. Please provide the Agency with actual test reports which support the summaries provided within the “Summary report of qualification testing” document as well as the additional verification activities cited within your response to the question above. Note: if a particular verification activity was conducted according to test methods specified in ISO 11608-1:2012, you may supply a statement of conformity to ISO11608-1:2012 in lieu of actual test report documents.

10. Your submission does not appear to contain shipping information for the combination product. Please provide information which supports that the complete combination
product, including the device constituent parts, is capable of meeting essential performance requirements after exposure to representative shipping conditions.

11. Section 3.2.P.8 of your submission contains stability information for the combination product. While you appear to have conducted assessments of dose accuracy after aging of the primary drug container closure, it is not clear if those assessments were conducted with aged device product. The Agency expects that you will provide information which supports that your complete combination product, including the device constituent parts, is capable of meeting essential performance requirements after aging to a period equal to or greater than the labeled expiry.

   a. Please provide complete aging information for the device constituent parts of the combination product.

   b. If you have validated aging of the device and drug constituent parts of the combination products separately, provide rationale for why the primary container closure and device assembly process does not adversely impact the primary container closure or device components of the combination product.

12. Section 3.2.P.8 of your submission contains stability information for the combination product. While you appear to have conducted assessments of dose accuracy after aging of the primary drug container closure, it is not clear if those assessments were conducted with aged device product. We expect that you will provide information which supports that your complete combination product, including the device constituent parts, is capable of meeting essential performance requirements after aging to a period equal to or greater than the labeled expiry.

Clinical Pharmacology

13. Submit the subject level (also known as study level) pharmacodynamic data (i.e., glucose infusion rate) for Trial 4026, preferably as SAS transport (*.xpt) files.

PREScribing INFORMATION

Your proposed prescribing information (PI) must conform to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57. As you develop your proposed PI, we encourage you to review the labeling review resources on the PLR Requirements for Prescribing Information and PLLR Requirements for Prescribing Information websites including:
• 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 in the PI on pregnancy, lactation, and females and males of reproductive potential
• Regulations and related guidance documents
• A sample tool illustrating the format for Highlights and Contents
• The Selected Requirements for Prescribing Information (SRPI) – a checklist of 42 important format items from labeling regulations and guidances and
• FDA’s established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

On December 4, 2014, the Food and Drug Administration published the “Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling,” also known as the Pregnancy and Lactation Labeling Rule (PLLR). The PLLR went into effect on June 30, 2015. According to PLLR, Risk Summary statements for sections 8.1 (Pregnancy), 8.2 (Lactation), and 8.3 (Females and Males of Reproductive Potential) must be based on available human and nonclinical data. The Risk Summary must also state when there are no human data or when available human data do not establish the presence or absence of drug-associated risk (21 CFR 201.57(c)(9)(i)(B)(1)).

Together with submission of the proposed labeling for PLLR compliance, applicants should provide the following information to support the labeling content: a review and summary of the relevant published literature, summary of cases reported in the pharmacovigilance database (if applicable), interim ongoing or final report on a closed pregnancy registry (if applicable).

During our preliminary review of your submitted labeling, you did not provide a review and summary of the available literature to support the changes in the Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of labeling. Thus, your proposed PLLR labeling changes cannot be agreed upon until the information request is fulfilled. No partial PLLR conversions may be made.

Submit the following information on insulin degludec and liraglutide use in pregnant and lactating women by December 27, 2015:

• a review and summary of all available published literature regarding insulin degludec and liraglutide
• a revised labeling incorporating the above information (in Microsoft Word format) that complies with PLLR.

We have also identified the following labeling issue and have the following comment:
The preferred presentation for cross-references in the Full Prescribing Information is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in italics and enclosed within brackets. For example, “[see Warnings and Precautions (5.2)]”. References such as [see Table 1 in Dosage and Administration (2.1)] in line 245 should not include a reference to Table 1. References such as (see Data, Animal Data) on line 532 should be revised to follow the preferred presentation. Please review all cross-references and revise them accordingly.

**We request that you resubmit labeling (in Microsoft Word format) that addresses this issue by December 27, 2015.** The resubmitted labeling will be used for further labeling discussions. Use the SRPI checklist to correct any formatting errors to ensure conformance with the format items in regulations and guidances.

Please respond only to the above requests for information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

We acknowledge your request for a waiver of the requirement that the Highlights of Prescribing Information be limited to no more than one-half page. We will consider your request during labeling discussions.

**PROMOTIONAL MATERIAL**

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI), Medication Guide, and patient PI. Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

OPDP Regulatory Project Manager  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Prescription Drug Promotion (OPDP)  
5901-B Ammendale Road  
Beltsville, MD 20705-1266  

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: [http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf](http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf)).

Do not submit launch materials until you have received our proposed revisions to the package insert (PI), Medication Guide, and patient PI, and you believe the labeling is close to the final version.
For more information regarding OPDP submissions, please see [http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm](http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm). If you have any questions, call OPDP at 301-796-1200.

We acknowledge receipt of your request for a full waiver of pediatric studies for this application. Once we have reviewed your request, we will notify you if the full waiver request is denied and a pediatric drug development plan is required.

If you have any questions, call Marisa Petruccelli, Regulatory Project Manager, at (240) 402-6147.

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

/s/

JEAN-MARC P GUETTIER
11/27/2015
Good afternoon,

I have an information request regarding NDA 208583 insulin degludec and liraglutide.

1. For the pivotal studies: **3697 and 3912**, please provide a combined table comparing and contrasting the following criteria. Please fill in responses in the column titled “Description”. This column should include a comparison of both studies, rather than a listing of items by study.

   **Table 1 - Common characteristics among all phase 3 studies**

<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Location</td>
<td>i.e. both studies were multinational, multicenter trials</td>
</tr>
<tr>
<td>Design</td>
<td>(i.e. Open/blinded label, centrally randomized, active-comparator, parallel group studies)</td>
</tr>
<tr>
<td>Blinding</td>
<td>How was blinding accomplished? If blinding was performed.</td>
</tr>
<tr>
<td>Comparator</td>
<td></td>
</tr>
<tr>
<td>Randomization ratio</td>
<td></td>
</tr>
<tr>
<td>Stratification of randomization</td>
<td>(i.e. by screening HbA1c (&lt;8.0% versus ≥8.0%), other)</td>
</tr>
<tr>
<td>Duration</td>
<td>i.e 6-month main study period followed by a 6-month controlled safety extension period</td>
</tr>
<tr>
<td>Primary objective</td>
<td></td>
</tr>
<tr>
<td>Primary efficacy variable</td>
<td></td>
</tr>
<tr>
<td>Planned method for primary efficacy analysis</td>
<td></td>
</tr>
<tr>
<td>Define the efficacy population used in the primary analysis, (i.e. intent-to-treat population or modified intention to treat)</td>
<td>How was the efficacy population defined?</td>
</tr>
<tr>
<td>Safety population</td>
<td>How was the safety population defined?</td>
</tr>
<tr>
<td>Glucometer used</td>
<td></td>
</tr>
<tr>
<td>Insulin delivery device</td>
<td>How was insulin delivered? I.e. pen?</td>
</tr>
<tr>
<td>Primary efficacy endpoints</td>
<td></td>
</tr>
<tr>
<td>Secondary efficacy endpoints</td>
<td></td>
</tr>
<tr>
<td>Inclusion and exclusion criteria</td>
<td></td>
</tr>
<tr>
<td>Prespecified titration of IdegLira</td>
<td></td>
</tr>
<tr>
<td>Prespecified titration of insulin</td>
<td></td>
</tr>
<tr>
<td>Prespecified titration of liraglutide</td>
<td></td>
</tr>
</tbody>
</table>

Reference ID: 3848809
Table 2 – concomitant antidiabetic medications allowed by protocol

<table>
<thead>
<tr>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>basal insulin</td>
</tr>
<tr>
<td>Other antidiabetic therapy</td>
</tr>
<tr>
<td>Antidiabetic therapy that was NOT allowed by protocol</td>
</tr>
</tbody>
</table>

Table 3 – Statistical methodology

<table>
<thead>
<tr>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary endpoint</td>
</tr>
<tr>
<td>Secondary endpoints</td>
</tr>
</tbody>
</table>

2. Also compare and contrast the safety monitoring committees (and specify if these were blinded) used in the studies (i.e. Study x had a hypoglycemia board committee, but study Y did not....)
3. Compare and contrast what were the pre-specified safety endpoints between the studies
4. Please answer questions 1-3 comparing the OTHER non-pivotal phase 3 studies (3851, 3951, 3952). For these comparisons do not just list items by study, but rather contrast the similarities and differences between studies.

Please provide a response to this request by **December 2, 2015**.

Please contact me with any questions.

Thank you,
Marisa

**Marisa Petruccelli**
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Phone: 240-402-6147
Fax: 301-796-9712
marisa.petruccelli@fda.hhs.gov
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MARISA PETRUCCELLI
11/18/2015
NDA 208583

PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE

Novo Nordisk Inc.
800 Scudders Mill Road
Plainsboro, NJ 08536

ATTENTION: Rick Spring
Associate Director, Regulatory Affairs

Dear Mr. Spring:

Please refer to your New Drug Application (NDA) dated September 12, 2015, received September 14, 2015, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Insulin Degludec and Liraglutide Injection, 100 units and 3.6 mg per mL.

We also refer to your correspondence, dated and received September 14, 2015, requesting review of your proposed proprietary name, Xultophy.

We have completed our review of the proposed proprietary name, Xultophy and have concluded that it is conditionally acceptable.

If any of the proposed product characteristics as stated in your September 14, 2015, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you require information on submitting requests for proprietary name review or PDUFA performance goals associated with proprietary name reviews, we refer you to the following:


If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Terrolyn Thomas, MS, MBA, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (240) 402-3981. For any other information regarding this application, contact Marisa Petruccelli, Regulatory Project Manager in the Office of New Drugs, at (240) 402-6147.

Sincerely,

{See appended electronic signature page}

Todd Bridges, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

TODD D BRIDGES
11/12/2015
MEMORANDUM OF TELECONFERENCE

Teleconference Date: October 14, 2015

Application Number: NDA 208583
Product Name: insulin degludec and liraglutide
Sponsor/Applicant Name: Novo Nordisk

Subject: Clarification on Contents of ISS

FDA Participants
Lisa Yanoff, M.D., Clinical Team Leader
Tania Condarco, M.D., Clinical Reviewer
Anna Kettermann, Dipl. Math, MA, Biometrics Reviewer

Sponsor/Applicant Participants
Rick Spring, Associate Director, Regulatory Affairs, US
Nina Liang, Associate Director, Regulatory Affairs, US

1.0 BACKGROUND:

On October 13, 2015, FDA requested a brief tcon with the applicant to inquire about the following:

In the ISS, we see the topline adjusted adverse event rates included in 7.11, but we were not able to find where these specific events are listed (i.e. adjusted pooled PT, adjusted SOC listings of adverse events). We would like to speak with whoever prepared the data package to ask about the inclusion/location of this information.

On October 14, 2015, the applicant sent the following via email as background to the call:

“We think the following may guide the team to the information desired. We also referred to the pre-NDA meeting minutes where it was stated:

FDA agreed that trial by trial analyses are acceptable for the ‘versus components’ pivotal trials (Trials 3697 and 3912), and that pooled analyses are acceptable for the ‘versus comparators’ phase 3 trials provided that the proper statistical adjustments are made to avoid confounding by study. FDA agreed that integrated analysis should be done for safety areas of interest, including deaths, serious adverse events, and adverse events due to withdrawals”.

In our comparison of IDegLira versus comparators (pooling of all 5 trials), the rates were adjusted to account for the unequal randomization and this was done for safety areas of interests, deaths, SAEs, and AEs leading to withdrawals. These are highlighted below.
Adjusted Rates found in the following ISS sections as well in Appendix 7.11:
Pg. 96, 2.1.1.5 Presentation of Adverse Events (explains approach for adjusted rates)
Overall AEs
SAEs
Overall event rates in safety areas of special interest
2.1.2 Common AEs
2.1.2.2 Completed Phase 3 trials
2.1.3.1 Fatal adverse event (under Deaths)
2.1.4.3 Serious Adverse Events

Pg. 145, Table 2-16 Analyses of medical events of special interest.
The following sections from the table have adjusted rates:
2.1.7 CV
2.1.8 Pancreatitis
2.1.9 Neoplasms
2.1.10 Thyroid disease
2.1.11 Altered renal function
2.1.12 Immunogenicity
2.1.13 Medication errors
2.1.5 AEs leading to withdrawal

In addition, does the table on pg. 1519 of ISS Appendix 7.2 Table 19: Adverse events by SOC, HLGT and PT - treatment-emergent - completed phase 3 trials represent what the team is looking for?

2.0 DISCUSSION:

FDA explained that in the ISS, Section 7.11 shows pooled and adjusted rates for adverse events, but does not include a more granular breakdown by MEDRA hierarchy of the actual adverse events. Using ‘Table 19: Adverse events by SOC, HLGT and PT - treatment-emergent - completed phase 3 trials’ on page 1519 of the ISS as an example, FDA explained that we need tables with this level of detail, listing the actual events by SOC and PT for all adjusted events for all safety areas of interest, including deaths, serious adverse events, and adverse events due to withdrawals (as stated in the pre-NDA meeting minutes) and including common adverse events. Novo Nordisk agreed to generate tables with this level of detail and provide this to the FDA as soon as possible. FDA pointed out that Novo Nordisk should generate this more detailed safety information under the assumption that the method they used to adjust adverse events is acceptable; the acceptability of this method has not been reviewed yet.

FDA also mentioned that the proposed labeling does not included the pooled analyses, which will be a review issue.

3.0 ACTION ITEMS:
Novo Nordisk will submit the requested, more-detailed information as soon as possible.
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MARISA PETRUCELLI
10/14/2015
NDA 208583

NDA ACKNOWLEDGMENT

Novo Nordisk Inc.
Attention: Robert B. Clark
Vice President, Regulatory Affairs
800 Scudders Mill Road
Plainsboro, NJ 08536

Dear Mr. Clark:

We have received your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: insulin degludec and liraglutide [rDNA origin] injection

Date of Application: September 12, 2015

Date of Receipt: September 14, 2015

Our Reference Number: NDA 208583

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on November 13, 2015, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:
Secure email between CDER and applicants is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications.

If you have any questions, call me at (240) 402-6147.

Sincerely,

{See appended electronic signature page}

Marisa Petruccelli
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MARISA PETRUCELLI
09/21/2015
IND109121

MEETING MINUTES

Novo Nordisk Inc.
Attention: Nina Liang, PhD
Associate Director, Regulatory Affairs
800 Scudders Mill Road
Plainsboro, NJ 08536

Dear Dr. Liang:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for IDegLira (insulin degludec/liraglutide) injection.

We also refer to the Pre-NDA meeting between representatives of your firm and the FDA on June 16, 2015. The purpose of the meeting was to discuss nonclinical and clinical topics regarding this IND.

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 Marisa Petruccelli, Regulatory Project Manager at (240) 402-6147.

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
MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: Pre-NDA
Meeting Date and Time: June 16, 2015, 1:30-2:30 PM
Meeting Location: FDA White Oak, Building 22, Room 1417
Application Number: 109121
Product Name: Insulin degludec/liraglutide injection, referred to as IDegLira
Indication: Adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus
Sponsor/Applicant Name: Novo Nordisk Inc.
Meeting Chair: Jean-Marc Guettier, M.D.
Meeting Recorder: Marisa Petruccelli

FDA ATTENDEES
Office of Drug Evaluation II

Mary Parks, M.D., Deputy Director

Division of Metabolism and Endocrinology Products

Jean-Marc Guettier, M.D., Division Director
Lisa Yanoff, M.D., Clinical Team Leader
Tania Condurco, M.D., Clinical Reviewer
Stephanie Leuenroth-Quinn, PhD, Acting Nonclinical Team Leader
Miyun Tsai-Turton, PhD, MS, Nonclinical Reviewer
Julie Van der Waag, MPH, Chief, Project Management Staff
Marisa Petruccelli, Project Manager

Office of Pharmaceutical Quality

Suong Tran, PhD, Quality/CMC Lead

Office of Biostatistics

Gregory Levin PhD, Acting Biometrics Team Leader
Anna Kettermann, Dipl. Math, MA, Biometrics Reviewer
Office of Clinical Pharmacology

Manoj Khurana, PhD, Clinical Pharmacology Team Leader
Ritesh Jain, PhD, Clinical Pharmacology Reviewer

Office of Surveillance and Epidemiology

Sarah Vee, Pharm.D, Safety Evaluator, Division of Medical Error Prevention and Analysis

Office of Combination Products

Bindi Nikhar, M.D., Associate Clinical Director

Eastern Research Group

Christopher Sese, Independent Assessor

SPONSOR ATTENDEES

Kamilla Begtrup, Principal Statistician
Ole Eskerod, VP, Medical & Science, Insulin and Diabetes Outcomes
Jenny Færch, Programming Specialist
Christian Foged, Project VP, Insulin and Diabetes Outcomes
Peter Jelnes, Senior Safety Surveillance Advisor
Irene Langebakke, International Medical Director, Insulin & Diabetes Outcomes
Nina Liang, Associate Director, Regulatory Affairs, US
Henriette Mersebach, Executive Director, Clinical Development and Research, US
Finn Møllegaard, CVP, Regulatory Affairs, Insulins
Anne Phillips, SVP, Clinical Development, Medical Affairs, Regulatory Affairs, US
Per­mille Poulsen, Director, Medical & Science, Insulin & Diabetes Outcomes
Marianne Bork Samuelsen, Department Manager, Regulatory, Insulin and GLP-1
Rick Spring, Associate Director, Regulatory Affairs, US
Michael Søberg Christensen, CVP Regulatory Affairs CMC

1.0 BACKGROUND

IDegLira is a fixed drug-drug ratio and device combination product containing the basal insulin analog insulin degludec (IND 76496 and NDA 203314 Tresiba (insulin degludec injection), currently under review) and the marketed GLP-1 receptor agonist liraglutide (NDA 22341, Victoza (liraglutide [rDNA origin] injection, approved on January 25, 2010). The IDegLira product intended for the market contains 100 U insulin degludec and 3.6 mg liraglutide per mL, and Novo Nordisk plans to market the product in a 3 mL pre-filled pen injector for the treatment of type 2 diabetes mellitus.

On August 23, 2013, Novo Nordisk submitted a Type C meeting request regarding the content and appropriate timing of filing an NDA for IDegLira. On September 3, 2013, FDA denied this request, stating that “The interim data from the degludec dedicated cardiovascular outcomes
trial are critical to the assessment of benefit-risk for the combination product. A new drug application for IDEgLira would not be considered complete without these interim data. Absent these data, an application for IDEgLira would not be filed on the basis that it would not be complete”. The resubmission of NDA 203314 included the interim clinical trial data from the dedicated, double-blind, cardiovascular outcomes trial, EX1250-4080 (DEVOTE) and cross-reference to this data will be made for IDEgLira. Novo Nordisk plans to submit the NDA for IDEgLira in the fall of 2015, prior to the user fee goal date for NDA 203314, for review under “the Program”.

The purpose of this meeting is to discuss nonclinical and clinical topics in preparation for filing an NDA for IDEgLira.

Note that the name IDEgLira is neither a proposed proprietary name nor the established name. However, because the name IDEgLira was used throughout the briefing package, this name is used in this document solely for convenience.

2. DISCUSSION

2.1. Nonclinical

Question 1: Does the Agency agree that documentation from the above nonclinical program and cross referencing to the insulin degludec and liraglutide NDAs are sufficient for filing of the IDEgLira NDA?

FDA Response to Question 1: Yes, the nonclinical program for IDEgLira together with cross referencing to the insulin degludec and liraglutide NDAs are sufficient for IDEgLira NDA filing.

Novo Nordisk Response: We acknowledge your comment. Further discussion with the Agency is not needed.

Meeting Discussion: No further discussion.

2.2. Clinical Pharmacology

Question 2: Does the Agency agree that the clinical pharmacology program for IDEgLira, including population pharmacokinetics analysis and cross-referencing to the insulin degludec and liraglutide clinical pharmacology programs is sufficient for the NDA submission?

FDA Response to Question 2: Yes, from an NDA filing perspective, we agree that the clinical pharmacology program is sufficient for NDA submission.

Novo Nordisk Response: We acknowledge your comment. Further discussion with the Agency is not needed.

Meeting Discussion: No further discussion.
2.3. Clinical

**Question 3:** Does the Agency agree that the number of exposed subjects and the duration of exposure in the IDegLira clinical development program are adequate to support the NDA filing?

**FDA Response to Question 3:** The number of patients exposed and the duration of treatment with IDegLira, in the completed phase 3 trials, is sufficient to support filing of the NDA. However, as previously stated in Pre-IND correspondence, it is possible that the number of patients and duration of exposure will not be adequate if an efficacy or safety concern arises when we review the degludec NDA.

In addition, as previously stated in the end-of-phase 2 meeting, it will be important to evaluate those patients who received less than the minimum clinically effective doses of liraglutide, after the titration period, and in your NDA you should present exposure data in terms of doses of insulin and liraglutide achieved.

**Novo Nordisk Response:**
We acknowledge your comments. The data will be incorporated in the NDA.

**Meeting Discussion:** No further discussion.

**Question 4:** Does the Agency agree to the planned presentation for the completed phase 3 IDegLira trials in the Summary of Clinical Efficacy/ISE?

**FDA Response to Question 4:** No, we do not agree. We note that the last-observation-carried-forward (LOCF) technique is your primary imputation method across the phase 3 trials, and we acknowledge that this was accepted by the Agency at the end-of-phase 2 meeting in 2010. However, the Division’s thinking regarding the LOCF approach and missing data has changed since the publication in 2010 of a report on missing data by the National Academy of Sciences (NAS), *The Prevention and Treatment of Missing Data in Clinical Trials*. The report states “The panel believes that in nearly all cases, there are better alternatives to [LOCF]...which are based on more reasonable assumptions and hence result in more reliable inferences about treatment effects”. In order to reliably evaluate the intention-to-treat estimand (i.e., the difference in HbA1C in all randomized patients regardless of adherence or use of rescue), LOCF relies on the strong, implausible, and unverifiable assumption that patient outcomes after treatment discontinuation remain constant through the landmark visit. In addition, as a single-imputation approach, LOCF does not appropriately take into account the statistical uncertainty in the imputation process. Because of our concerns with LOCF, additional analyses will be critical to support the effectiveness of IDegLira.

In particular, you should conduct analyses that include all data in all randomized patients, regardless of adherence to treatment or use of rescue medications. We also recommend additional analyses with multiple imputation of missing data that take into account treatment adherence, i.e., analyses that do not rely on the assumption that the statistical
behavior of outcomes in patients who have discontinued study therapy is similar to the behavior of on-treatment outcomes. We request that you submit a plan for the analyses that you will conduct to address missing data for our review.

Novo Nordisk Response:
We acknowledge your comments. Novo Nordisk would like to discuss this response at the face-to-face meeting, specifically our plan for the additional analyses that will be conducted to address missing data. Please see the attached slide (Novo Nordisk Response to FDA Response to Question 4) to support the discussion and statistical analysis plan.

Meeting Discussion: FDA requested that the sponsor provide additional details on the ‘copy control’ method. Provided that the ‘copy control’ method is the same as the ‘jump to reference’ method described in the Carpenter et al. paper cited below, the FDA finds the proposed analysis reasonable (although not necessarily sufficient on its own). FDA also recommended that the sponsor conduct tipping point analyses for primary endpoints (and secondary endpoints if the sponsor is seeking labeling claims for secondary endpoints). FDA asked that the sponsor describe all approaches in detail and provide code. FDA also re-emphasized its concern with the use of LOCF and noted that the choice of analysis to most reliably estimate the treatment effect in labeling would be a review issue.


Question 5: Does the Agency agree with the proposed presentation of the data and pooling strategy in the ISS and the proposed database cut-off dates?

FDA Response to Question 5: No we do not agree.

appropriately account for study differences in your pooling strategy and through stratification by study in integrated analyses. At the meeting, please clarify your exact pooling strategy and how you will address issues associated with simple pooling of data in integrated analyses and reports.

Novo Nordisk Response:
We acknowledge your comments. Novo Nordisk would like to further discuss this response at the face-to-face meeting and provide clarification of our safety data presentation, including our pooling strategy. Please see the attached slides (Novo Nordisk Response to FDA Response to Question 5) to support the discussion.

Meeting Discussion: FDA explained the need to remove the statistical artifact in order to reliably detect true safety signals. FDA agreed that trial by trial analyses are acceptable for the ‘versus components’ pivotal trials (Trials 3697 and 3912), and that pooled analyses are acceptable for the ‘versus comparators’ phase 3 trials provided that the proper
statistical adjustments are made to avoid confounding by study. FDA agreed that integrated analysis should be done for safety areas of interest, including deaths, serious adverse events, and adverse events due to withdrawals, and that additional integrated analysis can be done at the discretion of Novo Nordisk, and may be requested by FDA after submission. FDA indicated that it would provide a reference that describes possible statistical approaches (based on stratification by study) and suggests FDA requested that in the NDA the sponsor provide explanation for any safety signal detected in individual trial analysis but not in the integrated analysis and vice versa.

2.3 Regulatory/Administrative Questions

Question 6: Does the Agency agree with the proposal for datasets and data listings to be submitted in the NDA?

FDA Response to Question 6: Your proposal appears reasonable, but we recommend that analysis datasets be submitted in CDISC ADAM format. In addition, you should submit programming code for your primary and key secondary and sensitivity analyses for all phase 3 trials.

Novo Nordisk Response: We acknowledge your comments, but we will not be able to submit analysis datasets in CDISC ADAM format. Analysis datasets will be provided in legacy format as described in the meeting package. Novo Nordisk will provide the programming code for all the primary, key secondary, and sensitivity analyses for all phase 3 trials included in the legacy analysis datasets as requested.

Meeting Discussion: No further discussion.

Post-Meeting Comment: We acknowledge that you will be unable to submit your analysis in CDISC ADAM format. We refer you to the following 2014 guidance: “Providing Regulatory Submissions in Electronic Format — Standardized Study Data Guidance for Industry.” Also refer to the FDA Data Standards website: http://www.fda.gov/ FORINDUSTRY/DataStandards/StudyDataStandards/default.htm.

Please be aware that study data contained in your submission must be submitted electronically in a format that FDA can process, review, and archive.

Question 7: Does the Agency agree with the proposal for the BIMO information to be submitted in the NDA?

FDA Response to Question 7: No, we do not agree. We acknowledge your plans to provide general study information and clinical site summary data for the completed phase 3 trials listed in your Table 1. As noted, you will follow the specifications outlined in the FDA document “Specifications for Preparing and Submitting Summary Level Clinical Site Data for CDER’s Inspection Planning”, version 1.2, which is linked to the FDA’s draft Guidance.
for Industry: Providing Submissions in Electronic Format—Summary Level Clinical Site Data for CDER's Inspection Planning. This information helps to facilitate the timely identification of clinical investigator sites for on-site clinical inspection. In addition, please submit the site-specific individual subject data listings for all sites that enrolled subjects in the phase 3 studies noted above as they are essential to plan and to conduct clinical inspections efficiently.

Novo Nordisk Response:
We acknowledge your comments. Novo Nordisk agrees to provide the site-specific individual subject data listings for all sites that enrolled subjects in the phase 3 studies.

Meeting Discussion: No further discussion.

**Question 8:** Does the Agency agree with the proposal for CRFs and Narratives to be submitted in the NDA?

**FDA Response to Question 8:** Your approach seems reasonable. In addition, narratives for deaths, serious adverse events, adverse events leading to discontinuation, adverse events of special interest (e.g., hypersensitivity reactions, medullary thyroid carcinoma, pancreatitis, severe hypoglycemia events, etc.) should be manually-generated and written up in the format of a standard medical case history (i.e., not computer generated).

For ease of review, individual CSR sections (i.e. data tables/figures), should contain hyperlinks to narratives.

For ease of review, create a list of patients for whom narratives are provided with hyperlinks to the narrative. The list should be in the following format:

<table>
<thead>
<tr>
<th>Patient ID (Hyperlink to narrative)</th>
<th>Reason(s) for Narrative (i.e., Death; SAE, SAE leading to treatment discontinuation, Severe hypoglycemia, etc.)</th>
<th>Preferred term(s) (PT) associated with the event</th>
<th>Assigned treatment group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Organize the table according to “Reason for narrative,” (i.e., categories) and identify patients who fall in multiple categories for a narrative.

Note that in your presentations of reasons for discontinuation in your individual CSRs and in the integrated summaries, the category of “other” without further explanation is not acceptable. In your report you should provide a table with patient ID and verbatim terms for all discontinuations due to “other”.

Reference ID: 3788768
Novo Nordisk Response:
We acknowledge your comments. As the clinical trial reports are finalized, a full list of narratives with individual hyperlinks will be provided as an appendix to the ISS and presented as outlined above. The additional information on discontinuations due to "other" will be included with the NDA.

Meeting Discussion: No further discussion.

Question 9: Does the Agency agree to the content, application format, and the cross-reference strategy?

FDA Response to Question 9:

a) We agree to the content and application format for the CMC information on the drug products in the NDA, and to the cross-reference to the CMC information on the drug substances insulin degludec and liraglutide in NDA 203314 and NDA 22341.

We remind you that stability data on the complete drug/drug/device combination product (i.e., cartridge assembled in the final pen injector) should be included in the initial NDA for our filing review. The data should be sufficient to assure the performance of the pen injector, including dose accuracy, throughout the proposed long-term and in-use storage conditions.

IDegLira is a drug/drug/device combination product and as such subject to 21 CFR Part 4- Current Good Manufacturing Practice Requirements for Combination Products.

Novo Nordisk Response:
We acknowledge your comments. Novo Nordisk would like to confirm at the face-to-face meeting that the information provided below is adequate to address the preliminary comments received in relation to the stability data for the complete drug/drug/device combination product to be included in the NDA.

To support the performance of the drug/drug/device combination product (i.e. 3 mL cartridge assembled in the PDS290 IDegLira pen-injector) throughout the proposed shelf life and in-use storage period, the following data will be included in the NDA application:

- Dose accuracy data up to end of shelf life (24 months at 5°C) for the drug/drug/device combination product.
- Dose accuracy data at the end of the in-use period (3 weeks at 30°C), including simulated handling, for the drug/drug/device combination product. In-use testing is performed after storage at long term conditions until end of shelf life.

Furthermore, to support the proposed shelf life (24 months at 5°C) and the in-use period (3 weeks at 30°C), the following stability data have been generated on the drug product in the primary container (3 mL cartridge):

- Stability data at long term (up to 24 months at 5°C) and accelerated (6 months at 25°C) storage conditions.
• In-use data, during 3 weeks at 30°C, including simulated handling. In-use testing is performed after storage at long term conditions until end of shelf life.

Meeting Discussion: FDA acknowledges the plan to submit stability and performance data requirements for the combination product. See the post-meeting comments below regarding these requirements.

The sponsor may choose to cross-reference previous applications in which information regarding the device has been reviewed and found to be acceptable by the Agency. For follow up questions, the sponsor should contact the Regulatory Project Manager.

Post-Meeting Comments:
Regarding stability of device components of the combination product, you state that you will provide real time stability information for the combination product as assessed by dose accuracy testing. The Agency has the following comments regarding your approach:

a. You state that the combination product will be assessed using methods as outlined within ISO11608-1. This consensus standard is recognized by the Agency and contains useful design and test information; however, it is not an acceptable substitution for comprehensive design input and verification activities for your products. The Agency expects that you will demonstrate that all essential performance and safety requirements for your device are appropriately characterized and verified within your submission, both after manufacture and at a time period commensurate with the date of expiration. Note that provision of accelerated or forced aging studies may be acceptable to assess stability of some of the device performance and safety elements.

b. You have not provided a description of the dose accuracy requirements for the combination product. Within your planned NDA, the Agency expects that you will clearly state the dose accuracy requirements for your combination product and provide information supporting the clinical acceptability of such requirements. Please note that citation of “standard” dose accuracy specifications alone will not be sufficient to justify product dose accuracy.

b) Please provide complete details regarding the PDS290 IDegLira pen injector.

Novo Nordisk Response:
We acknowledge your comment. The following table lists the documentation for the PDS290 IDegLira pen injector to be submitted in the NDA.

<table>
<thead>
<tr>
<th>3.2.P.7 Container Closure System</th>
</tr>
</thead>
<tbody>
<tr>
<td>Technical Description</td>
</tr>
<tr>
<td>Comparison to FlexTouch</td>
</tr>
</tbody>
</table>
Rubber Plunger Component Report for 21-310-00

Cap 8 mm with rubber disc. Component report EMK0155

Cartridge 3 ml, System Report for EMK0502

Cartridge 3 ml, Component Report for 20-323-17

Summary Report of Qualification Testing

Dose Accuracy Data

Validation of Depth and Route of Injection

Risk Management Report Analysis Input to Usability Test - UT94 - PDS290 IDegLira pen-injector

Summative Usability Test of PDS290 IDegLira pen-injector, Test ID: DV0262-UT94-2014 - test plan

Summative Usability Test of PDS290 IDegLira pen-injector, Test ID DV0262-UT94-2014 - Report

Validation of Device Use -UT94- PDS290 IDegLira pen-injector, Final Report

Meeting Discussion: No further discussion.

c) Additional eCTD comments for combination products:

Other than data analogous to batch records, all device constituent and combination product information data should be integrated in the eCTD with conceptually similar drug constituent information. The data should be organized based on the following principles:

1. For eCTD format and use of the electronic submission system, please adhere to eCTD headings as defined per ICH and FDA specifications. In the specifications, these may be identified as leaf nodes or elements. Specifically, any title that is associated with a numerical item should not change; i.e., Item 3.2.P.7 should say “Container Closure System.”

2. Do not use "node extensions" to create new elements. Although this is described in the eCTD specification, and may be acceptable in some regions, it is not acceptable in submissions to FDA.
3. When including and referencing device information, we recommend the following:

a. You may reference files under 3.2.P.7, which are not currently listed as numerical items in ICH and FDA specifications and guidance.

b. In Module 3.2.P.7, you could include a leaf titled similar to the following, “Table of Contents for pen-injector”. This leaf/document could provide reference links to the other files in module 3.2.P.7.

c. The leaf titles should be clear, concise, and indicative of the document’s content.

4. Module 1.4.4 “Cross-reference to other applications” is a location where you can provide references to other applications and you can include copies of an application’s table of contents, reference tables, or other similar documents. If you are cross referencing another company’s application or master file, include the appropriate letters of authorization from the other companies in modules 1.4.1 - 1.4.3 (1.4.1 “Letter of authorization”, 1.4.2 “Statement of right of reference”, 1.4.3 “List of authorized persons to incorporate by reference”). If there are standards you will reference in the Performance Specifications which also meet these criteria, then please put them in module 1.4.4. The Performance Specifications section should link to this information.

5. All device information pertaining to manufacturing or assembly of the finished combination product and documents necessary to demonstrate compliance with 21 CFR Part 4 and the applicable 21 CFR part 820 regulations should be located in Section 3.2.P.3.

   a. The list of manufacturing facilities provided on the Form FDA 356h, or as an attachment to the form, should explicitly describe the manufacturing, assembly, or testing processes taking place at each site involved with the device constituent part.

   b. Suggestions on the types of documents to submit for review of required sections of 21 CFR Part 820 (based upon the combination product 21 CFR Part 4 GMP operating system at the facility) can be found in the guidance document titled “Quality System Information for Certain Premarket Application Reviews; Guidance for Industry and FDA Staff,” issued on February 3, 2003. The complete document may be found at http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm070897.htm.

6. We recommend that you provide an “Information to Reviewers” or “Reviewers Guide” document in Module 1.2 Cover letters. This document would be separate from the cover letter and placed after the cover letter and should provide a high level overview (with reference links) of the submission’s content and list where the information is located in the eCTD. For example, it should identify where drug, device and combination product is located.
Novo Nordisk Response:
We acknowledge your comments for the eCTD structure for combination products, Module 1.4.4, device information pertaining to manufacturing and assembly, and the request to provide a Reviewer’s Guide. The requested information will be included in the NDA.

Meeting Discussion: No further discussion.

Question 10: Does the Agency agree that IDegLira fixed combination meets the regulatory definition of a New Chemical Entity (NCE) per the FDA guidance and would therefore be eligible for “The Program” under PDUFA V?

FDA Response to Question 10: Eligibility for ‘The Program’ under PDUFA V is based on status as a New Molecular Entity (NME), which is different than a New Chemical Entity (NCE).

As defined under 21 CFR 314.108, ‘New chemical entity means a drug [product] that contains no active moiety that has been approved by FDA in any other application submitted under section 505(b) of the act.’

As defined by FDA policy, a New Molecular Entity (NME) is an active moiety that has not been previously approved or legally marketed as the active moiety in the United States in any drug product, either as a single ingredient, as part of a combination product, or as part of a mixture of stereoisomers.

If you submit the NDA for IDegLira while the NDA for insulin degludec is still pending, we will classify the NDA for IDegLira as both an NME and a new combination, qualifying it for review under The Program.

Novo Nordisk Response:
We acknowledge your comments and appreciate the clarification provided. Further discussion with the Agency is not needed.

Meeting Discussion: No further discussion.

Question 11: Does the Agency agree with Novo Nordisk’s plan for submission of an agreed upon initial PSP to the IDegLira NDA?

FDA Response to Question 11: You must have FDA confirmation of an agreed PSP before you submit your NDA, otherwise it may be grounds for a refuse-to-file action. Please also note that although you must have an agreed iPSP before you submit your NDA, waivers and deferrals for pediatric studies are granted at the time of approval of a marketing application.

Novo Nordisk Response:
We acknowledge your comments. Further discussion with the Agency is not needed.
Meeting Discussion: No further discussion.

**Question 12:** Does the Agency agree on the approach for submission of the IDegLira REMS?

**FDA Response to Question 12:** FDA agrees with your proposal to submit a REMS that has components of the Victoza approved REMS. A complete review of the proposed REMS in conjunction with the full clinical review of the NDA will be necessary to determine whether the proposed REMS is acceptable, since additional information regarding risks and safe product use may emerge during the review of your NDA. In addition to your proposed REMS document, submit all planned materials (e.g., proposed communication and education materials) identified within the plan that will be necessary to implement your proposal.

**Novo Nordisk Response:**
We acknowledge your comments. The proposed REMS document and planned materials will be included in the NDA.

**Meeting Discussion:** No further discussion.
3.0 DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

- The content of a complete application was discussed.

All applications are expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities included or referenced in the application.

- A preliminary discussion on the need for a REMS was held and it was concluded that a complete review of the proposed REMS in conjunction with the full clinical review of the NDA will be necessary to determine whether the proposed REMS is acceptable, since additional information regarding risks and safe product use may emerge during the review of the NDA. In addition to the proposed REMS document, the sponsor should submit all planned materials (e.g., proposed communication and education materials) identified within the plan that will be necessary to implement this proposal.

- Major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission. You stated you intend to submit a complete application and therefore, there are no agreements for late submission of application components.

4.0 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.

5.0 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 (PLL R) (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 PLLR Requirements for Prescribing Information and PLLR Requirements for Prescribing Information websites including:

- 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 in the PI for human drug and biological products
- 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 42 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.

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

6.0 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.”

<table>
<thead>
<tr>
<th>Site Name</th>
<th>Site Address</th>
<th>Federal Establishment Indicator (FEI) or Registration Number (CFN)</th>
<th>Drug Master File Number (if applicable)</th>
<th>Manufacturing Step(s) or Type of Testing [Establishment function]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Corresponding names and titles of onsite contact:

<table>
<thead>
<tr>
<th>Site Name</th>
<th>Site Address</th>
<th>Onsite Contact (Person, Title)</th>
<th>Phone and Fax number</th>
<th>Email address</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
7.0 NME STATUS
FDA has made a preliminary determination that the application for this product would be reviewed as a new molecular entity (NME) and therefore subject to the Program, under PDUFA V. 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.

8.0 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).

1. 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.

Attachment 1
Technical Instructions:
Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format

A. Data submitted for OSI review belongs in Module 5 of the eCTD. For items I and II in the chart below, the files should be linked into the Study Tagging File (STF) for each study. Leaf titles for this data should be named “BIMO [list study ID, followed by brief description of file being submitted].” In addition, a BIMO STF should be constructed and placed in Module 5.3.5.4, Other Study reports and related information. The study ID for this STF should be “bimo.” Files for items I, II and III below should be linked into this BIMO STF, using file tags indicated below. The item III site-level dataset filename should be “clinsite.xpt.”

<table>
<thead>
<tr>
<th>DSI Pre-NDA Request Item¹</th>
<th>STF File Tag</th>
<th>Used For</th>
<th>Allowable File Formats</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>data-listing-dataset</td>
<td>Data listings, by study</td>
<td>.pdf</td>
</tr>
<tr>
<td>I</td>
<td>annotated-crf</td>
<td>Sample annotated case report form, by study</td>
<td>.pdf</td>
</tr>
<tr>
<td>II</td>
<td>data-listing-dataset</td>
<td>Data listings, by study (Line listings, by site)</td>
<td>.pdf</td>
</tr>
<tr>
<td>III</td>
<td>data-listing-dataset</td>
<td>Site-level datasets, across studies</td>
<td>.xpt</td>
</tr>
</tbody>
</table>

B. In addition, within the directory structure, the item III site-level dataset should be placed in the M5 folder as follows:

```
= [m5]
  = datasets
    = bimo
      = site-level
```

C. It is recommended, but not required, that a Reviewer’s Guide in PDF format be included. If this Guide is included, it should be included in the BIMO STF. The leaf title should be “BIMO Reviewer Guide.” The guide should contain a description of the BIMO elements being submitted with hyperlinks to those elements in Module 5.

¹ Please see the OSI Pre-NDA/BLA Request document for a full description of requested data files
References:

eCTD Backbone Specification for Study Tagging Files v. 2.6.1

FDA eCTD web page
(http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm)

For general help with eCTD submissions: ESUB@fda.hhs.gov

9.0 ISSUES REQUIRING FURTHER DISCUSSION
The sponsor may request further discussion of the comments provided by the Center for Devices and Radiological Health as post-meeting comments.

10.0 ACTION ITEMS

<table>
<thead>
<tr>
<th>Action Item/Description</th>
<th>Owner</th>
<th>Due Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Official Meeting Minutes</td>
<td>FDA</td>
<td>July 16, 2015</td>
</tr>
</tbody>
</table>

11.0 ATTACHMENTS AND HANDOUTS
The slides presented to support the discussion of questions 4 and 5 are included below.
Question 4: Sensitivity analyses to evaluate robustness of efficacy results obtained using LOCF

- The confirmatory trials included in the NDA were not designed to and did not collect data after treatment discontinuation, retrieve drop-out analysis is therefore not possible

- Planned sensitivity analyses
  - Multiple imputation (copy difference from control)
    - withdrawn (WD) IDegLira subjects assumed to be switched to comparator treatment or treatment inferior to comparator (for non-inferiority comparisons only)
    - Mirrors an intention-to-treat principle and includes all randomised subjects
  - Multiple imputation (copy control)
    - withdrawn IDegLira subjects assumed to respond as if treated with comparator treatment or treatment inferior to comparator (for non-inferiority comparisons only) for the entire trial
    - Mirrors an intention-to-treat principle and includes all randomised subjects
  - Repeated measurement analyses
    - result had all subjects remained in trial and on randomised treatment
    - Mirrors a per-protocol principle and includes randomised subjects with at least one post baseline observation

Reference ID: 3788768
Question 4: Endpoints in scope for sensitivity analyses

- $\text{HbA}_{1c}$
- $\text{HbA}_{1c} < 7.0\%$, and $\text{HbA}_{1c} \leq 6.5\%$
- insulin dose
- fasting plasma glucose
- confirmed hypoglycaemia
- body weight
Question 5: Clarification of safety data presentation

- **Purpose**
  - Establish safety profile *versus components* (IDeg and liraglutide)
  - Establish safety profile *versus comparators* (basal insulin, GLP-1 RA and placebo)

- **Methodology**
  - Pooling of data to increase sensitivity for detection of signals
  - Trial by trial assessment to account for trial related differences
  - No statistical analyses applied
### Question 5: Clarification of safety data presentation in ISS

<table>
<thead>
<tr>
<th></th>
<th>Common AEs</th>
<th>Safety areas of interest</th>
<th>Other Laboratory data</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Versus components</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pivotal trials</td>
<td>Trial by trial: IDEgLira vs. IDeg and liraglutide</td>
<td>Pooled*: IDEgLira vs. IDeg and liraglutide</td>
<td>Trial by trial: IDEgLira vs. IDeg and liraglutide</td>
</tr>
<tr>
<td>Trials 3697 and 3912</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Versus comparators</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All phase 3 trials</td>
<td>Pooled*: IDEgLira vs. basal insulin, GLP-1 RA and placebo</td>
<td>Pooled*: IDEgLira vs. basal insulin, GLP-1 RA and placebo</td>
<td>Pooled*: IDEgLira vs. basal insulin, GLP-1 RA and placebo</td>
</tr>
<tr>
<td>Trials 3697, 3951, 3912, 3952, 3851</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Reference ID: 3788768

*All trial specific findings will be discussed as deemed relevant*
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
07/07/2015
PIND 109121

Novo Nordisk Inc.
Attention: Mary Ann McElligott, Ph.D.
Associate Vice President, Regulatory Affairs
100 College Road West
Princeton, NJ 08540

Dear Dr. McElligott:

Please refer to your Pre-Investigational New Drug Application (PIND) file for insulin degludec/liraglutide (IDegLira) fixed-ratio combination injection.

We also refer to the meeting between representatives of your firm and the FDA on November 9, 2010. The purpose of the meeting was to discuss the development program for IDegLira.

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

If you have any questions, call me at (301) 796-5332.

Sincerely,

{See appended electronic signature page}

Pooja Dharia, Pharm.D.
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure

Meeting Minutes
MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: End of Phase 2

Meeting Date and Time: Tuesday, November 9, 2010
Meeting Location: 3:00 P.M. to 4:00 P.M., EST

Application Number: PIND 109121
Product Name: IDeqLira (insulin degludec/liraglutide) injection
Indication: Type 2 Diabetes Mellitus
Sponsor/Applicant Name: Novo Nordisk, Inc.

Meeting Chair: Hylton Joffe, M.D., M.M.Sc.
Meeting Recorder: Pooja Dharia, Pharm.D.

FDA ATTENDEES

Division of Metabolism and Endocrinology Products (DMEP)
Mary Parks, M.D.  Director
Jean-Marc Guettier, M.D.  Clinical Reviewer
Lisa Yanoff, M.D.  Clinical Reviewer
Hylton Joffe, M.D., M.M.Sc.  Clinical Team Leader
Ilan Irony, M.D.  Clinical Team Leader
Karen Davis Bruno, Ph.D.  Pharmacology/Toxicology Team Leader
Pooja Dharia, Pharm.D.  Regulatory Project Manager

Office of Clinical Pharmacology
Lokesh Jain, Ph.D.  Clinical Pharmacology Reviewer, Division of Clinical Pharmacology 2 (DCP2)
Sally Choe, Ph.D.  Clinical Pharmacology Team Leader, DCP2

Office of Biostatistics
Todd Sahlroot, Ph.D.  Deputy Director, Division of Biometrics II (DBII)
Janice Derr, Ph.D.  Statistical Reviewer, DBII

Office of New Drug Quality Assessment
Suong Tran, Ph.D.  Pharmaceutical Assessment Lead, Division of New Drug Quality Assessment I

Reference ID: 2873941
Meeting Minutes
EOP2 Meeting
November 9, 2010

John Duan, Ph.D. Biopharmaceutics Reviewer
Angelica Dorantes, Ph.D. Biopharmaceutics Team Leader

Office of Surveillance and Epidemiology
Margarita Tossa, M.S. Safety Regulatory Project Manager
Walter Fava, R.Ph. Safety Evaluator, Division of Medication Error Prevention and Analysis (DMEPA)
Carlos Mena-Grillasca Safety Team Leader, DMEPA

Office of Combination Products
Lana Shiu, M.D. Senior Medical Advisor

SPONSOR ATTENDEES
Lars Iversen Senior Preclinical Project Manager, Biopharm Toxicology and Safety Pharmacology
Ulrik Sparegodt Senior CMC Project Manager
Lisbeth Vesterg Jacobsen Head of Clinical pharmacology, GLP-1 & Obesity
Pernille Poulsen International Medical Director, GLP-1 & Obesity
Jesper Madsen Statistics Specialist
Martin Lange Vice President, Medical & Science, Degludec
Niklas Öhrner Project Vice President
Peter Kristensen Senior Vice President of Global Development
Marianne Bork Samuelsen Senior Regulatory Project Manager
Inger Mollerup Corporate Vice President
Mads Frederik Rasmussen Executive Director, Diabetes - Clinical Development & Research, US
Meena Rao Director, Regulatory Affairs, US
Patricia Wilson Sr. Manager, Regulatory Affairs, US
Robert Fischer Senior Director, Regulatory Affairs, Princeton

Reference ID: 2873941
1.0 BACKGROUND

IDegLira is a combination product comprised of three constituent parts: a pen-injector device and a fixed-ratio combination of insulin degludec and liraglutide subcutaneous injection for the treatment of patients with type 2 diabetes mellitus (T2DM). Insulin degludec is a long-acting basal insulin analog in Phase 3 clinical development under IND 076496. Liraglutide, a glucagon-like peptide (GLP-1) receptor agonist, was approved as Victoza under NDA 022341 in January 2010.

A Phase 1 trial, evaluating the safety, tolerability, pharmacokinetics and pharmacodynamics of single-dose administration of IDegLira compared to the individual drug constituents has been completed.

Currently, Novo Nordisk wishes to gain feedback on their proposed Phase 3a pivotal clinical trial for IDegLira.

2. DISCUSSION

Novo Nordisk’s questions are repeated below with FDA’s pre-meeting responses in bold font, followed by meeting discussion in italicized font. The sponsor’s post-meeting comments are in underlined font and post-meeting comments from FDA are in underlined, bold font.

1. Does the Agency agree that, in addition to the available nonclinical information on insulin degludec and liraglutide, respectively, the 13 week repeated dose toxicity study in rats with IDegLira will be sufficient to support the clinical development program and marketing authorization?

   **FDA Response:** Yes. Based on your descriptive study summary with regard to the nonclinical development of insulin degludec, liraglutide, and IDegLira in the meeting package, the nonclinical data appear sufficient to support the clinical development of IDegLira. However, the adequacy of support is a review issue pending the submission of all your nonclinical study reports for IDegLira.

   **Discussion:** No discussion occurred.

2. Does the Agency agree that the proposed clinical pharmacology program for IDegLira, including cross-referencing to the insulin degludec and liraglutide clinical pharmacology programs, respectively, is sufficient to support an application for marketing authorization?

   **FDA Response:** Yes. The proposed clinical pharmacology program seems sufficient for clinical development of IDegLira. However, the need for additional information would be determined based on review of the insulin degludec NDA and additional information supporting IDegLira.
Meeting Minutes
EOP2 Meeting
November 9, 2010

Discussion: No discussion occurred.

3. Does the Agency agree that the proposed plans for population pharmacokinetic evaluation together with the results from the NN9068-3632 trial will be sufficient to address the pharmacokinetics of IDegLira?

FDA Response: We recommend that you evaluate the suitability of the sampling scheme to satisfy the intended objectives of population pharmacokinetic analysis using techniques such as simulation.

Discussion: No discussion occurred.

4. Does the Agency agree that the proposed IDegLira phase 3a trial design including the statistical approach, together with OAD background treatment data generated for insulin degludec and liraglutide, respectively, is sufficient to support the proposed indication?

FDA Response: No, we do not agree. In addition to demonstrating safety, your program should be designed to demonstrate that each component of the combination product contributes to the claimed effect. We do not find that demonstrating non-inferior glycemic efficacy would be sufficient to meet this requirement. Some of the secondary endpoints you propose to use as evidence of contribution to the claimed effect have not been validated clinically and are subject to biases in your open-label design.

Your pivotal trial should set out, as its primary objective, to demonstrate superiority on HbA1c for IDegLira over each of the individual components. One approach may be to enroll patients who are currently inadequately controlled on a basal insulin who may better tolerate upward titration of IDegLira, liraglutide, and degludec.

Discussion: FDA reiterated that a pivotal study in the IDegLira development program should aim to demonstrate superiority of the combination product over each of the single drug constituents based on HbA1c. The sponsor stated that it expects to be able to show superiority of IDegLira over liraglutide but that it would be difficult in the proposed trial to show superiority of IDegLira to degludec alone because the upper limit of the insulin dose is 50 units in the IDegLira arm whereas the degludec alone arm has no upper limit on the insulin dose. FDA stated that it would be acceptable to limit the maximal insulin dose in the degludec alone arm to 50 units also so that superiority of IDegLira to both individual drug constituents can feasibly be tested. The sponsor was concerned that limiting the maximum dose to 50 units in the degludec alone arm would not reflect standard clinical practice where insulin doses are only limited by hypoglycemia. However, FDA assured the sponsor that it is appropriate to set a maximum insulin dose for degludec in the pivotal trial because the primary objective of this trial is to show each constituent in the combination product contributes to the overall effect of the combination...
product. FDA also recommended that the sponsor consider enrolling patients who are not naïve to insulin so that it would be more likely that a substantial proportion of the participants would reach the maximal insulin dose in the IDegLira and degludec alone arms. Otherwise, the insulin doses may differ considerably between the degludec and IDegLira arms, which could confound the ability to show superiority of IDegLira over degludec alone. FDA acknowledged difficulties blinding all treatment arms given that liraglutide has only 3 dose steps whereas degludec can be dosed up to 50 units. Therefore, FDA recommended that the sponsor consider blinding the degludec and IDegLira arms only.

Because diabetes is a progressive disease, clarify the role of IDegLira in patients who require more glucose-lowering than can be achieved with the maximum dose of IDegLira and how these patients should be managed clinically. In addition, it is likely in clinical practice that patients who are failing IDegLira may choose to add prandial insulin, yet the efficacy and safety of doing so is not being tested in your proposed development program. Please clarify.

Discussion: The sponsor stated that IDegLira is intended for patients who are naïve to both insulin and a GLP-1 receptor agonist. FDA expressed doubts that this intended population represents those who are likely to use IDegLira, if approved. For example, iDegLira would also likely be an attractive option for patients treated with either basal insulin or a GLP-1 receptor agonist and who require intensification of anti-diabetic therapy. In addition, the convenience of one daily injection with iDegLira instead of two/three daily injections with a co-administered basal insulin and GLP-1 receptor agonist would also likely be an attractive option to both patients and healthcare providers. Finally, intensification of anti-diabetic therapy with prandial insulin in patients failing IDegLira is a possibility. FDA expressed concern that no data will be obtained in the currently proposed IDegLira program to inform prescribers on IDegLira’s risk-benefit profile in these other settings (see Question 7 discussion points).

Patients receiving less than the minimum clinically effective dose of liraglutide are not expected to derive benefit from the combination product but will be exposed to risks. Clarify your rationale for your choice of the liraglutide starting dose.

Discussion: No discussion occurred.

We note that you require only 12 weeks of treatment for patients to be eligible for inclusion in the Per Protocol population of the 6-month trial. A more typical definition is based on patients who have received at least 20 weeks of treatment. Revise or clarify the basis for using only 12 weeks for the Per Protocol population.

Post-Meeting Comment from Sponsor’s Minutes: The sponsor notes that they have used 12 weeks for the Per Protocol population in their other insulin trials, including the
degludec program and that most of the HbA1c reduction occurs within the first 12 weeks of therapy.

**FDA Response to Sponsor’s Post-Meeting Comment: Use of 12 weeks for the Per Protocol population is acceptable.**

5. Does the Agency agree with the proposed background medication dose levels of metformin and pioglitzone?

**FDA Response:** We agree with the proposed doses of the background anti-diabetic medications. Please clarify how many patients will be receiving background pioglitzone. In addition, clarify why you are not including patients on background sulfonylurea. If IDegLira is approved, it is likely that some patients may continue on sulfonylureas when IDegLira is initiated. Including patients treated with background sulfonylurea therapy will provide important safety information, such as the risk of hypoglycemia with concomitant use of IDegLira.

*Discussion: No discussion occurred.*

Post-Meeting Comment from Sponsor’s Minutes: The sponsor states that 125 patients (15%) in the proposed phase 3a IDegLira program will be exposed to both metformin and pioglitzone and that 705 patients (85%) will be exposed to metformin alone. The sponsor plans to cross-reference studies for NDA 76,496 (i.e., liraglutide) and IND 76496 (i.e., degludec) to address safety concerns regarding concomitant use of liraglutide, degludec and sulfonylurea.

**FDA Response to Sponsor’s Post-Meeting Comment:** The number of patients who will be exposed to IDegLira in combination with pioglitzone (~60) is too small to permit a meaningful assessment of efficacy and safety and should at least be doubled. We agree with your plan to stratify randomization based on pioglitzone use. You should aim to demonstrate similar trends with regard to efficacy in this subgroup compared to the overall population. With regard to concomitant sulfonylurea use, we do not agree that it is sufficient to cross-reference the liraglutide and degludec NDAs because neither NDA is studying co-administration of both liraglutide and degludec in sulfonylurea-treated patients.

6. Does the Agency agree to the proposed inclusion and exclusion criteria for the proposed IDegLira phase 3a trial?

**FDA Response:** Your overall inclusion and exclusion criteria appear reasonable although the intended patient population for IDegLira is unclear. Clarify whether IDegLira is intended only for patients who are naïve to both a glucagon-like peptide (GLP)-1 agonist and basal insulin or whether you intend for IDegLira to also be used in patients with inadequate glycemic control on a GLP-1 agonist or on basal insulin. In addition, ensure that the patient population you study will allow you to
adequately examine IDegLira’s entire dosing range (see our response to Question 9 below).

Discussion: See Question 4 discussion points.

7. Does the Agency agree to the proposed withdrawal criteria?

FDA Response: Your withdrawal criteria are reasonable. Please clarify how you will handle patients who meet withdrawal criteria. In general, we recommend that these patients be rescued with additional therapy (in this case, prandial insulin) but that they remain in the trial for the entire trial duration to bolster the safety database. For the primary efficacy endpoint, you should treat HbA1c data after rescue as missing and use last-observation-carried-forward.

Discussion: The sponsor expects a low withdrawal rate in the study. Patients who meet withdrawal criteria will be discontinued from the study and an alternative therapy left to the discretion of the treating physician will be initiated. A discussion concerning implementation of glycemic rescue with prandial insulin followed. The sponsor does not favor implementation of rescue with prandial insulin in the trial due to lack of current knowledge regarding use of liraglutide in combination with prandial insulin and because of the theoretical risk of hypoglycemia when IDegLira is used in combination with prandial insulin. FDA notes that these are precisely the reasons for why such a regimen should be tested in a clinical trial and asked whether useful safety information with concomitant prandial insulin administration could be obtained from the current trial. The sponsor stated that given the low expected need for glycemic rescue they did not believe useful information would be obtained. FDA then recommended that information on coadministered IDegLira and prandial insulin be obtained in another trial.

8. Does the Agency agree to the proposed titration algorithms for the phase 3a trial, and the proposed IDegLira starting dose?

FDA Response: The starting dose is reasonable. Please clarify how frequently patients will be asked to monitor fingerstick blood glucoses. Clarify whether fasting glucose refers to the pre-breakfast value or any value in the post-absorptive period (i.e., > 4-hours after meals). Clarify whether the three drugs will be administered at the same time of the day. Please clarify how you will handle skipped or missing fingerstick blood glucose data. Provide details on how you ensure compliance with the titration algorithm and provide an analysis of titration compliance in your final study report. Confirm that doses of study medication will be relatively stable during the last three months of the trial to ensure that the endpoint HbA1c measurement accurately reflects glycemic control.

Discussion: No discussion occurred.
Post-Meeting Comment from Sponsor’s Minutes: Fingerstick blood glucoses will be monitored once daily pre-breakfast. Fasting glucose refers to pre-breakfast glucose. The trial products can be administered at any time of the day but for a given patient are to be administered at the same time each day. Dose adjustment will be based on the mean of 3, 2, or 1 consecutive pre-breakfast values if there are no, one or two values missing respectively. No dose adjustment will occur if no values are obtained. Compliance with titration will be ensured by weekly clinic or phone visits, a weekly titration deviation report, and review by a titration committee. The sponsor notes that small adjustments of insulin doses may occur after the first 12 weeks of the trial.

FDA Response to Sponsor’s Post-Meeting Comment: Your overall plan is reasonable. The time of day of injection should be recorded so that exploratory analyses of efficacy and safety can be conducted, as needed. If there is considerable dose adjustment of insulin in the last 12 weeks of the trial we may question whether the HbA1c value at endpoint accurately reflects glycemic control.

9. Does the Agency agree that the number of exposed subjects and duration of exposure in the IDegLira phase 3a trial, together with available clinical data from the insulin degludec and Victoza® development programs, is sufficient to assess IDegLira clinical safety (including CV safety) and to support marketing authorization?

FDA Response: The number of patients and exposure duration appear reasonable based on our current state of knowledge regarding liraglutide and degludec. However, it is possible that the number of patients and duration of exposure may not be adequate if an efficacy or safety concern arises when we review the degludec NDA. In terms of pharmacokinetic exposure, clarify whether the dose range up to the maximum dose will be adequately represented in your study (i.e., proportion of patients you expect to reach IDeg/0.6 mg Lira, IDeg/1.2 mg Lira, and IDeg/1.8 mg Lira at end of study).

Discussion: The sponsor expects to be able to cover the entire dose range but did not provide estimates of the proportion of patients who will achieve the IDeg/0.6 mg Lira, IDeg/1.2 mg Lira, and IDeg/1.8 mg Lira doses. Enrolling patients who are not insulin naive may also ensure that a substantial number of patients achieve the maximum IDegLira and degludec doses at study end.

10. Does the Agency agree with the proposed safety monitoring strategy, including plans for antibody measurements?

FDA Response: Your proposed safety monitoring strategy appears reasonable based on our current state of knowledge regarding liraglutide and degludec. In terms of immunogenicity, clarify how the presence of circulating drug product impacts your ability to detect anti-liraglutide and anti-degludec antibodies.

Discussion: No discussion occurred.
Post-Meeting Comment from Sponsor’s Minutes: The sponsor states that the same approach discussed with FDA for degludec will also be used for the IDegLira program. For liraglutide, the sponsor states that the assay fulfills the recommendations set out in the Mire-Sluis white paper (AR Mire-Sluis et al: Journal of Immunological Methods 289 (2004) 1 – 16).

FDA Response to Sponsor’s Post-Meeting Comment: Based on the limited information in the sponsor’s post-meeting comment, it is unclear whether the proposed approach for liraglutide is consistent with what has been done for the Victoza program, including the required postmarketing cardiovascular trial. The sponsor should clarify further.

11. Does the Agency agree with the proposed pen scale, representing IDegLira dose steps as defined above?

FDA Response: Based on the trial dosing and titration outlined in section 9.2.4 of the briefing packet dated October 7, 2010, we agree that the pen scale of one unit increments appears adequate provided that '1 unit' increments cover the dose range and titration that will ultimately be submitted for the dosage and administration section of the labeling. However, we note that there is a risk for users to misdial the dose and this risk should be assessed in Human Factors/Usability studies.

If the dosage and administration changes and dose adjustments of less than one unit are required, then the pen scale will not be adequate.

We acknowledge that you will consider our previous comments concerning conducting adequate risk analysis in your human factors/usability studies communicated for INDs 076496 and 073198 on August 25, 2010.

We request a working model of the pen device PDS290 and would like you to submit a copy of the human factors protocol to the IND for review prior to implementing the study.

Discussion: No discussion occurred.

Additional Comments:

12. We remind you of the Pediatric Research Equity Act (PREA) of 2007 which requires all applications for a new active ingredient, new dosage form, new indication, new route of administration, or new dosing regimen to contain an assessment of the safety and effectiveness of the drug for the claimed indications in all relevant pediatric subpopulations unless the requirement is waived or deferred. We recommend that you start planning your pediatric development program.
Discussion: No discussion occurred.

13. You have performed testing in previous NDA submissions to demonstrate that the PDS 290 pen can operate with the needles in the current submission. However, the potential for the needle to dislodge from the PDS 290 should be considered as part of the human factors testing/usability studies. The User can easily mis-couple the auto injector and needle, prior to operating the device. The Human Factors/Usability testing should demonstrate that this use risk, along with all other use risks have been identified, tested and mitigated. As stated in comments to you as part of previous submissions, you must perform a comprehensive use risk hazard analysis, prioritization and testing of the PDS 290 to demonstrate that the user can safely use the product to deliver the desired dose. The Center for Devices and Radiological Health (CDRH) guidance regarding human factors is available at http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm094460.htm.

Discussion: No discussion occurred.

14. Your submission states that the PDS 290 Pen Injector is similar to the pen injectors that are proposed for use with several of your company’s other products. Based on the description of the device provided in this submission, it is unclear whether the dose selected by the user will represent the accurate dose for IDegLira. For example, if the user were to select “2” on the dose dial for IDegLira, how much volume of drug will be delivered? Will this volume be different than the volume dispensed when the user selects “2” on the PDS 290 pen injector filled with another Novo Nordisk product? Please demonstrate that the PDS 290 can accurately deliver the dose that the user requests.

Discussion: No discussion occurred.

Post-Meeting Comment from Sponsor’s Minutes: For any given dose scale number, the PDS290 pen injector will deliver the same volume of IDegLira, insulin, and liraglutide. If the user selects “2” on the dose scale, 0.02 mL will be delivered. The PDS290 pen for IDegLira will be tested for dose accuracy.

FDA Response to Sponsor’s Post-Meeting Comment: We agree with your response to Question 14. This means that the volume of drug administered when a specific setting is set on the device is consistent. The labeling for the device appears to clearly identify the concentration of the prefilled product.

In addition, however, please provide information to validate the depth of the injection as subcutaneous. Also, for general information we reference “Guidance to Industry: Technical considerations for Pen, Jet and Related Injectors Intended for use with Drugs and Biological Products (Draft 2009)”
15. We are aware of several adverse event reports associated with the Novo Nordisk Flex Pen. Some of the identified root causes for the device failures were failure of the device to deliver the drug, device breakage, device sticking, detachment of device component and fluid leak. Please confirm that the Novo Nordisk Flex Pen is the same as or is based on the PDS 290 device described in your recent IND and NDA submissions. Please identify whether you have changed your device design, manufacturing, labeling or any other aspect of the device based on these adverse events. For each change, please identify the reason for the change and describe the change to the device. Please identify if you have performed any communication with the user base of the Flex Pen regarding corrections to the labeling, additional warnings or cautionary statements, or outright replacements of the pen injector, due to the adverse events.

Discussion: The sponsor noted that the Flex Pen is the predecessor pen. FDA responded that the sponsor must submit information on how the design has improved upon the Flex Pen. The sponsor must submit complete performance testing.

5.0 ATTACHMENTS AND HANDOUTS

Attachment 1: Proposed primary and confirmatory secondary endpoints based on FDA preliminary comments
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

POOJA DHARIA
12/08/2010

Reference ID: 2873941
LATE-CYCLE COMMUNICATION DOCUMENTS
NDA 208583

Novo Nordisk Inc.
Attention: Robert B. Clark
Vice President, Regulatory Affairs
800 Scudders Mill Road
Plainsboro, NJ 08536

Dear Mr. Clark:

Please refer to your New Drug Application (NDA) dated September 14, 2015, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for insulin degludec and liraglutide injection.

We also refer to the Late-Cycle Meeting (LCM) between representatives of your firm and the FDA on May 9, 2016.

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

If you have any questions, call Marisa Petruccelli, Regulatory Project Manager at (240) 402-6147.

Sincerely,

Lisa Yanoff, M.D.
Clinical Team Leader
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure:
Late Cycle Meeting Minutes
MEMORANDUM OF LATE-CYCLE MEETING MINUTES

Meeting Date and Time: May 9, 2016, 2:00pm
Meeting Location: FDA White Oak, Building 22, Room 1419

Application Number: NDA 208583
Product Name: insulin degludec and liraglutide injection
Applicant Name: Novo Nordisk, Inc.

Meeting Chair: Lisa Yanoff, M.D.
Meeting Recorder: Marisa Petruccelli

FDA ATTENDEES
Jean-Marc Guettier, M.D., Division Director
Jennifer R. Pippins, M.D., M.P.H, Deputy Director for Safety
Lisa Yanoff, M.D., Clinical Team Leader
Tania Condarco, M.D., Clinical Reviewer
Smita Abraham, M.D., Clinical Reviewer
Julie Van der Waag, MPH, Chief, Project Management Staff
Marisa Petruccelli, Project Manager

Center for Devices and Radiological Health
Sapana Patel, PharmD, Pharmacist, General Hospital Devices Branch

Office of Clinical Pharmacology
Manoj Khurana, PhD, Clinical Pharmacology Team Leader
Sang Chung, PhD, Clinical Pharmacology Reviewer
Nitin Mehrotra, M.Pharm., PhD, Pharmacometrics Team Leader

Office of Biostatistics
Mark Rothmann PhD, Biometrics Team Leader
Anna Kettermann, Dipl. Math, MA, Biometrics Reviewer

Office of Combination Products
Bindi Nikhar, M.D., Associate Clinical Director

Office of Surveillance and Epidemiology
Amarilys Vega, MD, MPH, Medical Officer, Division of Risk Management
Ariane Conrad, PharmD, BCACP, CDE, FASCP, Safety Evaluator, Division of Medication Error Prevention and Analysis (DMEPA)
Yelena Maslov, PharmD, Team Leader, DMEPA
Ali Niak, M.D., Medical Officer, Division of Pharmacovigilance
1.0 BACKGROUND

NDA 208583 was submitted on September 14, 2015, for insulin degludec and liraglutide injection.

Proposed indication: As an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

PDUFA goal date: September 14, 2016

FDA issued a Background Package in preparation for this meeting on April 29, 2016.

2.0 DISCUSSION

1. Introductory Comments

Welcome, Introductions, Ground rules, Objectives of the meeting
2. Discussion of Substantive Review Issues

Substantive review issues identified to-date have to do with the nature of the proposed product for the indication being sought. The issues are similar to those raised and discussed in guidance meetings/written responses during product development and have to do with the clinical and practical utility of the product proposed. These issues will be discussed at the Advisory Committee (AC) meeting to be convened on May 24, 2016. Other than any pending responses to information requests, the Agency does not require additional data from Novo Nordisk at this time to complete the review of the application.

3. Additional Applicant Data

Discussion:
Novo Nordisk updated the Agency on its tentative plans to submit the results of the labeling comprehension study on June 3, 2016.

4. Information Requests

The Center for Devices and Radiological Health (CDRH) has the following request in follow-up to the response you provided on April 28, 2016:

The Agency recommends that you perform testing on the final finished device and not on the raw materials as manufacturing and processing could alter the physicochemical characteristics of the device that could lead to changes in the biocompatibility response. In order to use a risk assessment to address the necessary biocompatibility endpoints, in this case cytotoxicity, sensitization, and irritation, both the materials as well as manufacturing should be included. You have provided information on either manufacturing for the various components; however, the reviewer was unable to locate all the necessary information. The reviewer has included a table, summarizing the information provided and highlighting the missing information. Please provide the CAS # (and if available MSDS sheets) and provide a risk assessment of the sensitization and irritation potential for:

- [ ] the cartridge holder
- [ ] the dose button
- [ ] the dose button
- [ ] the dial

Additionally, please provide a rationale for why the manufacturing and processing will not impact the biocompatibility. Alternatively, you may perform the requested testing on the final finish device (or components).
<table>
<thead>
<tr>
<th>Component</th>
<th>Cytotoxicity testing on final component</th>
<th>Sensitization and Irritation testing on final component</th>
<th>Risk information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Housing and cap</td>
<td></td>
<td>Not needed</td>
<td>Not needed</td>
</tr>
<tr>
<td>Cartridge holder</td>
<td>Testing performed</td>
<td>Testing not performed; rationale that cytotoxicity was negative not adequate; need additional information on materials</td>
<td>Information not provided</td>
</tr>
<tr>
<td>Dial</td>
<td>Testing performed</td>
<td>Testing not performed; rationale that cytotoxicity was negative not adequate; need additional information on materials</td>
<td>Testing performed on base material used for the dial in compliance with ISO-10993-10</td>
</tr>
<tr>
<td>Dose button 1</td>
<td>Testing performed</td>
<td>Testing not performed; rationale that cytotoxicity was negative not adequate; need additional information on materials</td>
<td>MSDS sheet provided</td>
</tr>
</tbody>
</table>

Reference ID: 3939930
Discussion:
The Agency acknowledged receipt of Novo Nordisk’s May 5, 2016, response to this information request. Note: Since the date of this meeting, the Agency has reviewed the May 5 response and has no additional questions at this time.

5. Discussion of Upcoming Advisory Committee Meeting

FDA’s preparations for the upcoming AC meeting are ongoing, and we have no further information to communicate at this time. The high level issues to be discussed at the AC meeting are noted above.

Discussion:

Novo Nordisk and the Agency discussed how the topic of the LEADER trial, a multicenter, international, randomized, double-blind, placebo-controlled trial investigating the long-term effects of Victoza (1.2 and 1.8 mg) compared to placebo, both in addition to standard of care, in people with type 2 diabetes at high risk of cardiovascular events, should be handled at the AC meeting.

It was discussed that Dr. Guettier would include a disclaimer in his opening remarks that the LEADER trial has not yet been reviewed by the Agency and is not to be considered in this AC meeting. Novo Nordisk stated that it does not intend to discuss the LEADER trial beyond what has already been disclosed in the March 4, 2016, press release. If pressed to answer more specific questions, Novo Nordisk intends to state that the outcome of the trial was positive, but that specific results are not being shared yet.

Novo Nordisk noted a few discrepancies in the AC background document provided by the Agency and will provide specific comments to the Agency through the Designated Federal Official, LaToya Bonner.
6. REMS or Other Risk Management Actions

**Overall**
Edits made to the materials align the Xultophy REMS with the Saxenda REMS. We remind you that the REMS materials must align with the final version of the Xultophy Prescribing Information.

**REMS Document**
We are revising the Xultophy REMS Document to align with the Saxenda REMS document. The Xultophy REMS Document is currently going through the pre-clearance process. Additional comments will be provided to Novo Nordisk once the REMS document is pre-cleared.

**REMS Letters**
Please see the FDA’s minor revisions in tracked changes to the REMS Letter for Healthcare Providers and REMS Letter for Professional Societies [attached to the Late Cycle Meeting Background Package].

**Factsheet**
The FDA has made minor changes to the REMS Factsheet to align the Factsheet with the proposed Prescribing Information. See the revisions in tracked changes in the REMS Factsheet [attached to the Late Cycle Meeting Background Package].

**Slides**
Revise the slides so they are aligned with the Saxenda REMS slides. Presentation of Xultophy REMS information should reflect the presentation of the Saxenda REMS slides, instead of the Victoza REMS slides. For example, the first slide should contain only the information related to the definition and purpose of the REMS program. The next slide should contain information related to the potential risk of medullary thyroid carcinoma, including subheading for the Boxed Warning. Information about appropriate patient selection and patient management should follow on the next slides. The risk of acute pancreatitis should be its own slide with the information about appropriate patient selection and patient management following on another slide. See our comments and revisions to the REMS slides [attached to the Late Cycle Meeting Background Package].

**REMS Website**
Remove the Important Safety Information from the top of the REMS webpage. As the Prescribing Information is also included at the top of the webpage, having this information is redundant. The bullets appear too close together in the screenshot. Provide more space
between the bullets. Please see our comments on the REMS website [attached to the Late Cycle Meeting Background Package].

REMS Supporting Document
Revise the REMS Supporting Document to reflect modifications to the REMS Document (pending completion of pre-clearance process) and REMS appended materials.

Discussion:
The Agency received Novo Nordisk’s response to these comments on May 6, 2016 and is reviewing this response. The Agency shared its plans to provide comments on the REMS document soon after the May 9, 2016 meeting. Note: Comments on the REMS document were provided to Novo Nordisk on May 11, 2016, and Novo Nordisk responded on May 20, 2016.

7. Review Plans
FDA will continue review of the NDA and, at this time, there appear to be no significant review issues that would prevent FDA from taking an action on or before the PDUFA goal date.

Discussion:
The Agency commented that the AC needs to occur before the review of this application can continue. The Agency added that no major information requests are anticipated that would cause a delay in the review timeline. Labeling review is being deferred until the AC has taken place, but is not expected to be delayed any further at this time.

8. Wrap-up and Action Items
The AC meeting was held on May 24, 2016.

This application has not yet been fully reviewed by the signatory authority, division director, and Cross-Discipline Team Leader (CDTL) and therefore, this meeting did not address the final regulatory decision for the application.

- The Agency will review the results of the labeling comprehension study that Novo Nordisk intends to submit and provide comments to Novo Nordisk.

9. Additional Discussion:
The Agency conveyed that statistical issues previously discussed caused difficulty in the review of this application. It was suggested for the benefit of future applications that steps be taken early on, in clinical trial management, and in preparation of the submission, to improve the way missing data is handled and analyzed. Novo Nordisk acknowledged this concern and will work internally, and with the Agency in future pre-NDA meetings, to address this concern.
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

LISA B YANOFF
06/01/2016