CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203313Orig1s000
203314Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 203313 SUPPL # N/A HFD # 510

Trade Name Ryzodeg 70/30

Generic Name 70% insulin degludec and 30%insulin aspart injection

Applicant Name Novo Nordisk

Approval Date, If Known

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.

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:

c) Did the applicant request exclusivity?

YES ☐ NO ☒

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

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?

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.

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# 203314	Tresiba (insulin degludec injection)
NDA# 20986	Novolog
NDA# 21172	Novolog Mix 70/30
NDA# 21810	Novolog Mix 50/50

Please note: NDA 203313 for Ryzodeg (70% insulin degludec and 30% insulin aspart injection) and NDA 203314 for Tresiba (insulin degludec injection) are being approved on the same day.

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:

(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:

(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?

YES ☐ NO ☐

If yes, explain:

(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:

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.")

Investigation #1-5 YES ☐ NO ☐

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?

Investigation #1-5 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"):

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?

All investigations identified in response to question 3(c) !

IND # 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?

Not applicable

(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:

==========

Name of person completing form: Callie Cappel-Lynch
Title: Regulatory Project Manager
Date: September 4, 2015

Name of Office/Division Director signing form: Lisa Yanoff, on behalf of Jean-Marc Guettier
Title: Team Leader, Acting

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/

CALLIE C CAPPEL-LYNCH
09/18/2015

LISA B YANOFF
09/18/2015

EXCLUSIVITY SUMMARY

NDA # 203314 SUPPL # N/A HFD #

Trade Name Tresiba

Generic Name insulin degludec injection

Applicant Name Novo Nordisk

Approval Date, If Known

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

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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.

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:

c) Did the applicant request exclusivity?

YES ☐ NO ☒

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

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?

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).

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(Answer either #1 or #2 as appropriate)

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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#

NDA#

NDA#

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.

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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:

(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:

(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?

YES ☐ NO ☐

If yes, explain:

(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:

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.")

Investigation #1 YES ☐ NO ☐

Investigation #2 YES ☐ NO ☐

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

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?

Investigation #1 YES ☐ NO ☐

Investigation #2 YES ☐ NO ☐

If you have answered "yes" for one or more investigation, identify the NDA in which a

similar investigation was relied on:

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"):

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?

Investigation #1 !
 !

IND # YES ☐ ! NO ☐
 ! Explain:

Investigation #2 !
 !

IND # YES ☐ ! NO ☐
 ! Explain:

(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?

Investigation #1 !
 !

YES ☐ ! NO ☐
Explain: ! Explain:

Investigation #2 !
!
YES ☐ ! NO ☐
Explain: ! Explain:

(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:

==========

Name of person completing form: Callie Cappel-Lynch
Title: Regulatory Project Manager
Date: September 4, 2015

Name of Office/Division Director signing form: Lisa Yanoff, on behalf of Jean-Marc Guettier
Title: Team Leader, Acting

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

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/s/

CALLIE C CAPPEL-LYNCH
09/18/2015

LISA B YANOFF
09/18/2015

From: CappelLynch, Callie
To: "SHSK (Shawn Hoskin)"
Subject: RE: Tresiba labeling
Date: Friday, September 25, 2015 11:55:00 AM
Attachments: 9.25.15 FDA edits Ryzodeg-pi-clean.doc
9.25.15 FDA edits Ryzodeg-pi-tracked.doc

Hi Shawn,

Please see the attached labeling for Ryzodeg. We also request revised labeling be submitted within 1 hour.

Thanks,
Callie

From: SHSK (Shawn Hoskin) [mailto:shsk@novonordisk.com]
Sent: Friday, September 25, 2015 11:48 AM
To: CappelLynch, Callie
Subject: RE: Tresiba labeling

Thanks Callie – I confirm receipt

From: CappelLynch, Callie [mailto:Callie.CappelLynch@fda.hhs.gov]
Sent: Friday, September 25, 2015 11:33 AM
To: SHSK (Shawn Hoskin)
Subject: Tresiba labeling
Importance: High

Hi Shawn,

Please see the attached labeling with FDA edits. We ask that you submit revised labeling within the hour. If you have any questions, please let me know.

Thanks,
Callie

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

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/s/

CALLIE C CAPPEL-LYNCH
09/25/2015

From:	CappelLynch, Callie
To:	SHSK (Shawn Hoskin) (shsk@novonordisk.com)
Subject:	Tresiba labeling
Date:	Friday, September 25, 2015 11:33:00 AM
Attachments:	9.25.15 FDA edits Tresiba-pi-u100-u200-clean.doc 9.25.15 FDA edits Tresiba-pi-u100-u200-tracked.doc
Importance:	High

Hi Shawn,

Please see the attached labeling with FDA edits. We ask that you submit revised labeling within the hour. If you have any questions, please let me know.

Thanks,
Callie

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

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/s/

CALLIE C CAPPEL-LYNCH
09/25/2015

From:	CappelLynch, Callie
To:	SHSK (Shawn Hoskin) (shsk@novonordisk.com)
Subject:	Tresiba PI FDA comments
Date:	Thursday, September 24, 2015 8:39:00 AM
Attachments:	9.24.15 FDA Edits Tresiba pi-u100-u200-clean.doc 9.24.15 FDA Edits Tresiba pi-u100-u200-tracked.doc
Importance:	High

Hi Shawn,

Please see the attached Tresiba PI with FDA comments. Please send revised labeling by COB today. If you have any questions, please contact me.

Thanks,
Callie

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

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/s/

CALLIE C CAPPEL-LYNCH
09/24/2015

From:	CappelLynch, Callie
To:	"SHSK (Shawn Hoskin)"
Subject:	Ryzodeg PI and PPI FDA comments
Date:	Thursday, September 24, 2015 12:26:00 PM
Attachments:	9.24.15 FDA edits Ryzodeg-pi-clean.doc 9.24.15 FDA edits Ryzodeg-pi-tracked.doc 9.24.15 FDA edits Ryzodeg-ppi-clean.doc 9.24.15 FDA edits Ryzodeg-ppi-tracked.doc
Importance:	High

Hi Shawn,

Please see the attached labeling with FDA edits. We request that you send revised labeling by COB today. If you have any questions, please contact me.

Thanks,
Callie

-----Original Message-----
From: SHSK (Shawn Hoskin) [mailto:shsk@novonordisk.com]
Sent: Thursday, September 24, 2015 12:10 PM
To: CappelLynch, Callie
Subject: RE: Tresiba PI FDA comments

Hi Callie,

I can confirm that the submission yesterday for both products contained all of the carton and container labels for the presentations we are currently seeking approval for.

In the original NDA submission (b) (4) so those labels were not included in yesterday's submission.

Feel free to give me a call if you have any questions. Thanks.

Kind regards,
Shawn

-----Original Message-----
From: CappelLynch, Callie [mailto:Callie.CappelLynch@fda.hhs.gov]
Sent: Thursday, September 24, 2015 11:31 AM
To: SHSK (Shawn Hoskin)
Subject: RE: Tresiba PI FDA comments

Hi Shawn,

I just want to confirm that the carton and container labeling recently submitted contained all proposed carton and container labeling for both products and that there was not any additional in the original submission. Just trying to make sure everything is in order so if you could confirm that would be great.

Thanks,
Callie

-----Original Message-----
From: SHSK (Shawn Hoskin) [mailto:shsk@novonordisk.com]
Sent: Thursday, September 24, 2015 8:57 AM
To: CappelLynch, Callie
Subject: Re: Tresiba PI FDA comments

Ok, thanks. Appreciate it.

Kind regards,
Shawn

Sent from my iPhone

> On Sep 24, 2015, at 8:52 AM, CappelLynch, Callie <Callie.CappelLynch@fda.hhs.gov> wrote:
>
> I would expect so, but can't give you a time frame yet. I'll update you as soon as possible.
>
> Thanks,
> Callie
>
> -----Original Message-----
> From: SHSK (Shawn Hoskin) [mailto:shsk@novonordisk.com]
> Sent: Thursday, September 24, 2015 8:51 AM
> To: CappelLynch, Callie
> Subject: Re: Tresiba PI FDA comments
>
> Thanks Callie - I confirm receipt. Do you think there will be other labeling for review later today (i.e. Ryzodeg 70/30 PI, or PPI/IFUs)?
>
> Kind regards,
> Shawn
>
> Sent from my iPhone
>
>> On Sep 24, 2015, at 8:41 AM, CappelLynch, Callie <Callie.CappelLynch@fdahhs.gov> wrote:
>>
>> Hi Shawn,
>>
>> Please see the attached Tresiba PI with FDA comments. Please send revised labeling by COB today. If you have any questions, please contact me.
>>
>> Thanks,
>> Callie
>> <9.24.15 FDA Edits Tresiba pi-u100-u200-clean.doc>
>> <9.24.15 FDA Edits Tresiba pi-u100-u200-tracked.doc>
>

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

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/s/

CALLIE C CAPPEL-LYNCH
09/24/2015

From: CappelLynch, Callie
To: SHSK (Shawn Hoskin) (shsk@novonordisk.com)
Subject: RE: Labeling comment
Date: Monday, September 21, 2015 3:01:00 PM

Hi Shawn,

Sorry for any confusion, but please use the following statement instead of the one presented in the email below.

'At the end of 26 weeks, TRESIBA provided greater reduction in mean HbA1c compared to sitagliptin ($p < 0.001$).'

Thanks,
Callie

From: CappelLynch, Callie
Sent: Monday, September 21, 2015 2:55 PM
To: SHSK (Shawn Hoskin) (shsk@novonordisk.com)
Subject: Labeling comment
Importance: High

Hi Shawn,

Please see the labeling comment below. If you have any questions, please contact me.

We note the following textual error for the degludec vs. sitagliptin trial which had a superiority design: The label states: (b) (4)

We recommend that the language be changed to '**At the end of 26 weeks, TRESIBA provided greater HbA1c reduction compared to sitagliptin (p<0.001).**'

Thanks,
Callie

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

/s/

CALLIE C CAPPEL-LYNCH
09/21/2015

From:	CappelLynch, Callie
To:	"SHSK (Shawn Hoskin)"
Subject:	RE: Thanks RE: NDA 203313 and 203314 status check
Date:	Friday, September 18, 2015 6:12:00 PM
Attachments:	Clean 9.18.15 FDA Edits Tresiba PI.doc Clean 9.18.15 FDA Edits Ryzodeg PI.doc Track Changes 9.18.15 FDA Edits Ryzodeg PI.doc Track Changes 9.18.15 FDA Edits Tresiba PI.doc
Importance:	High

Hi Shawn,

Please see the attached labeling with FDA comments. We request that you send back revised labeling by COB Tuesday or earlier, if possible. If you have one done before that other it would be acceptable to send at different times.

If you have any questions, please let me know.

Thanks,
Callie

-----Original Message-----
From: SHSK (Shawn Hoskin) [mailto:shsk@novonordisk.com]
Sent: Friday, September 18, 2015 11:12 AM
To: CappelLynch, Callie
Subject: Thanks RE: NDA 203313 and 203314 status check

Thanks Callie. Appreciate it.

Kind regards,
Shawn

-----Original Message-----
From: CappelLynch, Callie [mailto:Callie.CappelLynch@fda.hhs.gov]
Sent: Friday, September 18, 2015 11:01 AM
To: SHSK (Shawn Hoskin)
Subject: RE: NDA 203313 and 203314 status check

Hi Shawn,

We expect to have labeling by the end of the day today, but I'll update you if that doesn't look like it will happen. Regarding any other additional issues, there are no outstanding issues that I am aware of, but I'll check in with the team today.

Thanks,
Callie

-----Original Message-----
From: SHSK (Shawn Hoskin) [mailto:shsk@novonordisk.com]
Sent: Friday, September 18, 2015 8:15 AM
To: CappelLynch, Callie
Subject: Re: NDA 203313 and 203314 status check

Hi Callie,

Welcome back!

I just wanted to follow-up on the revised PI's we submitted September 4. Should we anticipate additional discussion on the PI's, and if yes, do you know when we will receive the FDAs comments?

Is there anything else outstanding that we need to address with the Division prior to the September 26 PDUFA date?

Kind regards,
Shawn

Sent from my iPad

On Sep 8, 2015, at 5:50 PM, CappelLynch, Callie
<Callie.CappelLynch@fda.hhsgov<mailto:Callie.CappelLynch@fda.hhs.gov>> wrote:

No problem, thanks for sending! I also want to let you know that I will be on leave starting at 3pm tomorrow through September 17th . I'll return to work on Friday, September 18th. While I'm away Rich Whitehead will be covering, but Elisabeth Hanan will be taking lead on all PMR/PMC related issues for these application. Please cc them as appropriate on all matters that need attention during my absence as I will not have access to email.

Thanks,
Callie

From: SHSK (Shawn Hoskin) [mailto:shsk@novonordisk.com]
Sent: Tuesday, September 08, 2015 5:41 PM
To: CappelLynch, Callie
Subject: RE: NDA 203313 and 203314 PMR/PMC

Hi Callie,

Sorry - these should have been sent to you via email at the same time as the submission through the gateway. Here you go.

Kind regards,
Shawn

From: CappelLynch, Callie [mailto:Callie.CappelLynch@fda.hhs.gov]
Sent: Tuesday, September 08, 2015 3:57 PM
To: SHSK (Shawn Hoskin)
Subject: NDA 203313 and 203314 PMR/PMC

Hi Shawn,

We received your submission containing the PMR/PMC documents for NDA 203313 and 203314. Would you be able to send me, through email, a word copy with track changes?

Thanks,
Callie

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/s/

CALLIE C CAPPEL-LYNCH
09/21/2015

From: CappelLynch, Callie
To: "SHSK (Shawn Hoskin)"
Subject: RE: Thanks RE: NDA 203313 and 203314 status check
Date: Monday, September 21, 2015 8:41:00 AM

Hi Shawn,

We have the following clarification regarding the data presentation for tables in section 14 of the PI for both Tresiba and Ryzodeg 70/30. Please use the adjusted means for HbA1c results in the tables based on your prespecified primary efficacy analyses. Include a footnote in each table that provides the analysis model and factors/covariates. The footnote should not show the method for handling of missing data, but please provide the percent of subjects in each treatment group for whom data was missing at the time of the primary efficacy analysis measurement in the footnote.

Thanks,
Callie

-----Original Message-----
From: CappelLynch, Callie
Sent: Friday, September 18, 2015 6:13 PM
To: 'SHSK (Shawn Hoskin)'
Subject: RE: Thanks RE: NDA 203313 and 203314 status check
Importance: High

Hi Shawn,

Please see the attached labeling with FDA comments. We request that you send back revised labeling by COB Tuesday or earlier, if possible. If you have one done before that other it would be acceptable to send at different times.

If you have any questions, please let me know.

Thanks,
Callie

-----Original Message-----
From: SHSK (Shawn Hoskin) [mailto:shsk@novonordisk.com]
Sent: Friday, September 18, 2015 11:12 AM
To: CappelLynch, Callie
Subject: Thanks RE: NDA 203313 and 203314 status check

Thanks Callie. Appreciate it.

Kind regards,
Shawn

-----Original Message-----
From: CappelLynch, Callie [mailto:Callie.CappelLynch@fda.hhs.gov]
Sent: Friday, September 18, 2015 11:01 AM
To: SHSK (Shawn Hoskin)
Subject: RE: NDA 203313 and 203314 status check

Hi Shawn,

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Thanks,
Callie

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From: SHSK (Shawn Hoskin) [mailto:shsk@novonordisk.com]
Sent: Friday, September 18, 2015 8:15 AM
To: CappelLynch, Callie
Subject: Re: NDA 203313 and 203314 status check

Hi Callie,

Welcome back!

I just wanted to follow-up on the revised PI's we submitted September 4. Should we anticipate additional discussion on the PI's, and if yes, do you know when we will receive the FDAs comments?

Is there anything else outstanding that we need to address with the Division prior to the September 26 PDUFA date?

Kind regards,
Shawn

Sent from my iPad

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Callie

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Shawn

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Sent: Tuesday, September 08, 2015 3:57 PM
To: SHSK (Shawn Hoskin)
Subject: NDA 203313 and 203314 PMR/PMC

Hi Shawn,

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Thanks,

Callie

APPEARS THIS WAY ON ORIGINAL

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/s/

CALLIE C CAPPEL-LYNCH
09/21/2015

From:	CappelLynch, Callie
To:	SHSK (Shawn Hoskin) (shsk@novonordisk.com)
Subject:	FDA comments on Ryzodeg and Tresiba PPI and IFU
Date:	Monday, September 21, 2015 3:52:00 PM
Attachments:	clean 9.21.15 FDA edits Ryzodeg PPI.doc clean 9.21.15 FDA edits Tresiba PPI.doc Clean FDA edits 9.21.15 Ryzodeg IFU.docx clean FDA edits 9.21.15 Tresiba U-100 IFU.doc clean FDA edits 9.21.15 Tresiba U-200 IFU.doc track changes 9.21.15 FDA edits Ryzodeg PPI.doc track changes 9.21.15 FDA edits Tresiba PPI.doc Track Changes FDA edits 9.21.15 Ryzodeg IFU.docx track changes FDA edits 9.21.15 Tresiba U-100 IFU.doc track changes FDA edits 9.21.15 Tresiba U-200 IFU.doc
Importance:	High

Hi Shawn,

Please see the attached labeling with FDA comments. We ask that you provide revised labeling by COB tomorrow. If you have any questions, please contact me.

Thanks,
Callie

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/s/

CALLIE C CAPPEL-LYNCH
09/21/2015

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 203313

PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE

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

ATTENTION: Shawn Hoskin
Senior Director, Regulatory Affairs

Dear Mr. Hoskin:

Please refer to your New Drug Application (NDA) dated and received March 26, 2015, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for 70% Insulin Degludec and 30% Insulin Aspart Injection, 100 units/mL.

We also refer to your correspondence dated and received August 21, 2015, requesting review of your proposed proprietary name, Ryzodeg 70/30.

We have completed our review of the proposed proprietary name, Ryzodeg 70/30 and have concluded that it is conditionally acceptable.

If any of the proposed product characteristics as stated in your August 21, 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:

- Guidance for Industry Contents of a Complete Submission for the Evaluation of Proprietary Names (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf)
- 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, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (240) 402-3981. For any other information regarding this application, contact Callie Cappel-Lynch, Regulatory Project Manager in the Office of New Drugs, at (301) 796-8436.

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

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/s/

TODD D BRIDGES
09/04/2015

MEMORANDUM OF MEETING MINUTES

MEETING DATE:	August 19, 2015
TIME:	3:00 PM (EST)
LOCATION:	White Oak, Building 22, Room 6157
APPLICATION:	NDA 203313
DRUG NAME:	Ryzodeg (insulin degludec and insulin aspart) Injection, 100 units/mL
TYPE OF MEETING:	Teleconference
MEETING CHAIR:	Jean-Marc Guettier
MEETING RECORDER:	Terrolyn Thomas

FDA ATTENDEES:

Jean-Marc Guettier, Division Director, Division of Metabolism and Endocrinology Products
Lisa Yanoff, Medical Officer, Division of Metabolism and Endocrinology Products
Callie CappelLynch, Regulatory Project Manager, Division of Metabolism and Endocrinology Products
Lubna Merchant, Associate Director, Division of Medication Error Prevention and Analysis
Yelena Maslov, Team Leader, Division of Medication Error Prevention and Analysis
Sarah Vee, Reviewer, Division of Medication Error Prevention and Analysis
Monika Houstoun, Regulatory Director, Division of Metabolism and Endocrinology Products
Tania Condarco, Medical Officer, Division of Metabolism and Endocrinology Products
Terrolyn Thomas, Senior Safety Project Manager, Office of Surveillance and Epidemiology

SPONSOR ATTENDEES:

Bob Clark, Vice President, US Regulatory Affairs
Shawn Hoskin, Senior Director, US Regulatory Affairs
Nina Liang, Associate Director, US Regulatory Affairs
Martin Lange, Corporate Project Vice President, Insulin and Diabetes Outcomes
Jane Moll Pedersen, Department Director, Global Regulatory Affairs

BACKGROUND:

The sponsor submitted a request for Proprietary Name Request on April 8, 2015 to review the proposed proprietary name, Ryzodeg. DMEP proposed to add a modifier 70/30 to the proprietary name, Ryzodeg to be consistent with current naming approach for the mixed insulins.

MEETING OBJECTIVES:

The purpose of this meeting is to request the sponsor submit an amendment to add the modifier 70/30 to the proposed proprietary name.

DISCUSSION:

FDA explained their rationale to include a modifier 70/30 in the proposed proprietary Ryzodeg, to be consistent with current naming approach for the mixed insulins.

The sponsor asked clarification on the process of resubmitting the name as well as updated label and labeling, FDA clarified that the name would need to be submitted as a new proprietary name request and the labels and labeling can be updated at a later date.

REGULATORY OPTIONS:

DMEPA options for sponsor to move with proposed name, usually:

- To submit an amendment with the proposed proprietary name with the modifier 70/30.

ACTION ITEMS:

- Applicant will submit amendment with proposed changes.

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/s/

JEAN-MARC P GUETTIER
09/01/2015

From:	CappelLynch, Callie
To:	SHSK (Shawn Hoskin) (shsk@novonordisk.com)
Subject:	NDA 203313 and 203314 Labeling comments
Date:	Friday, August 28, 2015 12:53:00 PM
Attachments:	8.28.15 clean Ryzodeg proposed-pi.doc 8.28.15 clean Tresiba proposed-pi-u100-u200.doc 8.28.15 track changes Ryzodeg proposed-pi.doc 8.28.15 track changesTresiba proposed-pi-u100-u200.doc
Importance:	High

Hi Shawn,

Please see the attached labeling for NDA 203313 and 203314 with FDA comments. I have included a track changes and clean version of each label. We ask that you work off the clean labels and return revised labeling to us by COB next Friday, September 4, 2015. The TRESIBA label has been more extensively reviewed and therefore we ask that you change the RYZODEG label to conform, where appropriate, to the TRESIBA label.

If you have any questions, please contact me.

Thanks,
Callie

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

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/s/

CALLIE C CAPPEL-LYNCH
08/31/2015

From: CappelLynch, Callie
To: SHSK (Shawn Hoskin) (shsk@novonordisk.com)
Subject: information request NDA 203313 and 203314
Date: Monday, August 24, 2015 2:02:00 PM
Importance: High

Hi Shawn,

Please see the information request below for NDA 203313 and 203314. We ask that you provide response by COB Friday August 28, 2015. If you have any questions, please let me know.

1. You state "*All PDS290 pen-injector components which come into direct or indirect contact with users consist of* (b) (4) To support the biocompatibility of the device (b) (4) to the currently marketed FlexPen® and FlexTouch® pen-injectors, please provide a material certification statement from the device manufacturer as below:

   (b) (4)

2. The (b) (4) have been modified from the previous NDA/BLA approved devices. It appears that these modified patient contacting device components have introduced new materials including (b) (4). However, the material information provided in your 15 June 2015 response is unclear and inadequate. To address the safety concern, please clearly identify all materials used in the modified (b) (4). Please specify the new materials that are not used in the previously approved pen-injectors. Please provide the chemical identity, composition, CAS number if there is, currently known health problems associated with the chemical and toxicological data, for each of the new materials identified above. This information may be contained in the Material Safety Data Sheets (MSDS) or Technical Specification Sheets.

3. Based on analysis of the raw materials used, you state "*the Tresiba®/Ryzodeg® FlexTouch® pen-injectors do not pose a risk of cytotoxicity, skin irritation and sensitization, or any other biological hazard as defined in EN ISO 10993-1 and are safe for the intended use*". However, you have not provided any biocompatibility testing for the modified pen-injector in its final finished form. Please be advised that biocompatibility testing or risk analysis based on raw materials may have limitations and may not represent the final finished subject device or device components. Based on the FDA recognized standard ISO 10993-1: 2009/(R)2013 Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process, biocompatibility testing shall be performed on the final product, or representative samples from the final product or materials processed in the same manner as the final

product (including sterilization). ISO 10993-1 also indicates that biocompatibility of the final product shall be re-evaluated if there is any change a) in the source or in the specification of the materials used in the manufacture of the product; b) in the formulation, processing, primary packaging or sterilization of the product; c) in the manufacturer's instructions or expectations concerning storage, e.g. changes in shelf life and/or transport; etc.

To demonstrate that the modified PDS290 pen-injector is biocompatible, please provide complete biocompatibility study reports of the following using the final finished new device components, based on the exposure type and duration and a worst case scenario:

- *In vitro* cytotoxicity (ISO 10993-5)
- Skin irritation or intracutaneous reactivity (ISO 10993-10)
- Sensitization (ISO 10993-10)

Thanks,
Callie

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/s/

CALLIE C CAPPEL-LYNCH
08/24/2015

From: CappelLynch, Callie
To: SHSK (Shawn Hoskin) (shsk@novonordisk.com)
Subject: NDA 203313 and 203314 information request
Date: Thursday, August 20, 2015 8:52:00 AM
Importance: High

Hi Shawn,

Please see the below Information Request regarding antibody data for NDA 203313 and NDA 203314. These data should be submitted no later than COB Wednesday, August 26, 2015.

1. Provide a table containing data on antibody incidence rates and, if available, antibody titers for each study that assessed immunogenicity in Type I or Type 2 diabetes. The tables for each study should describe:

a. Number of patients (absolute number and percent) treated with degludec (TRESIBA), degludec + insulin aspart (RZYODEG), or comparator.

   i. who were positive for ADA at any time during the study

   ii. who were positive for ADA at baseline

   iii. who had sustained ADA (defined as two or more positive for ADA samples or remained positive at the end of the study).

   iv. For all subjects that have at least 1 positive sample provide the ADA titers if available in a table organized by treatment group, patient and sampling time.

a. Number of patients (absolute number and percent) treated with degludec (TRESIBA), degludec + insulin aspart (RZYODEG), or comparator.
   i. who were positive for AIA at any time during the study

   ii. who were positive for AIA at baseline

   iii. who had sustained AIA (defined as two or more positive for ADA samples or remained positive at the end of the study).

   iv. For all subjects that have at least 1 positive sample provide the AIA titers if available in a table organized by treatment group, patient and sampling time

b. Table showing whether there is a correlation between ADA or AIA with adverse events

c. Table showing whether there is a correlation between ADA or AIA and changes in efficacy with changes in antibody levels and/or titer.

There are different immunological profiles expected for type 1 diabetes (T1DM) versus type 2 diabetes (T2DM). Therefore, your incidence rate and titer data will need to be tabulated individually for each study, and also averaged across T1DM versus T2DM studies for TRESIBA studies, and similarly, for RYZODEG studies.

2. Your submission stated the sensitivity of each assay but does not state that an appropriate suitability control was used routinely to ensure that the sensitivity of the assays was consistent during the run of the study samples. Describe the system suitability controls that are routinely included as part of assay runs.

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/s/

CALLIE C CAPPEL-LYNCH
08/20/2015

From:	CappelLynch, Callie
To:	NLIA (Nina Liang) (nlia@novonordisk.com); SHSK (Shawn Hoskin) (shsk@novonordisk.com)
Subject:	NDA 203313 and 203314 information request
Date:	Thursday, August 13, 2015 2:05:00 PM
Importance:	High

Hi Shawn and Nina,

Please see the below information request for NDA 203313 and 203314. We request that you respond by COB Thursday August 20, 2015. If you have any questions, please contact me.

1. The application does not appear to clearly identify which manufacturing sites are responsible for the design, manufacturing and assembly of the final combination product with the inclusion of the device constituent parts for the final combination product. Please provide a table with all the manufacturers involved, with their address, FEI, and responsibilities.
2. The finished combination product manufacturer has inadequately addressed the requirement for 21 CFR 820.50, purchasing controls. Specifically, the firm did not provide any procedures or descriptions of your purchasing controls. No information about agreements with suppliers or controls over supplies was identified while there are many suppliers involved in the manufacturing of the finished combination product. Please provide a summary of the purchasing controls.
3. The description of the finished combination product manufacturer's management controls was inadequate. They did not specify which firm has the ultimate responsibility for the final combination product in compliance with 21 CFR 820.20. Please provide a summary descriptions of the management controls.
4. The application has inadequately addressed the requirement for Design Controls, 21 CFR 820.30. It did not provide documentation describing the design of the finished product. Please provide a summary description of the design controls and transfer of the design to the finished combination product manufacturer, if applicable.
5. The application does not identify CAPA procedures or systems. The finished combination product manufacturer does not provide any details or a summary of its procedure(s) for its Corrective and Preventive Action (CAPA) System as required by 21 CFR Part 820.100. Please provide a summary description of the CAPA system.
6. The application does not identify acceptance activity procedures. The finished combination product manufacturer did not provide details or a summary of its procedure(s) for its Acceptance activities as required by the Receiving, In-process and Finished Device Acceptance under 21CFR 820.80. Please provide a summary description of the acceptance activities.
7. Please describe the incoming, in-process and release activities planned to ensure that manufactured products will be safe and effective.

You may find useful information regarding the types of documents to provide in the document called 'Quality System Information for Certain Premarket Application Reviews; Guidance for Industry and FDA Staff,' (2003). This document may be found at
http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm070897.htm

Thanks,
Callie

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/s/

CALLIE C CAPPEL-LYNCH
08/13/2015

From: CappelLynch, Callie
To: SHSK (Shawn Hoskin) (shsk@novonordisk.com)
Subject: NDa 203313 and 203314 Labeling Comments
Date: Tuesday, July 21, 2015 3:44:00 PM

Hi Shawn,

Please see the labeling comments below regarding the carton and container labeling for NDA 203313 and 203314. We ask that you send revised copies by COB August 4, 2015. If you have any question, please contact me.

Ryzodeg (NDA 203313)

A. Container Labels

1. Revise the fonts of the proprietary and established names so that the established name is at least one half as large as the letters comprising the proprietary name or designation with which it is joined, and the established name shall have a prominence commensurate with the prominence with which such proprietary name or designation appears, taking into account all pertinent factors, including
typography, layout, contrast, and other printing features per 21 CFR 201.10(g)(2).

2. Revise the strength presentation adjacent to the proprietary name to read "100 units/mL (U-100)" (b) (4)

3. Relocate the strength statement to appear below the safety warning, "For Single Patient Use Only".

4. The safety warning, "For Single Patient Use Only", should be placed immediately below the established name so that there is no intervening matter between the established name and the warning. This will ensure that the warning is in the same viewing angle and field as the drug name and less likely to be overlooked. We recommend using a red-shaded and bolded letters in a contrasting colored box to
enhance visibility and prominence.

5. Unbold the statement "Rx Only".

B. Carton Labeling (FlexTouch Pen)

1. See comments B1 through B5.

2. Revise the location and increase the prominence of the NDC number so that it appears

above the proprietary name to assist healthcare providers in identifying the product.

Tresiba (NDA 203314)

A. Container Labels

1. Revise the fonts of the proprietary and established names so that the established name is at least one half as large as the letters comprising the proprietary name or designation with which it is joined, and the established name shall have a prominence commensurate with the prominence with which such proprietary name or designation appears, taking into account all pertinent factors, including
typography, layout, contrast, and other printing features per 21 CFR 201.10(g)(2).

2. Revise the strength presentation adjacent to the proprietary name to read "100 units/mL (U-100)" or "200 units/mL (U-200)" (b) (4)

3. Relocate the strength statement to appear below the safety warning, "For Single Patient Use Only".

4. The safety warning, "For Single Patient Use Only", should be placed immediately below the established name so that there is no intervening matter between the established name and the warning. This will ensure that the warning is in the same viewing angle and field as the drug name and less likely to be overlooked. We recommend using a red-shaded and bolded letters in a contrasting colored box to
enhance visibility and prominence.

5. Unbold the statement "Rx Only".

B. Carton Labeling

1. See Comments B 1 through B 5.

2. Revise the location and increase the prominence of the NDC number so that it appears above the proprietary name to assist healthcare providers in identifying the product.

Thanks,
Callie

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/s/

CALLIE C CAPPEL-LYNCH
07/21/2015

From: CappelLynch, Callie
To: SHSK (Shawn Hoskin) (shsk@novonordisk.com)
Subject: NDA 203313 and 203314 Information Request
Date: Friday, June 26, 2015 12:26:00 PM

Hi Shawn,

Please see the below information request for NDA 203313 and 203314. We ask that you provide response ASAP, but no later than 2 weeks from today.

Please provide the 510k number(s) for the [redacted] (b) (4)

It is our understanding that your pivotal trials were all conducted with the PDS290 device. (b) (4) [redacted]

Thanks,
Callie

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/s/

CALLIE C CAPPEL-LYNCH
06/26/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 203313
NDA 203314

INFORMATION REQUEST

Novo Nordisk Inc.
Attention: Shawn Hoskin
Senior Director, Regulatory Affairs
800 Scudders Mill Road
P.O. Box 846
Plainsboro, NJ 08536

Dear Mr. Hoskin:

Please refer to your New Drug Application (NDA) resubmission dated March 26, 2015, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Ryzodeg (insulin degludec/insulin aspart [rDNA origin]), injection, 100 U/mL and Tresiba (insulin degludec [rDNA origin]), injection, 100 U/mL and 200 U/mL.

We also refer to your amendments dated April 23, 29, May 14, 21, 22, June 5, and 16, 2015.

We are reviewing your application and have the following comments and information requests:

You are proposing to market insulin degludec (IDeg) and insulin degludec/aspart (IDeg/Asp) (b) (4) [redacted]. We have the following medication error concerns related to this proposal that should be addressed prior to the approval of Tresiba and Ryzodeg (b) (4) [redacted]:

(b) (4) [redacted]

(b) (4)

To resolve this significant medication error issue you will need to address the following:

1. Develop additional means of (b) (4) and submit your proposed plan for review by the Agency.

2. Depending on your proposal, a differentiation Human Factors study may be needed to ensure sufficient differentiation among the devices.

If you have any questions, please contact Callie Cappel-Lynch, Regulatory Project Manager, at (301) 796-8436.

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

[1] Do Different Body Colors and Labels of Insulin Pens Enhance a Patient's Ability to Correctly Identify Pens for Injecting Long-Acting versus Short-Acting Inuslins?, Lefkowitz, M. J Diabetes Sci Technol Vol 5, Issue 1, January 2011

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/s/

JEAN-MARC P GUETTIER
06/24/2015

From: CappelLynch, Callie
To: SHSK (Shawn Hoskin) (shsk@novonordisk.com)
Subject: NDA 203313 and 203314 Information Request
Date: Wednesday, June 10, 2015 1:00:00 PM

Hi Shawn,

Please see the below information request for NDA 203313 and 203314. Please provide response within 1 week. If you have any questions, please contact me.

1. FlexTouch (PDS290) appears to have been on the market since 2013 via Levemir sNDA S-33 and Novolog sNDA S-61. What other NDA/BLA product have been marketed in the U.S. using this platform injector? What do you change internally in terms of your operating mechanism (springs and such) to accommodate a new drug/biologic each time?

2. You provided a comparison table in your NDA comparing FlexPen and FlexTouch, however, you have not specified what are the internal mechanical differences. We are looking for specifications in your submission for spring force/trigger force/injection force.

3. What is the shelf life of your injector device and where is that information located in the submission?

4. What is the Life Cycle of your injector meaning just before expiry of your device and it is distributed from the shelf to the user then how many injection can your device perform? Is the testing performed to 2x or 3x? Where is this testing information located in your submission?

Thanks,
Callie

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/s/

CALLIE C CAPPEL-LYNCH
06/10/2015

From: CappelLynch, Callie
To: SHSK (Shawn Hoskin) (shsk@novonordisk.com)
Subject: RE: NDA 203313 and 203314 Information Request
Date: Wednesday, June 10, 2015 4:43:00 PM

Hi Shawn,

Please see additional clarification on the request below.

Although the injector device uses a non-replaceable cartridge, it is not a one-time use and discard injector in that patients can dial numerous doses on the injector before emptying out the cartridge. Thus the Agency is seeking data (not exactly the Life Cycle per ISO 11608-1) regarding the maximum of number of actuations/drug delivery doses can this injector device perform per the life time of the fixed cartridge.

We are also looking for the biocompatibility (ISO 10993) testing and data for this surface contacting injector device.

Lastly, did you track device performance during the clinical trials in terms of device-related medication errors, device malfunctions or failures or adverse events related to the device use? If yes, please provide the detailed data and root cause analysis as well as the location of this information in the 2 submissions.

Thanks,
Callie

From: CappelLynch, Callie
Sent: Wednesday, June 10, 2015 1:00 PM
To: SHSK (Shawn Hoskin) (shsk@novonordisk.com)
Subject: NDA 203313 and 203314 Information Request

Hi Shawn,

Please see the below information request for NDA 203313 and 203314. Please provide response within 1 week. If you have any questions, please contact me.

1. FlexTouch (PDS290) appears to have been on the market since 2013 via Levemir sNDA S-33 and Novolog sNDA S-61. What other NDA/BLA product have been marketed in the U.S. using this platform injector? What do you change internally in terms of your operating mechanism (springs and such) to accommodate a new drug/biologic each time?

2. You provided a comparison table in your NDA comparing FlexPen and FlexTouch, however, you have not specified what are the internal mechanical differences. We are looking for specifications in your submission for spring force/trigger force/injection force.

3. What is the shelf life of your injector device and where is that information located in the submission?

4. What is the Life Cycle of your injector meaning just before expiry of your device and it is distributed from the shelf to the user then how many injection can your device perform? Is the testing performed to 2x or 3x? Where is this testing information located in your submission?

Thanks,
Callie

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/s/

CALLIE C CAPPEL-LYNCH
06/10/2015

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 203314

PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE

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

ATTENTION: Shawn Hoskins
Senior Director, Regulatory Affairs

Dear Mr. Hoskins:

Please refer to your New Drug Application (NDA) dated and received March 26, 2015, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Insulin Degludec Injection, 100 units/mL and 200 units/mL.

We also refer to your correspondence dated and received March 26, 2015, requesting review of your proposed proprietary name, Tresiba.

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

If any of the proposed product characteristics as stated in your March 26, 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:

- Guidance for Industry Contents of a Complete Submission for the Evaluation of Proprietary Names (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf)
- 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, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (240) 402-3981. For any other information regarding this application, contact Callie Cappel-Lynch, Regulatory Project Manager in the Office of New Drugs, at (301) 796-8436.

Sincerely,

{See appended electronic signature page}

Todd Bridges, RPh
Deputy 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

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/s/

TODD D BRIDGES
06/08/2015

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 203313

PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE

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

ATTENTION: Shawn Hoskin
Senior Director, Regulatory Affairs

Dear Mr. Hoskin:

Please refer to your New Drug Application (NDA) dated and received March 26, 2015, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for 70% Insulin Degludec and 30% Insulin Aspart Injection, 100 units/mL.

We also refer to your correspondence dated and received March 26, 2015, requesting review of your proposed proprietary name, Ryzodeg.

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

If any of the proposed product characteristics as stated in your March 26, 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:

- Guidance for Industry Contents of a Complete Submission for the Evaluation of Proprietary Names (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf)
- 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, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (240) 402-3981. For any other information regarding this application, contact Callie Cappel-Lynch, Regulatory Project Manager in the Office of New Drugs, at 301-796-8436.

Sincerely,

{See appended electronic signature page}

Todd Bridges, RPh
Deputy 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

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/s/

TODD D BRIDGES
06/06/2015

From: Chen, Elizabeth
To: "SHSK (Shawn Hoskin)"
Cc: CappelLynch, Callie
Subject: RE: NDA 203313 and 203314 - FDA Information Request
Date: Wednesday, June 03, 2015 6:06:00 PM

Dear Shawn,

Please see the following (additional) Information Request:

1) In the Safety Update, for table 52 in appendix 1.7, titled "Allergic reactions (narrow and broad scope) by SOC and PT (MedDRA version 17.0)- treatment-emergent-completed phase 3 trials – subjects with T2DM –IDeg +IDegAsp vs. comparator—summary – safety update – safety analysis set"
   Provide the narratives for the following PT terms:
      Exfoliative rash
      Angioedema
      Skin exfoliation
      Face oedema

2) In the Safety Update, for table 46 in appendix 1.7, titled "Allergic reactions (narrow and broad scope) by SOC and PT (MedDRA v. 17.0) –treatment-emergent - completed phase 3 trials – T1DM – IDeg+IDegAsp vs. comparator – summary – safety update- safety analysis set,"
   provide the narratives for the following PT terms:
      Face oedema
      Angioedema

3) In the Safety Update, for table 2-41 titled "Allergic reactions (narrow and broad scope) by SOC and PT (MedDRA v. 17.0) –treatment-emergent - completed phase 3 trials – T1DM – IDeg+IDegAsp vs. comparator – summary – safety update- safety analysis set," provide the narratives for all the patients listed.

Again, please provide a response within 7 days. (Callie should be included on this response, as she will be back in the office at that time.)

Please confirm receipt of this request.

Regards,
Elizabeth Chen

From: SHSK (Shawn Hoskin) [mailto:shsk@novonordisk.com]
Sent: Tuesday, June 02, 2015 12:45 PM
To: Chen, Elizabeth
Cc: CappelLynch, Callie

Subject: RE: NDA 203313 and 203314 - FDA Information Request

Hi Elizabeth,

I confirm receipt of this request. I'll let both you and Callie know when we submit the response to the NDAs. Thanks.

Kind regards,
Shawn

From: Chen, Elizabeth [mailto:Elizabeth.Chen@fda.hhs.gov]
Sent: Tuesday, June 02, 2015 12:35 PM
To: SHSK (Shawn Hoskin)
Cc: CappelLynch, Callie
Subject: NDA 203313 and 203314 - FDA Information Request

Dear Shawn,

My name is Elizabeth Chen, and I am covering for Callie Cappel-Lynch while she is out of the office. I have the following requests for information from the clinical reviewer here at FDA.

In order to make sure your review gets completed in a timely fashion, please provide the following:

1) For the DEVOTE trial, please describe the methodology (i.e. variables selected) to create table 14.3.1.4, using the datasets submitted in the NDA.
2) For the DEVOTE trial, please provide a file which contains **only** the narratives for the patients who discontinued due to AEs.

Please provide a response within 7 days. Callie should be included on this response, as she will be back in the office at that time.

Please confirm receipt of this request.

Regards,
Elizabeth Chen

Elizabeth Chen, Pharm.D.
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
elizabeth.chen@fda.hhs.gov
PH: 240-402-3729

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/s/

ELIZABETH R CHEN
06/03/2015

From: CappelLynch, Callie
To: SHSK (Shawn Hoskin) (shsk@novonordisk.com)
Subject: NDA 203314 and 203313 Information Request
Date: Tuesday, May 19, 2015 1:18:00 PM

Hi Shawn,

Please see the information request for NDA 203313 and 203314 below. We are requesting response within 1 week.

For the DEVOTE trial, please clarify why, in the Adverse event dataset (adae.xpt), the following patients **only** have a 'reported term for adverse event' **without** corresponding PT or SOC terms.

USUBID	Reported term for adverse event
EX1250-4080/178001	HEPATOCELLULAR CARCINOMA SEGMENTS 5-6
EX1250-4080/196006	ACUTE TROMBOSIS WITH MI WITHIN THE NEWLY IMPLEMENTED STENT
EX1250-4080/292010	MULTIPLE STENOSIS OF LEFT FEMORAL SUPERFICIAL ARTERY
EX1250-4080/627007	VOMITING WITH SEVERE HEADACHE
EX1250-4080/706015	INTENSIVE THERAPIES POST ORTHOPLASTY
EX1250-4080/715009	FATAL CARDIAC ARREST
EX1250-4080/763012	GASTROESOPHAGEAL ADENOCARCINOMA, STAGE 2
EX1250-4080/782048	ATYPICAL CHEST PAIN AND CONGESTIVE HEART FAILURE (CHF) EXACERBATION
EX1250-4080/846004	TOTAL THYROIDECTOMY
EX1250-4080/905008	PROLONGED HOSPITALIZATION FOR AORTIC VALVE REPLACEMENT
EX1250-4080/907003	PERMANENT PACEMAKER IMPLEMENTATION
EX1250-4080/944003	EXACERBATION OF CHRONIC COPD
EX1250-4080/176003	SUBJECT HAD A EPISODE OF DYSPNEA ASSOCIATED WITH RIGHT BACK PAIN.HE WENT TO E.R. ON DECEMBER 21 2014 AND HE WAS HOSPITLIZED,HE HAD CORONARY ARTHERY BY PASS GRAPH.(X3) HE WAS RELEASED ON 03 JANUARY 15
EX1250-4080/256007	CONGESTIVE CARDIAC FAILURE SECONDARY TO ANEMINA
EX1250-4080/378001	CHRONIC OBSTRUCTIVE PULMONARY DISEASE EXACERBATED
EX1250-4080/727028	VENTRAL HERNIA X 2
EX1250-4080/738020	CHOLELITHYASIS
EX1250-4080/755013	CONGESTIVE HEART AGGRAVATED
EX1250-4080/783003	CERVICAL SPONDYLOSIS WITH MYELOPATHY
EX1250-4080/819008	BRONCHITIS WITH MRSA
EX1250-4080/848003	CLOSED R-DISTAL TIBIA & R-PROXIMAL FIBULAR SHAFT FXS DUE TO A FALL SECONDARY TO SYNCOPE, POSSIBLY ARRHYTHMIC EVENT
EX1250-4080/883012	ADMIT FOR EVALUATION OF ATYPICAL CHEST PAIN
EX1250-4080/888017	CARDIAC ARREST DUE TO RCA PLAQUE RUPTURE
EX1250-4080/926003	TEMPORARY AMNESIA

If you have any questions, please contact me.

Thanks,
Callie

APPEARS THIS WAY ON ORIGINAL

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/s/

CALLIE C CAPPEL-LYNCH
05/19/2015

From: CappelLynch, Callie
To: SHSK (Shawn Hoskin) (shsk@novonordisk.com)
Subject: NDA 203313 and 203314 Information Request
Date: Friday, May 15, 2015 9:40:00 AM

Hi Shawn,

Please see the below information request for NDA 203313 and 203314. We are requesting response within 1 week.

Please perform a custom SMQ search (using the PT terms in Table 1) of the Adverse Event databases of the **ISS** and the **Safety Update** of the completed Phase 3 trials, for treatment Emergent events, in the Safety analysis set.

Please report the output as shown in Table 2. Please fill in the highlighted portions.

Table 1.

CARDIOGENIC SHOCK
CARDIAC ASTHMA
CARDIAC FAILURE
CARDIAC FAILURE ACUTE
CARDIAC FAILURE CHRONIC
CARDIAC FAILURE CONGESTIVE
CARDIOPULMONARY FAILURE
COR PULMONALE
LEFT VENTRICULAR FAILURE
RIGHT VENTRICULAR FAILURE
DYSPNOEA PAROXYSMAL NOCTURNAL
ORTHOPNOEA
ACUTE LEFT VENTRICULAR FAILURE
Acute right ventricular failure
Cardiac cirrhosis
Chronic right ventricular failure
Cor pulmonale
HEPATIC CONGESTION
Ventricular failure
ACUTE PULMONARY OEDEMA
PULMONARY OEDEMA
Non-cardiogenic pulmonary edema

Table 2

	IDeg			IDeg			Comparator			Comparator		
	Safety Update			**ISS**			**Safety Update**			**ISS**		

	N(%)	Events	R	N(%)	Events	R	N(%)	Events	R	N(%)	Events	N(%)
T1DM												
T2DM												
	IDeg+IDegAsp			IDeg+IDegAsp			Comparator			Comparator		
T1DM												
T2DM												

N= number of subjects with adverse events
% proportion of subjects in analysis set having adverse events
R= number of events divided by subject years of exposure multiplied by 100

If you have any questions, please contact me.

Thanks,
Callie

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/s/

CALLIE C CAPPEL-LYNCH
05/15/2015

From: CappelLynch, Callie
To: SHSK (Shawn Hoskin) (shsk@novonordisk.com)
Subject: NDA 203313 and 203314 Information Request
Date: Monday, May 11, 2015 11:38:00 AM

Hi Shawn,

Please see the information request below. We are requesting response within 1 week.

Please clarify if the "second consensus communication" shown in Appendix 3: Event Adjudication Flowchart (page 30 in EX1250-4080), is made up of the same, or different adjudicators as the "first consensus communication".

If you have any questions, please contact me.

Thanks,
Callie

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/s/

CALLIE C CAPPEL-LYNCH
05/11/2015

From: CappelLynch, Callie
To: SHSK (Shawn Hoskin) (shsk@novonordisk.com)
Subject: NDA 203313 and 203314 Information Request
Date: Friday, May 08, 2015 9:53:00 AM

Hi Shawn,

Please see the information request below. We are requesting response by COB May 15, 2015.

Please provide narrative for the following event:
One fatal event('Cardiac arrest') was considered non-treatment-emergent and not included in the above table: Trial id =NN1250-3579-3643, Subject ID = 914014.

If you have any questions, please contact me.

Thanks,
Callie

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/s/

CALLIE C CAPPEL-LYNCH
05/08/2015

From: CappelLynch, Callie
To: SHSK (Shawn Hoskin) (shsk@novonordisk.com)
Subject: NDA 203313 and 203314 Information Request
Date: Friday, April 24, 2015 3:57:00 PM

Hi Shawn,

Please see the information request below for NDA 203313 and 203314. We are requesting response by COB May 1, 2015. If you have any questions, please let me know.

Per the Data Access Management Plan (DAMP), Alan Moses was involved in the steering committee (blinded) and the IDRT (ublinded). Please clarify the time line (i.e. the dates) that Dr. Moses was involved in each of these groups. The DAMP also states that Dr. Moses was **designated** to be part of these two groups, could you clarify how confidentiality was ensured, even when Dr. Moses participated in both unblinded and blinded portions of the trial?

Thanks,
Callie

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/s/

CALLIE C CAPPEL-LYNCH
04/24/2015

From: CappelLynch, Callie
To: SHSK (Shawn Hoskin) (shsk@novonordisk.com)
Subject: Information request for NDA 203314/203313
Date: Thursday, April 23, 2015 9:12:00 AM
Attachments: image001.emz
image004.png

Hi Shawn,

Please see the information request below. We are requesting response by COB, Thursday April 30, 2015. If you have any questions, please contact me.

1. Please clarify if the Safety Surveillance Global Safety group is blinded or unblinded.
2. Please clarify the communication between the DMC, safety surveillance global safety NN, internal NN degludec safety committee, steering committee, (b) (4) and EAC in a diagram (an example is shown below).

Figure 1 - DEVOTE - DMC communication scheme

Tania Condarco MD
Medical Reviewer (DMEP)
Phone: 301-796-1295

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/s/

CALLIE C CAPPEL-LYNCH
04/23/2015

From: CappelLynch, Callie
To: "SHSK (Shawn Hoskin)"
Subject: RE: Information Request NDA 203313 and 203314
Date: Thursday, April 23, 2015 10:14:00 AM

Hi Shawn,

Please see the response to your clarification question below. If you have additional questions, please contact me.

The purpose of our request is to understand your analyses and process. Please provide SAS programs and associated macros used for the CV Cox regression primary analysis and its sensitivity analyses (on-treatment analyses etc.). The programs don't have to be executable on FDAs IT environment but need to be documented or self-explanatory.

Thanks,
Callie

From: SHSK (Shawn Hoskin) [mailto:shsk@novonordisk.com]
Sent: Wednesday, April 22, 2015 10:24 AM
To: CappelLynch, Callie
Subject: RE: Information Request NDA 203313 and 203314

Hi Callie,

Here is the clarification we are requesting:

- Is the purpose of providing the computer programs (SAS) to allow FDA to run the analyses, or alternatively to look at the code, or to understand the process which was used with the external statistical vendor (b) (4)? The information we would need to provide are different depending on this.
    - Currently the SAS programs (for CV cox regression primary analysis, the pipeline sensitivity analysis, and the on-treatment analyses) are set up pointing to internal libraries and macros and therefore would not run on FDAs IT environment without modification

Kind regards,
Shawn

From: CappelLynch, Callie [mailto:Callie.CappelLynch@fda.hhs.gov]
Sent: Monday, April 20, 2015 3:53 PM
To: SHSK (Shawn Hoskin)
Subject: Information Request NDA 203313 and 203314

Hi Shawn,

We request that you provide the computer programs used for the analysis of cardiovascular safety in the DEVOTE trial. We are requesting response within 10 days. If you have any questions, please contact me.

Thanks,
Callie

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/s/

CALLIE C CAPPEL-LYNCH
04/23/2015

From: CappelLynch, Callie
To: SHSK (Shawn Hoskin) (shsk@novonordisk.com)
Subject: Information Request NDA 203313 and 203314
Date: Monday, April 20, 2015 3:53:00 PM

Hi Shawn,

We request that you provide the computer programs used for the analysis of cardiovascular safety in the DEVOTE trial. We are requesting response within 10 days. If you have any questions, please contact me.

Thanks,
Callie

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/s/

CALLIE C CAPPEL-LYNCH
04/20/2015

From:	CappelLynch, Callie
To:	SHSK (Shawn Hoskin) (shsk@novonordisk.com)
Cc:	CappelLynch, Callie
Subject:	NDA 203313 and 203314 Labeling Comments
Date:	Wednesday, April 08, 2015 3:23:27 PM

Hi Shawn,

Please see the PLR labeling format deficiencies listed below for NDA 203313 and 203314. We ask that you submit revised labeling by April 29, 2015. If you have any questions, please contact me.

Thanks,
Callie

NDA 203313:

HIGHLIGHTS GENERAL FORMAT

1. The length of HL must be one-half page or less unless a waiver has been granted in a previous submission. The HL Boxed Warning does not count against the one-half page requirement. Instructions to complete this item: If the length of the HL is one-half page or less, select "YES" in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page, select "NO" unless a waiver has been granted.

   Comment: *Highlight section is longer than 1/2 page. If you have already submitted a waiver request, please disregard this comment.*

2. A horizontal line must separate HL from the Table of Contents (TOC). A horizontal line must separate the TOC from the FPI.
   Comment: *Horizontal lines are not present*

3. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between the product title and Initial U.S. Approval. See Appendix A for a sample tool illustrating white space in HL.

   Comment: *White space is not present before major headings.*

Highlights Limitation Statement

4. The **bolded** HL Limitation Statement must include the following verbatim statement: "**These highlights do not include all the information needed to use (insert name of drug product) safely and effectively. See full prescribing information for (insert name of drug product).**" The name of drug product should appear in UPPER CASE letters.

Comment: *Drug product is not in upper case letters.*

Contents: Table of Contents (TOC)

5. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (through), articles (a, an, and the), or conjunctions (for, and)].

Comment: *All subsections are not in title case*

FULL PRESCRIBING INFORMATION: GENERAL FORMAT

6. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below (section and subsection headings should be in UPPER CASE and title case, respectively). If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

Comment: *All subsections are not presented in title case.*

PATIENT COUNSELING INFORMATION Section in the FPI

7. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION section). The reference should appear at the beginning of Section 17 and include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Medication Guide, Instructions for Use).

Comment: *Does not includes types of FDA approved patient labeling*

NDA 203314

HIGHLIGHTS GENERAL FORMAT

1. The length of HL must be one-half page or less unless a waiver has been granted in a previous submission. The HL Boxed Warning does not count against the one-half page requirement. Instructions to complete this item: If the length of the HL is one-half page or less, select "YES" in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page, select "NO" unless a waiver has been granted.

Comment: *Highlight section is longer than 1/2 page If you have already submitted a waiver request, please disregard this comment.*

2. A horizontal line must separate HL from the Table of Contents (TOC). A horizontal line must separate the TOC from the FPI.

Comment: *Horizontal line is not present betweel TOC and FPI*

3. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between the product title and Initial U.S. Approval. See Appendix A for a sample tool illustrating white space in HL.

Comment: *White space is not present before major headings.*

Highlights Limitation Statement

4. The **bolded** HL Limitation Statement must include the following verbatim statement: "**These highlights do not include all the information needed to use (insert name of drug product) safely and effectively. See full prescribing information for (insert name of drug product).**" The name of drug product should appear in UPPER CASE letters.

Comment: *Drug product is not in upper case letters.*

Contents: Table of Contents (TOC)

5. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (through), articles (a, an, and the), or conjunctions (for, and)].

Comment: *All subsections are not in title case*

FULL PRESCRIBING INFORMATION: GENERAL FORMAT

6. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below (section and subsection headings should be in UPPER CASE and title case, respectively). If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

Comment: *All subsections are not presented in title case.*

PATIENT COUNSELING INFORMATION Section in the FPI

7. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION section). The reference should appear at the beginning of Section 17 and include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Medication Guide, Instructions for Use).

Comment: *Does not includes types of FDA approved patient labeling*

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/s/

CALLIE C CAPPEL-LYNCH
04/09/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 203313
NDA 203314

ACKNOWLEDGE –
CLASS 2 RESUBMISSION

Novo Nordisk Inc.
Attention: Shawn Hoskin
Senior Director, Regulatory Affairs
P.O. Box 846
Plainsboro, NJ 08536

Dear Mr. Hoskin:

We acknowledge receipt on March 26, 2015, of your resubmission to your supplemental new drug applications submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Ryzodeg (insulin degludec/insulin aspart [rDNA origin]), injection, 100 U/mL and Tresiba (insulin degludec [rDNA origin]), injection, 100 U/mL and 200 U/mL.

We consider this a complete, class 2 response to our February 8, 2013, action letter. Therefore, the user fee goal date is September 26, 2015.

If you have any questions, call me at (301) 796-8436.

Sincerely,

{See appended electronic signature page}

Callie Cappel-Lynch, Pharm.D.
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

CALLIE C CAPPEL-LYNCH
04/07/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 203313
NDA 203314

**MEETING REQUEST-
WRITTEN RESPONSES**

Novo Nordisk Inc.
Attention: Shawn Hoskin
Senior Director, Regulatory Affairs
P.O. Box 846
Plainsboro, NJ 08536

Dear Mr. Hoskin:

Please refer to your New Drug Applications (NDAs) dated September 29, 2011, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Ryzodeg (insulin degludec/insulin aspart [rDNA origin]), injection, 100 U/mL and Tresiba (insulin degludec [rDNA origin]), injection, 100 U/mL and 200 U/mL

We also refer to your submission dated January 2, 2015, containing a Type C meeting request. The purpose of the requested meeting was to discuss the interim cardiovascular data obtained from the dedicated CV outcome trial DEVOTE and determine if these data would be sufficient to support resubmission of NDAs 203313 and 203314.

Further reference is made to our Meeting Granted letter dated January 13, 2015, wherein we stated that written responses to your questions would be provided in lieu of a meeting.

The enclosed document constitutes our written responses to the questions contained in your February 17, 2015, background package.

If you have any questions, call Callie Cappel-Lynch, Regulatory Project Manager at (301) 796-8436.

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:
Written Responses

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

WRITTEN RESPONSES

Meeting Type:	Type C Meeting
Meeting Category:	Guidance
Application Number:	NDA 203313 NDA 203314
Product Name:	Ryzodeg (insulin degludec/insulin aspart [rDNA origin]), injection, 100 U/mL Tresiba (insulin degludec [rDNA origin]), injection, 100 U/mL and 200 U/mL
Indication:	Treatment of diabetes mellitus
Sponsor/Applicant Name:	Novo Nordisk
Regulatory Pathway:	505(b)(1)

1.0 BACKGROUND

On September 29, 2011, Novo Nordisk submitted New Drug Applications for insulin degludec (conditionally accepted proprietary name: TRESIBA) and a fixed-dose combination of insulin degludec and insulin aspart (conditionally accepted proprietary name: RYZODEG). Insulin degludec (IDeg) is a long-acting (basal) insulin analog available as IDeg U100 and IDeg U200. Ryzodeg is a fixed-dose combination of insulin degludec and insulin aspart (IAsp), a short–acting insulin analog. Insulin aspart was approved on June 7, 2000, under the proprietary name NovoLog (NDA 020986). Ryzodeg is composed of 70% IDeg and 30% IAsp (U100). Both Ryzodeg and Tresiba are intended for once daily subcutaneous use in adults with type-1 and type-2 diabetes mellitus. The dosage of both drugs is to be individualized based on glycemic response, with no upper dosage-limit.

On May 16, 2012, Novo Nordisk submitted a major amendment which resulted in extending the review goal date to October 29, 2012. An advisory committee meeting was held on November 8, 2012, to discuss the safety and efficacy of both products. On February 8, 2013, a Complete Response Letter was issued for both NDAs. In this Complete Response Letter Novo Nordisk was advised to submit additional clinical trial data from a dedicated, double-blind, cardiovascular outcomes trial (CVOT) using glargine as the comparator.

On April 4, 2013, an End of Review meeting was held. At that time the applicant agreed to conduct a CVOT.

At this time the interim data from this trial is available. The purpose of this meeting is to discuss the interim cardiovascular data obtained from the dedicated CVOT, DEVOTE, and determine if these data would be sufficient to support resubmission of NDAs 203313 and 203314

2.0 QUESTIONS AND RESPONSES

2.1. Clinical

Question 1: Does the Agency agree that the DEVOTE interim data justify resubmission?

FDA Response to Question 1: Based information provided in the briefing book it appears you have addressed the deficiencies in the 8 February 2013, Complete Response Letter.

Question 2: Is the Agency aware of any additional precautions which should be put in place to preserve the integrity of the ongoing DEVOTE trial?

FDA Response to Question 2: The data access plan you submitted in November appeared reasonable. Access to interim results should be limited to as few individuals as possible. We note that (b) (4) and an external cardiology expert have also been given access to interim results but were not identified in the original data access plan. We recommend that any changes to the plan or to the list of individuals with access to unblinded interim data be communicated to us prior to implementation of the change.

Question 3: Does the Agency agree that information from the interim analysis of DEVOTE will be redacted from reviews posted on the Agency's web page, and if requests are received via the Freedom of Information Act, the Agency will keep information from the interim analysis of DEVOTE confidential until completion, submission, and Agency review of the full trial?

FDA Response to Question 3: As already indicated in our responses dated May 23, 2014, we appreciate your concerns with regard to protecting the integrity of ongoing studies. A determination about the disclosure of the interim CVOT data included in FDA reviews will be made at the time of approval based on the circumstances of the study at that time.

Question 4: Does the Agency agree with the proposal for mutually communicating requests received from other Regulatory Authorities for information relating to the DEVOTE interim analysis?

FDA Response to Question 4: We agree that unblinded information will be shared with another foreign Regulatory Authority pursuant to a confidentiality agreement with that Authority under conditions of strict confidentiality only. We agree to notify Novo Nordisk if the results are disclosed to any other Authority.

You state in your briefing book that you; *"will notify the FDA of the limited number of Authorities where results of the interim analysis will be disclosed".* Clarify the number and name of the Authorities where results of the interim analysis will be disclosed and the purpose of such disclosures (i.e., particularly in regions where the drug is already marketed). Specify the types of 'solid assurance' you will seek from theses Authorities to ensure interim results are not disclosed.

2.2. Communication with the unblinded Interim DEVOTE Reporting Team

Question 5: Does the Agency have any questions regarding this set-up, and does the Agency agree that this approach appropriately protects against accidental unblinding of the blinded Novo Nordisk NDA team during review of the resubmission?

FDA Response to Question 5: We agree with this approach.

2.3. Regulatory

Question 6: Does the Agency agree that the proposed resubmission contents are sufficient to support filing of the Class 2 resubmission for NDAs 203314 and 203313?

FDA Response to Question 6: We agree. In addition, please see the additional FDA comments below related to the resubmission.

Question 7: Based on the preliminary review of the DEVOTE interim CV MACE and general safety data provided in Section 8 of this background Meeting Package, can the Agency provide their current thinking on the likelihood of having an Advisory Committee meeting to discuss the benefit/risk profile of IDeg?

FDA Response to Question 7: The decision for convening a second Advisory Committee will be made after we have had the opportunity to review your resubmission package.

Question 8: If the Agency determines that a second Advisory Committee meeting is necessary, does the Agency agree that it should take place in a completely closed session? If the Agency disagrees, what data elements would/could potentially be relevant to discuss in an open session, given the potential for inadvertent disclosure?

FDA Response to Question 8: It is premature to discuss this prior to review of the resubmission. As commented in our May 23, 2014, responses and in our response to Question 3, we acknowledge the need to protect the integrity of ongoing studies, but this will need to be balanced with the need for transparency. We will discuss how to approach this issue if it is determined that a second Advisory Committee meeting is needed.

Additional FDA Comments:

1. **The resubmission should contain data that address the deficiencies listed in the Complete Response Letter. Requests for new claims that require review of efficacy (i.e. (b) (4) and studies assessing the U200 formulation [3943, 3816]) should be submitted separately as efficacy supplements, after the NDAs are approved, or as separate NDAs, if you choose request these new claims while NDAs 203313 and 203314 are pending.**

2. **As already indicated in the advice/information request dated May 23, 2014, analyses of important safety parameters (e.g., Deaths, SAEs, SUSARs, AE leading to withdrawal, hypoglycemia) from the pediatric, IDeg-U200 studies, and IDegLira programs that could inform overall safety of IDeg should be included and presented in the update. These data can be considered separately and compared to data in the adult IDeg/IDegAsp pool.**

3. **Please submit updated standard liver safety analyses with central tendency and categorical changes in liver enzymes and biochemical Hy's law cases.**

4. **We will expect the updated safety data for IDeg and IDegAsp to be pooled and presented in a manner that will facilitate comparison to the safety data from the original NDA submission.**

3.0 PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (PSP) 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.

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.

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/s/

JEAN-MARC P GUETTIER
03/20/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 203313
NDA 203314

MEETING REQUEST GRANTED
WRITTEN RESPONSES ONLY

Novo Nordisk Inc.
Attention: Shawn Hoskin
Senior Director, Regulatory Affairs
P.O. Box 846
Plainsboro, NJ 08536

Dear Mr. Hoskin:

Please refer to your New Drug Applications (NDAs) dated September 29, 2011, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for

- Ryzodeg (insulin degludec/insulin aspart [rDNA origin]), injection, 100 U/mL
- Tresiba (insulin degludec [rDNA origin]), injection, 100 U/mL and 200 U/mL

We also refer to your January 2, 2015, correspondence requesting a meeting to discuss the interim cardiovascular data obtained from the dedicated CV outcome trial DEVOTE and determine if these data would be sufficient to support resubmission of NDAs 203313 and 203314. Based on the statement of purpose, objectives, and proposed agenda, we consider the meeting a Type C meeting.

We have determined that written responses to your questions would be the most appropriate means for responding to the meeting request. Therefore, a meeting will not be scheduled. Our goal date for providing our written responses is March 18, 2015.

Submit background information (three paper copies or one electronic copy to the application and 8 paper desk copies to the RPM) as soon as possible but no later than 1 month prior to our goal date for sending written responses (as stated above) for our review and response. If the materials presented in the background package are inadequate to answer the questions or if we do not receive the package by February 18, 2015, we may cancel the agreement to provide written responses. If we cancel the agreement to provide written responses, a new meeting request will be required.

Submit 8 desk copies to the following address:

Callie Cappel-Lynch
Food and Drug Administration
Center for Drug Evaluation and Research
White Oak Building 22, Room: 3362
10903 New Hampshire Avenue
Silver Spring, Maryland
Use zip code **20903** *if shipping via United States Postal Service (USPS).*
Use zip code **20993** *if sending via any carrier other than USPS (e.g., UPS, DHL, FedEx).*

If you have any questions, call me at (301) 796-8436.

Sincerely,

{See appended electronic signature page}

Callie Cappel-Lynch, Pharm.D.
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

CALLIE C CAPPEL-LYNCH
01/13/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 76496
IND 73198

**MEETING REQUEST-
WRITTEN RESPONSES**

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 Investigational New Drug Applications (INDs) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for insulin degludec (rDNA origin) injection and insulin degludec/insulin aspart (rDNA origin) injection.

We also refer to your submission dated March 14, 2014, containing a Type C meeting request. The purpose of the requested meeting was to discuss the interim analysis of the DEVOTE CVOT, the handling of the unblinded data, the interim analysis setup, and the safety update which would be submitted in support of a potential Class 2 resubmission of NDA 203313 and 203314.

Further reference is made to our Meeting Granted letter dated March 19, 2014, wherein we stated that written responses to your questions would be provided in lieu of a meeting.
The enclosed document constitutes our written responses to the questions contained in your April 25, 2014, background package.

If you have any questions, call Callie Cappel-Lynch, Regulatory Project Manager at (301) 796-8436.

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:
Written Responses

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

WRITTEN RESPONSES

Meeting Type:	Type C
Meeting Category:	Guidance
Application Numbers:	IND 76496 and IND 73198
Product Names:	degludec (rDNA origin) injection and insulin degludec/insulin aspart (rDNA origin) injection
Indication:	Treatment of diabetes mellitus
Sponsor/Applicant Name:	Novo Nordisk
Regulatory Pathway:	505(b)(1)

1.0 BACKGROUND

On September 29, 2011, Novo Nordisk submitted New Drug Applications for insulin degludec (conditionally accepted proprietary name: TRESIBA) and a fixed-dose combination of insulin degludec and insulin aspart (conditionally accepted proprietary name: RYZODEG). Insulin degludec (IDeg) is a long-acting (basal) insulin analog available as IDeg U100 and IDeg U200. Ryzodeg is a fixed-dose combination of insulin degludec and insulin aspart (IAsp), a short–acting insulin analog. Insulin aspart was approved on June 7, 2000, under the proprietary name NovoLog (NDA 020986). Ryzodeg is composed of 70% IDeg and 30% IAsp (U100). Both Ryzodeg and Tresiba are intended for once daily subcutaneous use in adults with type 1 and type 2 diabetes mellitus. The dosage of both drugs is to be individualized based on glycemic response, with no upper dosage-limit.

On May 16, 2012, Novo Nordisk submitted a major amendment which resulted in extending the review goal date to October 29, 2012. An advisory committee meeting was held on November 8, 2012, to discuss the safety and efficacy of both products. On February 8, 2013, a Complete Response Letter was issued for both NDAs.

On April 4, 2013, an End of Review meeting was held with Novo Nordisk to discuss the deficiencies in the Complete Response Letter. Novo Nordisk agreed to conduct a Cardiovascular Outcomes Trial in order to address the deficiencies. At this time the sponsor is requesting a meeting to discuss the analysis of this trial.

2.0 QUESTIONS AND RESPONSES

2.1. Clinical

Question 1: For the DEVOTE interim clinical trial data (EX1250-4080), which is intended to support a Class 2 resubmission of NDA 203314 and 203313, does the Agency agree with the

Novo Nordisk proposal [redacted] (b) (4)

FDA Response to Question 1: For evaluation of cardiovascular risk, we request that you submit the following subject-level datasets in the NDA resubmission in order to thoroughly evaluate the cardiovascular safety of IDeg.

1) **Demographics and other baseline risk factors**
2) **Patient disposition including reason of premature treatment discontinuation**
3) **Adverse events**
4) **Time to event dataset for MACE, including randomization date, treatment start date,**
   treatment end date, date of MACE, and last direct contact date.

We may require additional unblinded information to complete our review of the application(s). Therefore, we recommend that you designate personnel within the unblinded DEVOTE reporting team who will be able to provide additional information if needed. We will communicate with the blinded/firewalled NDA team for other issues related to the application(s).

Question 2: Does the Agency agree to this proposal for "on-treatment" analyses?

FDA Response to Question 2: The proposed "on-treatment" and "on-treatment + 30 days" analyses are acceptable. [redacted] (b) (4) [redacted] (b) (4) **. The appropriate censoring should be,**

1) **On-treatment: Only first-occurred MACE events that occur during the treatment period will be counted as events. For those subjects with no such event, they will be censored at the treatment discontinuation date.**

2) **On-treatment + 30 days: Only first-occurred MACE events that occur during the treatment period plus 30 days post treatment will be counted as events. For those subjects with no such event, they will be censored at the time of treatment discontinuation plus 30 days.**

Question 3: Does the Agency agree to the methodology described for the interim analysis and final analysis in the SAPs as presented in Appendix 2 and 3?

FDA Response to Question 3: We have the following comments:

1) **The proposed primary on-study analysis is acceptable. In the on-study analysis, subjects will be censored at last direct contact. Please specify clearly what date the last direct contact refers to (on-site, through telephone contact with patients, relatives or their physicians?)**

2) **We recommend conducting "on-treatment" and "on-treatment + 30 days" analyses (please refer to our response to Question 2) as sensitivity analysis for both final analysis and interim analysis. The proposed per-protocol analysis would be expected to have little implication in the CV risk evaluation.**

3) **Please specify clearly the patient population and censoring scheme of the two sensitivity analyses proposed on Page 9 of Appendix 3.**

Question 4: Does the Agency agree that the proposed mitigations are appropriate and sufficient to minimize the potential bias in the ongoing DEVOTE trial?

FDA Response to Question 4: Your proposed mitigations appear appropriate and sufficient. At the time of NDA resubmission we request you provide all documentation of the processes put in place for submitting interim results to the FDA (for example, provide the documentation specified in Section 8 of "Operational setup of the DEVOTE interim analysis" of your briefing package). See also our response to Question 1.

Question 5: Does the Agency agree to the proposed format of reporting the interim analysis?

FDA Response to Question 5: We agree with the proposal that the unblinded data and report will be submitted as a separate sequence to the NDAs. Please refer to our response to Question 1 for additional information which should be submitted at the same time. Please submit the DMC meeting minutes to the NDAs at the time of resubmission.

Question 6: Does the Agency agree that information from the interim analysis of DEVOTE will be redacted from reviews posted on the Agency's web page, and if requests are received via the Freedom of Information Act the Agency will keep information from the interim analysis of DEVOTE confidential?

FDA Response to Question 6: We appreciate your concerns with regard to protecting the integrity of ongoing studies. Additional internal discussion on how to balance the need for transparency and the need to protect the integrity of the trial will be needed before we are able to provide a response to this question.

Question 7: In the case that a Class 2 resubmission is made and the data support the approval of NDAs 203314 and 203313 (i.e. the data does not indicate concern of cardiovascular safety with use of IDeg), does the Agency agree that information from the interim analysis of DEVOTE would not be used in labeling until after submission of the final DEVOTE trial report?

FDA Response to Question 7: See our response to Question 6.

Question 8: Has the Agency considered how the integrity of DEVOTE will be protected if a second Advisory Committee meeting were called to discuss the cardiovascular safety of IDeg?

FDA Response to Question 8: We have considered possible ways to protect the integrity of DEVOTE in the event of a second Advisory Committee meeting. One possibility could be

to discuss data from DEVOTE in a closed portion of the session with sponsor representation only by the members from the firewalled/unblinded DEVOTE team. All other information would be discussed in an open session. Final determination of how to address this will require additional internal discussion.

Question 9: Does the Agency agree with the proposed strategy for grouping of the trials, the pooling strategy, the proposed submission of post-marketing safety data, and the proposed database cut-off?

FDA Response to Question 9: The proposed strategy for grouping of the trials, the pooling strategy, the proposed submission of post-marketing safety data, and the proposed database cut-off seems acceptable. In addition, submit pooled hypoglycemia data for the separate T1DM and T2DM populations.

Question 10: Does the Agency agree that it is sufficient to include only trials in the IDeg or IDegAsp development program in the safety updates, and address IDeg data from IDegLira trials in a separate NDA?

FDA Response to Question 10: We will expect the safety data for IDeg and IDegAsp to be pooled and presented in a manner that will facilitate comparison to the safety data from the original NDA submission. Analyses of important safety parameters (e.g., Deaths, SAEs, SUSARs, AE leading to withdrawal, hypoglycemia) from the IDegLira program that could inform overall safety of IDeg should be included and presented in the update. These data can be considered separately and compared to data in the IDeg/IDegAsp pool.

Question 11: Does the Agency agree that the interim data, together with the safety updates as outlined above will be adequate for the Agency's evaluation of cardiovascular safety of IDeg?

FDA Response to Question 11: Provided you have addressed our comments, the information will likely be adequate to review the cardiovascular safety of IDeg.

Question 12: (b) (4) pediatric trials NN1250-3561 and NN5401-3816 (b) (4)

FDA Response to Question 12: Analyses of important safety parameters (e.g., Deaths, SAEs, SUSARs, AE leading to withdrawal, hypoglycemia) from the pediatric program that could inform overall safety of IDeg should be included and presented in the update. These data can be considered separately and compared to data in the adult IDeg/IDegAsp pool.

Question 13: Does the Agency agree to the proposed content of the resubmissions reflected in the draft Table of Contents for IDeg and IDegAsp?

FDA Response to Question 13: No, we do not agree. We also request an updated written summary of clinical safety in addition to the proposed safety updates.

Question 14: Is the proposed dataset format and content for the resubmission acceptable to the Agency?

FDA Response to Question 14: In general, this is acceptable. For efficiency and timely review, we suggest that you submit the safety update datasets in SDTM and ADaM format.

Question 15: Is the proposed dataset format for the DEVOTE dataset acceptable to the Agency?

FDA Response to Question 15: The proposed dataset format is acceptable. See our response to Question 1 for datasets requested for the DEVOTE trial.

3.0 PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (PSP) within 60 days of an End of Phase (EOP2) meeting. 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.

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 Pediatric and Maternal Health Staff 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.

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/s/

JEAN-MARC P GUETTIER
05/23/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 203313
NDA 203314

MEETING MINUTES

Novo Nordisk Inc.
Attention: Robert Clark
Vice President, Regulatory Affairs
P.O. Box 846
Plainsboro, NJ 08536

Dear Mr. Clark:

Please refer to your New Drug Applications (NDAs) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for:

- Ryzodeg (insulin degludec/insulin aspart [rDNA origin]), injection, 100 U/mL and
- Tresiba (insulin degludec [rDNA origin]), injection, 100 U/mL and 200 U/mL.

We also refer to the telecon between representatives of your firm and the FDA on October 3, 2012. The purpose of the meeting was to discuss Human Factors testing for the PDS 290 pen injector.

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

If you have any questions, call Callie Cappel-Lynch, Regulatory Project Manager at (301) 796-8436.

Sincerely,

{See appended electronic signature page}

Jean-Marc Guettier, MD
Director, Acting
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: **C**
Meeting Category: **Guidance**

Meeting Date and Time: **October 3, 2012 (9:00 – 10:00 am)**
Meeting Location: **Teleconference**

Application Number: **NDA 203313 & NDA 203314**
Product Name: **Ryzodeg & Tresiba**
Indication: **Treatment of Diabetes Mellitus**
Sponsor/Applicant Name: **Novo Nordisk**

Meeting Chair: **Mary H. Parks, M.D.**
Meeting Recorder: **Rachel Hartford**

FDA ATTENDEES (alphabetic)

Richard Abate	
Jean-Marc Guettier, MD	Clinical Team Leader, Division of Metabolism and Endocrinology Products (DMEP)
Rachel Hartford	Regulatory Project Manager, DMEP
Carol Holquist, RPh	Director, Division of Medication Error and Prevention Analysis (DMEPA), Office of Surveillance and Epidemiology (OSE)
Yelena Maslov, Pharm.D.	Team Leader, DMEPA, OSE
Quynh Nhu Nguyen	Combination Products Human Factors Specialist, Center for Devices and Radiological Health, Office of Device Evaluation
Mary H. Parks, M.D.	Director, DMEP
Margarita Tossa, M.S.	Regulatory Project Manager, OSE

SPONSOR ATTENDEES

<u>Novo Nordisk Inc. (USA)</u>	
Robert B Clark	Vice President, US Regulatory Affairs

Alan C Moses, MD	Corporate Vice President, Global Chief Medical Officer
Shawn Hoskin	Director, Regulatory Affairs
Rick Spring	Sr. Manager, Regulatory Affairs
Novo Nordisk A/S (Denmark)	
Mads Krogsgaard Thomsen	Executive Vice President and Chief Science Officer
Susanne Rugh	Corporate Vice President, Degludec Management
Jesper Kløve	Senior Vice President, Device R&D
Søren Mikkelsen	Corporate Vice President, Prefilled Device Development
Peter Bonne Eriksen	Senior Vice President, Regulatory Affairs
Inger Mollerup	Corporate Vice President, Regulatory Affairs
Jane Møll Pedersen	Global Regulatory Director
Dorrit Espersen Juul	Global Regulatory Director
Kirsten Nielsen Tallerup	Department Manager, Regulatory Affairs Prefilled Devices
Mads Axelsen	International Medical Director
Per K Christensen	Director, Insulin and Devices
Gitte Ter-Borch	International Trial Manager Specialist
Birgitte Berg, Director	Clinical Operation Insulin & Devices-1
Sara Juana Niemann	Development Engineer, PDS290 Developement
Rasmus Klinck	Medical Writer

1.0 BACKGROUND

A Human Factors Discipline Review letter was issued on July 9, 2012, for Ryzodeg and Tresiba containing the following italicized text.

> *Our review of the Human Factors portion of your submissions is complete, and we have identified the following deficiencies.*
>
> *While the UT86 report demonstrated that through improving the Instructions For Use (IFU) and training materials the use errors can be reduced, the results of the study show use errors that can result in incorrect dosing that require further mitigation. We are most concerned with the following findings:*
>
> - *1 participant did not set dose correctly and committed use error*
>
> *You reported that this participant was an elderly, pen-experienced, and untrained participant. The participant was on basal-bolus insulin therapy with Lantus vial and syringe as basal insulin and NovoLog FlexPen as bolus insulin. It should be noted that the Novolog FlexPen delivers 1 unit increments of insulin when dialed. When using his vial and syringe, he has to convert number of units to the correct volume. The test results reported that this participant dialed and administered an incorrect dose during two different tasks during normal injection and during end-of content/split dose between two pens. You also reported that one participant experienced a close call with this step. Because this type of use error can result in incorrect dosing during actual use and while you have taken helpful measures to reduce the potential of use errors, it appears that you do not directly address the potential risk of users converting the number of units required based on the prescribed dose. Implement further mitigation via modifying the IFU to inform the users that regardless of the concentration of insulin used, the PDS290 pen-injectors are designed to deliver the specified number of insulin units as prescribed, and that the users do not need to perform any dose conversion.*
>
> - *1 participant misinterpreted the dose delivered after detecting blocked needle*
>
> *You reported that this participant was an elderly, pen-experienced and untrained participant. The participant set the dose correctly (instructed dose - 36 units of 200 U/ml Tresiba) and attempted to administer the injection. However, due to the blocked needle, the participant incorrectly concluded that he had delivered 10 units, and that he needed to deliver 26 additional units to administer the full 36 unit dose. The participant replaced the needle on the pen-injector and administered 26 units, rather than 36 units. Because this type of use error can result in incorrect dosing in actual use and while you have taken helpful measures to reduce the potential of use errors, it appears that you do not directly address the potential of risk of users misinterpreting the amount of insulin delivered in situations where the needle is blocked. You also reported that two participants experienced close call with this step.*

As previously communicated in our General Advice letter dated May 3, 2012, this finding indicated that the user might not be aware of the potential for dose counter malfunction associated with blocked needles i.e. the device dose counter may wrongly report that up to a maximum of 7 units have been delivered. This could result in clinically significant dosing errors after the user discovers that the needle on the device is blocked. We conclude that the dose counter, which serves as a visual feedback to the users, is not optimally designed as it can mislead users and cause confusion with regards to dosing after the device problem (i.e. blocked needle) is discovered. If there are no design alternatives to reduce this risk further, implement further mitigation via modifying the IFU to inform the users that in case of a blocked needle, the dose counter will display a value that is different from the original dose that the user has set. In addition, the IFU should provide specific instructions for use to resolve a blocked needle situation.

- *2 participants did not hold the needle at the injection site for the specified time*

  You reported that one participant who was an elderly, pen-experienced and trained participant, committed one use error during her fifth task (blocked needle). The other participant was an adult, pen-naïve and untrained participant who committed one use error during the first task (normal injection). The participants both set the dose correctly and administered the injection, but held the needle in the cushion for less than one second after the dose counter had returned to"0". You also reported that one participant experienced close call with this step.

  As previously communicated in our General Advice letter dated May 3, 2012, we are concerned that you instruct patients to hold the needle for 6 seconds. However, in the study, you defined that it is only a use error if the participant did not keep the needle in the skin for at least 1 second after the dose counter returns to "0." If proper injection is defined as holding the needle for 6 seconds, then the study should demonstrate that users can hold the device for 6 seconds.

Based on the errors that one of your participants experienced in setting the dose with this device, we conclude that your product is prone to dosing errors and additional risks are associated with the U200 strength of Tresiba pen injector. Our evaluation of the submitted data also noted the number of users completing tasks with Tresiba FlexTouch 200 units/mL were inadequate (10 total users, 5 trained and 5 untrained).

Additionally, please note that the purpose of a design validation (human factors) study is to demonstrate that the device can be used by representative users under simulated use conditions without producing patterns of failures that could result in negative clinical impact to patients or injury to device users.

Thus, further evaluation is necessary of the Tresiba FlexTouch 200 units/mL pen injector and should include the changes to the IFU described in this letter as well as:

- *The intended adult and elderly patients with severe insulin resistance who require large daily doses of insulins and who are likely to make up the majority of your potential users. Since the patient users of Tresiba FlexTouch 200 unit/ mL will most likely be prior insulin users (pen injector or syringe and vial), you do not need to include insulin naïve patients in your study. If naïve patients are included, please ensure they are a separate user group. Lastly, patients with prior Humulin U-500 experience must be noted and do not need to be excluded from the study.*

- *Both trained (15 participants) and untrained (15 participants) patients who have prior insulin experience should be evaluated. The untrained group should have the option to read the instructions for use rather than required to read it to better simulate "real use" untrained scenario. All participants should be informed during the training and/or familiarization period that the strength of the insulin is "200 units/mL."*

- *If visually impaired participants are not included in this study, the tasks for patient user groups should include visual impairment simulation.*

- *Finally, include both trained (15 participants) and untrained (15 participants) inpatient nurses as healthcare providers that use the Tresiba FlexTouch 200 units/mL as this user group has not been assessed in any of the prior studies.*

Novo Nordisk intends to modify the PDS290 IFU and validate the changes in a focused HF/usability validation test PDS290-UT103-2012 (UT103). The purpose of this meeting is to reach agreement on the IFU changes and design of UT103.

2. DISCUSSION

Usability Test Protocol Design

Question 1: Does the Agency agree that the proposed focused usability test design evaluating only Tresiba® FlexTouch® 200 U/mL pen injector is sufficient to validate the changes made to the IFU and the results would also support Tresiba® FlexTouch® 100 U/mL and Ryzodeg® FlexTouch® 100 U/mL?

FDA Preliminary Response: Yes, we agree that the proposed usability protocol focused on the changes to the IFU for use with the Tresiba FlexTouch 200 U/mL pen injector is sufficient to validate change to the IFU and support the U100 Tresiba and Ryzodeg products. However, once the testing has demonstrated that those changes are effective, you will also need to consider whether the changes should be incorporated to the corresponding IFU for use with the Tresiba FlexTouch 100 U/mL and Ryzodeg FlexTouch 100 U/mL pen injectors. If for example, the change to the IFU is based on use of the PDS290, incorporate

changes. If however, the change to the IFU is based on product strength, do not incorporate changes.

Meeting Discussion: The applicant confirmed that they will implement all changes, based on the use of the PDS290, that are demonstrated to be effective in the Tresiba U-200 IFU also in the Tresiba U100 and Ryzodeg IFUs. FDA confirmed that this is acceptable.

Question 2: Does the Agency agree with the number and composition of participants to be tested in UT103?

FDA Preliminary Response: No we do not agree. The Division of Medication Error and Prevention Analysis (DMEPA) finds that the number and composition of adult and elderly subjects and subjects with disease related impairments (vision, and manual dexterity etc.) are adequate. However, patients using this product will include both insulin sensitive and insulin resistant individuals. Therefore, please ensure that these two types of participants are adequately represented in your study. We recommend that 30 trained and 30 untrained participants with diabetes mellitus and insulin experience be included. In each of the trained and untrained groups 50% of patients should be users with relatively high insulin resistance (i.e., those requiring 50 units of insulin per dose or more) and 50% should be users requiring less than <50 units of insulin per dose but no defined minimum units per dose. In other words, for the group of 30 untrained individuals, 15 patients should be insulin resistant and 15 patients should be insulin sensitive.

Although the Center for Devices and Radiologic Health (CDRH) agrees with your proposed number and composition of participants to be tested in the UT103 as it is a supplemental usability testing to previous usability tests, and to demonstrate that the proposed IFU are effectively in minimizing use errors, the requested increase in number of patient user participants by DMEPA would demonstrate the IFU is valid. CDRH recommends that you ensure equal representation of the different patient user groups (insulin sensitive diabetic patients, and insulin resistant diabetic patients), and patients with disease related impairments (vision, and manual dexterity). Also ensure that you divide all study participants into two equal groups: trained versus untrained.

Meeting Discussion: The applicant proposed that insulin "resistant" be defined as patients who required > 50 units of insulin daily rather than a single dose, FDA agreed to this change in definition.

Question 3: Does the Agency agree that the test population included in UT103 (adult/elderly with pen-injector and/or vial and syringe experience and inpatient nurses with pen-injector experience) is sufficient?

FDA Preliminary Response: See Question 2.

Meeting Discussion: No discussion occurred.

Question 4: Does the Agency agree with the proportion of adult/elderly participants with high insulin resistance and visual/simulated visual impairment to be tested in UT103?

FDA Preliminary Response: See Question 2.

Meeting Discussion: No discussion occurred.

Question 5: Does the Agency agree that both trained and untrained participants should be informed during the training and/or familiarization period that the concentration of the insulin is 200 U/mL and (b) (4)

FDA Preliminary Response: No, we do not agree. We agree that the participants can be informed of the product's concentration (200 units/mL). (b) (4) ".

In addition, note that we consider the (b) (4) as training (b) (4) .

The use of the term (b) (4) may imply to the user that they should review the materials and thus is considered training by guiding the users to the resource materials. Use alternate wording to introduce the testing scenario in the protocol (8.1.6) and remove the word (b) (4) from the administrator's script. For example, consider the following script:
"….You have all of the materials you need to inject insulin, and it is time to give yourself an injection. The point is to approach the scenario as realistically as possible. Take as much time as you might normally take with the materials, handling them in any way you wish. Assume that you are working alone, so please do not ask me for assistance. However, there is a telephone available *[point to telephone in supply area]* in case you need to place a call for assistance. I will be sitting over at the other end of the table. Tell me when you are ready to begin and I will give you the first task instruction card."

Meeting Discussion: The applicant expressed concern that the untrained user group will only be provided with a strength without stating the fact that the dose conversion is not needed. They pointed out that this may bias patients and produce dosing errors. FDA disagreed that this will bias participants because in actual use environment, the users may not be told that dose conversion is not needed and if errors during HF study do occur, this will be indicative of what types of errors may occur in a real world environment due to differences in product concentration. The applicant proposed a split among untrained user to identify whether providing a strength without information regarding dose conversion will produce any errors. They proposed 15 users will be told the strength and 15 users will not be told the strength. FDA agreed.

Question 6: Does the Agency agree with the use scenarios and the respective steps to be tested in UT103?

FDA Preliminary Response: We find your proposed scenarios for normal injections and block needle injections to be acceptable. However, CDRH indicated in the Discipline Review letter that we were concerned with the end-of-content/split-dosing injections. Clarify why you do not intend to include this scenario in the supplemental study.

In addition, with respect to the training check (section 7.4), you indicated that additional training will be provided to test participants as necessary, and if a participant is deemed ineligible, they will not be asked to participate in the actual hands-on test. Clarify why you believe this methodology is representative of actual use, and how you plan to implement the additional training in actual use. Also, clarify who will determine that a user is ineligible using the proposed product in actual use. If participant is deemed ineligible following the training session, include which participants were so deemed and the reasons for excluding the participant recorded on the "Training Record - People with Diabetes" with the submission of the data for UT103.

Furthermore, with respect to baseline injections (section 8.1.2), you indicated that participants will be asked to perform two baseline injections prior to simulated injections. Additionally, we are concerned that this baseline test may impact the results of the simulated use test. Conduct this testing after the simulated use test.

Meeting Discussion: The applicant clarified that the end-of-content/split-dosing scenario will not be included in the supplemental study because the IFU was modified and retested in UT86, where there were no use errors reported. The applicant also clarified that in actual use, it is the clinic's responsibility to decide if the patient can self-inject, and it is through certified diabetes education. FDA indicated that this sounds reasonable. The applicant stated that they will remove the baseline test, and FDA found this to be acceptable.

Question 7: Does the Agency agree with the proposal to test all user groups in Scenario 1 (normal injection) steps but only the adult/elderly user group in Scenario 2 (blocked needle) steps as inpatient nurses would not reuse needles in a "real use" scenario?

FDA Preliminary Response: Yes, we agree with your proposal.

Meeting Discussion: No discussion occurred.

Question 8: Does the Agency agree that the approach to validate the mitigations (IFU content and ancillary instructional video) associated with the Tresiba® FlexTouch® pen 200 U/mL use error "Did not set dose correctly" is adequate?

FDA Preliminary Response: Your approach to validate the IFU changes and additional ancillary instructional video associated with setting the dose scenario for the Tresiba FlexTouch pen 200 U/mL appears adequate.

Meeting Discussion: No discussion occurred.

Question 9: Does the Agency agree that the approach to validate the mitigations (IFU content and ancillary instructional video) associated with the blocked needle scenario is adequate?

FDA Preliminary Response: Your approach to validate the IFU changes and additional ancillary instructional video associated with the blocked needle scenario for the Tresiba FlexTouch pen 200 U/mL appears adequate.

Meeting Discussion: No discussion occurred.

Question 10: Does the Agency agree that the approach to validate the mitigations (IFU content and ancillary instructional video) via user performance testing is adequate, noting that trained and untrained participants might or might not read the IFU in the course of preparing to perform or performing the tasks?

FDA Preliminary Response: Since one of the focus for the this supplemental test is on the changes to the IFU and since assessment of user understanding of critical messages in the labeling cannot be done through observation of participant behavior, we ask that you validate the participants in the trained arm of your study prior to the simulated use portion of your study given that they will be exposed to the revised IFU during training. Ensure that you ask explicit and detailed questions about the content of or inferential questions about information that was implied by the text. It is important that these questions not be leading (i.e. don't make the correct responses obvious) and for this reason, we discourage forced-choice responses. The participants should also provide subjective feedback regarding any wording in the labeling they found confusing, misleading, or incomplete. Additionally, the clarity of the IFU should be evaluated with respect to findings on task failures/use errors observed in the study.

Data collection – Use error "Did not hold the needle at the injection site for the specified time"

Meeting Discussion: The applicant proposed that following training the participants who read the IFUs were asked to explain what they read for understanding. FDA agreed.

Question 11: Does the Agency agree that the use error criteria described above is acceptable?

FDA Preliminary Response: No, we do not agree. Note that for purposes of performance assessment, we consider task failure as action/lack of action that could lead to patient harm. Modify your definition in section 4.6. Ensure that the task failures that will be recorded represent failures that could cause harm during actual use. Upon review of the IFU, we note that the IFU states "a drop is normal after an injection." If "real use" of this pen injector should result in no more than a drop of insulin remaining the needle, then, we recommend revising the criteria to be consistent with the IFU. A task failure should be recorded if the needle is withdrawn after counting to a number less than 6 after the counter

returns to "0" and more than a drop (e.g. two or more drops) is observed coming out of the needle upon removal.

Meeting Discussion: FDA asked additional clarifying questions regarding the delivery of insulin so that the description of the error in the IFU was described correctly. The applicant asked to clarify the performance failure definition. FDA indicated that the protocol should clearly define the performance success and failures and ensure that that failures being recorded represent the failures that could cause harm during actual use. The applicant indicated that they will follow up with modified definitions to the project manager after the meeting. FDA agreed to review those definitions and provide feedback if needed.

Question 12: Does the Agency agree that the usability protocol PDS290-UT103-2012 sufficiently addresses the concerns listed in the Agency's Discipline Review letter?

FDA Preliminary Response: With the noted changes, we agree that the protocol addresses our concerns. We also request that a copy of the ancillary instructional video be included when the data from UT103 is submitted as a reference for our reviewers.

Meeting Discussion: No discussion occurred.

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/s/

JEAN-MARC P GUETTIER
11/18/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 076496

SPECIAL PROTOCOL ASSESSMENT – (b) (4)

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 Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act (FDCA or the Act) for insulin degludec [rDNA origin], injection, 100 U/mL and 200 U/mL.

(b) (4)

We also have the following responses to your questions:

(b) (4)

Question 2: Does the Division agree that the proposed double-blind trial design and patient population is suitable to generate reliable hypoglycemia data, and the data from Trial NN1250-3998 (b) (4)

FDA Response to Question 2:
FDA agrees with your proposal for a double-blind design. We do not agree that the (b) (4) **The study population should be enriched with susceptible individuals at high risk for developing severe hypoglycemia (e.g., those patients with: a history of recurrent severe events, hypoglycemic symptom "unawareness," end-organ dysfunction such as renal failure, long-standing diabetes, long-standing insulin use, and loss of insulin secretory function captured using fasting C-peptide). In addition, we do not agree with your proposal** (b) (4) **evaluation of hypoglycemic risk should be based on the entire treatment intervention phase (i.e., titration and maintenance phases). The titration and maintenance phases provide relevant clinical information that should be captured in the primary analysis.**

Question 3: Does the Division agree with the primary endpoint (b) (4) (b) (4) in trial NN1250-3998?

FDA Response to Question 3:
No, we do not agree with your proposal (b) (4) (b) (4) **The trial should be designed to demonstrate a benefit for an endpoint based on severe hypoglycemic events (refer to additional comments). Only after a clinically meaningful reduction in severe hypoglycemia is demonstrated over the entire 24-hour period, would assessment of a secondary benefit for a specific nocturnal period (i.e., an agreed-upon, pre-defined segment of a 24-hour time period) be permissible. Also see our response to Question 9.**

Question 4: Does the Division agree with the definition and proposed documentation of severe hypoglycemia?

FDA Response to Question 4:
We do not entirely agree with your definition for severe hypoglycemia. The full ADA Workgroup definition for severe hypoglycemia also includes the following:

> ***"These episodes may be associated with sufficient neuroglycopenia to induce seizure or coma. Plasma glucose concentrations may not be available during an event, but neurological recovery following the return of plasma glucose to normal is considered sufficient evidence that the event was induced by a low plasma glucose concentration."***

The definition implies that severe hypoglycemia is associated with neurological dysfunction resulting in an immediate threat to life. Subjects to whom carbohydrates or glucagon were administered by a third party but who did not have neurological impairment may or may not have had a severe hypoglycemic episode. To ensure each episode constitutes a true severe hypoglycemic event, data on the prodromal signs and symptoms, the need for third

party assistance, and documentation of neurological recovery or other outcome should be captured and available for each event. To minimize bias in this process, we recommend that an independent, blinded adjudication committee prospectively adjudicate each episode.

Additionally, your proposed ascertainment and documentation plans are not described in sufficient details to allow a meaningful assessment of their adequacy. Rigorous methods for identifying, capturing, assessing, documenting, and adjudicating hypoglycemic events should be described in your study protocol. A charter detailing a blinded adjudication process by an independent panel of experts should also be provided.

Question 5: Does the Division agree that the cut-off level of (b) (4) mg/dl is acceptable to define a hypoglycemic episode in trial NN1250-3998?

FDA Response to Question 5:
No, we do not agree that a glucose cut-off level of (b) (4) mg/dL (b) (4) (b) (4) as you have proposed, is acceptable to define confirmed hypoglycemia in your study. You have selected a hypoglycemic endpoint which relies on a low glucose value (b) (4) (b) (4) To increase the specificity of your "confirmed hypoglycemia" definition we recommend that you revise your definition to require the coincident occurrence of hypoglycemic symptoms and low glucose value.

Question 6: Does the Division agree with the proposal in Trial NN1250-3998 to define symptomatic nocturnal confirmed hypoglycemia as (b) (4) (b) (4)

FDA Response to Question 6:
No, we do not agree with your proposed definition of symptomatic nocturnal confirmed hypoglycemia (b) (4) The definition of the nocturnal time period should consider the time-action profiles of the two insulin products being tested. Refer to our response to Question 8.

Question 7: Can the Division confirm that utilizing a cross-over design aiming for equivalent PG in the two crossover periods for the test and comparator products is acceptable to allow comparisons between groups in frequency and severity of hypoglycemia?

FDA Response to Question 7:
The proposed cross-over design may be acceptable. However, the assumptions in analyzing the cross-over design should be assessed statistically to demonstrate the absence of a carryover effect. Additionally, the internal validity of the study can potentially be demonstrated, in part, by ensuring that the intensity of the treatment regimen (e.g., insulin exposure) and overall glycemic control (e.g., HbA1c, FPG) are comparable in the two crossover periods. Specifically, non-inferiority in regards to glycemic control (i.e., HbA1c) must be demonstrated before statistical testing of the primary study endpoint can be

considered. Lack of comparability in treatment intensity and glycemic control between the study periods will invariably raise doubts regarding the validity of any claims of a hypoglycemia-reduction advantage.

Question 8: Does the Division agree that requiring all subjects to inject their basal insulin in the evening between the supper meal and bedtime, in a double-blind trial setting where the time of injection will be documented, represents a valid evaluation to assess the inherent qualities of both insulin products and assess their impact on nocturnal hypoglycemia?

FDA Response to Question 8:
The two insulin products being compared in this study do not have identical pharmacokinetic (PK) and pharmacodynamic (PD) properties, and the time-action profiles of these two insulin products will be different. Therefore, timing of the insulin administration could potentially affect the time interval during which subjects would be at highest risk for hypoglycemic episodes. Given the inherent PK and PD differences in insulin degludec and insulin glargine, the timing of the insulin dosage and the definition of the nocturnal period both could potentially confound interpretation of the study data. Your study design should address how these potential confounders can be minimized. As an example, you could consider having ½ the study subjects inject their basal insulin in the morning.

Question 9: Does the Division have any additional comments on the trial design or statistical considerations of trial NN1250-3998?

FDA Response to Question 9:
As addressed in the response to Question 3, the primary study endpoint should be a clinically meaningful and statistically significant reduction in severe hypoglycemia demonstrated over the entire duration of exposure (b) (4) (b) (4) **in the course of a well-designed clinical trial. Only when statistical significance is achieved on the primary endpoint can testing proceed to a pre-defined secondary endpoint of nocturnal hypoglycemia. If hypothesis testing is planned for the secondary study endpoints, the alpha allocation will need to be pre-specified along with the specific alpha adjustment strategy to ensure a one-sided study-wise type I error rate of 0.025. Without pre-specified adjustment for multiplicity, analyses for your key secondary endpoints (i.e., those for which you may seek claims) will be considered exploratory and the findings will be regarded as hypothesis generating.**

In the absence of a statistically significant result for the primary analysis of your primary study endpoint, results based on secondary endpoints, subgroups, or additional analyses of the primary endpoint cannot result—either singly or in combination—in an efficacy claim. In the event that there is a statistically significant result for the primary analysis of the primary study endpoint, and FDA determines that flaws in the design and/or modifications in the study over time do not confound the reliability and confidence in the results, those secondary endpoints that are significant after proper adjustment for multiplicity could potentially be considered for inclusion in the label.

(b) (4)

We recommend that the primary analysis method be a comparison of the *proportion* of subjects in each treatment period who experience at least one hypoglycemic episode rather than event numbers or rates. Since the planned trial utilizes a cross-over design, one may use McNemar's test as the primary analysis. A negative binomial regression model, which was used in your previous Phase 3a program for all the individual trial analyses, may be used as a supportive analysis. Accordingly, sample size will need to be recalculated based on the recommendations outlined in this letter.

Also, your study proposal suggests that patients will contribute to the primary analysis (b) (4) **Instead, we recommend that patients contribute to the primary analysis "as randomized."**

(b) (4)

FDA Response to Question 10:
At this time, it is premature for FDA to comment on your proposed labeling.

(b) (4)

FDA Response to Question 11:
At this time, it is premature for FDA to comment on your proposed labeling.

Question 12: Does the Division have any comments regarding inclusion of both CV and hypoglycemia data together in a Class 2 resubmission with a targeted 6 month PDUFA goal date?

FDA Response to Question 12:
No. The decision regarding what to include in a resubmission is at your sole discretion.

Additional Comments:

In addition to the responses to your specific questions, we have the following comments:

1. **Efficacy analyses evaluating a potential benefit of reduced hypoglycemic risk should be based on an objective, specific, and clinically meaningful definition of hypoglycemia (e.g., ADA severe hypoglycemia) and not** (b) (4)

(b) (4)

(b) (4)

2. **Hypoglycemia should be designated as a medical event of special interest (i.e., severe and serious hypoglycemia). In addition to your proposed reporting plan, the safety database should be queried on an ongoing basis for serious adverse event preferred terms consistent with hypoglycemic events and terms representing conditions that could have resulted from hypoglycemia (e.g., sudden death, seizure, trauma, fracture, fall, motor vehicle accident). Source data should be reviewed and summarized to determine whether hypoglycemia contributed to these events.**

3. **Your definition of a confirmed hypoglycemic episode for the T2DM study suggests that, in part, it will include a biochemically confirmed "plasma glucose value" of (b) (4) (b) (4) with or without symptoms consistent with hypoglycemia. Clarify if this will truly be a plasma-derived glucose measurement, or if it will in most cases be a self-monitored blood glucose measurement (SMBG)?**

If you choose to revise this protocol and submit another request for special protocol assessment prior to study initiation, it should address all the issues itemized above and be prominently labeled as a **"Special Protocol Assessment – Resubmission."** In addition, your cover letter should clearly reference the date and type of your original SPA submission as well as the following SPA reference number: 3 To facilitate review of your SPA resubmission, send a copy of the cover letter to Callie Cappel-Lynch.

If you wish to discuss our responses, you may request a meeting. Such a meeting will be categorized as a Type A meeting and will be limited to the discussion of this protocol. For additional information, refer to FDA's "Guidance for Industry: Formal Meetings Between the FDA and Sponsors or Applicants" at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm153222.pdf.

If you have any questions, call Callie Cappel-Lynch, Regulatory Project Manager, at (301) 796 8436.

Sincerely,

{See appended electronic signature page}

Jean-Marc Guettier, MD
Director, Acting
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
08/30/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

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NDA 203313
NDA 203314

MEETING MINUTES

Novo Nordisk Inc.
Attention: Robert B. Clark
Vice President, Regulatory Affairs
P.O. Box 846
Plainsboro, NJ 08536

Dear Mr. Clark:

Please refer to your New Drug Applications (NDAs) dated September 29, 2011, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for

- Ryzodeg (insulin degludec/insulin aspart [rDNA origin]), injection, 100 U/mL
- Tresiba (insulin degludec [rDNA origin]), injection, 100 U/mL and 200 U/mL

We also refer to the meeting between representatives of your firm and the FDA on April 4, 2013. The purpose of the meeting was to discuss the deficiencies described in our Complete Response letter dated February 8, 2013, and to discuss actions to be taken to address these deficiencies.

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 Callie Cappel-Lynch, Regulatory Project Manager, at (301) 796-8436.

Sincerely,

{See appended electronic signature page}

Mary H. Parks, M.D.
Director
Division of Metabolism and Endocrinology Products
Office of New Drugs
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes for End-of-Review meeting held on April 4, 2013.

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

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MEMORANDUM OF MEETING MINUTES

Meeting Type:	A
Meeting Category:	End of Review
Meeting Date and Time:	April 4, 2013 (2:00 – 4:00pm)
Meeting Location:	WO Bldg 22, RM 1415
Application Number:	NDA 203313 & NDA 203314
Product Name:	Ryzodeg (insulin degludec/insulin aspart [rDNA origin]), injection, 100 U/mL Tresiba (insulin degludec [rDNA origin]), injection, 100 U/mL and 200 U/mL
Indication:	Treatment of diabetes mellitus
Sponsor/Applicant Name:	Novo Nordisk
Meeting Chair:	Jean-Marc Guettier
Meeting Recorder:	Callie Cappel-Lynch

FDA ATTENDEES

Office of New Drugs

Curtis Rosebraugh, M.D., M.P.H.	Director, Office of Drug Evaluation II
Mary Parks, M.D.	Director, Division of Metabolism and Endocrinology Products (DMEP)
Karim Calis, PharmD, M.P.H.	Clinical Reviewer, DMEP
Jean-Marc Guettier, M.D.	Diabetes Clinical Team Leader, DMEP
Callie Cappel-Lynch, Pharm.D.	Regulatory Project Manager, DMEP
Mehreen Hai, Ph.D.	Acting Chief, Project Management Staff, DMEP
Rachel Hartford	Team Leader, RPM Enrichment Enhanced Communications Team

Office of Biometrics

Cynthia Liu, M.A.	Statistical Reviewer, Division of Biometrics II
Dongmei Liu, Ph.D.	Statistical Reviewer, Division of Biometrics II
Todd Sahlroot, Ph.D.	Deputy Director, Division of Biometrics II
Eugenio Andraca-Carrera, Ph.D.	Statistical Reviewer, Division of Biometrics VII
Bo Li, Ph.D.	Statistical Reviewer Division of Biometrics VII
Mat Soukup, Ph.D.	Team Leader Division of Biometrics VII

SPONSOR ATTENDEES

Novo Nordisk A/S (Denmark):

Mads Krogsgaard Thomsen	Executive Vice President and Chief Science Officer
Peter Bonne Eriksen	Senior Vice President, Regulatory Affairs
Peter Kristensen	Senior Vice President, Global Development
Inger Mollerup	Corporate Vice President, Regulatory Affairs
Martin Lange	Corporate Vice President, Degludec Projects
Lars Endahl	Principal Scientist, Biostatistics
Rasmus Rabol	International Medical Director, Medical and Science

Novo Nordisk Inc. (USA):

Jerzy Gruhn,	President/Novo Nordisk US
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1.0 BACKGROUND

On September 29, 2011, Novo Nordisk submitted New Drug Applications for insulin degludec (conditionally accepted proprietary name: TRESIBA) and a fixed-dose combination of insulin degludec and insulin aspart (conditionally accepted proprietary name: RYZODEG). Insulin degludec (IDeg) is a long-acting (basal) insulin analog available as IDeg U100 and IDeg U200. Ryzodeg is a fixed-dose combination of insulin degludec and insulin aspart (IAsp), a short–acting insulin analog. Insulin aspart was approved on June 7, 2000, under the proprietary name NovoLog (NDA 020986). Ryzodeg is composed of 70% IDeg and 30% IAsp (U100). Both Ryzodeg and Tresiba are intended for once daily subcutaneous use in adults with type-1 and type-2 diabetes mellitus. The dosage of both drugs is to be individualized based on glycemic response, with no upper dosage-limit.

On May 16, 2012, Novo Nordisk submitted a major amendment which resulted in extending the review goal date to October 29, 2012. An advisory committee meeting was held on November 8, 2012, to discuss the safety and efficacy of both products. On February 8, 2013 a Complete Response Letter was issued for both NDAs. The deficiencies are repeated below in italicized text.

We have completed our review of this application, as amended, and have determined that we cannot approve this application in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

CLINICAL

1. Cardiovascular Safety

A consistent and persistent signal of excess cardiovascular (CV) risk associated with insulin degludec and insulin degludec/aspart relative to comparators is observed across multiple analyses.

You were informed on February 24, 2009, at your End-of-Phase 2 meeting, to collect and analyze the CV data from your clinical trials as outlined in the December 2008 FDA Guidance for Industry Diabetes Mellitus – Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071627.pdf). You submitted your statistical analysis plan (SAP) for evaluation of CV risk on February 19, 2010, to IND 073198 and IND 076496, stating that all confirmatory Phase 3a trials AND their planned extensions would be combined and that these combined data would be considered as one data set for the purpose of CV risk assessment. Under Section 4.2.2 of the SAP you stated that "the combined data set will be the basis for summaries, analyses and presentation of MACE."

At the time of NDA submission, your CV meta-analysis did not include data from these planned extensions with the exception of Study 3645. A total of 16 studies were included in the meta-analysis referred to as "the original meta-analysis." This analysis, based on 80 CV events including CV death, nonfatal stroke, nonfatal myocardial infarction (MI), or unstable angina pectoris (hereafter referred to as MACE+), yielded a HR (95% CI) of 1.10 (0.68-1.77). Your analysis excluded three additional events in the insulin degludec treatment groups which occurred 9, 11, and 18 days after last day of treatment even though your SAP did not specify exclusion of such events. Our analysis including these three events yielded a HR (95% CI) of 1.17 (0.73, 1-87). Both analyses suggested an unfavorable risk signal leading to a request for additional information on April 27, 2012.

As a result of this request, you submitted an updated analysis on May 11, 2012. This analysis was based on 17 trials and included data from seven controlled extensions as specified in your original SAP. The one additional trial (Study 3896) was a 26-week trial comparing insulin degludec/aspart to glargine in patients with type 2 diabetes mellitus (T2DM) on other background oral anti-diabetic therapies. In this trial, the process of CV event collection and adjudication was similar to that of the trials included in the pre-planned meta-analysis and it was therefore deemed appropriate to include this trial in the updated meta-analysis. The endpoint was a composite of MACE+ individual components. The updated meta-analysis provided 60% additional CV events and increased the total patient-years of exposure (PYE) from 5444 to 7716 PYE. We carefully reviewed the characteristics of the study population originally randomized and compared these to characteristics of the population continuing into the planned extensions. Patient demographics as well as disease characteristics remained balanced between treatment groups and between those originally randomized and those who continued into the extension phases. Furthermore, no evidence of selection bias for continued participation in

either treatment groups was noted when discontinuation rates or reasons for discontinuation were examined. As a result, we concluded that this updated database provided reliable and robust data to assess CV risk and accordingly conducted an updated meta-analysis on these data. Despite the increased exposure and additional events, the original signal of CV risk was not attenuated. The following table summarizes the results for MACE+ and MACE, which includes only CV death, nonfatal MI, and nonfatal stroke. While your SAP identified MACE+ as the primary composite endpoint, inclusion of unstable angina introduces events which are less objective in their evaluation and may be less specific to an underlying atherosclerotic process. Inclusion of less objectively evaluated events, and those that may be less specific, in a planned comparison pre-specified to rule out an excess amount of risk (i.e., non-inferiority comparison) increases the likelihood of showing no treatment difference (i.e., bias to the null). This point is exemplified in Tables 1 and 2 below wherein the hazard ratio is consistently greater in analyses of MACE than MACE+ leading us to conclude that in the face of a potential CV signal, a more rigorous assessment should be based on MACE endpoints.

Table 1. CV Meta-analyses of Original Database and Updated Database on both MACE+ and MACE Endpoints

	Original Database		***Updated Database***	
	IDeg/IDeg-Asp N=5647 (PYE 3569.9)	***Comparator N=3312 (PYE 1873.9)***	***IDeg/IDeg-Asp N=5794 (PYE 5153.6)***	***Comparator N=3461 (PYE 2562.7)***
MACE+	*53 (14.8)*	*27 (14.4)*	*95 (18.4)*	*37 (14.4)*
MI	*20 (5.6)*	*7 (3.7)*	*34 (6.6)*	*9 (3.5)*
Stroke	*11 (3.1)*	*4 (2.1)*	*24 (4.6)*	*6 (2.3)*
CV Death	*8 (2.2)*	*4 (2.1)*	*12 (2.3)*	*6 (2.3)*
UAP	*14 (3.9)*	*12 (6.4)*	*25 (4.8)*	*16 (6.2)*
MACE+ HR (95% CI)	*1.10 (0.68, 1.77)*		*1.30 (0.88, 1.93)*	
MACE	*39 (10.9)*	*15 (8.0)*	*70 (13.6)*	*21 (8.2)*
MI	*20 (5.6)*	*7 (3.7)*	*34 (6.6)*	*9 (3.5)*
Stroke	*11 (3.1)*	*4 (2.1)*	*24 (4.6)*	*6 (2.3)*
CV Death	*8 (2.2)*	*4 (2.1)*	*12 (2.3)*	*6 (2.3)*
MACE HR (95% CI)	*1.39 (0.76, 2.57)*		*1.67 (1.01, 2.75)*	

*We also conducted a meta-analysis of all clinical trials and their planned extensions as **you proposed** in your statistical analysis plan. The results are summarized in the following table.*

Table 2. CV Meta-analysis based on Novo Nordisk's Statistical Analysis Plan

	Degludec/Degludec-Asp	***Comparator***
MACE+ Events	*93*	*36*
HR (95% CI)	*1.29 (0.87, 1.91)*	
MACE		

Events	*68*	*20*
HR (95% CI)	*1.65 (0.99, 2.75)*	

The data summarized in both Tables 1 and 2 support the conclusion of a consistent and persistent signal of excess CV risk associated with insulin degludec and insulin degludec/aspart relative to comparators observed across multiple analyses.

You have de-emphasized the findings in the updated meta-analysis citing decreasing sample size and unexplained changes in hazard rates in the comparator group after Week 52. However, we note that even in Table 1 the original meta-analysis, which would have excluded all but one planned extension phase, did not show a favorable effect of insulin degludec and insulin degludec/aspart on CV risk.

2. Hypoglycemia Risk Reduction

We were unable to identify a unique benefit of insulin degludec and insulin degludec/aspart over existing insulin therapies to offset a potential adverse CV effect. Although you have presented data and analyses to NDA 203314 (insulin degludec) in support of a hypoglycemic risk reduction, we do not agree with your conclusion that insulin degludec provides a clinically meaningful reduction in the risk of developing hypoglycemia over other available once-daily basal insulin for the following reasons:

a. *The reliability and generalizability of the estimates are limited due to reliance on point of care derived data obtained from trials with an open-label design and due to exclusion of populations of patients at increased risk of developing hypoglycemia.*

b. *There was not a consistent trend to suggest a hypoglycemia benefit across definitions of hypoglycemia and in particular for specific, objective, definitions of hypoglycemia (i.e., severe hypoglycemia).*

c. *A clear hypoglycemia benefit was not seen in the population most susceptible to developing hypoglycemia (i.e., type 1 diabetes mellitus [T1DM]) in analyses of individual trials and in the meta-analysis of glargine comparator trials. In fact, subjects with T1DM randomized to insulin degludec in the three pivotal T1DM trials were three times more likely to withdraw due to hypoglycemia than subjects randomized to comparators; were numerically more likely to experience at least one event of hypoglycemia; and had more numerous events of hypoglycemia per exposure time. These findings were found to be inconsistent with the observation that at the trial end, subjects with T1DM randomized to insulin degludec in all three pivotal trials used on average numerically lower total units of insulin per day compared to subjects randomized to comparators.*

d. *Although you stated in your advisory committee briefing material that "hypoglycemia is the primary limiting factor to achieving glycemic control with insulin"[1] and repeated this*

[1] Novo Nordisk November 8, 2012 Advisory Committee Briefing Materials for NDA 203313, page 32.

position in your advisory committee meeting presentations, you were not able to demonstrate that the purported hypoglycemic risk reduction associated with insulin degludec use led to better glycemic control based on HbA1c reduction from baseline or proportion of individual patients achieving HbA1c target. In four trials comparing glycemic efficacy of insulin degludec to insulin glargine in a basal-only insulin regimen (Studies 3579, 3672, 3586, and 3668), the LS mean treatment difference in HbA1c reduction consistently favored insulin glargine.

e. *The presumed benefit of insulin degludec on confirmed nocturnal hypoglycemia may have been confounded by differences in pharmacodynamic profiles between insulin degludec and insulin glargine. You captured events for this subgroup analysis as those occurring between midnight and 0600. The Tmax for glucose lowering is approximately 12 hrs for insulin degludec and 4 hrs for glargine. Because insulin degludec was administered only in the evenings (with evening meal or before bedtime), its peak affect and risk for hypoglycemia may not have been captured within the time band specified for identifying nocturnal hypoglycemia. Although glargine could be administered anytime of the day in these trials, its administration in the evening might result in a biased ascertainment not favoring glargine. You did not capture information on time of day for glargine administration in your trials; however, an exploratory analysis by FDA in which the time band for collecting nocturnal hypoglycemic events was extended by two hours showed an attenuated reduction in hypoglycemic risk associated with degludec suggesting that a treatment difference may be related to time of insulin injection, not inherent qualities of the insulin products.*

Path Forward

To address the above cardiovascular safety deficiencies, you will need to submit additional clinical trial data from a dedicated, double-blind, cardiovascular outcomes trial using glargine as the comparator. The trial should be powered to exclude an excess cardiovascular risk based on a composite of cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke (MACE), not MACE+. The risk margin to exclude that is necessary for approval should be discussed with the Agency at an End-of-Review meeting. At a minimum, the resubmission must include enough MACE events to definitively exclude a hazard of 80% with a reassuring point estimate. We encourage you to seek Agency feedback regarding trial design and statistical analysis plan before trial initiation.

To address a claim for hypoglycemic risk reduction with insulin degludec, you will need to demonstrate a clinically meaningful reduction in such risk over other available once-daily basal insulin that can be attributed to the unique pharmacokinetics/ pharmacodynamics (PK/PD) characteristics of insulin degludec.

FACILITY INSPECTIONS

During a recent inspection of the Novo Nordisk A/S, Novo Alle, DK-2880 Bagsvaerd, Denmark, manufacturing facility for this application, our field investigator conveyed deficiencies to the

representative of the facility. Satisfactory resolution of these deficiencies is required before this application may be approved.

2. DISCUSSION

MACE endpoint

Novo Nordisk agrees with the Agency that for a definitive CV outcomes trial, a three component MACE endpoint (CV death, myocardial infarction, and stroke) will be used as the primary endpoint. CV death, non-fatal myocardial infarction and non-fatal stroke will be prospectively adjudicated. Events will be adjudicated using methods similar to those used in the insulin degludec phase 3a development program and according to a Charter similar to the one the Agency agreed upon for that program.

Question 1: Does the Agency agree that the three component MACE endpoint (strict MACE) is the only CV endpoint evaluated by statistical analysis and the adjudication procedures used previously are appropriate and adequate for the proposed CV outcomes trial?

FDA Response: We agree with the use of a strict MACE composite endpoint for your primary analysis. Until we review your complete study protocol, Statistical Analysis Plan, the CEC Charter, a detailed description of the adjudication procedures, and other related study information (e.g., full description of CV-related safety parameters), we cannot comment on the adequacy of your overall study design, data analysis plan, or planned adjudication process.

Meeting Discussion: Agreement regarding use of the strict MACE composite endpoint for the primary analysis was reaffirmed. Novo Nordisk asked for clarification regarding specific types of CV-related safety parameters that might be requested by FDA. While other CV-related biomarkers were raised by FDA staff as endpoints of interest to measure in this trial, it was agreed to that the primary endpoints of interest are MACE and that effects on these other biomarkers are unlikely to assist in the review should an unfavorable imbalance in CV events be observed in the CV outcomes trial.

Population

Novo Nordisk intends to enroll a population of patients with established T2DM who are at high risk of cardiovascular events. Patients should be appropriate for basal insulin treatment and can be included if they currently are treated with insulin or if they require intensification of their current OAD or GLP-1 based therapy. Novo Nordisk intends to use criteria for defining a high risk CV population similar to those used for recruitment in the LEADER® trial using liraglutide. (b) (4)

Patients will be enrolled into the insulin degludec CV outcomes trial according to the following inclusion criteria:

- Type 2 diabetes mellitus diagnosed clinically Appropriate for basal insulin therapy at investigator's discretion
- Current treatment with one or more oral or injectable antidiabetic agents
- HbA1c > 6.5% (48 mmol/mol) within last 6 months for patients not currently treated with insulin
- Age ≥ 50 years at screening and at least one of the below criteria:
    - prior myocardial infarction
    - prior stroke or prior transient ischemic attack (TIA)
    - prior coronary, carotid or peripheral arterial revascularization
    - 50% stenosis on angiography or other imaging of coronary, carotid or lower extremity arteries
    - history of symptomatic coronary heart disease documented by positive exercise stress test or any cardiac imaging, or unstable angina with ECG changes
    - asymptomatic cardiac ischemia documented by positive nuclear imaging test or exercise test or dobutamine stress echo
    - chronic heart failure, NYHA class II-III
    - chronic renal failure, defined as a glomerular filtration rate of 30 - 60 mL/min/1.73 m2 per CKD-Epi

OR

- Age ≥ 60 years at screening and at least one of the below criteria:
    - microalbuminuria or proteinuria
    - hypertension and left ventricular hypertrophy by ECG or imaging
    - left ventricular systolic and diastolic dysfunction by imaging
    - ankle/brachial index < 0.9

Question 2: Does the Agency agree that this population of patients would be appropriate for a proposed pre-approval CV outcomes trial?

FDA Response: We agree that a population of individuals with established type 2 diabetes who are at high risk for cardiovascular events would be appropriate for your proposed CV outcomes trial. The specific subject inclusion and exclusion criteria will be reviewed when we receive the complete study protocol for your proposed trial (See response to Question 4 regarding minimum insulin requirements). The trial population should reflect the population of patients for whom degludec is intended (i.e., ~ 70% of patients should have inadequate glycemic control despite multiple antihyperglycemic agents).

Meeting Discussion: No discussion occurred.

US patient representation

Novo Nordisk intends to recruit approximately one third of the study population in US. The CV specific inclusion/exclusion criteria designed to achieve the expected rate of CV MACE may

impact recruitment with respect to demographic variables like age and potentially also race and ethnicity. We expect that the US population participating in the trial will be representative of a background US diabetes population with moderate to high risk of CV disease.

Question 3: Does the Agency agree to this approach?

FDA Response: We agree that a minimum of one-third of the study population should be derived from study sites within the United States. Trial participants should be representative of the U.S. type 2 diabetes population with cardiovascular disease.

Meeting Discussion: No discussion occurred.

Glycemic target

By FDA regulatory guidance, diabetes efficacy trials with insulin have been open-label and conducted as treat-to-target designed trials (FDA Guidance for Industry, Diabetes Mellitus, 2008). There is no precedence for conducting a dedicated CVOT with insulin in patients with advanced T2DM. Current treatment guidelines recommend that target levels of glycemic control must be adjusted based on background risk of the individual patients and higher glycemic targets should be set in order to reduce the risk of hypoglycemia in patients who are prone to adverse acute CV events (Inzucchi et al, Diabetes Care, 2012). The glycemic target of the insulin degludec phase 3a program of 4-5 mM (72-90 mg/dL) is not appropriate for this high risk population and it is therefore unlikely that patients will reach the same level of glycemic control in the insulin degludec CV outcomes trial as was achieved in the insulin degludec phase 3a program. The suggested approach for the insulin degludec CVOT is to ensure optimization of glycemic control for the individual patients while balancing the risk of too tight control in this high risk population. This is done by the individual investigator based on recommendations from Novo Nordisk and consistent with the American Diabetes Association guidelines that patients should aim for achieving a fasting plasma glucose <130 mg/dL and an HbA1c below 7.5%.

Question 4: Does the Agency agree that the CV safety of insulin degludec can be established in this high-risk population despite aiming for higher glycemic targets in accordance with ADA recommendations compared to the completed insulin degludec phase 3a program?

FDA Response: The 2013 ADA Standards of Medical Care in Diabetes (*Diabetes Care, 36 (1) 2013)* recommend an HbA1c treatment goal of < 7% for the majority of type 2 diabetics. Less stringent HbA1c goals may be appropriate for those with a history of severe hypoglycemia, limited life expectancy, advanced microvascular or macrovascular complications, extensive comorbid conditions, and those with long-standing diabetes in whom the general goal is difficult to attain. While the population expected to be enrolled in your CVOT will be at moderate to high risk of CVD, it will be unlikely to include those patients for which the 2013 ADA guidelines recommend less stringent treatment goals. For this reason, we do not agree with your proposed fasting plasma glucose goal of < 130 mg/dL or HbA1c goal < 7.5%.

Assessing CV safety of insulin degludec requires adequate exposure to insulin degludec and achievement of reasonable glycemic targets. In your CV outcomes trial, you should enroll subjects who require at minimum 20 units of insulin per day, and insulin dose should be titrated using the same glycemic target as that used in your Phase 3 program. This glycemic target would not be inappropriate for the high-cardiovascular-risk population you propose to study. It should be noted that nearly 20% of the participants in your Phase 3 degludec trials with type 2 diabetes had a history of pre-existing cardiovascular disease and many others had multiple cardiovascular disease risk factors. In addition, the majority of patients in the Phase 3 program did not achieve an HbA1c of 7% or less and the rate of severe hypoglycemia was low. Finally, the glycemic target in the degludec program was similar to the target used in the ORIGIN trial, another large insulin CVOT carried out in patients with established cardiovascular disease which suggested a neutral effect of glargine on cardiovascular risk.

In addition, if you intend to compare hypoglycemic risk between degludec and glargine , we recommend that you use an insulin dosing scheming and a target glycemic goal that will allow capture of a sufficient number of specific hypoglycemic events.

Meeting Discussion: The two points of discussion focused on eligibility criteria pertaining to the minimum insulin dose required at study entry and on the glycemic target for the proposed study. Novo Nordisk proposed several insulin dose entry criteria which take pre-trial history of insulin use and/or the baseline HbA1c level into account. The brief description of the modified entry criteria appeared reasonable; however, the FDA defers judgment on their acceptability until after review of the full protocol. Novo Nordisk proposed to target a fasting self-monitored blood glucose level of 90 mg/dL for dose titration. The proposal appeared reasonable however the FDA defers judgment on the acceptability of the glucose target until after review of the full protocol.

Post Meeting Comment: Ensure subjects with a prior history of insulin use who are receiving > 20 units are adequately represented in the study. We recommend insulin-naïve individuals not constitute more than 1/3 of the total planned enrollees. Submit, along with the full protocol, the plan to monitor the adequacy of dose titration in your study and contrast this plan to the monitoring plan used in the degludec Phase III program.

Blinding/Comparator

In the CRL, the Agency requested a double-blind trial conducted to assess the cardiovascular safety of insulin degludec. Novo Nordisk agrees that a double-blind trial represents the most scientifically rigorous approach to comparing the CV safety of two insulins. Conducting a double-blind CV outcomes trial with an active comparator requires that the delivery system for the insulin injections will appear identical in the two arms and that the dosing accuracy and quality of the products will not be impacted by the blinding procedure.

One option of blinding is by using vial and syringe. Blinding using this approach may imperil the integrity of the final analysis due to anticipated higher drop-out rate. Improving retention rates

yields more robust data with which to analyze the risk of CV events (Panel on Handling Missing Data in Clinical Trials and Committee on National Statistics. The Prevention and Treatment of Missing Data in Clinical Trials. Washington DC: The National Academy Press, 2010.). Using vial and syringe may also affect the in-trial medication adherence since several studies have demonstrated that pen devices are associated with higher adherence as compared to vial and syringe (Asche et al, Diabetes Technology and Therapeutics, 2010). Furthermore, recruiting insulin requiring subjects from investigators practicing modern diabetes care to a trial where insulin is administered using vial and syringe, will substantially limit the number of investigators and subjects willing to participate. Offering a vial and syringe treatment in a trial could lead to a decrease in patient acceptance of treatment since insulin pens now represents the preferred device for diabetic patients (Korytkowski et al, Clin Ther, 2003).

Globally, insulin pen devices are preferred by the majority of patients, and in most countries outside the US and South America, vial and syringe use is virtually unknown to patients and to physicians/diabetes educators. Based on world-wide sales figures, vial and syringe constitute only (b) (4)% of the total Lantus® sale and (b) (4)% of total Levemir® sale, with the US being the main contributor to vial and syringe sale in a steady downward trend.

Insulin pens are preferred due to their advantages with regard to patient safety (Lee et al, Clin Ther, 2006), ease of use (Korytkowski et al, Clin Ther, 2003), treatment satisfaction (Stockl et al., Curr Med Res Opin 2007), adherence (Asche et al, Diabetes Technology and Therapeutics, 2010) and clinical outcomes (Lee et al. J Eval Clin Pract 2009). However, due to inherent design differences between the Lantus® SoloSTAR® pen and the Novo Nordisk FlexTouch® used for insulin degludec, blinding of these two devices is not possible. Further, cartridges for insulin degludec and insulin glargine differ to an extent that the dimension and color of the pistons as well as their internal dimensions prohibit use of the same durable pen device for the two different cartridges. These differences would affect both the ability to blind the study as well as the dose accuracy in a clinically meaningful way.

In order to secure a double-blind trial that can be executed with appropriate retention of subjects, Novo Nordisk proposes (b) (4)

Question 5: In order to ensure proper blinding and to ensure a scientifically valid and robust trial, does the Agency agree to conducting a pre-approval double-blind trial vs. (b) (4) ? A draft trial outline is included to support the Agency's review.

FDA Response: No, we do not agree. The only comparator we will accept is insulin glargine. Insulin glargine was the predominant comparator in the degludec Phase 3 experience, accounting for more than 70% of all active comparators. As a result, the signal identified is in large part based on the comparison of degludec to glargine. In addition, in one recent large cardiovascular outcomes trial, insulin glargine was reported to have a neutral effect on CV endpoints. Finally, glargine is labeled for once daily administration. Therefore, insulin glargine is the only comparator we will accept to establish the CV safety of insulin degludec. We strongly urge you to carry out the trial in a double-blind fashion and you should be prepared to discuss why you have not considered the option of insulin delivery via an undifferentiated pen device and/or use of a double-dummy injection schedule to achieve this goal.

Meeting Discussion: The Sponsor reiterated their rationale for proposing (b) (4) *as the comparator in the proposed trial and outlined some of the challenges of blinding insulin glargine. However, FDA confirmed that insulin glargine—for the reasons outlined above—is the only comparator that will be accepted for this trial. The Sponsor was asked to systematically consider all options for conducting a blinded trial with insulin glargine as the sole comparator.*

Trial Design

In the CRL, the Agency proposes a pre-approval trial powered to exclude an excess cardiovascular risk of 80% with a reassuring point estimate. Sample size calculations show that a total of 150 MACE events will provide 95% power to definitively exclude an excess hazard of 80%; i.e. there is a 95% probability that the upper 95% confidence limit is below 1.8, assuming that the true underlying hazard ratio is 1.0. Moreover, the 150 events will provide around 85% probability for having a reassuring point estimate, defined as any point estimate below 1.2 for the hazard ratio.

Approximately 151 events will be accrued in a trial of 25 months duration comprising 4650 patients with an annualized event rate of 2.1 per 100 PYE (corresponding to the underlying risk in the recruited patient population), provided that the recruitment is uniform across the entire recruitment period, and finalized in 12 months. Further, it is assumed that the annualized rate of patients lost to follow-up is 1%. The below table shows how the total number of events will vary with varying annualized MACE rates and with varying duration of the recruitment period.

Recruitment time (assuming uniform recruitment)	Annualized MACE rates in both treatment groups (events per 100 PYE)				
	1.5	1.8	2.1	2.4	2.7
9 months	117	140	163	185	208
12 months	108	130	151	172	193
15 months	100	120	139	159	178

Novo Nordisk proposes [redacted] (b) (4)

Question 6a: Does the Agency agree that the described [redacted] (b) (4) trial design is appropriate to [redacted] (b) (4) and that this is adequate for resubmission?

FDA Response: For us to consider your resubmission as complete, you will need to exclude the 1.8 risk margin with a reassuring point estimate. However, [redacted] (b) (4) [redacted] (b) (4) **(See Response to Question 6b regarding overall objective of your cardiovascular outcomes trial).**

We have the following additional statistical comments:

- **You should follow all subjects for the duration of the trial even after they discontinue the randomized treatment. You should collect data on rescue medication(s) and any potential CV events of interest.**
- **You should propose a primary and secondary analysis population. Analysis populations should include both "on study" and "on treatment" populations. The "on study" analysis population should include all events that occur while subjects are on treatment and also those that occur while off treatment while patients are still being followed. The "on treatment" analysis population should include only events that occur while a subject is receiving the randomized treatment including a pre-defined censoring window.**

Meeting discussion: The sponsor requested clarification on the definitions of "on study" and "on treatment" analysis populations. The FDA stated these were similar to the naming conventions of ITT and PP analysis populations, respectively. The FDA stated that an "on study" analysis population can be considered primary, especially in the case of powering the trial, however, the "on treatment" analysis population is still considered to be important in the assessment of cardiovascular risk.

Question 6b: Does the Agency agree that the successful outcome of such a study, i.e. upper bound of (b) (4)

(b) (4)

FDA Response: We do not agree. Your development program to date has identified a concerning CV safety signal relative to glargine. As noted in our Complete Response letter, a 39% excess risk for MACE was observed at time of your NDA submission and increased to 67% with your updated database. This concerning CV safety signal distinguishes you from other recently approved anti-diabetic therapies where pre-marketing CV risk assessments have not shown hazard ratios exceeding 1.0. Consequently, you must design your cardiovascular safety trial with the primary objective of excluding a risk margin of 1.3.

While we will accept for resubmission and potentially approve your product based on an interim analysis excluding a CV risk margin of 1.8, assuming a reassuring point estimate and no other countervailing safety signals identified in the resubmission, you will be required to exclude an excess hazard of 30% postmarketing. Please note that while a reassuring point estimate remains a review issue, the consistent finding of excess MACE associated with degludec in your pre-marketing application advises us to interpret any point estimate exceeding 1.0 in your resubmission with concern.

Meeting Discussion: The Sponsor asked FDA to elaborate on the fact that resubmission, as stated in the complete response letter, will be contingent on demonstrating a "reassuring" point estimate at the interim analysis and sought further clarification on what that point estimate would be. The FDA stated that the "reassuring" point estimate will be a review issue and further clarified its position as follows. The FDA noted that the path forward highlighted in the letter and in response to questions posed at the end-of-review meeting allows Novo Nordisk to potentially use incomplete cardiovascular safety data (i.e., interim data) to support resubmission of the degludec and degludec/aspart applications. The FDA stated that the degludec program differs from other programs which also rely on interim cardiovascular safety data for filing and initial approval because a credible cardiovascular safety signal has already been identified. The FDA will thus review and interpret the result of the planned interim cardiovascular safety analysis derived from the dedicated CVOT in light of this fact. The FDA will be concerned if, for example, the point estimate derived from this second cardiovascular safety assessment, based on the more robust MACE endpoint, again suggests harm. The FDA will also be concerned if, based on the results of this interim analysis, it is unlikely that the final analysis will allow definitive exclusion of a hazard ratio of 1.3.

Protocol review time

Novo Nordisk will prepare a final protocol for FDA review based on the agreements reached with the Agency at the End of Review meeting.

Question 7: Does the Agency commit to a rapid review and turnaround time for the final protocol submitted by Novo Nordisk based on the agreements reached at the EoR meeting?

FDA Response: We will aim to review the proposed study protocol within 60 days of receiving your complete, near final, study protocol along with all other related supporting documents (Statistical Analysis Plan, CEC charter, etc.).

Meeting Discussion: The FDA reiterated its commitment to timely and productive feedback.

Other comments

Question 8: Does the Agency have additional advice for the design of this trial?

FDA Response: Please see our responses above.

Meeting Discussion: Not discussed during meeting.

Procedural question

Novo Nordisk believes that the following aspects of the NDAs have been satisfactorily evaluated and reviewed by FDA (device, CMC, nonclinical and clinical pharmacology, efficacy and safety other than CV) and that barring some future unexpected finding, NN considers these sections of the NDAs to be complete and not subject to further review.

Question 9: Does the Agency agree?

FDA Response: Future re-submissions should address all the deficiencies highlighted in the Complete Response letter.

Meeting Discussion: No discussion occurred.

Resolution of the December 2012 Warning Letter

In mid-December 2012, Novo Nordisk received a Warning Letter from FDA related to an inspection at a manufacturing facility in Bagsværd, Denmark. The company responded to the Warning Letter on December 28, 2012. The company has reached out to the FDA contact during

the first quarter of 2013 to see if additional information or clarifications were necessary; the Novo Nordisk response appears to be still under review.

Question 10: Given that over 60 days have passed since Novo Nordisk responded to the FDA Warning Letter related to the Bagsværd, Denmark manufacturing facility, can FDA provide any additional information to the company on the status of the topic, including the process and timing to completely resolve the issues raised by the Agency and close out the Warning Letter?

FDA Response: The FDA cannot comment on the status of an open review to the firm's response at this time. The outcome of the review will be communicated to the manufacturing facility in Bagsværd, Denmark when it is complete.

Meeting Discussion: No discussion occurred.

Communication

Novo Nordisk works diligently to always interact with regulatory authorities in a professionally scientific and transparent manner. We believe that this approach is fundamental in how we work to develop our medicines and monitor them carefully following approval. We greatly value the expertise of FDA and we recognize the FDA principles contained in PDUFA V in terms of enhanced communication and transparency with drug sponsors.

Question 11a: Does FDA have any advice or guidance to Novo Nordisk in terms of the company's approach to the quality of its applications, timeliness of responses and general interactions with FDA?

FDA Response: None at this time.

Meeting Discussion: The Sponsor asked if FDA had additional questions or comments. FDA commented that the Sponsor's updated investigator's brochure does not adequately reflect FDA's level of concern regarding the CV safety signal. FDA requested that the investigator's brochure be revised accordingly and asked that a copy of the informed consent—presenting a balanced assessment of potential study risks and benefits—be submitted with the proposed CV outcomes trial.

Question 11b: Can FDA comment on any enhanced communication principles in place that can be applied to the degludec applications moving forward?

FDA Response: The Program for enhanced review transparency and communication applies to all new molecular entity new drug applications and original biologics license applications, including applications that are resubmitted following a Refuse-to-File action received from October 1, 2012, through September 30, 2017. The goal of the Program is to improve the efficiency and effectiveness of the first cycle review process. The degludec re-submission will be a second cycle review and will not be reviewed under the Program.

Meeting Discussion: No discussion occurred.

3.0 PREA REQUIREMENTS

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit a Pediatric Study Plan (PSP) within 60 days of an End-of-Phase 2 (EOP2) meeting held on or after November 6, 2012. If an EOP2 meeting occurred prior to November 6, 2012 or an EOP2 meeting will not occur, then:

- if your marketing application is expected to be submitted prior to January 5, 2014, you may either submit a PSP 210 days prior to submitting your application or you may submit a pediatric plan with your application as was required under the Food and Drug Administration Amendments Act (FDAAA).
- if your marketing application is expected to be submitted on or after January 5, 2014, the PSP should be submitted as early as possible and at a time agreed upon by you and FDA. We strongly encourage you to submit a PSP prior to the initiation of Phase 3 studies. In any case, the PSP must be submitted no later than 210 days prior to the submission of your application.

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. For additional guidance on submission of the PSP, including a PSP Template, please refer to: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm . In addition, you may contact the Pediatric and Maternal Health Staff at 301-796-2200 or email pdit@fda.hhs.gov.

4.0 ISSUES REQUIRING FURTHER DISCUSSION

No issues requiring further discussion.

5.0 ACTION ITEMS

No action items were identified.

6.0 ATTACHMENTS AND HANDOUTS

The sponsor's slides are attached.

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

/s/

MARY H PARKS
05/01/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 203313
NDA 203314

MEETING PRELIMINARY COMMENTS

Novo Nordisk
Attention: Robert B. Clark
Vice President, Regulatory Affairs
P.O. Box 846
Plainsboro, NJ 08536

Dear Mr. Clark:

Please refer to your New Drug Applications (NDAs) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for

- Ryzodeg (insulin degludec/insulin aspart [rDNA origin]), injection, 100 U/mL
- Tresiba (insulin degludec [rDNA origin]), injection, 100 U/mL and 200 U/mL

We also refer to your correspondence dated and received March 1, 2013, requesting an End-of-Review meeting.

Our preliminary responses to your meeting questions are enclosed.

You should provide me with a hardcopy or electronic version of any materials (i.e., slides or handouts) to be presented and/or discussed at the meeting.

If you have any questions, call me at (301) 796-8436.

Sincerely,

{See appended electronic signature page}

Callie Cappel-Lynch, Pharm. D.
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

ENCLOSURE: Preliminary Meeting Comments

PRELIMINARY MEETING COMMENTS

Meeting Type:	A
Meeting Category:	End of Review
Meeting Date and Time:	April 4, 2013 (2:00 – 4:00pm)
Meeting Location:	WO Bldg 22, RM 1415
Application Numbers:	NDA 203313 & NDA 203314
Product Names:	Ryzodeg (insulin degludec/insulin aspart [rDNA origin]), injection, 100 U/mL Tresiba (insulin degludec [rDNA origin]), injection, 100 U/mL and 200 U/mL
Indication:	Treatment of diabetes mellitus
Sponsor/Applicant Name:	Novo Nordisk

Introduction:
This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. However, if these answers and comments are clear to you and you determine that further discussion is not required, you have the option of cancelling the meeting (contact me). If you choose to cancel the meeting, this document will represent the official record of the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda and/or changing the format of the meeting (e.g., from face to face to teleconference). It is important to remember that some meetings, particularly milestone meetings, can be valuable even if the premeeting communications are considered sufficient to answer the questions. Note that if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, we may not be prepared to discuss or reach agreement on such changes at the meeting although we will try to do so if possible. If any modifications to the development plan or additional questions for which you would like CDER feedback arise before the meeting, contact me to discuss the possibility of including these items for discussion at the meeting.

1.0 BACKGROUND

On September 29, 2011, Novo Nordisk submitted New Drug Applications for insulin degludec (conditionally accepted proprietary name: TRESIBA) and a fixed-dose combination of insulin degludec and insulin aspart (conditionally accepted proprietary name: RYZODEG). Insulin degludec (IDeg) is a long-acting (basal) insulin analog available as IDeg U100 and IDeg U200. Ryzodeg is a fixed-dose combination of insulin degludec and insulin aspart (IAsp), a short–

acting insulin analog. Insulin aspart was approved on June 7, 2000, under the proprietary name NovoLog (NDA 020986). Ryzodeg is composed of 70% IDeg and 30% IAsp (U100). Both Ryzodeg and Tresiba are intended for once daily subcutaneous use in adults with type-1 and type-2 diabetes mellitus. The dosage of both drugs is to be individualized based on glycemic response, with no upper dosage-limit.

On May 16, 2012, Novo Nordisk submitted a major amendment which resulted in extending the review goal date to October 29, 2012. An advisory committee meeting was help on November 8, 2012, to discuss the safety and efficacy of both products. On February 8, 2013 a Complete Response Letter was issued for both NDAs. The deficiencies are repeated below in italicized text.

We have completed our review of this application, as amended, and have determined that we cannot approve this application in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

CLINICAL

1. Cardiovascular Safety

A consistent and persistent signal of excess cardiovascular (CV) risk associated with insulin degludec and insulin degludec/aspart relative to comparators is observed across multiple analyses.

You were informed on February 24, 2009, at your End-of-Phase 2 meeting, to collect and analyze the CV data from your clinical trials as outlined in the December 2008 FDA Guidance for Industry Diabetes Mellitus – Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071627.pdf). You submitted your statistical analysis plan (SAP) for evaluation of CV risk on February 19, 2010, to IND 073198 and IND 076496, stating that all confirmatory Phase 3a trials AND their planned extensions would be combined and that these combined data would be considered as one data set for the purpose of CV risk assessment. Under Section 4.2.2 of the SAP you stated that "the combined data set will be the basis for summaries, analyses and presentation of MACE."

At the time of NDA submission, your CV meta-analysis did not include data from these planned extensions with the exception of Study 3645. A total of 16 studies were included in the meta-analysis referred to as "the original meta-analysis." This analysis, based on 80 CV events including CV death, nonfatal stroke, nonfatal myocardial infarction (MI), or unstable angina pectoris (hereafter referred to as MACE+), yielded a HR (95% CI) of 1.10 (0.68-1.77). Your analysis excluded three additional events in the insulin degludec treatment groups which occurred 9, 11, and 18 days after last day of treatment even though your SAP did not specify exclusion of such events. Our analysis including these three events yielded a HR (95% CI) of 1.17 (0.73, 1-87). Both analyses suggested an unfavorable risk signal leading to a request for additional information on April 27, 2012.

As a result of this request, you submitted an updated analysis on May 11, 2012. This analysis was based on 17 trials and included data from seven controlled extensions as specified in your original SAP. The one additional trial (Study 3896) was a 26-week trial comparing insulin degludec/aspart to glargine in patients with type 2 diabetes mellitus (T2DM) on other background oral anti-diabetic therapies. In this trial, the process of CV event collection and adjudication was similar to that of the trials included in the pre-planned meta-analysis and it was therefore deemed appropriate to include this trial in the updated meta-analysis. The endpoint was a composite of MACE+ individual components. The updated meta-analysis provided 60% additional CV events and increased the total patient-years of exposure (PYE) from 5444 to 7716 PYE. We carefully reviewed the characteristics of the study population originally randomized and compared these to characteristics of the population continuing into the planned extensions. Patient demographics as well as disease characteristics remained balanced between treatment groups and between those originally randomized and those who continued into the extension phases. Furthermore, no evidence of selection bias for continued participation in either treatment groups was noted when discontinuation rates or reasons for discontinuation were examined. As a result, we concluded that this updated database provided reliable and robust data to assess CV risk and accordingly conducted an updated meta-analysis on these data. Despite the increased exposure and additional events, the original signal of CV risk was not attenuated. The following table summarizes the results for MACE+ and MACE, which includes only CV death, nonfatal MI, and nonfatal stroke. While your SAP identified MACE+ as the primary composite endpoint, inclusion of unstable angina introduces events which are less objective in their evaluation and may be less specific to an underlying atherosclerotic process. Inclusion of less objectively evaluated events, and those that may be less specific, in a planned comparison pre-specified to rule out an excess amount of risk (i.e., non-inferiority comparison) increases the likelihood of showing no treatment difference (i.e., bias to the null). This point is exemplified in Tables 1 and 2 below wherein the hazard ratio is consistently greater in analyses of MACE than MACE+ leading us to conclude that in the face of a potential CV signal, a more rigorous assessment should be based on MACE endpoints.

Table 1. CV Meta-analyses of Original Database and Updated Database on both MACE+ and MACE Endpoints

	Original Database		***Updated Database***	
	IDeg/IDeg-Asp N=5647 (PYE 3569.9)	***Comparator N=3312 (PYE 1873.9)***	***IDeg/IDeg-Asp N=5794 (PYE 5153.6)***	***Comparator N=3461 (PYE 2562.7)***
MACE+	*53 (14.8)*	*27 (14.4)*	*95 (18.4)*	*37 (14.4)*
MI	*20 (5.6)*	*7 (3.7)*	*34 (6.6)*	*9 (3.5)*
Stroke	*11 (3.1)*	*4 (2.1)*	*24 (4.6)*	*6 (2.3)*
CV Death	*8 (2.2)*	*4 (2.1)*	*12 (2.3)*	*6 (2.3)*
UAP	*14 (3.9)*	*12 (6.4)*	*25 (4.8)*	*16 (6.2)*
MACE+ HR (95% CI)	*1.10 (0.68, 1.77)*		*1.30 (0.88, 1.93)*	
MACE	*39 (10.9)*	*15 (8.0)*	*70 (13.6)*	*21 (8.2)*
MI	*20 (5.6)*	*7 (3.7)*	*34 (6.6)*	*9 (3.5)*
Stroke	*11 (3.1)*	*4 (2.1)*	*24 (4.6)*	*6 (2.3)*
CV Death	*8 (2.2)*	*4 (2.1)*	*12 (2.3)*	*6 (2.3)*

MACE *HR (95% CI)*	*1.39 (0.76, 2.57)*	*1.67 (1.01, 2.75)*

*We also conducted a meta-analysis of all clinical trials and their planned extensions as **you proposed** in your statistical analysis plan. The results are summarized in the following table.*

Table 2. CV Meta-analysis based on Novo Nordisk's Statistical Analysis Plan

	Degludec/Degludec-Asp	***Comparator***
MACE+ *Events*	*93*	*36*
HR (95% CI)	*1.29 (0.87, 1.91)*	
MACE *Events*	*68*	*20*
HR (95% CI)	*1.65 (0.99, 2.75)*	

The data summarized in both Tables 1 and 2 support the conclusion of a consistent and persistent signal of excess CV risk associated with insulin degludec and insulin degludec/aspart relative to comparators observed across multiple analyses.

You have de-emphasized the findings in the updated meta-analysis citing decreasing sample size and unexplained changes in hazard rates in the comparator group after Week 52. However, we note that even in Table 1 the original meta-analysis, which would have excluded all but one planned extension phase, did not show a favorable effect of insulin degludec and insulin degludec/aspart on CV risk.

2. Hypoglycemia Risk Reduction

We were unable to identify a unique benefit of insulin degludec and insulin degludec/aspart over existing insulin therapies to offset a potential adverse CV effect. Although you have presented data and analyses to NDA 203314 (insulin degludec) in support of a hypoglycemic risk reduction, we do not agree with your conclusion that insulin degludec provides a clinically meaningful reduction in the risk of developing hypoglycemia over other available once-daily basal insulin for the following reasons:

a. *The reliability and generalizability of the estimates are limited due to reliance on point of care derived data obtained from trials with an open-label design and due to exclusion of populations of patients at increased risk of developing hypoglycemia.*

b. *There was not a consistent trend to suggest a hypoglycemia benefit across definitions of hypoglycemia and in particular for specific, objective, definitions of hypoglycemia (i.e., severe hypoglycemia).*

c. *A clear hypoglycemia benefit was not seen in the population most susceptible to developing hypoglycemia (i.e., type 1 diabetes mellitus [T1DM]) in analyses of individual trials and in the meta-analysis of glargine comparator trials. In fact, subjects with T1DM randomized to insulin degludec in the three pivotal T1DM trials were three times more likely to withdraw due to hypoglycemia than subjects randomized to comparators; were numerically more likely to experience at least one event of hypoglycemia; and had more numerous events of hypoglycemia per exposure time. These findings were found to be inconsistent with the observation that at the trial end, subjects with T1DM randomized to insulin degludec in all three pivotal trials used on average numerically lower total units of insulin per day compared to subjects randomized to comparators.*

d. *Although you stated in your advisory committee briefing material that "hypoglycemia is the primary limiting factor to achieving glycemic control with insulin"[1] and repeated this position in your advisory committee meeting presentations, you were not able to demonstrate that the purported hypoglycemic risk reduction associated with insulin degludec use led to better glycemic control based on HbA1c reduction from baseline or proportion of individual patients achieving HbA1c target. In four trials comparing glycemic efficacy of insulin degludec to insulin glargine in a basal-only insulin regimen (Studies 3579, 3672, 3586, and 3668), the LS mean treatment difference in HbA1c reduction consistently favored insulin glargine.*

e. *The presumed benefit of insulin degludec on confirmed nocturnal hypoglycemia may have been confounded by differences in pharmacodynamic profiles between insulin degludec and insulin glargine. You captured events for this subgroup analysis as those occurring between midnight and 0600. The Tmax for glucose lowering is approximately 12 hrs for insulin degludec and 4 hrs for glargine. Because insulin degludec was administered only in the evenings (with evening meal or before bedtime), its peak affect and risk for hypoglycemia may not have been captured within the time band specified for identifying nocturnal hypoglycemia. Although glargine could be administered anytime of the day in these trials, its administration in the evening might result in a biased ascertainment not favoring glargine. You did not capture information on time of day for glargine administration in your trials; however, an exploratory analysis by FDA in which the time band for collecting nocturnal hypoglycemic events was extended by two hours showed an attenuated reduction in hypoglycemic risk associated with degludec suggesting that a treatment difference may be related to time of insulin injection, not inherent qualities of the insulin products.*

Path Forward

To address the above cardiovascular safety deficiencies, you will need to submit additional clinical trial data from a dedicated, double-blind, cardiovascular outcomes trial using glargine as the comparator. The trial should be powered to exclude an excess cardiovascular risk based on a composite of cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke (MACE), not MACE+. The risk margin to exclude that is necessary for approval should be

[1] Novo Nordisk November 8, 2012 Advisory Committee Briefing Materials for NDA 203313, page 32.

discussed with the Agency at an End-of-Review meeting. At a minimum, the resubmission must include enough MACE events to definitively exclude a hazard of 80% with a reassuring point estimate. We encourage you to seek Agency feedback regarding trial design and statistical analysis plan before trial initiation.

To address a claim for hypoglycemic risk reduction with insulin degludec, you will need to demonstrate a clinically meaningful reduction in such risk over other available once-daily basal insulin that can be attributed to the unique pharmacokinetics/ pharmacodynamics (PK/PD) characteristics of insulin degludec.

FACILITY INSPECTIONS

During a recent inspection of the Novo Nordisk A/S, Novo Alle, DK-2880 Bagsvaerd, Denmark, manufacturing facility for this application, our field investigator conveyed deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this application may be approved.

2. DISCUSSION

MACE endpoint

Novo Nordisk agrees with the Agency that for a definitive CV outcomes trial, a three component MACE endpoint (CV death, myocardial infarction, and stroke) will be used as the primary endpoint. CV death, non-fatal myocardial infarction and non-fatal stroke will be prospectively adjudicated. Events will be adjudicated using methods similar to those used in the insulin degludec phase 3a development program and according to a Charter similar to the one the Agency agreed upon for that program.

Question 1: Does the Agency agree that the three component MACE endpoint (strict MACE) is the only CV endpoint evaluated by statistical analysis and the adjudication procedures used previously are appropriate and adequate for the proposed CV outcomes trial?

FDA Response: We agree with the use of a strict MACE composite endpoint for your primary analysis. Until we review your complete study protocol, Statistical Analysis Plan, the CEC Charter, a detailed description of the adjudication procedures, and other related study information (e.g., full description of CV-related safety parameters), we cannot comment on the adequacy of your overall study design, data analysis plan, or planned adjudication process.

Population

Novo Nordisk intends to enroll a population of patients with established T2DM who are at high risk of cardiovascular events. Patients should be appropriate for basal insulin treatment and can be included if they currently are treated with insulin or if they require intensification of their current OAD or GLP-1 based therapy. Novo Nordisk intends to use criteria for defining a high risk CV population similar to those used for recruitment in the LEADER® trial using liraglutide. (b) (4)

Patients will be enrolled into the insulin degludec CV outcomes trial according to the following inclusion criteria:

- Type 2 diabetes mellitus diagnosed clinically Appropriate for basal insulin therapy at investigator's discretion
- Current treatment with one or more oral or injectable antidiabetic agents
- HbA1c > 6.5% (48 mmol/mol) within last 6 months for patients not currently treated with insulin
- Age ≥ 50 years at screening and at least one of the below criteria:
    - prior myocardial infarction
    - prior stroke or prior transient ischemic attack (TIA)
    - prior coronary, carotid or peripheral arterial revascularization
    - 50% stenosis on angiography or other imaging of coronary, carotid or lower extremity arteries
    - history of symptomatic coronary heart disease documented by positive exercise stress test or any cardiac imaging, or unstable angina with ECG changes
    - asymptomatic cardiac ischemia documented by positive nuclear imaging test or exercise test or dobutamine stress echo
    - chronic heart failure, NYHA class II-III
    - chronic renal failure, defined as a glomerular filtration rate of 30 - 60 mL/min/1.73 m2 per CKD-Epi

OR

- Age ≥ 60 years at screening and at least one of the below criteria:
    - microalbuminuria or proteinuria
    - hypertension and left ventricular hypertrophy by ECG or imaging
    - left ventricular systolic and diastolic dysfunction by imaging
    - ankle/brachial index < 0.9

Question 2: Does the Agency agree that this population of patients would be appropriate for a proposed pre-approval CV outcomes trial?

FDA Response: We agree that a population of individuals with established type 2 diabetes who are at high risk for cardiovascular events would be appropriate for your proposed CV outcomes trial. The specific subject inclusion and exclusion criteria will be reviewed when we receive the complete study protocol for your proposed trial (See response to Question 4

regarding minimum insulin requirements). The trial population should reflect the population of patients for whom degludec is intended (i.e., ~ 70% of patients should have inadequate glycemic control despite multiple antihyperglycemic agents).

US patient representation

Novo Nordisk intends to recruit approximately one third of the study population in US. The CV specific inclusion/exclusion criteria designed to achieve the expected rate of CV MACE may impact recruitment with respect to demographic variables like age and potentially also race and ethnicity. We expect that the US population participating in the trial will be representative of a background US diabetes population with moderate to high risk of CV disease.

Question 3: Does the Agency agree to this approach?

FDA Response: We agree that a minimum of one-third of the study population should be derived from study sites within the United States. Trial participants should be representative of the U.S. type 2 diabetes population with cardiovascular disease.

Glycemic target

By FDA regulatory guidance, diabetes efficacy trials with insulin have been open-label and conducted as treat-to-target designed trials (FDA Guidance for Industry, Diabetes Mellitus, 2008). There is no precedence for conducting a dedicated CVOT with insulin in patients with advanced T2DM. Current treatment guidelines recommend that target levels of glycemic control must be adjusted based on background risk of the individual patients and higher glycemic targets should be set in order to reduce the risk of hypoglycemia in patients who are prone to adverse acute CV events (Inzucchi et al, Diabetes Care, 2012). The glycemic target of the insulin degludec phase 3a program of 4-5 mM (72-90 mg/dL) is not appropriate for this high risk population and it is therefore unlikely that patients will reach the same level of glycemic control in the insulin degludec CV outcomes trial as was achieved in the insulin degludec phase 3a program. The suggested approach for the insulin degludec CVOT is to ensure optimization of glycemic control for the individual patients while balancing the risk of too tight control in this high risk population. This is done by the individual investigator based on recommendations from Novo Nordisk and consistent with the American Diabetes Association guidelines that patients should aim for achieving a fasting plasma glucose <130 mg/dL and an HbA1c below 7.5%.

Question 4: Does the Agency agree that the CV safety of insulin degludec can be established in this high-risk population despite aiming for higher glycemic targets in accordance with ADA recommendations compared to the completed insulin degludec phase 3a program?

FDA Response: The 2013 ADA Standards of Medical Care in Diabetes (*Diabetes Care, 36 (1) 2013)* recommend an HbA1c treatment goal of < 7% for the majority of type 2 diabetics. Less stringent HbA1c goals may be appropriate for those with a history of severe hypoglycemia, limited life expectancy, advanced microvascular or macrovascular

complications, extensive comorbid conditions, and those with long-standing diabetes in whom the general goal is difficult to attain. While the population expected to be enrolled in your CVOT will be at moderate to high risk of CVD, it will be unlikely to include those patients for which the 2013 ADA guidelines recommend less stringent treatment goals. For this reason, we do not agree with your proposed fasting plasma glucose goal of < 130 mg/dL or HbA1c goal < 7.5%.

Assessing CV safety of insulin degludec requires adequate exposure to insulin degludec and achievement of reasonable glycemic targets. In your CV outcomes trial, you should enroll subjects who require at minimum 20 units of insulin per day, and insulin dose should be titrated using the same glycemic target as that used in your Phase 3 program. This glycemic target would not be inappropriate for the high-cardiovascular-risk population you propose to study. It should be noted that nearly 20% of the participants in your Phase 3 degludec trials with type 2 diabetes had a history of pre-existing cardiovascular disease and many others had multiple cardiovascular disease risk factors. In addition, the majority of patients in the Phase 3 program did not achieve an HbA1c of 7% or less and the rate of severe hypoglycemia was low. Finally, the glycemic target in the degludec program was similar to the target used in the ORIGIN trial, another large insulin CVOT carried out in patients with established cardiovascular disease which suggested a neutral effect of glargine on cardiovascular risk.

In addition, if you intend to compare hypoglycemic risk between degludec and glargine , we recommend that you use an insulin dosing scheming and a target glycemic goal that will allow capture of a sufficient number of specific hypoglycemic events.

Blinding/Comparator

In the CRL, the Agency requested a double-blind trial conducted to assess the cardiovascular safety of insulin degludec. Novo Nordisk agrees that a double-blind trial represents the most scientifically rigorous approach to comparing the CV safety of two insulins. Conducting a double-blind CV outcomes trial with an active comparator requires that the delivery system for the insulin injections will appear identical in the two arms and that the dosing accuracy and quality of the products will not be impacted by the blinding procedure.

One option of blinding is by using vial and syringe. Blinding using this approach may imperil the integrity of the final analysis due to anticipated higher drop-out rate. Improving retention rates yields more robust data with which to analyze the risk of CV events (Panel on Handling Missing Data in Clinical Trials and Committee on National Statistics. The Prevention and Treatment of Missing Data in Clinical Trials. Washington DC: The National Academy Press, 2010.). Using vial and syringe may also affect the in-trial medication adherence since several studies have demonstrated that pen devices are associated with higher adherence as compared to vial and syringe (Asche et al, Diabetes Technology and Therapeutics, 2010). Furthermore, recruiting insulin requiring subjects from investigators practicing modern diabetes care to a trial where insulin is administered using vial and syringe, will substantially limit the number of investigators and subjects willing to participate. Offering a vial and syringe treatment in a trial could lead to a

decrease in patient acceptance of treatment since insulin pens now represents the preferred device for diabetic patients (Korytkowski et al, Clin Ther, 2003).

Globally, insulin pen devices are preferred by the majority of patients, and in most countries outside the US and South America, vial and syringe use is virtually unknown to patients and to physicians/diabetes educators. Based on world-wide sales figures, vial and syringe constitute only (b) (4)% of the total Lantus® sale and (b) (4)% of total Levemir® sale, with the US being the main contributor to vial and syringe sale in a steady downward trend.

Insulin pens are preferred due to their advantages with regard to patient safety (Lee et al, Clin Ther, 2006), ease of use (Korytkowski et al, Clin Ther, 2003), treatment satisfaction (Stockl et al., Curr Med Res Opin 2007), adherence (Asche et al, Diabetes Technology and Therapeutics, 2010) and clinical outcomes (Lee et al. J Eval Clin Pract 2009). However, due to inherent design differences between the Lantus® SoloSTAR® pen and the Novo Nordisk FlexTouch® used for insulin degludec, blinding of these two devices is not possible. Further, cartridges for insulin degludec and insulin glargine differ to an extent that the dimension and color of the pistons as well as their internal dimensions prohibit use of the same durable pen device for the two different cartridges. These differences would affect both the ability to blind the study as well as the dose accuracy in a clinically meaningful way.

In order to secure a double-blind trial that can be executed with appropriate retention of subjects, Novo Nordisk proposes (b) (4)

.

Question 5: In order to ensure proper blinding and to ensure a scientifically valid and robust trial, does the Agency agree to conducting a pre-approval double-blind trial vs. (b) (4) ? A draft trial outline is included to support the Agency's review.

FDA Response: No, we do not agree. The only comparator we will accept is insulin glargine. Insulin glargine was the predominant comparator in the degludec Phase 3 experience, accounting for more than 70% of all active comparators. As a result, the signal identified is in large part based on the comparison of degludec to glargine. In addition, in

one recent large cardiovascular outcomes trial, insulin glargine was reported to have a neutral effect on CV endpoints. Finally, glargine is labeled for once daily administration. Therefore, insulin glargine is the only comparator we will accept to establish the CV safety of insulin degludec. We strongly urge you to carry out the trial in a double-blind fashion and you should be prepared to discuss why you have not considered the option of insulin delivery via an undifferentiated pen device and/or use of a double-dummy injection schedule to achieve this goal.

Trial Design

In the CRL, the Agency proposes a pre-approval trial powered to exclude an excess cardiovascular risk of 80% with a reassuring point estimate. Sample size calculations show that a total of 150 MACE events will provide 95% power to definitively exclude an excess hazard of 80%; i.e. there is a 95% probability that the upper 95% confidence limit is below 1.8, assuming that the true underlying hazard ratio is 1.0. Moreover, the 150 events will provide around 85% probability for having a reassuring point estimate, defined as any point estimate below 1.2 for the hazard ratio.

Approximately 151 events will be accrued in a trial of 25 months duration comprising 4650 patients with an annualized event rate of 2.1 per 100 PYE (corresponding to the underlying risk in the recruited patient population), provided that the recruitment is uniform across the entire recruitment period, and finalized in 12 months. Further, it is assumed that the annualized rate of patients lost to follow-up is 1%. The below table shows how the total number of events will vary with varying annualized MACE rates and with varying duration of the recruitment period.

Recruitment time **(assuming uniform recruitment)**	**Annualized MACE rates in both treatment groups** **(events per 100 PYE)**				
	1.5	**1.8**	**2.1**	**2.4**	**2.7**
9 months	117	140	163	185	208
12 months	108	130	151	172	193
15 months	100	120	139	159	178

Novo Nordisk proposes [redacted] (b) (4)

Question 6a: Does the Agency agree that the described (b) (4) trial design is appropriate to (b) (4) and that this is adequate for resubmission?

FDA Response: For us to consider your resubmission as complete, you will need to exclude the 1.8 risk margin with a reassuring point estimate. However, (b) (4) (b) (4) (See Response to Question 6b regarding overall objective of your cardiovascular outcomes trial).

We have the following additional statistical comments:

- **You should follow all subjects for the duration of the trial even after they discontinue the randomized treatment. You should collect data on rescue medication(s) and any potential CV events of interest.**
- **You should propose a primary and secondary analysis population. Analysis populations should include both "on study" and "on treatment" populations. The "on study" analysis population should include all events that occur while subjects are on treatment and also those that occur while off treatment while patients are still being followed. The "on treatment" analysis population should include only events that occur while a subject is receiving the randomized treatment including a pre-defined censoring window.**

Question 6b: Does the Agency agree that the successful outcome of such a study, i.e. upper bound of (b) (4) (b) (4)

FDA Response: We do not agree. Your development program to date has identified a concerning CV safety signal relative to glargine. As noted in our Complete Response letter, a 39% excess risk for MACE was observed at time of your NDA submission and increased to 67% with your updated database. This concerning CV safety signal distinguishes you from other recently approved anti-diabetic therapies where pre-marketing CV risk assessments have not shown hazard ratios exceeding 1.0. Consequently, you must design your cardiovascular safety trial with the primary objective of excluding a risk margin of 1.3.

While we will accept for resubmission and potentially approve your product based on an interim analysis excluding a CV risk margin of 1.8, assuming a reassuring point estimate and no other countervailing safety signals identified in the resubmission, you will be required to exclude an excess hazard of 30% postmarketing. Please note that while a reassuring point estimate remains a review issue, the consistent finding of excess MACE associated with degludec in your pre-marketing application advises us to interpret any point estimate exceeding 1.0 in your resubmission with concern.

Protocol review time

Novo Nordisk will prepare a final protocol for FDA review based on the agreements reached with the Agency at the End of Review meeting.

Question 7: Does the Agency commit to a rapid review and turnaround time for the final protocol submitted by Novo Nordisk based on the agreements reached at the EoR meeting?

FDA Response: We will aim to review the proposed study protocol within 60 days of receiving your complete, near final, study protocol along with all other related supporting documents (Statistical Analysis Plan, CEC charter, etc.).

Other comments

Question 8: Does the Agency have additional advice for the design of this trial?

FDA Response: Please see our responses above.

Procedural question

Novo Nordisk believes that the following aspects of the NDAs have been satisfactorily evaluated and reviewed by FDA (device, CMC, nonclinical and clinical pharmacology, efficacy and safety other than CV) and that barring some future unexpected finding, NN considers these sections of the NDAs to be complete and not subject to further review.

Question 9: Does the Agency agree?

FDA Response: Future re-submissions should address all the deficiencies highlighted in the Complete Response letter.

Resolution of the December 2012 Warning Letter

In mid-December 2012, Novo Nordisk received a Warning Letter from FDA related to an inspection at a manufacturing facility in Bagsværd, Denmark. The company responded to the Warning Letter on December 28, 2012. The company has reached out to the FDA contact during the first quarter of 2013 to see if additional information or clarifications were necessary; the Novo Nordisk response appears to be still under review.

Question 10: Given that over 60 days have passed since Novo Nordisk responded to the FDA Warning Letter related to the Bagsværd, Denmark manufacturing facility, can FDA provide any additional information to the company on the status of the topic, including the process and timing to completely resolve the issues raised by the Agency and close out the Warning Letter?

FDA Response: The Agency cannot comment on the status of an open review to the firm's response at this time. The outcome of the review will be communicated to the manufacturing facility in Bagsværd, Denmark when it is complete.

Communication

Novo Nordisk works diligently to always interact with regulatory authorities in a professionally scientific and transparent manner. We believe that this approach is fundamental in how we work to develop our medicines and monitor them carefully following approval. We greatly value the expertise of FDA and we recognize the FDA principles contained in PDUFA V in terms of enhanced communication and transparency with drug sponsors.

Question 11a: Does FDA have any advice or guidance to Novo Nordisk in terms of the company's approach to the quality of its applications, timeliness of responses and general interactions with FDA?

FDA Response: None at this time.

Question 11b: Can FDA comment on any enhanced communication principles in place that can be applied to the degludec applications moving forward?

FDA Response: The Program for enhanced review transparency and communication applies to all new molecular entity new drug applications and original biologics license applications, including applications that are resubmitted following a Refuse-to-File action received from October 1, 2012, through September 30, 2017. The goal of the Program is to improve the efficiency and effectiveness of the first cycle review process. The degludec re-submission will be a second cycle review and will not be reviewed under the Program.

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/s/

CALLIE C CAPPEL LYNCH
04/02/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 203313
NDA 203314

MEETING REQUEST GRANTED

Novo Nordisk
Attention: Robert B. Clark
Vice President, Regulatory Affairs
P.O. Box 846
Plainsboro, NJ 08536

Dear Mr. Clark:

Please refer to your New Drug Applications (NDAs) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for

- Ryzodeg (insulin degludec/insulin aspart [rDNA origin]), injection, 100 U/mL
- Tresiba (insulin degludec [rDNA origin]), injection, 100 U/mL and 200 U/mL

We also refer to your March 1, 2013, correspondence requesting an End-of-Review meeting. Based on the statement of purpose, objectives, and proposed agenda, we consider the meeting a type A meeting.

The meeting is scheduled as follows:

Date:	**April 4, 2013**
Time:	**2:00 – 4:00 pm**
Location:	**10903 New Hampshire Avenue** **White Oak Building 22, Conference Room: 1415** **Silver Spring, Maryland 20903**

CDER participants (alphabetic) (tentative):

Eugenio Andraca-Carrera, Ph.D.	Statistical Reviewer, Division of Biometrics VII
Karim Calis, PharmD, M.P.H	Clinical Reviewer, Division of Metabolism and Endocrinology Products (DMEP)
Callie Cappel Lynch, PharmD	Regulatory Project Manager, DMEP
Jean-Marc Guettier, M.D.C.M.	Clinical Team Leader, DMEP

Mehreen Hai, Ph.D.	Acting Chief Project Manager, DMEP
Steven Hertz, B.S.	Consumer Safety Officer, Division of Manufacturing and Product Quality
Bo Li, Ph.D.	Statistical Reviewer, Division of Biometrics VII
Cynthia Liu, M.A.	Statistical Reviewer, Division of Biometrics II (OBI II)
Dongmei Liu, Ph.D.	Statistical Reviewer, OBI II
Mary H. Parks, M.D.	Director, DMEP
Curtis Rosebraugh, M.D., M.P.H.	Director, Office of Drug Evaluation II
Todd Sahlroot, Ph.D.	Deputy Director, OBI II
Mat Soukup, Ph.D.	Team Leader, Division of Biometrics VII

Please e-mail me any updates to your attendees at rachel.hartford@fda.hhs.gov. For each foreign visitor, complete and email me the enclosed Foreign Visitor Data Request Form, **at least two weeks** prior to the meeting. A foreign visitor is any non-U.S. citizen who does not have Permanent Resident Status or a valid U.S. Federal Government Agency issued Security Identification Access Badge. If we do not receive the above requested information in a timely manner, attendees may be denied access.

A few days before the meeting, you may receive an email with a barcode generated by FDA's Lobbyguard system. If you receive this email, bring it with you to expedite your group's admission to the building. Ensure that the barcode is printed at 100% resolution to avoid potential barcode reading errors.

Please have all attendees bring valid photo identification and allow 15-30 minutes to complete security clearance. Upon arrival at FDA, provide the guards with either of the following numbers to request an escort to the conference room: Rachel Hartford x60331 or Callie Cappel Lynch x68436.

Submit 18 desk copies to the following address as soon as possible.

Rachel Hartford
Food and Drug Administration
Center for Drug Evaluation and Research
White Oak Building 22, Room: 3118

10903 New Hampshire Avenue
Silver Spring, Maryland
Use zip code ***20903*** *if shipping via United States Postal Service (USPS).*
Use zip code ***20993*** *if sending via any carrier other than USPS (e.g., UPS, DHL, FedEx).*

If you have any questions, call me at (301) 796-0331.

Sincerely,

{See appended electronic signature page}

Rachel Hartford
Senior Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure:
Foreign Visitor Data Request Form

FOREIGN VISITOR DATA REQUEST FORM

VISITORS FULL NAME (First, Middle, Last)	
GENDER	
COUNTRY OF ORIGIN/CITZENSHIP	
DATE OF BIRTH **(MM/DD/YYYY)**	
PLACE OF BIRTH **(city and country)**	
PASSPORT NUMBER COUNTRY THAT ISSUED PASSPORT ISSUANCE DATE: EXPIRATION DATE:	
VISITOR ORGANIZATION/EMPLOYER	
MEETING START DATE AND TIME	April 4, 2013 - 2:30pm
MEETING ENDING DATE AND TIME	April 4, 2013 - 4:30pm
PURPOSE OF MEETING	End-of-Review
BUILDING(S) & ROOM NUMBER(S) TO BE VISITED	WO-22, RM 1415
WILL CRITICAL INFRASTRUCTURE AND/OR FDA LABORATORIES BE VISITED?	No
HOSTING OFFICIAL **(**name, title, office/bldg, room number, and phone number)	Rachel Hartford Senior Regulatory Project Manager WO 22, RM 3118 301-796-0331
ESCORT INFORMATION (If different from Hosting Official)	

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/s/

RACHEL E HARTFORD
03/08/2013

Hartford, Rachel

From: Hartford, Rachel
Sent: Monday, November 19, 2012 10:56 AM
To: 'SHSK (Shawn Hoskin)'
Subject: Information Request for NDAs 203313 & 203314

Hello Shawn,

We have an information request for Ryzodeg and Tresiba and request you respond by Monday. After you have a chance to review, please let me know an expected response timeframe.

Using the Novo Nordisk definition of MACE (i.e., unstable angina, nonfatal MI, nonfatal stroke, or cardiovascular death), provide the following information for all adjudicated MACE for the *updated* analyses with the cut-off date of May 1, 2012:

For each subject with an adjudicated MACE (identified by Subject ID and Trial and/or Extension number, and also indicating the study drug to which they were randomized and type of MACE experienced), provide in tabular format ALL available measurements of the parameters listed below chronologically from baseline until end of study. Be sure to specify the timing of the measurements in terms of study day and their proximity to the onset of first MACE. Provide a separate table for each of the following categories:

- Glucose
  - Specify the type of glucose measurement (e.g., fasting plasma glucose, capillary, etc.)
- Lipids
  - Total-C, LDL-C, HDL-C, Triglycerides
- Cardiovascular Biomarkers
  - hs-CRP and brain natriuretic peptide (NT proBNP)
- Biochemistry
  - Electrolytes, creatinine
- Vital Signs
  - Heart Rate and Blood Pressure
- 12-lead Electrocardiogram
- Body Weight and BMI
- HbA1c

Rachel E. Hartford
Regulatory Project Manager
Office of New Drugs
Center for Drug Evaluation and Research

Food and Drug Administration
rachel.hartford@fda.hhs.gov
301-796-0331 (phone)
301-796-9712 (fax)

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/s/

RACHEL E HARTFORD
11/19/2012

Hartford, Rachel

From: Hartford, Rachel
Sent: Wednesday, November 14, 2012 4:14 PM
To: 'SHSK (Shawn Hoskin)'
Subject: Information Request - degludec

Hello Shawn,

Please see our information request below and provide an expected response timeframe.

Perform the following additional hypoglycemia analyses and submit analyses datasets along with your response:

1. In trial 3583 you show that subjects on degludec had lower average interstitial glucose at night compared to glargine and that no differences in peak to trough variability between degludec and glargine was seen in the nocturnal period. Present incidence and event count hypoglycemia data between midnight and 6:00 AM using the Novo Nordisk "Confirmed", ADA documented symptomatic and ADA severe definition for this subgroup of participant (N=158) who underwent continuous glucose monitoring (CGM).

2. Present incidence and event count hypoglycemia data between midnight and 6:00 AM using the Novo Nordisk "Confirmed", ADA documented symptomatic and ADA severe definition for the subgroup of participants in trial 3579 (N=193) and 3668 (N=239) who underwent CGM measurement.

3. Provide CGMS data (i.e., for both baseline measurements and end-of-trial measurements) in figure format (Y-axis=glucose in mg/dL; X-axis= time in 30 min increments) comparing degludec once daily to glargine for the entire 24 hour period for the subgroup of patients selected for CGM in trials 3583 (N=158), 3579 (N=193) and 3668 (N=239). Describe how CGMS glucose data was pooled for these analyses.

4. Provide model-based, patient-level, adjusted estimates (95% CI) for Novo Nordisk "Confirmed" hypoglycemic event rate ratio for each degludec once daily versus glargine comparisons (include degludec fixed arm versus glargine in trial 3668 and 3770) for a nocturnal time period defined as 12:00 to 8:00 AM for trials: 3583, 3770, 3582, 3579, 3586, 3672, 3668.

5. Repeat analysis described in #4 but this time only include fasting glucose values (i.e., exclude all values after the pre-breakfast value).

6. You propose that the relative increase in the rate of hypoglycemia observed in the early morning (i.e., 6-8 AM) is due to short acting insulin use. Please clarify your position. In your response, address the following:

    a. It is unclear how one distinguishes the relative contribution of basal versus prandial insulin on hypoglycemic risk when two insulins are circulating. At meal times, during waking hours, prandial insulin is "stacked" atop basal insulin and both should contribute to hypoglycemic risk.

    b. In the type 1 diabetes trial it is also unclear why the observed ~25-30% relative reduction in the rate of nocturnal Novo "Confirmed" hypoglycemic event had no effect on the rate of hypoglycemia in the overall 24 hour time period. This would suggest that basal insulin is not an important contributor to overall hypoglycemic risk and that reducing the risk of hypoglycemia associated with the basal insulin component alone has a limited impact on overall risk.

c. In trials 3579, 3672, 3586 and 3668 no prandial insulin was used. The benefit seen for the midnight to 6 AM nocturnal time period was attenuated when 2 hours was added to the nocturnal period. If you believe this can all be attributed to sulfonylurea use in some of these trials, please provide data (subgroup analyses) to support this.

Thanks,

Rachel

Rachel E. Hartford
Regulatory Project Manager
Office of New Drugs
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rachel.hartford@fda.hhs.gov
301-796-0331 (phone)
301-796-9712 (fax)

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/s/

RACHEL E HARTFORD
11/16/2012

11/08/12

Food and Drug Administration
Center for Drug Evaluation and Research

Summary Minutes of the Endocrinologic and Metabolic Drugs Advisory Committee Meeting
November 8, 2012

Location: FDA White Oak Campus, Building 31, the Great Room (Rm. 1503), White Oak Conference Center, Silver Spring, Maryland.

Topic: The committee discussed the safety and efficacy of new drug applications (NDA) 203313, insulin degludec/insulin aspart [rDNA origin] injection and (NDA) 203314, insulin degludec [rDNA origin] injection, manufactured by Novo Nordisk Incorporated. The proposed indication (use) for these applications is for the treatment of Type 1 and Type 2 diabetes mellitus.

These summary minutes for the November 8, 2012 Meeting of the Endocrinologic and Metabolic Drugs Advisory Committee of the Food and Drug Administration were approved on January 30, 2013.

I certify that I attended the November 8, 2012 meeting of the Endocrinologic and Metabolic Drugs Advisory Committee of the Food and Drug Administration and that these minutes accurately reflect what transpired.

-Signed-

Paul T. Tran, RPh
Designated Federal Officer, EMDAC

-Signed-

Kenneth Burman, MD
Acting Chairperson, EMDAC

8 Page(s) have been Withheld in Full immediately following this page. These pages are included in the FDA Advisory Committee Documents. Please refer to http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/ucm285142.htm

Hartford, Rachel

From: Hartford, Rachel
Sent: Wednesday, November 07, 2012 10:02 AM
To: 'SHSK (Shawn Hoskin)'
Subject: RE: NDA 203314/203313 (Tresiba/Ryzodeg) Follow-up from Oct. 3 t-con

Hello Shawn,

Both DMEPA and CDRH HF find the definition proposed below acceptable.

Thanks,

Rachel

From: SHSK (Shawn Hoskin) [mailto:shsk@novonordisk.com]
Sent: Friday, November 02, 2012 2:32 PM
To: Hartford, Rachel
Subject: RE: NDA 203314/203313 (Tresiba/Ryzodeg) Follow-up from Oct. 3 t-con

Dear Rachel,

Thanks for providing the FDA feedback on our previously proposed definition of “Task Failure”. We have considered the FDA response, and we are proposing to modify the definition of “Task Failure” in section 4.6 of the RMA for the reporting of the UT103 results as provided below. We believe that this will adequately address the comments received from FDA. We would greatly appreciate if you could confirm the acceptability of the definition for “Task Failure” proposed below with CDRH and DMEPA, and our process of first conducting performance assessment (i.e. determining task success or failure which could potentially lead to harm and not receiving the prescribed therapy) followed by a clinical evaluation of all task failures to determine the medical consequence of the task failure.

Kind regards,
Shawn

SECTION 4.6 RISK MANAGEMENT ANALYSIS (RMA)

In the UT103 a task is defined as all user steps included in the injection of insulin as described within each use scenario.

The task success and failures definitions used for the reporting of the performance in UT103 are:

- A task failure is when a participant performs a task with an action or lack of action that potentially could lead to harm and not receiving the prescribed therapy
- A task success is when a participant performs a task which would not lead to harm or receive the prescribed therapy

Hence, tasks in which the participant commits use errors which potentially can lead to harm will be reported as task failures.

All task failures will be evaluated in respect to causes of failures and will be assessed in relation to potential clinical seriousness of harm in a reasonable real life setting and whether modifications are

required.

In addition: Within each use scenario/Task in the usability test UT103 all use errors in all handling steps will be observed.

A use error is defined as:

- A Use error is a case in which a user performs a step in an incorrect manner that will not lead to the intended outcome.

All observed use errors will be reported as described below:

- A Potentially serious use error (S4 and S5) is a use error which potentially can be associated with a serious adverse event
- Non-serious use errors (S3) is a use error which potentially can be associated with a non-serious adverse event

Novo Nordisk will follow-up, evaluate and assess potential root cause for all use errors as part of the risk management process and provide a discussion of the potential clinical consequence, if any, in the final report.

From: Hartford, Rachel [mailto:Rachel.Hartford@fda.hhs.gov]
Sent: Tuesday, October 16, 2012 5:25 AM
To: SHSK (Shawn Hoskin)
Subject: RE: NDA 203314/203313 (Tresiba/Ryzodeg) Follow-up from Oct. 3 t-con

Hello Shawn,

The definitions you have provided are not very clear in capturing performance success and failure. It is very confusing to combine both terms failure and error in the same definition. In addition, we are unclear on what you mean by a non-serious adverse event.

For purposes of assessing performance in an HF/usability validation test, we consider task failure as action or lack of action that can lead to patient harm i.e. not receiving the prescribed therapy. So the participants either perform the task right (task success), OR the don't perform it and/or perform it in a way that can cause patient harm (task failure). For our review of a validation test, we expect that you clearly define performance success and failure, and make sure that the performance failures that you recording represent the failures that could cause harm during actual use. As such, you would need to follow-up on all failures to determine:

- the nature of failures, the causes of failures (i.e. aspects of the design of the device, its labeling, and/or training), and the clinical impact, and
- whether modifications are required

Every test participant who experiences a "failure" (does something that would have led to harm under actual conditions of use), should be interviewed about that failure to determine the cause of the failure from the perspective of the participant.

Thanks,

Rachel

From: SHSK (Shawn Hoskin) [mailto:shsk@novonordisk.com]
Sent: Wednesday, October 03, 2012 12:45 PM
To: Hartford, Rachel
Subject: NDA 203314/203313 (Tresiba/Ryzodeg) Follow-up from Oct. 3 t-con

Hi Rachel,

Please extend my thanks to the meeting participants for their productive and helpful feedback today.

As we discussed in the teleconference with Quynh Nguyen, we are proposing to modify the definition of task failure in section 4.6 of the RMA for the reporting of the UT103 results as follows:

(b) (4)

As per the *Draft Guidance for Industry and Food and Drug Administration Staff, Applying Human Factors and Usability Engineering to Optimize Medical Device Design* (Section 10.1.4 and 10.1.5) the test monitor will collect performance and subjective data during the validation test. All observations will be evaluated from the perspective of the test participants involved and the direct performance data shall support the analysis and conclusion. The data analysis will include subjective feedback regarding critical task experience, difficulties, “close calls,” and any task failures by test participants.

Therefore, in UT103 all “Task failures” (b) (4)) and “Non-serious use errors” will be recorded, analyzed, and reported. All will be evaluated from the perspective of the test participants involved, including subjective feedback, and the direct performance data shall support the analysis and conclusion. A clinical evaluation of “Task failures” (b) (4)) and “Non-serious use errors” will also be performed.

Novo Nordisk is intending to begin the UT103 study on Oct. 15, 2012. We will incorporate all agreements reached in today’s teleconference in the testing of UT103. We would greatly appreciate FDA feedback on the definition proposals above, which will impact the reporting of the results from UT103 (but not the conduct of the study).

In addition, I’d like to confirm that the only change we will make to the IFU tested in UT103 is the one we discussed today with you (adding the BG monitoring). We will not include any additional changes (which was briefly brought up at the end of the teleconference).

Please feel free to contact me if you have any questions or need anything else for the definition assessment above, and thanks again for the productive meeting.

Kind regards,
Shawn

_____

Shawn Hoskin
Director, Regulatory Affairs
Novo Nordisk Inc.
100 College Road West
Princeton, New Jersey 08540
USA
+1 609-987-4844 (direct)
(b) (6)
shsk@novonordisk.com

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RACHEL E HARTFORD
11/07/2012

Hartford, Rachel

From: Hartford, Rachel
Sent: Wednesday, October 31, 2012 12:23 PM
To: 'SHSK (Shawn Hoskin)'
Subject: FW: Information Request for NDA 203314

Attachments: Microsoft Office Excel Worksheet

Shawn,

Please let me know that you received the request below and if you will be able to provide your response by Monday.

Thanks,

Rachel

From: Hartford, Rachel
Sent: Wednesday, October 31, 2012 12:21 PM
To: 'SHSK (Shawn Hoskin)'
Subject: Information Request for NDA 203314

Hello Shawn,

Hope you fared well during and after the storm. The government buildings were closed Monday and Tuesday; but most everyone was able to work from home.

In your pivotal trials insulin glargine could be injected at any time of the day. For each of the trials in NDA 203314 except 3580 provide details regarding the timing of the once daily glargine injection according the example provided below. Please submit datasets used to derive this information along with the response to this information request.

	Breakfast	Lunch	Dinner	Bedtime	Total
Trial 3579: Timing of Glargine Once Daily Injection	n/N(%)	n/N(%)	n/N(%)	n/N(%)	n/N (100%)

Thank you,

Rachel

Rachel E. Hartford
Regulatory Project Manager
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
rachel.hartford@fda.hhs.gov
301-796-0331 (phone)
301-796-9712 (fax)

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/s/

RACHEL E HARTFORD
10/31/2012

Hartford, Rachel

From: Hartford, Rachel
Sent: Tuesday, October 16, 2012 5:36 AM
To: 'SHSK (Shawn Hoskin)'
Subject: Information Request - Stats

Good Morning,

In Table 70 (on page 146) of your briefing document, baseline characteristics of patients with MACE in the NDA submission were presented. We were unable to locate some baseline information provided in your NDA submission and amendment dated May 11, 2012. We request that you submit a dataset containing the baseline patient information of the 9850 subjects used in the updated analyses of MACE (i.e., original data + data from 9 additional trials). In this data set of the integrated data base please include the following information:

-- patient ID

-- trial or study ID

-- patient population indicator variables (full analysis set, safety set, per protocol set)

-- HbA1C(%) at baseline

-- prior cardiovascular disease at baseline (Two level categorical variable: 1=yes, 0=No)

-- hypertension at baseline (Two level categorical variable: 1=yes, 0=No)

-- mild or moderate renal impairment at baseline (Two level categorical variable: 1=yes, 0=No)

-- Concomitant medications at baseline, including the following

(1) lipid-lowering drug (Two level categorical variable: 1=yes, 0=No)

(2) Aspirin (Two level categorical variable: 1=yes, 0=No)

(3) Beta-blocker (Two level categorical variable: 1=yes, 0=No)

(4) renin-angiotensin system inhibitors (Two level categorical variable: 1=yes, 0=No)

In addition to not being able to locate the information, we were unable to ascertain how some of the baseline characteristics were defined. Please provide clear definition for how each of the following dichotomous variables was determined:

- prior cardiovascular disease at baseline
- hypertension at baseline
- mild or moderate renal impairment at baseline

Thanks,

Rachel

Rachel E. Hartford
Regulatory Project Manager
Office of New Drugs
Center for Drug Evaluation and Research

Food and Drug Administration
rachel.hartford@fda.hhs.gov
301-796-0331 (phone)
301-796-9712 (fax)

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/s/

RACHEL E HARTFORD
10/16/2012

Hartford, Rachel

From: Hartford, Rachel
Sent: Tuesday, October 02, 2012 4:11 PM
To: 'SHSK (Shawn Hoskin)'
Subject: Information Request

Hello Shawn,

We have the following information request for Ryzodeg and Tresiba.

Please submit detailed case narrative reports for all study participants who had adjudicated MACE using the new cut-off date of May 1, 2012, who were not included in the original NDA submission.

Thank you,

Rachel

Rachel E. Hartford
Regulatory Project Manager
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
rachel.hartford@fda.hhs.gov
301-796-0331 (phone)
301-796-9712 (fax)

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/s/

RACHEL E HARTFORD
10/02/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 203313
NDA 203314

MEETING PRELIMINARY COMMENTS

Novo Nordisk Inc.
Attention: Robert Clark
Vice President, Regulatory Affairs
P.O. Box 846
Plainsboro, NJ 08536

Dear Mr. Clark:

Please refer to your New Drug Applications (NDAs) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for:

- Ryzodeg (insulin degludec/insulin aspart [rDNA origin]), injection, 100 U/mL and
- Tresiba (insulin degludec [rDNA origin]), injection, 100 U/mL and 200 U/mL.

We also refer to your correspondence dated and received August 10, 2012, requesting a meeting to discuss Human Factors testing for the PDS 290 pen injector.

Our preliminary responses to your meeting questions are enclosed.

If you have any questions, call me at (301) 796-0331.

Sincerely,

{See appended electronic signature page}

Rachel Hartford
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

ENCLOSURE:
Preliminary Meeting Comments

PRELIMINARY MEETING COMMENTS

Meeting Type:	**C**
Meeting Category:	**Guidance**
Meeting Date and Time:	**October 3, 2012 (9:00 – 10:00 am)**
Meeting Location:	**Teleconference**
Application Number:	**NDA 203313 & NDA 203314**
Product Name:	**Ryzodeg & Tresiba**
Indication:	**Treatment of Diabetes Mellitus**
Sponsor/Applicant Name:	**Novo Nordisk**

Introduction:
This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the teleconference. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. However, if these answers and comments are clear to you and you determine that further discussion is not required, you have the option of cancelling the meeting (contact me). If you choose to cancel the meeting, this document will represent the official record of the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda and/or changing the format of the meeting (e.g., from face to face to teleconference). It is important to remember that some meetings, particularly milestone meetings, can be valuable even if the premeeting communications are considered sufficient to answer the questions. Note that if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, we may not be prepared to discuss or reach agreement on such changes at the meeting although we will try to do so if possible. If any modifications to the development plan or additional questions for which you would like CDER feedback arise before the meeting, contact me to discuss the possibility of including these items for discussion at the meeting.

1.0 BACKGROUND

A Human Factors Discipline Review letter was issued on July 9, 2012, for Ryzodeg and Tresiba containing the following italicized text.

> *Our review of the Human Factors portion of your submissions is complete, and we have identified the following deficiencies.*

While the UT86 report demonstrated that through improving the Instructions For Use (IFU) and training materials the use errors can be reduced, the results of the study show use errors that can result in incorrect dosing that require further mitigation. We are most concerned with the following findings:

- *1 participant did not set dose correctly and committed use error*

  You reported that this participant was an elderly, pen-experienced, and untrained participant. The participant was on basal-bolus insulin therapy with Lantus® vial and syringe as basal insulin and NovoLog® FlexPen® as bolus insulin. It should be noted that the Novolog® FlexPen® delivers 1 unit increments of insulin when dialed. When using his vial and syringe, he has to convert number of units to the correct volume. The test results reported that this participant dialed and administered an incorrect dose during two different tasks during normal injection and during end-of content/split dose between two pens. You also reported that one participant experienced a close call with this step. Because this type of use error can result in incorrect dosing during actual use and while you have taken helpful measures to reduce the potential of use errors, it appears that you do not directly address the potential risk of users converting the number of units required based on the prescribed dose. Implement further mitigation via modifying the IFU to inform the users that regardless of the concentration of insulin used, the PDS290 pen-injectors are designed to deliver the specified number of insulin units as prescribed, and that the users do not need to perform any dose conversion.

- *1 participant misinterpreted the dose delivered after detecting blocked needle*

  You reported that this participant was an elderly, pen-experienced and untrained participant. The participant set the dose correctly (instructed dose - 36 units of 200 U/ml Tresiba) and attempted to administer the injection. However, due to the blocked needle, the participant incorrectly concluded that he had delivered 10 units, and that he needed to deliver 26 additional units to administer the full 36 unit dose. The participant replaced the needle on the pen-injector and administered 26 units, rather than 36 units. Because this type of use error can result in incorrect dosing in actual use and while you have taken helpful measures to reduce the potential of use errors, it appears that you do not directly address the potential of risk of users misinterpreting the amount of insulin delivered in situations where the needle is blocked. You also reported that two participants experienced close call with this step.

  As previously communicated in our General Advice letter dated May 3, 2012, this finding indicated that the user might not be aware of the potential for dose counter malfunction associated with blocked needles i.e. the device dose counter may wrongly report that up to a maximum of 7 units have been delivered. This could result in clinically significant dosing errors after the user discovers that the needle on the device is blocked. We conclude that the dose counter, which serves as a visual feedback to the users, is not optimally designed as it can mislead users

and cause confusion with regards to dosing after the device problem (i.e. blocked needle) is discovered. If there are no design alternatives to reduce this risk further, implement further mitigation via modifying the IFU to inform the users that in case of a blocked needle, the dose counter will display a value that is different from the original dose that the user has set. In addition, the IFU should provide specific instructions for use to resolve a blocked needle situation.

- *2 participants did not hold the needle at the injection site for the specified time*

  You reported that one participant who was an elderly, pen-experienced and trained participant, committed one use error during her fifth task (blocked needle). The other participant was an adult, pen-naïve and untrained participant who committed one use error during the first task (normal injection). The participants both set the dose correctly and administered the injection, but held the needle in the cushion for less than one second after the dose counter had returned to"0". You also reported that one participant experienced close call with this step.

  As previously communicated in our General Advice letter dated May 3, 2012, we are concerned that you instruct patients to hold the needle for 6 seconds. However, in the study, you defined that it is only a use error if the participant did not keep the needle in the skin for at least 1 second after the dose counter returns to "0." If proper injection is defined as holding the needle for 6 seconds, then the study should demonstrate that users can hold the device for 6 seconds.

Based on the errors that one of your participants experienced in setting the dose with this device, we conclude that your product is prone to dosing errors and additional risks are associated with the U200 strength of Tresiba pen injector. Our evaluation of the submitted data also noted the number of users completing tasks with Tresiba FlexTouch 200 units/mL were inadequate (10 total users, 5 trained and 5 untrained).

Additionally, please note that the purpose of a design validation (human factors) study is to demonstrate that the device can be used by representative users under simulated use conditions without producing patterns of failures that could result in negative clinical impact to patients or injury to device users.

Thus, further evaluation is necessary of the Tresiba FlexTouch 200 units/mL pen injector and should include the changes to the IFU described in this letter as well as:

- *The intended adult and elderly patients with severe insulin resistance who require large daily doses of insulins and who are likely to make up the majority of your potential users. Since the patient users of Tresiba FlexTouch 200 unit/ mL will most likely be prior insulin users (pen injector or syringe and vial), you do not need to include insulin naïve patients in your study. If naïve patients are included, please ensure they are a separate user group. Lastly, patients with prior*

Humulin U-500 experience must be noted and do not need to be excluded from the study.

- *Both trained (15 participants) and untrained (15 participants) patients who have prior insulin experience should be evaluated. The untrained group should have the option to read the instructions for use rather than required to read it to better simulate "real use" untrained scenario. All participants should be informed during the training and/or familiarization period that the strength of the insulin is "200 units/mL."*

- *If visually impaired participants are not included in this study, the tasks for patient user groups should include visual impairment simulation.*

- *Finally, include both trained (15 participants) and untrained (15 participants) inpatient nurses as healthcare providers that use the Tresiba FlexTouch 200 units/mL as this user group has not been assessed in any of the prior studies.*

Novo Nordisk intends to modify the PDS290 IFU and validate the changes in a focused HF/usability validation test PDS290-UT103-2012 (UT103). The purpose of this meeting is to reach agreement on the IFU changes and design of UT103.

2. DISCUSSION

Usability Test Protocol Design

Question 1: Does the Agency agree that the proposed focused usability test design evaluating only Tresiba® FlexTouch® 200 U/mL pen injector is sufficient to validate the changes made to the IFU and the results would also support Tresiba® FlexTouch® 100 U/mL and Ryzodeg® FlexTouch® 100 U/mL?

FDA Response: Yes, we agree that the proposed usability protocol focused on the changes to the IFU for use with the Tresiba FlexTouch 200 U/mL pen injector is sufficient to validate change to the IFU and support the U100 Tresiba and Ryzodeg products. However, once the testing has demonstrated that those changes are effective, you will also need to consider whether the changes should be incorporated to the corresponding IFU for use with the Tresiba FlexTouch 100 U/mL and Ryzodeg FlexTouch 100 U/mL pen injectors. If for example, the change to the IFU is based on use of the PDS290, incorporate changes. If however, the change to the IFU is based on product strength, do not incorporate changes.

Question 2: Does the Agency agree with the number and composition of participants to be tested in UT103?

FDA Response: No we do not agree. The Division of Medication Error and Prevention Analysis (DMEPA) finds that the number and composition of adult and elderly subjects

and subjects with disease related impairments (vision, and manual dexterity etc.) are adequate. However, patients using this product will include both insulin sensitive and insulin resistant individuals. Therefore, please ensure that these two types of participants are adequately represented in your study. We recommend that 30 trained and 30 untrained participants with diabetes mellitus and insulin experience be included. In each of the trained and untrained groups 50% of patients should be users with relatively high insulin resistance (i.e., those requiring 50 units of insulin per dose or more) and 50% should be users requiring less than <50 units of insulin per dose but no defined minimum units per dose. In other words, for the group of 30 untrained individuals, 15 patients should be insulin resistant and 15 patients should be insulin sensitive.

Although the Center for Devices and Radiologic Health (CDRH) agrees with your proposed number and composition of participants to be tested in the UT103 as it is a supplemental usability testing to previous usability tests, and to demonstrate that the proposed IFU are effectively in minimizing use errors, the requested increase in number of patient user participants by DMEPA would demonstrate the IFU is valid. CDRH recommends that you ensure equal representation of the different patient user groups (insulin sensitive diabetic patients, and insulin resistant diabetic patients), and patients with disease related impairments (vision, and manual dexterity). Also ensure that you divide all study participants into two equal groups: trained versus untrained.

Question 3: Does the Agency agree that the test population included in UT103 (adult/elderly with pen-injector and/or vial and syringe experience and inpatient nurses with pen-injector experience) is sufficient?

FDA Response: See Question 2.

Question 4: Does the Agency agree with the proportion of adult/elderly participants with high insulin resistance and visual/simulated visual impairment to be tested in UT103?

FDA Response: See Question 2.

Question 5: Does the Agency agree that both trained and untrained participants should be informed during the training and/or familiarization period that the concentration of the insulin is 200 U/mL and (b) (4)?

FDA Response: No, we do not agree. We agree that the participants can be informed of the product's concentration (200 units/mL). (b) (4)

".

In addition, note that we consider the (b) (4)" as training (b) (4)

The use of the term [redacted] (b) (4) may imply to the user that they should review the materials and thus is considered training by guiding the users to the resource materials. Use alternate wording to introduce the testing scenario in the protocol (8.1.6) and remove the word [redacted] (b) (4) from the administrator's script. For example, consider the following script:
"….You have all of the materials you need to inject insulin, and it is time to give yourself an injection. The point is to approach the scenario as realistically as possible. Take as much time as you might normally take with the materials, handling them in any way you wish. Assume that you are working alone, so please do not ask me for assistance. However, there is a telephone available *[point to telephone in supply area]* in case you need to place a call for assistance. I will be sitting over at the other end of the table. Tell me when you are ready to begin and I will give you the first task instruction card."

Question 6: Does the Agency agree with the use scenarios and the respective steps to be tested in UT103?

FDA Response: We find your proposed scenarios for normal injections and block needle injections to be acceptable. However, CDRH indicated in the Discipline Review letter that we were concerned with the end-of-content/split-dosing injections. Clarify why you do not intend to include this scenario in the supplemental study.

In addition, with respect to the training check (section 7.4), you indicated that additional training will be provided to test participants as necessary, and if a participant is deemed ineligible, they will not be asked to participate in the actual hands-on test. Clarify why you believe this methodology is representative of actual use, and how you plan to implement the additional training in actual use. Also, clarify who will determine that a user is ineligible using the proposed product in actual use. If participant is deemed ineligible following the training session, include which participants were so deemed and the reasons for excluding the participant recorded on the "Training Record - People with Diabetes" with the submission of the data for UT103.

Furthermore, with respect to baseline injections (section 8.1.2), you indicated that participants will be asked to perform two baseline injections prior to simulated injections. Additionally, we are concerned that this baseline test may impact the results of the simulated use test. Conduct this testing after the simulated use test.

Question 7: Does the Agency agree with the proposal to test all user groups in Scenario 1 (normal injection) steps but only the adult/elderly user group in Scenario 2 (blocked needle) steps as inpatient nurses would not reuse needles in a "real use" scenario?

FDA Response: Yes, we agree with your proposal.

Question 8: Does the Agency agree that the approach to validate the mitigations (IFU content and ancillary instructional video) associated with the Tresiba® FlexTouch® pen 200 U/mL use error "Did not set dose correctly" is adequate?

FDA Response: Your approach to validate the IFU changes and additional ancillary instructional video associated with setting the dose scenario for the Tresiba FlexTouch pen 200 U/mL appears adequate.

Question 9: Does the Agency agree that the approach to validate the mitigations (IFU content and ancillary instructional video) associated with the blocked needle scenario is adequate?

FDA Response: Your approach to validate the IFU changes and additional ancillary instructional video associated with the blocked needle scenario for the Tresiba FlexTouch pen 200 U/mL appears adequate.

Question 10: Does the Agency agree that the approach to validate the mitigations (IFU content and ancillary instructional video) via user performance testing is adequate, noting that trained and untrained participants might or might not read the IFU in the course of preparing to perform or performing the tasks?

FDA Response: Since one of the focus for the this supplemental test is on the changes to the IFU and since assessment of user understanding of critical messages in the labeling cannot be done through observation of participant behavior, we ask that you validate the participants in the trained arm of your study prior to the simulated use portion of your study given that they will be exposed to the revised IFU during training. Ensure that you ask explicit and detailed questions about the content of or inferential questions about information that was implied by the text. It is important that these questions not be leading (i.e. don't make the correct responses obvious) and for this reason, we discourage forced-choice responses. The participants should also provide subjective feedback regarding any wording in the labeling they found confusing, misleading, or incomplete. Additionally, the clarity of the IFU should be evaluated with respect to findings on task failures/use errors observed in the study.

Data collection – Use error "Did not hold the needle at the injection site for the specified time"

Question 11: Does the Agency agree that the use error criteria described above is acceptable?

FDA Response: No, we do not agree. Note that for purposes of performance assessment, we consider task failure as action/lack of action that could lead to patient harm. Modify your definition in section 4.6. Ensure that the task failures that will be recorded represent failures that could cause harm during actual use. Upon review of the IFU, we note that the IFU states "a drop is normal after an injection." If "real use" of this pen injector should result in no more than a drop of insulin remaining the needle, then, we recommend revising the criteria to be consistent with the IFU. A task failure should be recorded if the needle is withdrawn after counting to a number less than 6 after the counter returns to "0" and more than a drop (e.g. two or more drops) is observed coming out of the needle upon removal.

Question 12: Does the Agency agree that the usability protocol PDS290-UT103-2012 sufficiently addresses the concerns listed in the Agency's Discipline Review letter?

FDA Response: With the noted changes, we agree that the protocol addresses our concerns. We also request that a copy of the ancillary instructional video be included when the data from UT103 is submitted as a reference for our reviewers.

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/s/

RACHEL E HARTFORD
10/01/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 203313
NDA 203314

MEETING REQUEST GRANTED

Novo Nordisk Inc.
Attention: Robert Clark
Vice President, Regulatory Affairs
P.O. Box 846
Plainsboro, NJ 08536

Dear Mr. Clark:

Please refer to your New Drug Applications (NDAs) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for:

- Ryzodeg (insulin degludec/insulin aspart [rDNA origin]), injection, 100 U/mL and
- Tresiba (insulin degludec [rDNA origin]), injection, 100 U/mL and 200 U/mL.

We also refer to your August 10, 2012, correspondence requesting a Guidance Meeting to discuss Human Factors testing for the PDS 290 pen injector. Based on the statement of purpose, objectives, and proposed agenda, we consider the meeting a type C meeting.

The teleconference is scheduled as follows:

Date: October 3, 2012
Time: 9:00 – 10:00 am
Phone Arrangements: Please provide a CALL-IN NUMBER and PASSCODE to the FDA

CDER Participants: (alphabetic) (tentative)

Jean-Marc Guitter, MD	Clinical Team Leader, Division of Metabolism and Endocrinology Products (DMEP)
Rachel Hartford	Regulatory Project Manager, DMEP
Yelena Maslov	Team Leader, Division of Medication Error and Prevention Analysis (DMEPA), Office of Surveillance and Epidemiology (OSE)

Quynh Nhu Nguyen	Combination Products Human Factors Specialist, Center for Devices and Radiological Health, Office of Device Evaluation
Mary H. Parks, M.D.	Director, DMEP

If you have any questions, call me at (301) 796-0331.

Sincerely,

{See appended electronic signature page}

Rachel Hartford
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

RACHEL E HARTFORD
09/11/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 203313
NDA 203314

DISCIPLINE REVIEW LETTER

Novo Nordisk Inc.
Attention: Robert Clark
Vice President, Regulatory Affairs
P.O. Box 846
Plainsboro, NJ 08536

Dear Mr. Clark:

Please refer to your New Drug Applications (NDAs) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for:

- Ryzodeg (insulin degludec/insulin aspart [rDNA origin]), injection, 100 U/mL and
- Tresiba (insulin degludec [rDNA origin]), injection, 100 U/mL and 200 U/mL.

We also refer to your amendment dated April 24, 2012, containing responses to our December 23, 2011, Information Request letter and the results of the focused summative usability test PDS290-UT86-2012 (UT86).

Our review of the Human Factors portion of your submissions is complete, and we have identified the following deficiencies.

While the UT86 report demonstrated that through improving the Instructions For Use (IFU) and training materials the use errors can be reduced, the results of the study show use errors that can result in incorrect dosing that require further mitigation. We are most concerned with the following findings:

- 1 participant did not set dose correctly and committed use error

  You reported that this participant was an elderly, pen-experienced, and untrained participant. The participant was on basal-bolus insulin therapy with Lantus vial and syringe as basal insulin and NovoLog FlexPen as bolus insulin. It should be noted that the Novolog FlexPen delivers 1 unit increments of insulin when dialed. When using his vial and syringe, he has to convert number of units to the correct volume. The test results reported that this participant dialed and administered an incorrect dose during two different tasks during normal injection and during end-of content/split dose between two pens. You also reported that one participant experienced a close call with this step.

Because this type of use error can result in incorrect dosing during actual use and while you have taken helpful measures to reduce the potential of use errors, it appears that you do not directly address the potential risk of users converting the number of units required based on the prescribed dose. Implement further mitigation via modifying the IFU to inform the users that regardless of the concentration of insulin used, the PDS290 pen-injectors are designed to deliver the specified number of insulin units as prescribed, and that the users do not need to perform any dose conversion.

- 1 participant misinterpreted the dose delivered after detecting blocked needle

  You reported that this participant was an elderly, pen-experienced and untrained participant. The participant set the dose correctly (instructed dose - 36 units of 200 U/ml Tresiba) and attempted to administer the injection. However, due to the blocked needle, the participant incorrectly concluded that he had delivered 10 units, and that he needed to deliver 26 additional units to administer the full 36 unit dose. The participant replaced the needle on the pen-injector and administered 26 units, rather than 36 units. Because this type of use error can result in incorrect dosing in actual use and while you have taken helpful measures to reduce the potential of use errors, it appears that you do not directly address the potential of risk of users misinterpreting the amount of insulin delivered in situations where the needle is blocked. You also reported that two participants experienced close call with this step.

  As previously communicated in our General Advice letter dated May 3, 2012, this finding indicated that the user might not be aware of the potential for dose counter malfunction associated with blocked needles i.e. the device dose counter may wrongly report that up to a maximum of 7 units have been delivered. This could result in clinically significant dosing errors after the user discovers that the needle on the device is blocked. We conclude that the dose counter, which serves as a visual feedback to the users, is not optimally designed as it can mislead users and cause confusion with regards to dosing after the device problem (i.e. blocked needle) is discovered. If there are no design alternatives to reduce this risk further, implement further mitigation via modifying the IFU to inform the users that in case of a blocked needle, the dose counter will display a value that is different from the original dose that the user has set. In addition, the IFU should provide specific instructions for use to resolve a blocked needle situation.

- 2 participants did not hold the needle at the injection site for the specified time

  You reported that one participant who was an elderly, pen-experienced and trained participant, committed one use error during her fifth task (blocked needle). The other participant was an adult, pen-naïve and untrained participant who committed one use error during the first task (normal injection). The participants both set the dose correctly and administered the injection, but held the needle in the cushion for less than one second after the dose counter had returned to“0”. You also reported that one participant experienced close call with this step.

As previously communicated in our General Advice letter dated May 3, 2012, we are concerned that you instruct patients to hold the needle for 6 seconds. However, in the study, you defined that it is only a use error if the participant did not keep the needle in the skin for at least 1 second after the dose counter returns to "0." If proper injection is defined as holding the needle for 6 seconds, then the study should demonstrate that users can hold the device for 6 seconds.

Based on the errors that one of your participants experienced in setting the dose with this device, we conclude that your product is prone to dosing errors and additional risks are associated with the U200 strength of Tresiba pen injector. Our evaluation of the submitted data also noted the number of users completing tasks with Tresiba FlexTouch 200 units/mL were inadequate (10 total users, 5 trained and 5 untrained).

Additionally, please note that the purpose of a design validation (human factors) study is to demonstrate that the device can be used by representative users under simulated use conditions without producing patterns of failures that could result in negative clinical impact to patients or injury to device users.

Thus, further evaluation is necessary of the Tresiba FlexTouch 200 units/mL pen injector and should include the changes to the IFU described in this letter as well as:

- The intended adult and elderly patients with severe insulin resistance who require large daily doses of insulins and who are likely to make up the majority of your potential users. Since the patient users of Tresiba FlexTouch 200 unit/ mL will most likely be prior insulin users (pen injector or syringe and vial), you do not need to include insulin naïve patients in your study. If naïve patients are included, please ensure they are a separate user group. Lastly, patients with prior Humulin U-500 experience must be noted and do not need to be excluded from the study.

- Both trained (15 participants) and untrained (15 participants) patients who have prior insulin experience should be evaluated. The untrained group should have the option to read the instructions for use rather than required to read it to better simulate “real use” untrained scenario. All participants should be informed during the training and/or familiarization period that the strength of the insulin is “200 units/mL.”

- If visually impaired participants are not included in this study, the tasks for patient user groups should include visual impairment simulation.

- Finally, include both trained (15 participants) and untrained (15 participants) inpatient nurses as healthcare providers that use the Tresiba FlexTouch 200 units/mL as this user group has not been assessed in any of the prior studies.

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. 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 not be able to consider your response before we take an action on your application during this review cycle.

If you have any questions, call Rachel Hartford, Regulatory Project Manager, at (301) 796-0331.

Sincerely,

{See appended electronic signature page}

Mary H. Parks, M.D.
Director
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

MARY H PARKS
07/09/2012

Hartford, Rachel

From: Hartford, Rachel
Sent: Wednesday, August 01, 2012 3:10 PM
To: 'SHSK (Shawn Hoskin)'
Subject: Information Request for Ryzodeg and Tresiba

Hello Shawn,

We have the following information request for Ryzodeg and Tresiba.

Submit an integrated dataset containing patient adverse event information for the 9850 subjects from all trials through to 1 May 2012 (i.e., consistent with the cut-off date used in the updated MACE analyses). The data set should contain multiple records for subjects who experienced more than one adverse event.

In this dataset please include the following information:

-- unique subject ID

-- trial or study ID (for subjects that enroll in the extension trial, include only the main trial ID – a flag will designate those events that occur during the extension trial as described below)

-- randomization arm

-- as treated arm

-- adverse events sequence number (a sequential number within subject to denote multiple adverse events)

-- fields for full MedDRA hierarchy (from LLT to SOC)

-- adverse event start date

-- adverse event end date

-- flag variable for main trial event (Two level categorical variable: 1 = main trial event, 0 = extension trial event)

-- flag variable to designate if event was adjudicated as MACE (Two level categorical variable: 1 = MACE, 0 = not MACE)

-- flag variable to designate if event was adjudicated as MACE+ (Two level categorical variable: 1 = MACE+, 0 = not MACE+)

-- drug initiation date

-- drug discontinuation date

-- observation end date (this corresponds to the date at which a subject is no longer followed. If a subject discontinues treatment and is no longer followed the observation end date should be the same as the date of drug discontinuation.)

-- indicator variable for early drug discontinuation (Two level categorical variable: 1 = early discontinuation and 0 = trial completion. If a subject completed main trial but chose not to participate in the extension trial then this should be recorded as 1 and should be reflected in the next data field "reason for early drug discontinuation")

-- reason for early drug discontinuation (categorical variable that includes a term to designate subjects that choose not to enroll in the extension trial in addition to original terminology of reason for discontinuation)

-- indicator variable for completion of main trial (Three level categorical variable: 1 = completed, 0 = not completed, 99 = for trials that did not include an extension)

-- indicator variable for enrollment in extension trials (Three level categorical variable: 1 = enrolled, 0 = not enrolled, 99 = for trials that did not include an extension)

Thanks,

Rachel

Rachel E. Hartford
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
rachel.hartford@fda.hhs.gov
301-796-0331 (phone)
301-796-9712 (fax)

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/s/

RACHEL E HARTFORD
08/01/2012

Hartford, Rachel

From: Hartford, Rachel
Sent: Monday, July 16, 2012 12:48 PM
To: 'SHSK (Shawn Hoskin)'
Subject: Ryzodeg and Tresiba carton and container labels

Hello Shawn,

Please see the comments below for the Ryzodeg and Tresiba carton and container labels.

Thanks,

Rachel

TRESIBA (NDA 203314)

A. Container Label for (b) (4)

(b) (4)

RYZODEG (NDA 203313)

(b) (4)

(b) (4)

Rachel E. Hartford
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
rachel.hartford@fda.hhs.gov
301-796-0331 (phone)
301-796-9712 (fax)

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/s/

RACHEL E HARTFORD
07/16/2012

Hartford, Rachel

From: Hartford, Rachel
Sent: Tuesday, July 03, 2012 10:41 AM
To: 'SHSK (Shawn Hoskin)'
Subject: Ryzodeg and Tresiba Information Request

Hello Shawn,

We were unable to locate data on the disposition of subjects for the new information provided in your amendment dated May 11, 2012. Submit a dataset containing patient disposition information of the 9850 subjects used in the updated analyses of MACE (i.e., original data + data from 9 additional trials). In this updated data set of the integrated data base include the following information:

-- patient ID

-- trial or study ID

-- patient population indicator variables (full analysis set, safety set, per protocol set)

-- drug initiation date

-- drug discontinuation date

-- observation end date (this corresponds to the date at which a subject is no longer followed. If a subject discontinues treatment and is no longer followed the observation end date should be the same as the date of drug discontinuation.)

-- indicator variable for early drug discontinuation (Two level categorical variable: 1 = early discontinuation and 0 = trial completion. If a subject completed main trial but chose not to participate in the extension trial then this should be recorded as 1 and should be reflected in the next data field "reason for early drug discontinuation")

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-- indicator variable for completion of main trial (Three level categorical variable: 1 = completed, 0 = not completed, 99 = for trials that did not include an extension)

-- indicator variable for enrollment in extension trials (Three level categorical variable: 1 = enrolled, 0 = not enrolled, 99 = for trials that did not include an extension)

The following set of scenarios and their representation in a tabular line listing are provided to add clarity for the requested data structure. If you have any questions as they relate to the data structure please contact us.

Scenario 1-3 (trial without extension, 6 months)

-- Subject 1: early drug discontinuation, no further follow-up

-- Subject 2: early drug discontinuation, followed-up for another 1 month

-- Subject 3: completed trial

Scenario 4 - 8 (trial with extension, 6 months + 6 months)

-- Subject 4: early drug discontinuation in main trial, no follow-up after treatment discontinuation

-- Subject 5: early drug discontinuation in main trial, followed-up for another 1 month

-- Subject 6: completed main trial, did not consent to be enrolled in extension trial

-- Subject 7: completed main trial, enrolled in extension trial and discontinued early in extension trial

-- Subject 8: completed main trial, enrolled in extension trial and completed the extension trial

Subject	Drug Initiation Date	Drug Discontinuation Date	Observation End Date	Early Discontinuation	Reason for Early Discontinuation	Main Trial completion	Enrolled in Extension trial
1	1/1/2011	3/1/2011	3/1/2011	1	Non-compliance with protocol	99	99
2	1/1/2011	3/1/2011	4/1/2011	1	Other	99	99
3	1/1/2011	7/1/2011	7/1/2011	0		99	99
4	1/1/2011	3/1/2011	3/1/2011	1	Non-compliance with protocol	0	0
5	1/1/2011	3/1/2011	4/1/2011	1	Other	0	0
6	1/1/2011	7/1/2011	7/1/2011	1	No Consent extension	1	0
7	1/1/2011	10/1/2011	10/15/2011	1	Adverse Event	1	1
8	1/1/2011	1/4/2012	1/4/2012	0		1	1

Thanks,

Rachel

Rachel E. Hartford
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
rachel.hartford@fda.hhs.gov
301-796-0331 (phone)
301-796-9712 (fax)

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/s/

RACHEL E HARTFORD
07/03/2012

6/15/2012

MANDATORY: Send a copy of the consult request form to the Office of Combination Products (OCP) as follows:

--Originating Center: When the consult request is initiated.

--Consulting Center: When the consult is completed.

Email: combination@fda.gov or FAX: 301-847-8619

For additional information: Contact OCP by email or by telephone (301-796-8930) or refer to OCP's intranet page http://inside.fda.gov:9003/ProgramsInitiatives/CombinationProducts/ReviewerTools/default.htm.

For Consulting Center Use Only:

Date Received: 5/1/2012
Assigned to: Quynh Nhu Nguyen
Date Assigned:
Assigned by:
Completed date: 6/18/2012
Reviewer Initials: QNN
Supervisory Concurrence: Molly Story for Mary Weick-Brady

Intercenter Request for Consultative or Collaborative Review Form

To (Consulting Center):
Center: CDRH
Division: ODE/DAGID
Mail Code: HF
Consulting Reviewer Name: QuynhNhu Nguyen
Building/Room #: WO66, Rm2531
Phone #: 301-796-6273
Fax #:
Email Address: quynht.nguyen@fda.hhs.gov
RPM/CSO Name and Mail Code:
QuynhNhu Nguyen

From (Originating Center):
Center: CDER
Division: DMEP
Mail Code: HF-510
Requesting Reviewer Name:
Building/Room #:
Phone#:
Fax #:
Email Address:
RPM/CSO Name and Mail Code: Rachel Hartford x60331
Requesting Reviewer's Concurring Supervisor's Name:

Receiving Division: If you have received this request in error, you must contact the request originator by phone immediately to alert the request originator to the error.

Date of Request: 1May12

Requested Completion Date: 15Jun12

Submission/Application Number: NDA 203313
(Not Barcode Number)

Submission Type: NDA
(510(k), PMA, NDA, BLA, IND, IDE, etc.)

Type of Product: ☑ Drug-device combination ☐ Drug-biologic combination ☐ Device-biologic combination ☐ Drug-device-biologic combination ☐ Not a combination product

Submission Receipt Date: 24Apr12

Official Submission Due Date: ______

Name of Product: Ryzodeg (70% insulin degludec / (b) (4) [redacted] insulin aspart)

Name of Firm: Novo Nordisk

Intended Use: (375 characters max) treatment of diabetes

Brief Description of Documents Being Provided (e.g., clinical data -- include submission dates if appropriate):

(525 characters max) Focused Summative Usability Test PDS290-UT86-2012

Documents to be returned to Requesting Reviewer? ☐ Yes ☑ No

Complete description of the request. Include history and specific issues, (e.g., risks, concerns), if any, and specific question(s) to be answered by the consulted reviewer. The consulted reviewer should contact the request originator if questions/concerns are not clear. Attach extra sheet(s) if necessary:

Type of Request: ☑ Consultative Review ☐ Collaborative Review

(940 characters max -- use additional sheet if necessary) Please review the Focused Summative Usability Test PDS290-UT86-2012.
EDR Location: \\CDSESUB1\EVSPROD\NDA203313\20331 3.enx
Supporting Document Number: 17
eCTD Sequence Number: 0016
Letter Date: 04/24/2012
Stamp Date: 4/24/2012

Reference ID: 3124445

Reference ID: 3148733

GEN 1200360, CON 128316

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/s/

RACHEL E HARTFORD
05/01/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 203313

REVIEW EXTENSION – MAJOR AMENDMENT

Novo Nordisk Inc.
Attention: Robert Clark
Vice President, Regulatory Affairs
P.O. Box 846
Plainsboro, NJ 08536

Dear Mr. Clark:

Please refer to your September 29, 2011, New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Ryzodeg (insulin degludec/insulin aspart [rDNA origin]), injection, 100 U/mL.

We received your May 16, 2012, solicited major amendment to this application. The receipt date is within three months of the user fee goal date. 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 **October 29, 2012**.

Dr. Mary Parks, Director of the Division of Metabolism and Endocrinology Products, notified you through the June 7, 2012, telephone conversation with Robert Clark, Vice President.

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 2008 THROUGH 2012." If major deficiencies are not identified during our review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by September 10, 2012.

If you have any questions, call me at (301) 796-0331.

Sincerely,

{See appended electronic signature page}

Rachel Hartford
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

RACHEL E HARTFORD
06/07/2012

Hartford, Rachel

From: Hartford, Rachel
Sent: Thursday, May 17, 2012 11:58 AM
To: 'SHSK (Shawn Hoskin)'
Subject: Information Request for Ryzodeg and Tresiba

Hello Shawn,

In your May 11, 2012 response to our April 27, 2012 information request, you indicated that your updated analyses include all available data as of a new cut-off date of May 1, 2012. You also indicated that these data are derived from nine clinical trials that were completed between January 31, 2011 and May 1, 2012.

1. Provide the completion dates for each of the nine trials. Confirm that all of the additional MACE events which occurred in these nine trials have been adjudicated, and that no events from these trials are still pending adjudication.

2. Describe the specific procedures that were used to identify and capture cardiovascular adverse events and to determine whether an event was or was not to be adjudicated.

In your May 11, 2012 response (page 5 of 24, paragraph 3), you state the following:

"This open-label design may be associated with reporting bias and in the present case this is illustrated by either lack of reporting or a considerably longer reporting time of potential MACE events (sent for adjudication) in the comparator arm than in the IDeg+IDegAsp arm – particularly during trial extensions."

3. Provide specific data to support your assertion about the lack of reporting or longer reporting time, and address why such reporting bias, if it exists, would favor the comparator. Also address why these reporting problems would be more pronounced in the trial extensions, given that you presumably continued the same intensive cardiovascular safety monitoring during the extension periods.

Thanks,

Rachel

Rachel E. Hartford
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
rachel.hartford@fda.hhs.gov
301-796-0331 (phone)
301-796-9712 (fax)

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/s/

RACHEL E HARTFORD
05/21/2012

Hartford, Rachel

From: Hartford, Rachel
Sent: Monday, May 21, 2012 12:30 PM
To: 'SHSK (Shawn Hoskin)'
Subject: NDA 203314 Information Request

Hello Shawn,

Perform additional hypoglycemia analyses on the original datasets (i.e., those used to perform analyses at time of NDA filing).

For each of the eight individual studies evaluating degludec once daily (including the flexible schedule arms), provide an updated set of analyses for 'confirmed nocturnal hypoglycemia' by defining the nocturnal time period as episodes occurring between 00:01-7:59 AM for one set of analyses and 9:59PM-05:59AM for another set of analyses. Present the data in table format and include N(%), Event, Event Rate for degludec and control groups.

Thanks,

Rachel

Rachel E. Hartford
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
rachel.hartford@fda.hhs.gov
301-796-0331 (phone)
301-796-9712 (fax)

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/s/

RACHEL E HARTFORD
05/21/2012

Hartford, Rachel

From: Hartford, Rachel
Sent: Monday, May 14, 2012 4:43 PM
To: 'SHSK (Shawn Hoskin)'
Subject: FW: Ryzodeg and Tresiba Information Request

Hello Shawn,

We received your May 11, 2012, response to our email below and request that you:

1- Submit datasets used in the updated analyses of MACE+ and MACE(i.e., original data + data from 9 additional trials).
2- Confirm that the data structure in the updated datasets are identical to the original submitted datasets.
3- Confirm that datasets used for additional analyses of original data are identical to the ones submitted at the time of original NDA filing.

Thank you,

Rachel

From: Hartford, Rachel
Sent: Friday, April 27, 2012 2:37 PM
To: 'SHSK (Shawn Hoskin)'
Subject: Ryzodeg and Tresiba Information Request

Hello Shawn,

We have reviewed the report of your analysis of cardiovascular events across the NN1250 and NN5401 Phase 3a Trials (5.3.5.3 Cardiovascular Meta-analysis) which was included in your original NDA submission dated September 29, 2011.

The report addressed the 16 therapeutic confirmatory trials of insulin degludec (IDeg) and insulin degludec/insulin aspart (IDegAsp) in subjects with type 1 (T1DM) and type 2 diabetes mellitus (T2DM) as of the cut-off date of January 31, 2011 in which you compared the pool of insulin degludec products (IDeg and IDegAsp) to the pool of comparator products (biphasic insulin aspart, sitagliptin, insulin detemir, and insulin glargine) in terms of the hazard ratio for major adverse cardiovascular events (MACE).

Your primary endpoint of time from randomization until first MACE was analyzed using a Cox proportional hazard model stratified by trial and with treatment (IDeg+IDegAsp and comparators) as explanatory variable. It is our understanding that all MACE included in your analyses were derived through a blinded, independent adjudication process. For purposes of your meta-analysis, MACE was defined as a composite endpoint derived from acute coronary syndrome including unstable angina pectoris and myocardial infarction (non-ST elevation myocardial infarction [NSTEMI] and ST-elevation myocardial infarction [STEMI]), stroke or cardiovascular death.

At this time, we are requesting additional information regarding your cardiovascular safety analyses and ask that you address the following requests within two weeks:

A. Repeat all of the original analyses (including sensitivity analyses) using the original dataset with a cut-off date of January 31, 2011. In these repeat analyses, define MACE as a composite of cardiovascular death, nonfatal MI, and nonfatal stroke only. Include all events reported up to 30 days after drug discontinuation.

B. Update your original cardiovascular safety analyses using data from trials or trial extensions that have been completed since the previous cut-off of January 31, 2011. Clearly delineate how this new dataset differs from the original dataset. Provide the new cut-off date and briefly describe (preferably in tabular format) all the additional trials, including the number of additional patients and patient-year exposure for each trial and overall for all included trials. Confirm that all additional events included in the dataset were prospectively and blindly adjudicated. Repeat the original analyses (including sensitivity analyses) using the new cut-off date and present these analyses using *both* your original broader definition of MACE and the Agency's definition (i.e., cardiovascular death, nonfatal MI, and nonfatal stroke). Include events reported up to 30 days after drug discontinuation.

C. Repeat all of the analyses with the expanded dataset as outlined in item 2 above (present analyses using both definitions of MACE and including events reported up to 30 days after drug discontinuation) *but* include only studies using other insulin products as a comparator (exclude the study employing sitagliptin as the comparator) and present the findings in two ways: 1) including the studies of patients with T1DM only and 2) including the studies of subjects with both T1DM and T2DM.

Best,

Rachel

Rachel E. Hartford
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
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rachel.hartford@fda.hhs.gov
301-796-0331 (phone)
301-796-9712 (fax)

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/s/

RACHEL E HARTFORD
05/14/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 203313
NDA 203314

GENERAL ADVICE

Novo Nordisk Inc.
Attention: Anne Phillips, M.D.
Corporate Vice President, Clinical, Medical and Regulatory Affairs
100 College Road West
Princeton, NJ 08540

Dear Dr. Phillips:

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

- Ryzodeg (insulin degludec/insulin aspart [rDNA origin]), injection, 100 U/mL and
- Tresiba (insulin degludec [rDNA origin]), injection, 100 U/mL and 200 U/mL.

We also refer to your January 17, 2012, submission, containing responses to our December 23, 2011, Information Request letter and a usability test synopsis PDS290-UT86-2012. We also refer to your February 15, 2012, submission, containing a superseding protocol for usability test PDS290-UT86-2012.

A. We are concerned with the results from your analysis of use errors specifically with the response provided to question # 6 of the FDA Information Request letter dated December 23, 2011. The proportion, and nature of the use errors previously identified, and the additional analysis, in particular those associated with the dose counter mechanism, as well as other reported issues that are outlined in bullets 1 through 6 immediately below, indicate that specific modifications are necessary that may not be limited to the Instructions For Use (IFU). You have not provided a rationale or evidence that the proposed IFU changes will adequately address the use-related issues observed in your previous study.

   1. Eleven participants did not set the dose correctly for their injection: You reported that 9 participants experienced device feedback issues associated with the dose counter. In the event of a blocked needle, when no actual insulin has been delivered, you show that the device dose counter may wrongly report that up to a maximum of 7 units have been delivered. Users were not aware of the potential for dose counter malfunction associated with blocked needles. This could result in clinically significant dosing errors after the user discovers that the needle on the device is blocked. We conclude that the dose counter, which serves as a visual feedback to the users, is not optimally designed as it can mislead users and cause confusion with regards to dosing after the device problem (i.e., blocked needle) is discovered.

2. Nine participants miscalculated the second dose when using two pens. You reported that of these participants, 1 child user did not know how to carry out the split dose task between two pens. This participant was described to be inexperienced and would have normally benefited from adult assistance to perform self-injection. As a result the test administrator provided assistance, and a correct dose was delivered. You state that the test set up reflects actual use in that assistance to a child user led to the ability of the child to perform self-injection. The test set-up let the child user attempt to self-inject with no assistance, once issues with self-injection were noted assistance from the moderator was provided to correct the issues.

   If children are not expected to self-inject, they should not self-inject. If they require assistance from caregiver, this condition should be proactively included in the study and should be evaluated in a realistic manner. Please provide an explanation. In addition, the need to ensure that children can dose properly should be clearly communicated in both the device labeling/instructions for use as well as in your communications to prescribing physicians. Please provide revised labeling/instructions for use and your proposed communications to prescribing physicians that address these concerns.

   In addition, 9 participants did not correctly calculate the dose for each of the two pens resulting in the wrong dose being delivered. The majority of these participants did not realize that they had mis-calculated and delivered an incorrect dose. Overall, these test findings demonstrate that many users can not adequately perform the split dose calculations despite current mitigation strategies.

3. Forty seven participants did not hold the needle in the skin for the recommended amount of time (i.e., 6 seconds). In addition to waiting for the dose counter to scale back to "0", you recommended that the needle be held in the skin for 6 seconds so as to ensure delivery of the full product dose. You indicated that the 6 seconds hold time can be regarded as a safety precaution. In the same response, you provided data summarizing results of dose accuracy testing. This data did not clearly show the amount of insulin delivered between 0-1 seconds, 1-2 seconds, 2-3 seconds, 3-4 seconds, 5-6 seconds, and >6 seconds. Decide whether the 6 second hold time is clinically relevant, and provide a rationale for why the high proportion of use errors reported in this scenario should not be of concern.

4. Eight participants experienced needlestick injuries: You report that the IFU adequately mitigates against this use error by alerting users of the potential for needlestick injuries and instructing them on the safe handling of the pen-injector and needle. However, participants continue to commit this use error indicating that current mitigation strategy is not effective.

5. Seven participants either did not remove the needle or reused the needle. You reported that to mitigate these use errors, the IFU states to always use a new needle, and to always remove the used needle. If the user fails to change the needle and omits performing the required priming step, the user may be alerted that the needle is blocked, when the dose counter does not return to "0". Consequently, these instructions have to be disregarded in

order to not detect a blocked needle. However, participants continued to commit use errors for not using a new needle, which indicated that current mitigations are not effective.

6. Three participants did not detect a blocked needle. You reported that a blocked needle will be very unlikely to occur for a user, who uses a new needle for each injection and carefully attaches the needle as recommended in the training material. However, as previously discussed in relation to the dose setting task, the dose counter is not designed to account for the decrease up to a maximum of 7 units when the needle is blocked.

B. The proposed study protocol PDS290-UT86-2012 is not acceptable as a HF/Usability validation study in its current form since it involves (b) (4), which does not represent realistic use. Furthermore, (b) (4), which can be used effectively for exploratory studies, does not represent realistic use and should not be used in a HF/usability validation study. We note that this type of approach was also employed in your prior study. Please note the following concerns regarding the proposed protocol:

1. In the Human Factors/usability validation study, we expect participants to use the instructions as they normally would while interacting with the device and the extent and level of training provided should be identical to the training users will receive in practice. Following the use scenario, subjective responses should be obtained from test participants by asking them directly about specific knowledge essential for use of the injection (to evaluate whether or not they obtained this from IFU or training) and about the helpfulness of the IFU and all performance failures and difficulties with use observed by the test facilitator (to obtain perspective of the test participants regarding these). We expect that users representing all user groups with unique abilities be represented in the validation study.

2. Your participant groups do not include any inpatient nursing staff. Include a user group made up of at least 15 inpatient nurses (not certified diabetes educators) in future studies, Nurses are a user group for the PDS290 device because hospitals use pen injectors to administer insulin to patients. These health care provider participants should be evaluated with and without device training.

3. With the exception of the Children user group, include an equal number of trained and untrained participants (who are not required to read the IFU) in each user group. Untrained participants should not be required to read the IFU, since this represents a form of training that may not always occur with the actual use of your product.

Guidance on human factors procedures to follow can be found in *Medical Device Use-Safety: Incorporating Human Factors Engineering into Risk Management,* available online at: http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm094460.htm. Note that we recently published a draft guidance document that, while not yet in effect, might also be useful in understanding our current thinking and our approach to human factors. It is titled, *Applying Human Factors and Usability Engineering to Optimize Medical*

Device Design and can be found online at: http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm259748.htm.

If you have any questions, call Rachel Hartford, Regulatory Project Manager, at (301) 796-0331.

Sincerely,

{See appended electronic signature page}

Mary H. Parks, M.D.
Director
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

MARY H PARKS
05/03/2012

Hartford, Rachel

From: Hartford, Rachel
Sent: Tuesday, May 01, 2012 11:53 AM
To: 'SHSK (Shawn Hoskin)'
Subject: Information Request - Degludec NDA 203314

Shawn,

The numbers of episodes for "ADA documented symptomatic hypoglycemia" differ between tables 260-262, appendix 6.2 of the ISE and those found in table 36 of the meta-analysis for hypoglycemia. Events defined as "Novo Nordisk confirmed episodes" are consistent between the two documents. Clarify this discrepancy.

Best,

Rachel

Rachel E. Hartford
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
rachel.hartford@fda.hhs.gov
301-796-0331 (phone)
301-796-9712 (fax)

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/s/

RACHEL E HARTFORD
05/01/2012

MANDATORY: Send a copy of the consult request form to the Office of Combination Products (OCP) as follows:
--Originating Center: When the consult request is initiated.
--Consulting Center: When the consult is completed.
Email: combination@fda.gov or FAX: 301-847-8619

For additional information: Contact OCP by email or by telephone (301-796-8930) or refer to OCP's intranet page http://inside.fda.gov:9003/ProgramsInitiatives/CombinationProducts/ReviewerTools/default.htm.

For Consulting Center Use Only:

Date Received: _____
Assigned to: _____
Date Assigned: _____
Assigned by: _____

Completed date: _____
Reviewer Initials: _____
Supervisory Concurrence: _____

Intercenter Request for Consultative or Collaborative Review Form

To (Consulting Center):
Center: CDRH
Division: ODE/DAGID
Mail Code: HF
Consulting Reviewer Name: QuynhNhu Nguyen
Building/Room #: WO66, Rm2531
Phone #: 301-796-6273
Fax #:
Email Address: quynht nguyen@fda hhs.gov
RPM/CSO Name and Mail Code: QuynhNhu Nguyen

From (Originating Center):
Center: CDER
Division: DMEP
Mail Code: HF-510
Requesting Reviewer Name:
Building/Room #:
Phone#:
Fax #:
Email Address:
RPM/CSO Name and Mail Code: Rachel Hartford x60331
Requesting Reviewer's Concurring Supervisor's Name:

Receiving Division: If you have received this request in error, you must contact the request originator by phone immediately to alert the request originator to the error.

Date of Request: 1May12
Requested Completion Date: 15Jun12

Submission/Application Number: NDA 203314
(Not Barcode Number)
Submission Type: NDA
(510(k), PMA, NDA, BLA, IND, IDE, etc.)

Type of Product: ☑ Drug-device combination ☐ Drug-biologic combination ☐ Device-biologic combination ☐ Drug-device-biologic combination ☐ Not a combination product

Submission Receipt Date: 24Apr12
Official Submission Due Date: _____

Name of Product: Ryzodeg (70% insulin degludec (b) (4) insulin aspart)
Name of Firm: Novo Nordisk

Intended Use: (375 characters max) treatment of diabetes

Brief Description of Documents Being Provided (e.g., clinical data -- include submission dates if appropriate):
(525 characters max) Focused Summative Usability Test PDS290-UT86-2012

Documents to be returned to Requesting Reviewer? ☐ Yes ☑ No

Complete description of the request. Include history and specific issues, (e.g., risks, concerns), if any, and specific question(s) to be answered by the consulted reviewer. The consulted reviewer should contact the request originator if questions/concerns are not clear. Attach extra sheet(s) if necessary:

Type of Request: ☑ Consultative Review ☐ Collaborative Review

(940 characters max -- use additional sheet if necessary) Please review the Focused Summative Usability Test PDS290-UT86-2012.
EDR Location: \\CDSESUB1\EVSPROD\NDA203314\203314.enx
Supporting Document Number: 17
eCTD Sequence Number: 0016
Letter Date: 04/24/2012
Stamp Date: 4/24/2012

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/s/

RACHEL E HARTFORD
05/01/2012

Hartford, Rachel

From: Hartford, Rachel
Sent: Friday, April 27, 2012 2:37 PM
To: 'SHSK (Shawn Hoskin)'
Subject: Ryzodeg and Tresiba Information Request

Hello Shawn,

We have reviewed the report of your analysis of cardiovascular events across the NN1250 and NN5401 Phase 3a Trials (5.3.5.3 Cardiovascular Meta-analysis) which was included in your original NDA submission dated September 29, 2011.

The report addressed the 16 therapeutic confirmatory trials of insulin degludec (IDeg) and insulin degludec/insulin aspart (IDegAsp) in subjects with type 1 (T1DM) and type 2 diabetes mellitus (T2DM) as of the cut-off date of January 31, 2011 in which you compared the pool of insulin degludec products (IDeg and IDegAsp) to the pool of comparator products (biphasic insulin aspart, sitagliptin, insulin detemir, and insulin glargine) in terms of the hazard ratio for major adverse cardiovascular events (MACE).

Your primary endpoint of time from randomization until first MACE was analyzed using a Cox proportional hazard model stratified by trial and with treatment (IDeg+IDegAsp and comparators) as explanatory variable. It is our understanding that all MACE included in your analyses were derived through a blinded, independent adjudication process. For purposes of your meta-analysis, MACE was defined as a composite endpoint derived from acute coronary syndrome including unstable angina pectoris and myocardial infarction (non-ST elevation myocardial infarction [NSTEMI] and ST-elevation myocardial infarction [STEMI]), stroke or cardiovascular death.

At this time, we are requesting additional information regarding your cardiovascular safety analyses and ask that you address the following requests within two weeks:

A. Repeat all of the original analyses (including sensitivity analyses) using the original dataset with a cut-off date of January 31, 2011. In these repeat analyses, define MACE as a composite of cardiovascular death, nonfatal MI, and nonfatal stroke only. Include all events reported up to 30 days after drug discontinuation.

B. Update your original cardiovascular safety analyses using data from trials or trial extensions that have been completed since the previous cut-off of January 31, 2011. Clearly delineate how this new dataset differs from the original dataset. Provide the new cut-off date and briefly describe (preferably in tabular format) all the additional trials, including the number of additional patients and patient-year exposure for each trial and overall for all included trials. Confirm that all additional events included in the dataset were prospectively and blindly adjudicated. Repeat the original analyses (including sensitivity analyses) using the new cut-off date and present these analyses using *both* your original broader definition of MACE and the Agency's definition (i.e., cardiovascular death, nonfatal MI, and nonfatal stroke). Include events reported up to 30 days after drug discontinuation.

C. Repeat all of the analyses with the expanded dataset as outlined in item 2 above (present analyses using both definitions of MACE and including events reported up to 30 days after drug discontinuation) *but* include only studies using other insulin products as a comparator (exclude the study employing sitagliptin as the comparator) and present the findings in two ways: 1) including the studies of patients with T1DM only and 2) including the studies of subjects with both T1DM and T2DM.

Best,

Rachel

Rachel E. Hartford
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
rachel.hartford@fda.hhs.gov
301-796-0331 (phone)

301-796-9712 (fax)

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/s/

RACHEL E HARTFORD
04/30/2012

Hartford, Rachel

From: Hartford, Rachel
Sent: Tuesday, April 17, 2012 12:56 PM
To: 'SHSK (Shawn Hoskin)'
Subject: Ryzodeg and Tresiba - Information Request

Hello Shawn,

Included in the submissions for each NDA is an (b) (4) for each presentation of the FlexTouch. Where does the (b) (4) go? Does it have a purpose?

Thanks,

Rachel

Rachel E. Hartford
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
rachel.hartford@fda.hhs.gov
301-796-0331 (phone)
301-796-9712 (fax)

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/s/

RACHEL E HARTFORD
04/17/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 203313
NDA 203314

GENERAL ADVICE

Novo Nordisk Inc.
Attention: Anne Phillips, M.D.
Corporate Vice President, Clinical, Medical and Regulatory Affairs
100 College Road West
Princeton, NJ 08540

Dear Dr. Phillips:

Please refer to your New Drug Applications (NDAs) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for:

- Ryzodeg (insulin degludec/insulin aspart [rDNA origin]), injection, 100 U/mL and
- Tresiba (insulin degludec [rDNA origin]), injection, 100 U/mL and 200 U/mL.

We also refer to your March 23 and April 4, 2012, submissions containing responses to our March 20, 2012 Discipline Review Letter.

We have reviewed the referenced material and have the following comments:

1. Clearly explain in the labeling that when the counter is reset to zero, the prescribed dose is not completely delivered until 6 seconds later.
2. Include a prominent warning to the patients in the labeling that if the needle is removed before counting to 6 seconds after the counter is reset to zero, then under-dosing will occur by as much as 20% and patients may have hyperglycemic consequences and require additional insulin administration.
3. Target the diabetic educators to highlight this under-dosing problem so that these educators can reinforce these points with their patients regarding the clinical adverse consequences of inadequate dosing.

If you have any questions, call Rachel Hartford, Regulatory Project Manager, at (301) 796-0331.

Sincerely,

{See appended electronic signature page}

Mary H. Parks, M.D.
Director
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

MARY H PARKS
04/16/2012

Hartford, Rachel

From: Hartford, Rachel
Sent: Tuesday, March 27, 2012 9:16 AM
To: 'SHSK (Shawn Hoskin)'
Subject: Ryzodeg and Tresiba IFUs

Hello Again,

The Tresiba and Ryzodeg (b) (4) IFU do not have figures. Submit revised IFU's with the figures included. Sequential patient instructions should be labeled as “Step 1, Step 2” etc. Figures should be labeled as “Figure A, Figure B” etc., and placed immediately adjacent to the related step.

Thanks,

Rachel

Rachel E. Hartford
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
rachel.hartford@fda.hhs.gov
301-796-0331 (phone)
301-796-9712 (fax)

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/s/

RACHEL E HARTFORD
03/30/2012

Hartford, Rachel

From: Hartford, Rachel
Sent: Tuesday, March 27, 2012 8:28 AM
To: 'SHSK (Shawn Hoskin)'
Subject: Sample Request

Hello Shawn,

We are requesting samples of the [redacted] (b) (4) for Ryzodeg and Tresiba. We are trying to determine if the [redacted] (b) (4) It is not clear in these applications how the label is applied.

Thanks,

Rachel

Rachel E. Hartford
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
rachel.hartford@fda.hhs.gov
301-796-0331 (phone)
301-796-9712 (fax)

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RACHEL E HARTFORD
03/30/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 203313
NDA 203314

DISCIPLINE REVIEW LETTER

Novo Nordisk Inc.
Attention: Anne Phillips, M.D.
Corporate Vice President, Clinical, Medical and Regulatory Affairs
100 College Road West
Princeton, NJ 08540

Dear Dr. Phillips:

Please refer to your September 29, 2011, New Drug Applications (NDAs) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for:

- Ryzodeg (insulin degludec/insulin aspart [rDNA origin]), injection, 100 U/mL and
- Tresiba (insulin degludec [rDNA origin]), injection, 100 U/mL and 200 U/mL.

During our review of the PDS290 prefilled pen portions of your submission, we have identified the following deficiency:

Bench Testing:

The dose accuracy testing submitted does not comply with ISO 111608-1, Pen-Injectors for Medical Use-Part 1: Pen-injectors- Requirements and Test Methods. This standard requires that the "Pen injector shall indicate, by visual, audible or tactile means or any combination of these, that the injection stroke has been completed." (b) (4) We do not believe that this dosing accuracy failure can be or should be mitigated by labeling. To resolve this issue you will need to provide a drug delivery device which is ISO 11608-1 compliant.

We are providing this comment to you before we complete our review of the entire application to give you preliminary notice of an issue that we have identified. In conformance with the prescription drug user fee reauthorization agreements, this comment does not reflect a final decision on the information reviewed and should not be construed to do so. This comment is 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 this issue during this review cycle, depending on the timing of your response, and

in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

If you have any questions, call Rachel Hartford, Regulatory Project Manager, at (301) 796-0331.

Sincerely,

{See appended electronic signature page}

Mary H. Parks, M.D.
Director
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

MARY H PARKS
03/20/2012

3/20/2012

03/30/12

MANDATORY: Send a copy of the consult request form to the Office of Combination Products (OCP) as follows:
-Originating Center: When the consult request is initiated.
--Consulting Center: When the consult is completed.
Email: combination@fda.gov or FAX: 301-847-8619

For additional information: Contact OCP by email or by telephone (301-796-8930) or refer to OCP's intranet page http://inside.fda.gov:9003/ProgramsInitiatives/CombinationProducts/ReviewerTools/default.htm.

For Consulting Center Use Only:

Date Received: 19-JAN-2012
Assigned to: DuyNhu Nguyen
Date Assigned: _____
Assigned by: MAE
Completed date: 20-JAN-2012
Reviewer Initials: GNJ
Supervisory Concurrence: Ron Kaye

Intercenter Request for Consultative or Collaborative Review Form

To (Consulting Center):
Center: CDRH
Division: ODE/DAGID/GHDB
Mail Code: HF Z-480
Consulting Reviewer Name:
Building/Room #:
Phone #:
Fax #:
Email Address:
RPM/CSO Name and Mail Code: Jaqueline Ryan

From (Originating Center):
Center: CDER
Division: DMEP
Mail Code: HF-510
Requesting Reviewer Name:
Building/Room #:
Phone#:
Fax #:
Email Address:
RPM/CSO Name and Mail Code: Rachel Hartford x60331
Requesting Reviewer's Concurring Supervisor's Name:

Receiving Division: If you have received this request in error, you must contact the request originator by phone immediately to alert the request originator to the error.

Date of Request: 19Jan12
Requested Completion Date: 20Mar12

Submission/Application Number: NDA 203313 (Not Barcode Number)
Submission Type: NDA (510(k), PMA, NDA, BLA, IND, IDE, etc.)

Type of Product: ☑ Drug-device combination ☐ Drug-biologic combination ☐ Device-biologic combination ☐ Drug-device-biologic combination ☐ Not a combination product

Submission Receipt Date: 29Sep11
Official Submission Due Date: _____

Name of Product: Ryzodeg
Name of Firm: Novo Nordisk

Intended Use: (375 characters max) treatment of diabetes mellitus

Brief Description of Documents Being Provided (e.g., clinical data -- include submission dates if appropriate):
(525 characters max) initial NDA submission

Documents to be returned to Requesting Reviewer? ☐ Yes ☑ No

Complete description of the request. Include history and specific issues, (e.g., risks, concerns), if any, and specific question(s) to be answered by the consulted reviewer. The consulted reviewer should contact the request originator if questions/concerns are not clear. Attach extra sheet(s) if necessary:

Type of Request: ☑ Consultative Review ☐ Collaborative Review

(940 characters max -- use additional sheet if necessary) Please review Novo's responses to your comments and respond to Novo's additional Question # 1.

EDR Location: \\CDSESUB1\EVSPROD\NDA203313\203313.enx eCTD Sequence Number: 0008

Reference ID: 3074027

Reference ID: 3109282

GEN1200180 CON 124063

3/20/2012 R. Hartford

MANDATORY: Send a copy of the consult request form to the Office of Combination Products (OCP) as follows:
--Originating Center: When the consult request is initiated.
--Consulting Center: When the consult is completed.
Email: combination@fda.gov or FAX: 301-847-8619

For additional information: Contact OCP by email or by telephone (301-796-8930) or refer to OCP's intranet page http://inside.fda.gov:9003/ProgramsInitiatives/CombinationProducts/ReviewerTools/default.htm.

For Consulting Center Use Only:

Date Received: 19-JAN-2012
Assigned to: Joseph Nhan Nguyen
Date Assigned:
Assigned by:

Completed date: 20-MAR-2012
Reviewer Initials: JNN
Supervisory Concurrence: Ron Kaye

Intercenter Request for Consultative or Collaborative Review Form

To (Consulting Center):
Center: CDRH
Division: ODE/DAGID/GHDB
Mail Code: HF Z-480
Consulting Reviewer Name:
Building/Room #:
Phone #:
Fax #:
Email Address:
RPM/CSO Name and Mail Code:
Jaqueline Ryan

From (Originating Center):
Center: CDER
Division: DMEP
Mail Code: HF-510
Requesting Reviewer Name:
Building/Room #:
Phone#:
Fax #:
Email Address:
RPM/CSO Name and Mail Code: Rachel Hartford x60331
Requesting Reviewer's Concurring Supervisor's Name:

Receiving Division: If you have received this request in error, you must contact the request originator by phone immediately to alert the request originator to the error.

Date of Request: 19Jan12
Requested Completion Date: 20Mar12

Submission/Application Number: NDA 203314
(Not Barcode Number)

Submission Type: NDA
(510(k), PMA, NDA, BLA, IND, IDE, etc.)

Type of Product: ☑ Drug-device combination ☐ Drug-biologic combination ☐ Device-biologic combination ☐ Drug-device-biologic combination ☐ Not a combination product

Submission Receipt Date: 29Sept1
Official Submission Due Date:

Name of Product: Tresiba
Name of Firm: Novo Nordisk

Intended Use: (375 characters max) treatment of diabetes mellitus

Brief Description of Documents Being Provided (e.g., clinical data -- include submission dates if appropriate):
(525 characters max) initial NDA submission

Documents to be returned to Requesting Reviewer? ☐ Yes ☑ No

Complete description of the request. Include history and specific issues, (e.g., risks, concerns), if any, and specific question(s) to be answered by the consulted reviewer. The consulted reviewer should contact the request originator if questions/concerns are not clear. Attach extra sheet(s) if necessary:

Type of Request: ☑ Consultative Review ☐ Collaborative Review

(940 characters max -- use additional sheet if necessary) Please review Novo's responses to your comments and respond to Novo's additional Question # 1.

EDR Location: \\CDSESUB1\EVSPROD\NDA203314\203314.enx eCTD Sequence Number: 0008

Reference ID: 3074013

Reference ID: 3109282

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 203313
NDA 203314

INFORMATION REQUEST

Novo Nordisk Inc.
Attention: Anne Phillips, M.D.
Corporate Vice President, CMR
100 College Road West
Princeton, NJ 08540

Dear Dr. Phillips:

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

- Ryzodeg (insulin degludec/insulin aspart [rDNA origin]), injection, 100 U/mL and
- Tresiba (insulin degludec [rDNA origin]), injection, 100 U/mL and 200 U/mL.

We are reviewing the CMC section of your submissions and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

NDA 203313

Drug Product

1. Provide information on the following:

    a. Levels of soluble di-hexameric forms of insulin degludec present in your drug product.
    b. The stoichiometry of (b) (4).
    c. Data to support the proposed levels of zinc and phenol for the proposed drug products.

2. Your CMC section does not contain information on the levels of individual insulin degludec related substances and impurities present in the drug product. ICH Q6B guidance states that if impurities are known to be introduced or formed during the production and/or storage of the drug product, the levels of these impurities should be determined and acceptance criteria established. Therefore, provide the following:

    a. Information on the levels of individual insulin degludec related substances and impurities present in batches used in phase 3 clinical studies and stability studies.

b. Explain which impurities are increasing during manufacturing, during long-term, accelerated and in-use stability studies.
c. Based on available data, propose a limit for each of the individual product related substances and impurities present in the product including limits for (b) (4) in the drug product.
d. Update your post-approval stability protocol to include limits for individual product related substances and impurities.
e. Clarify whether glycerol used in the formulation (b) (4) of the insulin degludec in your product.
f. Provide intact and reduced mass data for each of the individual impurities separated by the analytical method, A6020a.
g. Clarify whether your proposed test method is capable of quantitating individual product-related substances and impurities with adequate specificity, accuracy and precision in the proposed product.
h. Explain your choice of RP HPLC over other applicable methods (e.g., ion exchange chromatography) for the quantitation of charged variants.

3. Considering the expected insulin aspart content specification (b) (4)% of label claim at the end of shelf-life, your proposed combined limit for total Insulin aspart related substances and impurities (~(b) (4)% level) does not meet the purity expectations of drug product at the end of shelf-life. Therefore, revise your proposed limit for Insulin aspart related substances and impurities to meet the purity expectations or justify your proposed specifications.

NDA 203314

Drug Substance

1. Provide the chemical structure, general physico-chemical properties and a certificate of analysis of the (b) (4)

2. Justify the parenthetical description of Content (b) (4) in the Drug Substance specifications. This may be interpreted to mean inclusion of all (b) (4) variants in the sample, rather than only the main peak as defined by HPLC Method A7091a.

3. The shelf life of insulin degludec (b) (4) batch 126.454.09.1 should be revised to reflect the available long-term, real-time stability evaluation.

4. The shelf life of the current insulin degludec (b) (4) batch 064.454.09.2 should be revised to reflect the available long-term, real-time stability evaluation of either the previous (b) (4) batch 179.454.07.2 (if appropriate) or the current (b) (4) batch.

5. Explain how insulin degludec (b) (4) batch 064.454.09.2, produced in (b) (4), is traceable (for Content, Bioactivity) to the insulin degludec (b) (4) (b) (4) batch 126.454.09.1, which was produced (b) (4) later (b) (4)).

6. A shelf life of (b) (4) months will be granted for the drug substance when stored at (b) (4). This is based on acceptable long term stability results from real-time studies obtained for the drug substance from the Primary Stability batches. The (b) (4) in the manufacture of insulin degludec drug substance has changed significantly from earlier campaigns, therefore, data from Supportive Stability batches were not considered for expiry dating.

7. Provide data showing photostability of the insulin degludec drug substance.

Drug Product

1. Provide information on the following:
    a. Levels of soluble di-hexameric forms of insulin degludec present in your drug product.
    b. The stoichiometry of (b) (4) complex.
    c. Data to support the proposed levels of zinc and phenol for the proposed drug products.

2. Your CMC section does not contain information on the levels of individual insulin degludec related substances and impurities present in the drug product. ICH Q6B guidance states that if impurities are known to be introduced or formed during the production and/or storage of the drug product, the levels of these impurities should be determined and acceptance criteria established. Therefore, provide the following:

    a. Information on the levels of individual insulin degludec related substances and impurities present in batches used in phase 3 clinical studies and stability studies.
    b. Explain which impurities are increasing during manufacturing, during long-term, accelerated and in-use stability studies.
    c. Based on available data, propose a limit for each of the individual product related substances and impurities present in the product including limits for (b) (4) in the drug product.
    d. Update your post-approval stability protocol to include limits for individual product related substances and impurities.
    e. Clarify whether glycerol used in the formulation (b) (4) of the insulin degludec in your product.
    f. Provide intact and reduced mass data for each of the individual impurities separated by the analytical method, A6020a.
    g. Clarify whether your proposed test method is capable of quantitating individual product-related substances and impurities with adequate specificity, accuracy and precision in the proposed product.
    h. Explain your choice of RP HPLC over other applicable methods (e.g., ion exchange chromatography) for the quantitation of charged variants.

3. Considering the expected purity of your drug product is (b) (4)%, the combined limits for (b) (4) related substances, (b) (4) impurities and % HMWP would exceed the (b) (4)% total impurity level. Therefore, revise your proposed limit for (b) (4) related substances, (b) (4) impurities and % HMWP to meet the purity expectations.

4. Your proposal to have wider shelf-life specification for insulin degludec related substances and impurities is not supported by the observed stability profile of your primary stability batches (i.e., very little degradation is seen under real-time storage conditions). Revise your shelf-life specification to current release specification level or justify the same.

If you have any questions, call Swati Patwardhan, Regulatory Project Manager-Quality, at 301-796-4085.

Sincerely,

{See appended electronic signature page}

Ali Al Hakim, Ph.D.
Branch Chief, Branch VII
Division of New Drug Quality Assessment III
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

ALI H AL HAKIM
02/13/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 203314

PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE

Novo Nordisk Inc.
100 College Road West
Princeton, NJ 08540

Attention: Eddie Li, Ph.D.
Vice President, Regulatory Affairs

Dear Dr. Li:

Please refer to your New Drug Application (NDA) dated September 29, 2011, received on September 29, 2011, submitted under section 505(b) of the Federal Food, Drug and Cosmetic Act for Insulin Degludec 100 Units/mL and 200 Units/mL Injection.

We also refer to your October 5, 2011, correspondence, received October 5, 2011, requesting review of your proposed proprietary name Tresiba. We have completed our review of the proposed proprietary name, Tresiba, and have concluded that it is acceptable.

The proposed proprietary name, Tresiba, will be re-reviewed 90 days prior to approval of the NDA. If we find the name unacceptable following the re-review, we will notify you.

If **any** of the proposed product characteristics as stated in your October 5, 2011, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Margarita Tossa, Safety Regulatory Project Manger in the Office of Surveillance and Epidemiology, at (301) 796-4053. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, Rachel Hartford at (301) 796-0331.

Sincerely,

{See appended electronic signature page}

Carol Holquist, 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

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/s/

IRENE Z CHAN on behalf of CAROL A HOLQUIST
12/30/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 203313
NDA 203314

INFORMATION REQUEST

Novo Nordisk Inc.
Attention: Eddie Li, Ph.D.
Vice President, Regulatory Affairs
100 College Road West
Princeton, NJ 08540

Dear Dr. Li:

Please refer to your New Drug Applications (NDAs) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for:

- Ryzodeg (insulin degludec/insulin aspart [rDNA origin]), injection, 100 U/mL and
- Tresiba (insulin degludec [rDNA origin]), injection, 100 U/mL and 200 U/mL.

We also refer to your September 29, 2011, submissions.

We are reviewing the Device Human Factors sections of your submissions and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDAs.

Two separate studies were conducted: user differentiation and user handling. Each study consisted of the same group of 105 participants. Address the following for both NDAs:

1. Based on the table provided on page 40 of the Risk Management Analysis Input to Usability Test (Doc ID: 001006117, Dated May 2, 2011), it is not clear why, under the adults subgroup, the untrained participants did not undergo the differentiation evaluation. In addition, it is not clear why, under the Health Care Provider (HCP) subgroup, the trained HCP did not undergo the differentiation evaluation. Please clarify.

2. Also, the following items could not be located for review. Direct us to where this information is located within the NDAs or submit for review:

   - A breakdown of the number of participants for the different user groups, trained and untrained. Include in this breakdown, the number of participants with visual, dexterity, and hearing impairment.
   - A rationale for determining who should be receiving training, and who should not among the intended users

- A rationale for why [redacted] (b) (4) is an approach that represents realistic use

3. We understand that diabetic patients have medical conditions such as retinopathy and neuropathy, and these conditions may worsen over time. Provide a justification for why test participants included in the study are an adequate representation of the intended user group.

Regarding the study results for both studies, address the following specific concerns:

User Differentiation Study:

4. The study reported that three of 105 participants did not perform the task of selecting the correct carton with the intended insulin product. A total of five use errors were recorded, with one participant repeatedly committing the same error on three occasions, and this same participant committed three errors with the previous task of selecting the correct carton. Two participants had negative transfer from their use experience with other similar products, and one participant could not identify the green color carton. The study also reported that three of 105 participants did not perform the task of selecting the correct carton with the intended insulin product.

   The IFU includes a statement to have users [redacted] (b) (4) Based on the risk analysis, the clinical outcome can be hypoglycemia or hyperglycemia if a patient injects a different type of insulin other than intended and the error is undetected. There are different use scenarios for which this hazard exists – for example, either the pharmacist/HCP chooses the wrong carton and dispenses to the patient, and the patient does not recognize the wrong insulin carton; or the patient has more than one type of insulin available, and the patient chooses the wrong carton. The results are not clear in terms of which user group (children/adult/caregiver/HCP) the three participants were part of.

   It is concerning that not all users were able to successfully complete these tasks and that serious clinical impact can occur. We are concerned that participants were not able to identify the carton and pen-injector with the correct insulin despite the use of colors and instructions provided in the IFU, and therefore the risks associated with these aspects of use are not successfully mitigated. Further design optimization can be done to the pen label to clearly identify the insulin type and the dose.

User Handling Study:

5. A discrepancy was noted between the Validation of Device Use (UT59 and UT54 NN Report, Dated June 29, 2011) report and test report PDS290-UT54-2011. The test report PDS290-UT54-2011 provided in several tables a listing of different types of injectors (FlexPen, KwikPen, SoloStar), and various baseline tasks. It is not clear if the product

used for the final validation study represented the commercial product of the (b) (4) product. Please clarify.

6. The Validation of Device Use (UT59 and UT54 NN Report, Dated June 29, 2011) reported 94 of 105 participants committed 226 errors across tasks associated with delivering an injection and some of the errors resulted in needlestick injuries. We are most concerned with the following findings. Of the 105, participants,
   - 11 participants did not set the dose correctly for their injection resulting in 12 use errors.
   - 9 participants miscalculated the second dose when using two pens resulting in 9 use errors.
   - 2 participants did not hold the dose button down until it scales back to the 0 position resulting in 4 use errors
   - 47 participants did not hold the needle in the skin for an appropriate amount of time resulting in 171 use errors
   - 7 participants either did not remove the needle or reused the needle resulting in 10 use errors
   - 8 participants experienced needlestick injuries resulting in 10 use errors
   - 4 participants did not put the cap back on after use resulting in 4 use errors
   - 3 participants did not detect a blocked needle resulting in 3 use errors

   These use errors can result in underdosing or overdosing. Other use errors can result in needlestick injuries, contamination, and infection. You provided some root cause analysis along with the position that the current mitigations are effective and that the residual risks are minimal. However, to fully assess the extent of the use errors, additional clarification is necessary for the following items:

   a. For the use errors associated with 11 participants who did not set the dose correctly for their injection resulting in 12 use errors, the narrative provided in the root cause analysis section was not clear on how the use error occurred among the sequence of use interaction steps, and what "visual feedback" the users received or did not receive from the device. The report indicated that 7 of the use errors occurred after other use errors had previously occurred i.e. users neglected the priming step, or attempted to inject with a blocked needle. It was also not clear if any of the users recognized that a full dose had not been delivered, and what aspect of the device design allowed them to do so. Address the above concerns and provide a side-by-side comparison of the correct injection sequence versus the sequence for which all of the use errors occurred, and clearly describe how the user errors occurred along with screen shots of the device status at each of the steps, subjective feedback from users on the root cause of the use errors, and indicate which of these participants ultimately delivered/did not deliver a correct dose. Also provide a clarification on the "visual feedback" and clarification on the clinical significance of the one participant who injected both a priming dose and a prescribed dose. It appeared that one participant committed the error twice but the report did not provide details on this participant. Furthermore, stating that

the root causes were associated with user forgetfulness, habit, and misunderstanding, or that the root causes were not unique to the proposed pen-injector does not provide adequate evidence demonstrating that the device can be used safely and effectively.

b. For the use errors associated with 9 participants who miscalculated the second dose when using two pens resulting in 9 use errors, the report indicated that one use error was associated with one 10-year old participant who found the instructions to be confusing, failed the split dose task and was assisted by the moderator. A discrepancy was noted in your assessment of this use error. You stated in the report that in a real-life situation, a 10 year-old child may perform the injection but never have the full responsibility for insulin administration. However, in the Risk Management Analysis Input to Usability Test (Doc ID: 001006117, Dated May 2, 2011), you stated that Children (age 10 to 17) are considered as part of the 5 distinct user groups, who self inject without a parent's involvement. Because the report showed that a representative test user in the child subgroup could not successfully perform an injection, and because they represent a group where special considerations should be incorporated in the design of the product, we recommend that this use-related risk be fully mitigated. In addition, the remaining 8 use errors did not include the necessary subjective data that are focused on identifying the root cause of the failures and potential design improvements recommendations from the perspective of representative users. The report remained unclear in terms of which of these participants ultimately delivered/did not deliver a correct dose. Provide additional information that addresses the above concerns.

c. For the use errors associated with 2 participants who did not hold the dose button down until it scales back to the 0 position resulting in 4 use errors, this is a critical task in ensuring that the patients receive a full dose of intended insulin. One participant repeatedly misunderstood the dosing task three times, and believed that the full dose would be delivered by simply activating the dose button. Another participant did not hold the dose button down. While there were only two participants who committed this use error, the clinical impact is significant in that the patients would not receive a full dose. It is also not clear if these two participants held the needle in the skin for the 6 seconds task. It appears that the user interface including the IFU and labeling do not provide sufficient feedback to the users or prevent underdosing. Provide a proposal on how these errors can be addressed. Note that any further mitigation will need to be evaluated for effectiveness.

d. For the use errors associated with 47 participants who did not hold the needle in the skin for an appropriate amount of time resulting in 171 use errors, you indicated that dose accuracy testing showed that a full dose is delivered 1 second after the dose counter returns to "0" while the needle remains in the skin. However, for 123 of the 171 use errors, the needle was removed from the skin

after 1 second, and 48 of the 171 use errors occurred when the needle was removed from the skin under 1 second, which resulted in underdosing. It is unclear why you are specifying that the needle should be held in the skin for 6 seconds, yet stating that dose accuracy testing demonstrated that a full dose can be delivered 1 second after the dose counter returns to "0." The report did not include the necessary subjective data that are focused on identifying the root cause of the failures and potential design improvement recommendations from the perspective of representative users. Furthermore, stating that the root causes were associated with user forgetfulness, habit, and misunderstanding, etc. or that the root causes were not unique to the proposed pen-injector does not provide adequate evidence demonstrating that the device can be used safely and effectively. It appears that the user interface including the IFU and labeling do not provide sufficient feedback to the users or prevent underdosing. Provide a proposal on how these errors can be addressed. Note that any further mitigation will need to be evaluated for effectiveness.

e. For the use errors associated with 8 participants who experienced needlestick injuries resulting in 10 use errors, we request that you optimize the design and/or IFU and training to minimize the rate of occurrence of needlestick injuries.

f. For the use errors associated with 7 participants who either did not remove the needle from the device or reused the needle resulting in 10 use errors, you stated that these tasks are incorporated in the use of the product to prevent blocked needles, contamination, infection, and inaccurate dosing. Four participants committed 4 use errors in not removing the needle from the device, and 3 participants committed 3 use errors in reusing a previously inserted needle. Again, stating that the root causes were associated with user forgetfulness, habit, and misunderstanding, etc. or that the root causes were not unique to the proposed pen-injector does not provide adequate evidence demonstrating that the device can be used safely and effectively. Because these use errors can result in negative impact to the patients, provide a proposal on how these errors can be addressed. Note that any further mitigation will need to be evaluated for effectiveness.

g. For the use errors associated with 4 participants who did not put the cap back on after use resulting in 4 use errors, the sponsor stated that these errors can result in underdosing. We note that degradation caused by exposure to sunlight due to the cap not being mounted after use can result in underdosing. However, it is not clear what the clinical impact will be for patients injecting insulin that has been degraded, and how the patient would detect that the insulin has been degraded. We believe the device user interface can be further optimized to improve use performance.

h. For the use errors associated with 3 participants who did not detect a blocked needle resulting in 3 use errors, you stated that the resulting harm is that a patient may miss a dose. It is not clear if the pen-injector provides any feedback to the

user in this situation, and whether or not the users recognize that they did not receive any insulin. You also provided a clarification that the blocked needle task is an experimental artifact because in real life, the blocked needle only occurs if a patient reuses a needle or uses a defective needle. The testing showed that indeed 3 participants opted to reuse the needles, and therefore this is not an experimental artifact. Please indicate what aspects of the device design were or were not effective in mitigating use-related risks, and why potential improvement to the device design will not fully mitigate those use related risks.

i. You also reported deviations (page 95 of 102), and close calls (page 96 of 102). While these are "deviations" and "close-calls" that did no result in medical consequences, you did not provide a discussion of how users were able to recognize the potential failures and what steps they took to correct themselves. Please provide in your discussion how the design of the device and its labeling influenced the patient's behavior for self-correction.

7. We expect to review a report of the human factors/usability evaluation and validation testing with any pattern of use errors, and a conclusion based on the test results that the device is reasonably safe and effective for the intended users, uses and use conditions. We are concerned that your testing did not provide the level of evidence to conclude that the device can be used safely and effectively. You should take the results of these evaluations and use them to further optimize the training, IFU and/or device user interface so that use errors are effectively minimized. Improvements should be demonstrated through focused HF/usability validation.

Guidance on human factors procedures to follow can be found in *Medical Device Use-Safety: Incorporating Human Factors Engineering into Risk Management,* available online at: http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm094460.htm.

Note that we recently published a draft guidance document that, while not yet in effect, might also be useful in understanding our current thinking and our approach to human factors. It is entitled, *Applying Human Factors and Usability Engineering to Optimize Medical Device Design* and can be found online at: http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm259748.htm.

If you have any questions, call Rachel Hartford, Regulatory Project Manager, at (301) 796-0331.

Sincerely,

{See appended electronic signature page}

Mary H. Parks, M.D.
Director
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

MARY H PARKS
12/23/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 203313

PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE

Novo Nordisk Inc.
100 College Road West
Princeton, NJ 08540

Attention: Eddie Li, Ph.D.
Vice President, Regulatory Affairs

Dear Dr. Li:

Please refer to your New Drug Application (NDA) dated September 29, 2011, received on September 29, 2011, submitted under section 505(b) of the Federal Food, Drug and Cosmetic Act for 70% insulin degludec and 30% insulin aspart [rDNA origin] 100 Units/mL Injection.

We also refer to your October 5, 2011, correspondence, received October 5, 2011, requesting review of your proposed proprietary name Ryzodeg.

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

The proposed proprietary name, Ryzodeg, will be re-reviewed 90 days prior to approval. If **any** of the proposed product characteristics as stated in your September 23, 2011, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Margarita Tossa, Safety Regulatory Project Manger in the Office of Surveillance and Epidemiology, at (301) 796-4053. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, Rachel Hartford at (301) 796-0331.

Sincerely,

{See appended electronic signature page}

Carol Holquist, 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

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/s/

CAROL A HOLQUIST
12/22/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 203313

FILING COMMUNICATION

Novo Nordisk Inc.
Attention: Eddie Li, Ph.D.
Vice President, Regulatory Affairs
100 College Road West
Princeton, NJ 08540

Dear Dr. Li:

Please refer to your New Drug Application (NDA) dated and received September 29, 2011, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for Ryzodeg (insulin degludec/insulin aspart [rDNA origin]), injection, 100 U/mL.

We also refer to your amendments dated October 5(2), 24, and 25, 2011.

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 **July 29, 2012**.

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, midcycle, 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 June 8, 2012.

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.

We request that you submit the following information as soon as possible:

Clinical

1. You reference your December 21, 2010, background package and our March 21, 2011, advice letter but this approach does not adequately address in the NDA how you plan to fulfill the requirements of the Pediatric Research Equity Act (PREA). See "Required Pediatric Assessments" below.

Chemistry, Manufacturing, and Controls

2. Clarify what the reference is for the units of the dosage strength (b) (4)". In the proposed drug product specification, the content of insulin degludec in the formulation is measured as "nmol", and you state that 100 (b) (4) corresponds to 600 nmol/ml. Provide a reference for the units of the dosage strength (b) (4)", comparable to that submitted for your insulin detemir product (i.e., one unit (24 nmol) of insulin detemir corresponds to one IU of human insulin (6 nmol) based on clinical data).

3. Clarify how your proposed dosage strength of 100 (b) (4) for the combined content of insulin degludec and insulin aspart complies with 21 CFR 201.100, which requires the labeling to state "the quantity or proportion of each active ingredient in the drug product".

Office of Scientific Investigations (OSI)

4. You notified us that the Osvaldo Brusco site was closed due to Good Clinical Practices (GCP) concerns (Studies N1250-3579, N1250-3580, N1250-3582). How have data from this site been handled in analyses and reported in Clinical Study Reports?

5. In the clinsite.xpt dataset virtually all investigators are reported as having financial disclosure amounts; however, only a small subset of these sites are reported to have disclosable information in the Tables of Financial Disclosure. Please clarify.

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.

REQUIRED PEDIATRIC ASSESSMENTS

Under 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.

We note that you have not addressed how you plan to fulfill this requirement. Within 30 days of the date of this letter, please submit (1) a full waiver request, (2) a partial waiver request and a pediatric development plan for the pediatric age groups not covered by the partial waiver request, or (3) a pediatric drug development plan covering the full pediatric age range. All waiver requests must include supporting information and documentation. A pediatric drug development plan must address the indication proposed in this application.

If you request a full waiver, we will notify you if the full waiver is denied and a pediatric drug development plan is required.

If you have any questions, call Rachel Hartford, Regulatory Project Manager, at (301) 796-0331.

Sincerely,

{See appended electronic signature page}

Mary H. Parks, M.D.
Director
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

MARY H PARKS
11/30/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 203314

FILING COMMUNICATION

Novo Nordisk Inc.
Attention: Eddie Li, Ph.D.
Vice President, Regulatory Affairs
100 College Road West
Princeton, NJ 08540

Dear Dr. Li:

Please refer to your New Drug Application (NDA) dated and received September 29, 2011, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for Tresiba (insulin degludec [rDNA origin]), injection, 100 U/mL and 200 U/mL.

We also refer to your amendments dated October 5(2) and 24, 2011.

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 **July 29, 2012**.

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, midcycle, 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 June 8, 2012.

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.

We request that you submit the following information as soon as possible:

Clinical

1. Clarify why you are [redacted] (b) (4) Study 1250-3586 entitled "*A 26-week randomised, confirmatory, controlled, open label, multicentre, multinational treat-to-target trial comparing the efficacy and safety of NN1250 and insulin glargine, both injected once daily as add on to current OAD treatment in insulin naïve subjects with type 2 diabetes mellitus qualifying for more intensified treatment.*"

2. You reference your December 21, 2010, background package and our March 21, 2011, advice letter but this approach does not adequately address in the NDA how you plan to fulfill the requirements of the Pediatric Research Equity Act (PREA). See "Required Pediatric Assessments" below.

Chemistry, Manufacturing, and Controls

3. Clarify what the reference is for the units of the dosage strength [redacted] (b) (4) In the proposed drug product specification, the content of insulin degludec in the formulation is measured as "nmol", and you state that 100 [redacted] (b) (4) orresponds to 600 nmol/ml. Provide a reference for the units of the dosage strength [redacted] (b) (4), comparable to that submitted for your insulin detemir product (i.e., one unit (24 nmol) of insulin detemir corresponds to one IU of human insulin (6 nmol) based on clinical data).

Office of Scientific Investigations (OSI)

4. You notified us that the Osvaldo Brusco site was closed due to Good Clinical Practices (GCP) concerns (Studies N1250-3579, N1250-3580, N1250-3582). How have data from this site been handled in analyses and reported in Case Study Reports?

5. In the clinsite.xpt dataset virtually all investigators are reported as having financial disclosure amounts; however, only a small subset of these sites are reported to have disclosable information in Tables of Financial Disclosure. Please clarify.

Clinical Pharmacology

6. Provide raw data (as SAS transport files) used for the population pharmacokinetic (PK) analysis conducted for Study NN1250-3586. A description of each data item should be provided in a Define.pdf file. Any data point and/or subjects that have been excluded from the analysis should be flagged and maintained in the datasets.

7. Provide the NONMEM Model Codes for the population PK analysis conducted for Study NN1250-3586. In general, model codes or control streams and output listings should be provided for all major model-building steps, e.g., base structural model, covariates models, final model, and validation model. These files should be submitted as ASCII text files with *.txt extension (e.g.: myfile_ctl.txt, myfile_out.txt).

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.

REQUIRED PEDIATRIC ASSESSMENTS

Under 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.

We note that you have not addressed how you plan to fulfill this requirement. Within 30 days of the date of this letter, please submit (1) a full waiver request, (2) a partial waiver request and a pediatric development plan for the pediatric age groups not covered by the partial waiver request, or (3) a pediatric drug development plan covering the full pediatric age range. All waiver requests must include supporting information and documentation. A pediatric drug development plan must address the indication proposed in this application.

If you request a full waiver, we will notify you if the full waiver is denied and a pediatric drug development plan is required.

If you have any questions, call Rachel Hartford, Regulatory Project Manager, at (301) 796-0331.

Sincerely,

{See appended electronic signature page}

Mary H. Parks, M.D.
Director
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

MARY H PARKS
11/30/2011

Sharma, Khushboo

From: Sharma, Khushboo
Sent: Monday, October 24, 2011 2:06 PM
To: 'eili@novonordisk.com'
Cc: 'mpel@novonordisk.com'
Subject: Information Request NDA 203313

Dear Dr. Li

We are reviewing the Chemistry, Manufacturing and Controls section of your submission for NDA 203313 dated September 29, 2011. We have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your submission.

1. For NDA 203313 (insulin degludec and insulin aspart), please confirm that the the drug substance manufacturing/testing sites for insuplin aspart are included in Form 356h.

If your response can be found in the contents of your submission, just cite those sections of the submission that are relevant to the issues under consideration. Otherwise, please provide the appropriate information as an amendment to the submission. In addition, a copy of your response submitted by e-mail (khushboo.sharma@fda.hhs.gov) will expedite the review of your request. In your cover letter refer to the date on which this information was requested.

Please acknowledge the receipt of this email and provide the time line of the amendment submission.

Thank you,

Khushboo Sharma
Regulatory Health Project Manager
FDA/CDER/OPS/ONDQA
Division of New Drug Quality Assessment III
Phone (301)796-1270

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/s/

KHUSHBOO SHARMA
10/24/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 203313

NDA ACKNOWLEDGMENT

Novo Nordisk Inc.
Attention: Eddie Li, Ph.D.
Vice President, Regulatory Affairs
100 College Road West
Princeton, NJ 08540

Dear Dr. Li:

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: Ryzodeg (insulin degludec/insulin aspart [rDNA origin]), injection, 100 (b) (4)

Date of Application: September 29, 2011

Date of Receipt: September 29, 2011

Our Reference Number: NDA 203313

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 28, 2011**, 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:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolism and Endocrinology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm.

If you have any questions, call me at (301) 796-0331.

Sincerely,

{See appended electronic signature page}

Rachel Hartford
Regulatory Health Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

RACHEL E HARTFORD
10/12/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 203314

NDA ACKNOWLEDGMENT

Novo Nordisk Inc.
Attention: Eddie Li, Ph.D.
Vice President, Regulatory Affairs
100 College Road West
Princeton, NJ 08540

Dear Dr. Li:

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: Tresiba (insulin degludec [rDNA origin]), injection, 100 (b) (4)

Date of Application: September 29, 2011

Date of Receipt: September 29, 2011

Our Reference Number: NDA 203314

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 28, 2011**, 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:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolism and Endocrinology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

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If you have any questions, call me at (301) 796-0331.

Sincerely,

{See appended electronic signature page}

Rachel Hartford
Regulatory Health Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

RACHEL E HARTFORD
10/12/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 073198
IND 076496

MEETING MINUTES

Novo Nordisk Inc.
Attention: Anne Phillips, M.D.
Corporate Vice President – Clinical, Medical and Regulatory Affairs
100 College Road West
Princeton, NJ 08540

Dear Dr. Phillips:

Please refer to your Investigational New Drug Applications (INDs) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act (FDCA) for NN5401 insulin degludec/insulin aspart and NN1250 insulin degludec.

We also refer to the pre-NDA meeting between representatives of your firm and the FDA on June 17, 2011.

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 me at (301) 796-0331.

Sincerely,

{See appended electronic signature page}

Rachel Hartford
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

ENCLOSURE:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type:	Type B
Meeting Category:	Pre-NDA
Meeting Date and Time:	June 17, 2011 (2:00 – 3:30pm)
Meeting Location:	10903 New Hampshire Avenue White Oak Building 22, Conference Room: 1313 Silver Spring, Maryland 20903
Application #s/Names:	IND 073198 insulin degludec / insulin aspart IND 076496 insulin degludec
Sponsor/Applicant Name:	Novo Nordisk
Meeting Chair:	Mary H. Parks, M.D.
Meeting Recorder:	Rachel Hartford

FDA ATTENDEES

Ali Al Hakim, Ph.D.	Branch VII Chief, Division of New Drug Quality Assessment III (DNDQA-III), Office of New Drug Quality Assessment (ONDQA)
Richard Abate	Safety Evaluator, Division of Medication Error Prevention and Analysis (DMEPA), Office of Surveillance and Epidemiology (OSE)
Enid Galliers	Chief Project Management Staff, DMEP
Jean-Marc Guettier, M.D.	Clinical Reviewer, DMEP
Rachel Hartford	Regulatory Health Project Manager, DMEP
Hylton Joffe, M.D., M.M.Sc.	Diabetes Team I Leader, DMEP
Manoj Khurana, Ph.D.	Clinical Pharmacology Reviewer, Division of Clinical Pharmacology II (DCP II)

Cynthia Liu, M.S.	Statistician, Division of Biometrics II
Mary H. Parks, M.D.	Director, DMEP
Todd Sahlroot, Ph.D.	Statistics Team Leader, Division of Biometrics II
Nikhil Thakur	Combination Products Team Leader, Center for Devices and Radiological Health (CDRH), Office of Device Evaluation (ODE), Division of Anesthesiology, General Hospital, Infection Control, and Dental Devices (DAGID), General Hospital Devices Branch (GHDB)
Jayabharathi Vaidyanathan, Ph.D.	Acting Clinical Pharmacology Team Leader, Division of Clinical Pharmacology II (DCP II)

SPONSOR ATTENDEES

Peter Kristensen	Senior Vice President Global Development
Peter Bonne Eriksen	Senior Vice President Regulatory Affairs
Alan Moses	Corporate Vice President Global Chief Medical Officer
Anne Phillips	Corporate Vice President Clinical Development, Medical, Regulatory Affairs
Susanne Rugh	Project Corporate Vice President
Inger Mollerup	Corporate Vice President Regulatory Affairs
Søren Mikkelsen	Vice President Device Development
Martin Lange	International Medical Vice President
Mari-Anne Gall	International Medical Vice President
Mads Frederik Rasmussen	Executive Director Clinical Development Diabetes
Lars Endahl	Statistician
Hanne Haahr	Director Insulin Clinical Pharmacology
Jan Vanggaard Andersen	Senior Nonclinical Project Manager
Erica Nishimura	Scientific Director Diabetes Biology

Aage Hvass	Principal Scientist Diabetes Analytical Development
Jane Møll Pedersen	Global Regulatory Director
Dorrit Espersen Juul	Global Regulatory Director
Joseph O'Gara	Device Regulatory Affairs Officer
Dominique Lagrave	Senior Director Regulatory Operations and Innovation
Lois Kotkoskie	Senior Director Regulatory Affairs
Shawn Hoskin	Associate Director Regulatory Affairs

1. BACKGROUND

Novo Nordisk submitted IND 076496 for insulin degludec (IDeg), 100 U/mL and 200 U/mL on September 5, 2007. IND 073198 for insulin degludec/insulin aspart (IDegAsp), 100 U/mL was submitted on March 20, 2008. Both products are being developed to improve glycemic control in adults with Type 1 and Type 2 diabetes mellitus. A combined End-of-Phase 2 meeting was held on February 24, 2009.

Novo Nordisk plans to submit both NDAs at the same time in Fall 2011 and to include once daily and twice daily dosing regimens in the IDegAsp NDA. The purpose for this meeting is to discuss the content and format of the NDAs and to identify any issues that could hinder the review process or result in a refuse-to-file action.

2. DISCUSSION

FDA's preliminary responses to the questions enclosed in your May 12, 2011, meeting package were sent to you via email on June 16, 2011. Your questions appear below followed by our preliminary responses in **bold**. A summary of the discussion at the meeting is shown in *italics*. Post-meeting comments are shown in underlined regular font.

Insulin Degludec (IDeg)

CHEMISTRY, MANUFACTURING AND CONTROLS

Question 1: Presuming the acceptance of the data conclusions in the NDA, can the Agency comment on the proposed strategy to support the proposed (b) (4) month drug substance shelf life and (b) (4) ?

FDA Response: The proposed strategy will support the filing of the NDA. The adequacy of the data and the shelf life of the drug substance will be determined as part of FDA's review of the NDA. We do not agree with your proposal (b) (4) (b) (4). In accordance with Good Review Management Principles and Practices (GRMPPs) timelines, (b) (4)

Discussion: Novo Nordisk stated that they would like (b) (4) We responded that, as per the above response, (b) (4) .

Question 2: Presuming the acceptance of the data conclusions in the NDA, can the Agency comment on the proposed strategy to support the proposed 30 month drug product shelf life and [redacted] (b) (4)

FDA Response: The proposed strategy will support the filing of the NDA. The adequacy of the data and the shelf life of the single-entity drug product will be determined as part of FDA's review of the NDA. We do not agree with your proposal [redacted] (b) (4)

Discussion: See discussion under Question 1.

Background

In the NDA submission, Novo Nordisk will provide comparability protocols to support the following changes, which are intended to be implemented post-approval:

- Manufacture [redacted] (b) (4) of drug product at additional FDA approved sites for Novo Nordisk insulin production. Novo Nordisk will use the manufacturing process as described in the NDA at the additional sites.
- Assembly of drug product in PDS290 pen-injector at additional FDA approved Novo Nordisk manufacturing sites.

Implementation of the changes described in these comparability protocols will not be initiated until a final report is generated and signed by Quality Assurance (QA) and a company responsible person and only if all sites have a satisfactory current good manufacturing practice (cGMP) status at the time of implementation. Novo Nordisk is proposing to provide notification to the FDA at the time of implementation, and to submit the final reports to the product Annual Report at the next reporting period after sign-off and implementation.

Question 3: Does the Agency agree with the strategy of submitting comparability protocols for these types of changes in the NDA?

FDA Response: We have no objection to your plan to submit comparability protocols in the NDA. We will convey our comments on the reporting categories after reviewing all available information to be submitted in the NDA. However, be aware that annual reports are not an acceptable reporting category for the changes that you are proposing.

Discussion: No discussion occurred.

Question 4: Recognizing that the annual reporting categories will be determined upon review and approval of the comparability protocols, at this time can the Agency comment on the proposed implementation and reporting strategy?

FDA Response: See response to question 3.

Discussion: No discussion occurred.

DEVICE (PDS 290)

Background
As drug-device combination products, IDeg and IDegAsp PDS290 are subject for a review with split responsibilities between different Offices within the FDA. Novo Nordisk is aware that CDER DMEP has the lead for this review and that CDRH and CDER OSE also have a role in the review process. Novo Nordisk has an interest in achieving timely resolution of possible questions concerning Human Factor Engineering (HFE) studies.

Question 5: Novo Nordisk would appreciate if the Agency could provide insight in the review process and the timing relating to the PDS290 pen injector and the interaction between the affected offices including guidance on how Novo Nordisk can support this process?

FDA Response: The Division of Medication Error Prevention and Analysis (DMEPA) within the Office of Surveillance and Epidemiology and the Center for Devices and Radiological Health (CDRH) will concurrently review the PDS 290 injector and the associated Human Factors study data. DMEPA and CDRH work together to provide a unified set of comments with regard to Human Factors studies to streamline the Human Factors evaluation so that a single study can satisfy both groups' requirements. You should submit the data regarding the PDS 290 injector and the Human Factors study in clearly labeled sections of each application to assist reviewers in finding the required information needed to complete their reviews.

Discussion: No discussion occurred.

Question 6: If the Agency requests changes as part of label negotiations during the NDA review (i.e. to the carton, Instructions for Use or pen label), does the Agency agree that additional human factors testing of the revised label would not be necessary?

FDA Response: We do not agree that additional human factors testing of the revised labels would not be necessary. The need for additional human factors testing is a review issue and dependent on the required changes identified during review of the application.

Discussion: Novo Nordisk asked about the types of changes that would prompt the need for a new human factors study. We stated that if Novo Nordisk changes the label or labeling of the product (e.g. changing the proprietary name of the product), Novo Nordisk should incorporate this change into its risk analysis of use-related risks. Based on this analysis, Novo Nordisk should either provide the appropriate human factors testing to demonstrate that the use-related risk associated with the labeling change has been addressed, or Novo Nordisk should provide its rationale and evidence to demonstrate how the labeling change does not introduce any new use-related risk.

Background
Novo Nordisk is aware that a revised guidance on human factors testing may be available in the near future. For the human factors evaluation of the PDS290 pen-injector, we have based our human factors testing on the existing FDA guidances and standards together with the information

that FDA provided at our August 20, 2010 (Degludec Type C) meeting and January 13, 2011 (PDS290 end of review) meeting.

Question 7: Can the Agency share any new or changed requirements that may be included in a revised human factors testing guidance document, and comment how these would be applied to the upcoming PDS290 NDA review?

FDA Response: At this time, you are encouraged to refer to the existing Guidance Document. CDRH has provided comments to you regarding our expectations for Human Factors studies as part of the Agency's response to other submissions. Those general principles have not changed.

Discussion: No discussion occurred.

Question 8: Can the Agency provide their anticipated timeframe for release of this new guideline?

FDA Response: CDRH will announce the new Guidance on FDA's website (www.fda.gov). Please stay tuned to the website and other FDA announcements. There will probably be an opportunity to comment on the Guidance when it is published by FDA. Again, the details of the availability for comment, comment period, etc. will be forthcoming in future FDA announcements.

Discussion: No discussion occurred.

NONCLINICAL

Question 9: Does the Agency agree that the above nonclinical program is adequate for filing of the IDeg NDA?

FDA Response: Yes, the nonclinical program of IDeg appears reasonable for filing.

Discussion: No discussion occurred.

CLINICAL PHARMACOLOGY

Question 10: Does the Agency agree that the steady state data from Trial NN1250-3678 and the phase 3a Trial NN1250-3672 are sufficient to support approval of the 200 U/mL formulation for the once daily use of IDeg?

FDA Response: In the absence of a Phase 3, head-to-head comparison of the 100 U/mL and 200 U/mL dose strengths, the pharmacokinetic/pharmacodynamic trial NN1250-3678 which provides bridging information between the two formulations, becomes pivotal for claiming bioequivalence. Based on limited information the data appear adequate for filing.

In your phase 3 program, the U200 formulation was only studied in insulin-naive patients with type 2 diabetes. Given that patients with type 1 diabetes are less insulin-resistant than patients with type 2 diabetes, the adequacy of the available data to support approval of the 200 U/mL dose strength in type 1 diabetes will be a review issue.

Discussion: No discussion occurred.

CLINICAL

Question 11: Does the Agency agree that the 12-lead ECGs measured at baseline and at end of trial in NN1250-3579, with evaluation by a blinded independent central cardiology reading center, are adequate for assessing IDeg QT intervals and for filing of the IDeg and IDegAsp NDAs?

FDA Response: Your plan is adequate to support filing. Whether the data generated from this approach are adequate for assessing the effect of degludec and degludec/aspart on QT prolongation will be a review issue. Please submit analysis-ready data sets to facilitate review.

Discussion: Novo Nordisk agreed to submit a sample QT dataset within a week of the pre-NDA meeting so we could test analysis readiness.

Post-Meeting Comment: FDA has reviewed the sample QT dataset. The format of this dataset appears reasonable. To facilitate our review, we have the following recommendations:

- Include meaningful variable names and variable labels with unit/format information
- Provide a description of each variable in the "define.pdf" file. The unit for each numerical variable should be included
- Use the following format for date and time variables:
    - For date: Instead of using '20091023', please use '2009-10-23'
    - For time: Instead of using '907', '2145', please use '09:07', '21:45'
    - The time that the electrocardiogram is obtained should be recorded to the second.

Question 12: Does the Agency agree that the number of exposed subjects and the duration of exposure in the development program are adequate to support the NDA filing and adequately represents the US patient population?

FDA Response: The proposed number of exposed patients, the duration of exposure, and the representation of the United States patient population appear adequate to support NDA filing. However, the scope of your 4-month safety update is unclear. Therefore, the following comment was communicated to you via email on June 13: You mention that the

4-month safety update (i.e., database cut-off of March 31st 2011) for degludec and degludec/aspart will include blinded safety data from ongoing extension studies. Please clarify why the data will be blinded given that the phase 3 trials are open-label. In addition, clarify what types of adverse events and other safety data (e.g. lab data) will be included in the safety update and how those data will be presented. Update Table 5 (under Question 12) and Table 8 (under Question 26) to show how the patient exposures will increase when the safety update data are added to the data included at the time of NDA filing.

Enclosure 3 shows Novo Nordisk's pre-meeting responses to our above pre-meeting questions. The responses are acceptable except where noted otherwise.

Discussion: The discussion for this question focused on the amount, nature, analyses and planned presentation of additional data to be submitted in the 120-Day Safety Update. Novo Nordisk stated that data submitted in this safety update will not represent new patients but rather additional exposure of patients participating in extension trials. We agreed with Novo Nordisk's approach to focus the 120-Day Safety Update on major safety outcomes including deaths, serious adverse events, adverse events leading to withdrawal and adverse events of interest (cardiovascular events, neoplasms, severe hypoglycemic episodes, allergic/immunogenicity reactions and injection site reactions). To ensure that the data in the 120-Day Safety Update will be presented in a manner that will facilitate efficient review, we asked Novo Nordisk to submit shell tables to illustrate how these data will be presented.

Post Meeting Comment: On June 29, 2011, we received Novo Nordisk's sample shell tables and the strategy for presenting data in the 120-Day Safety Update. As agreed to at the meeting, Novo Nordisk confirmed that the 120-Day Safety Update will focus on deaths, serious adverse events, adverse events leading to withdrawal and adverse events of interest. For each of these analyses, Novo Nordisk proposes to show the original NDA data followed by the updated data in an identical table format. Various pooling strategies will be used (e.g., IDeg vs. comparator, IDegAsp vs. comparator, and/or IDeg + IDegAsp vs. comparator). We agree with this approach but request that Novo Nordisk also show adverse events leading to withdrawal for IDeg and IDegAsp combined vs. comparator for all patients and by type of diabetes (like is being done for deaths, serious adverse events, neoplasms, and allergic reactions). Besides showing the data in tabular format, we expect Novo Nordisk to highlight and discuss important differences between the data in the original NDA and the data in the 120-Day Safety Update.

Question 13: Does the Agency agree that the phase 3 program has included adequate exposure for the various races and ethnicities?

FDA Response: We agree provided no unexpected efficacy or safety concerns emerge particularly among those races/ethnicities with limited enrollment in your development program.

Discussion: No discussion occurred.

Question 14: Does the Agency agree to the approach for grouping the therapeutic confirmatory trials of IDeg and the presentation of these studies for all efficacy endpoints in the ISE?

FDA Response: We agree with your approach. Ensure that there are adequate hyperlinks between the narrative portion of the Integrated Summary of Efficacy and the supporting tables and figures. For our review of efficacy, we will focus on the results from the individual phase 3 trials.

Discussion: No discussion occurred.

Question 15: Can the Agency comment on the adequacy of the NN1250-3770 and 3668 trials to support the dosing of IDeg at any time of the day with a possibility to vary dosing time from day to day?

FDA Response: The design of these trials is adequate to support filing. We cannot comment on the adequacy of these trials to support varying the dosing time from day to day until we have reviewed the trial data in detail. There are several analyses that will be key for interpreting study results including, but not limited to, the following information that we requested via email on June 13, 2011: "With regard to Question 15 and the flexible dosing schedule please clarify: How data concerning compliance with the flexible dosing schedule was assessed and will be presented. What safety issues you have identified as potentially related to the flexible dosing schedule and considered in your safety analysis (i.e., hypoglycemia, hyperglycemia, etc...). How the effect of injection timing on safety outcomes will be presented [e.g., How injection intervals (i.e., 8 versus 40 hours) influence the rate of hypoglycemic or hyperglycemic events?]"

Enclosure 3 shows Novo Nordisk's pre-meeting responses to our above pre-meeting questions. The responses are acceptable except where noted otherwise.

Discussion: Novo Nordisk stated that safety data from the flexible dosing schedule will be presented by day of the week. Novo Nordisk agreed with our request to also present the safety data by pooling together days according to time of injection (i.e,. to pool all the days when study drug was dosed in the morning and compare to the pool of days when study drug was dosed in the evening). This pooling strategy will facilitate review of aggregate data following an 8 hour or 40 hour injection interval.

Question 16: Does the Agency agree with the proposed strategy for grouping of the IDeg trials and the proposed data-base cut-off?

FDA Response: Your general pooling strategy which groups clinical trials that are of similar design is appropriate. We agree that data for the subgroups you have identified (i.e., type of diabetes, antecedent insulin use and degludec strength) should be presented. However, the details of your pooling strategy are unclear. Therefore, the following comment was communicated to you via email on June 13: For the Integrated Summary of Safety for degludec and degludec/aspart, clarify which trials will be pooled for deaths, serious adverse events, withdrawals due to adverse events, common adverse events, immunogenicity reactions, hypoglycemia, and laboratory data. Please also clarify whether you intend to show both pooled and subgroup data for all (i.e., deaths, nonfatal serious adverse events, dropouts and discontinuations, significant adverse events, immunogenicity, labs, ECG etc…) or only for some safety outcomes.

Enclosure 3 shows Novo Nordisk's pre-meeting responses to our above pre-meeting questions. The responses are acceptable except where noted otherwise.

Discussion: Although Novo Nordisk's proposed pooling strategy appears reasonable, we reminded Novo Nordisk to include justification in the NDA for the various pooling strategies, taking into account similarities or differences in terms of the patient population studied, trial design, and types of comparator. Novo Nordisk confirmed that safety data will be presented in terms of total number of adverse events, incident cases and incidence rates. At our request, Novo Nordisk agreed to provide a common adverse event table using an incidence cutoff of ≥ 2% rather than the currently proposed (b) (4) *cutoff. Novo Nordisk also confirmed that the NDA will include adverse event tables that present all adverse events, regardless of incidence. We noted potential methodological issues with performing change from baseline analyses for laboratory data when the 26-week and 52-week trials are pooled. Therefore, we reached agreement that these laboratory analyses will be shown for the pool of 26-week trials and separately for the pool of 52-week trials.*

Question 17: Does the Agency agree with the proposed strategy for discussion of data for each of the trial groups?

FDA Response: See response to Question 16. For variables susceptible to be influenced by time on therapy (e.g., weight gain, immunogenicity) you should also include data for the completers population.

Discussion: Novo Nordisk agreed to include analyses for the completers population for the two outcomes listed above.

Post-Meeting Comment: Novo Nordisk's above proposal is acceptable. At this time we have not identified other safety issues that should be presented using the completers population. If such analyses are needed during our review of the NDA we will communicate this request to you in a timely manner.

Question 18: Does the Agency agree that the additional analyses, as described above, address the concerns raised in their Advice letter dated October 8, 2010, and the meta-analysis data provided will allow the Agency to make a determination on the comparative hypoglycemia observed between IDeg and IGlar in the phase 3a program?

FDA Response: We agree that you have addressed some of the methodological concerns raised in the October 8, 2010, advice letter. Whether the meta-analysis and other available hypoglycemia data will allow us to make a determination on the comparative hypoglycemia between degludec and glargine depends on review of the data.

For nocturnal hypoglycemia and overall hypoglycemia, you should also present the hypoglycemia results separately for symptomatic and asymptomatic events. When showing the results for nocturnal hypoglycemia, include results for overall hypoglycemia as well as results for hypoglycemia during the non-nocturnal hours.

There may be important differences between treatment groups that could confound the hypoglycemia results. Examples include timing of the insulin injection (e.g., glargine administered at night and degludec administered in the morning), type of glucose measurement (continuous glucose monitors, plasma glucose, or whole blood glucose), and differences in insulin dose. Clarify how you intend to address these potential confounders.

Discussion: Novo Nordisk reviewed the major findings surrounding hypoglycemic events in their program and was given the opportunity to clarify their position with respect to the effect of potential confounders on the observed findings. We asked Novo Nordisk to include in the NDA all needed information to interpret the hypoglycemia data, including analyses of hypoglycemic events in terms of number of events, event rates, and incidence rates. We also asked Novo Nordisk to analyze hypoglycemic events using the Wilcoxon test as a sensitivity analysis. This analysis can accommodate potential outliers, that is, patients with large numbers of hypoglycemic events.

Post-Meeting Comment: For all hypoglycemia analyses, also calculate event rates for each treatment group as the number of patients with at least one episode divided by total exposure for the treatment group and multiplied by 100.

Question 19: Can the Agency provide their perspective on the medical relevance of the time of day of hypoglycemic events in patients with type 1 and type 2 diabetes mellitus, and how this relates to the PD characteristics of a basal insulin?

FDA Response: We recognize that hypoglycemia, regardless of the timing during the course of the 24-hour day, has the potential to influence both benefit (achieving target HbA1c goal) and risk (e.g., death, serious impairment, injury, and increased risk of additional hypoglycemic events) associated with insulin therapy in diabetic patients. A hypoglycemic episode at any time of day can have important medical relevance, particularly if the episode is severe or leads to impairment or injury (e.g., while operating a motor vehicle). Basal insulins can lead to or contribute to hypoglycemia at any time during the 24-hour day if there is a mismatch between delivered dose and insulin requirements. We know, for example, that an insulin pump user may require adjustment of the basal insulin delivery rate at different times of the day to account for changes in insulin requirements that occur over the 24-hour period.

Discussion: No discussion occurred.

Question 20: Does the Agency agree that the proposed cardiovascular safety assessment is sufficient for NDA filing?

FDA Response: The strategy you outlined to assess cardiovascular safety is sufficient for NDA filing.

Discussion: No discussion occurred.

Insulin Degludec/Insulin Aspart (IDegAsp)

CHEMISTRY, MANUFACTURING AND CONTROLS

Question 21: Presuming the acceptance of the data conclusions in the NDA, can the Agency comment on the proposed strategy to support the proposed (b) (4) month drug product shelf life (b) (4))?

FDA Response: The proposed strategy will support the filing of the NDA. The adequacy of the data and the shelf life of the IDegAsp drug product will be determined as part of FDA's review of the NDA. We do not agree with your proposal (b) (4)

Discussion: See discussion under Question 1.

Note: The background package did not contain a question 22.

NONCLINICAL

Question 23: Does the Agency agree that the above nonclinical program is adequate for filing of the IDegAsp NDA?

FDA Response: Yes, the nonclinical program for IDegAsp appears reasonable for filing. You should reference nonclinical information in the proposed NDA for IDeg as well as NovoLog (NDA 20986) for the combination IDegAsp proposed NDA.

Discussion: No discussion occurred.

CLINICAL PHARMACOLOGY

Question 24: Based on the results presented for study NN5401-3857, does the Agency agree that the PK and PD profiles of IDegAsp are sufficiently different (at least 20%) from those of IDeg and IAsp to justify marketing of IDegAsp?

FDA Response: Provided the pharmacokinetic/pharmacodynamic study NN5401-3857 was conducted with the intended commercial formulations of IDegAsp and IDeg, this study will be adequate to support the proposed NDA for IDegAsp from a filing perspective. However, accepting the claim of "*sufficiently different (at least 20%) from those of IDeg and IAsp*" is a review issue.

Discussion: No discussion occurred.

Question 25 (identical to Question 11): Does the Agency agree that the 12-lead ECGs measured at baseline and at end of trial in NN1250-3579, with evaluation by a blinded independent central cardiology reading center, are adequate for assessing IDeg QT intervals and for filing of the IDeg and IDegAsp NDAs?

Discussion: We stated that the response to Question 11 applies to Question 25.

CLINICAL

Question 26: Does the Agency agree that the number of exposed subjects and the duration of exposure in the development program are adequate to support the NDA filing and adequately represents the US patient population?

FDA Response: The response to Question 12 is repeated here as it pertains to both degludec and degludec/aspart.

The proposed number of exposed patients, the duration of exposure, and the representation of the United States patient population appear adequate to support NDA filing. However, the scope of your 4-month safety update is unclear. Therefore, the following comment was communicated to you via email on June 13: You mention that the 4-month safety update (i.e., database cut-off of March 31st 2011) for degludec and degludec/aspart will include blinded safety data from ongoing extension studies. Please clarify why the data will be blinded given that the phase 3 trials are open-label. In addition, clarify what types of adverse events and other safety data (e.g. lab data) will be included in the safety update and how those data will be presented. Update Table 5 (under Question 12) and Table 8 (under Question 26) to show how the patient exposures will increase when the safety update data are added to the data included at the time of NDA filing.

Discussion: See Discussion and Post-Meeting Comment under Question 12.

Question 27: Does the Agency agree to the approach for grouping therapeutic confirmatory trials for IDegAsp and the presentation of these studies for all efficacy endpoints in the ISE?

FDA Response: We agree with your outlined approach. See response to Question 14.

Discussion: No discussion occurred.

Question 28: Does the Agency agree with the proposed strategy for grouping of the trials and the proposed data-base cut-off?

FDA Response: We agree with your general approach. Please see responses to Questions 16 and 17.

Discussion: No discussion occurred.

Question 29: Does the Agency agree with the proposed strategy for discussion of data for each of the trial groups?

FDA Response: We agree with your general approach. Please see responses to Questions 16 and 17.

Discussion: No discussion occurred.

Insulin Degludec (IDeg) and Insulin Degludec/Insulin Aspart (IDegAsp)

REGULATORY/ADMINISTRATIVE

Question 30: Does the Agency agree with this proposal to have one drug product folder for 100 U/mL and 200 U/mL?

FDA Response: Yes, we agree with your proposal as we previously recommended to you at the DIA Conference.

Discussion: No discussion occurred.

Question 31: Is this approach for datasets acceptable to the Agency?

FDA Response: Yes. Please make sure that the data format and variable names are consistent across trials.

Additional Clinical Pharmacology Response: You state that data sets for modeling and simulation will not be submitted. In your background package you did not specify the details of modeling and simulation (e.g., objectives and analyses conducted). Without this information, it is difficult to comment on your proposal. We encourage you to submit all available data as this may be helpful in the review of your submission.

Discussion: Novo Nordisk mentioned that they have conducted a population pharmacokinetic (PK) analysis using data from a clinical study in an Asian population and have not found anything significant with regard to covariates etc., and that they will not be using this information for any claims. Novo Nordisk stated that they intend to support the use in specific populations with results from other clinical pharmacology studies. We stated that while this modeling and simulation data may be useful, it is not required to be submitted in the NDA. We left it to Novo Nordisk's discretion as to whether to include the above mentioned analysis in the NDA. Novo Nordisk mentioned that this population PK data will be submitted with the trial datasets.

Question 32: Does the Agency agree with this proposal for patient tabulations?

FDA Response: No. Please submit individual patient tabulations (i.e., data listings) in PDF format with the study reports. We use the data listings to verify derived data if necessary. In order to efficiently plan and conduct inspections of clinical sites and sponsor, Office of Scientific Investigations (OSI) has specific requests concerning submission of datasets and data listings in the NDA that include submission of the individual patient tabulations in PDF format. As described in the attached documents, we request that you submit the PDF listings for the individual patient tabulations for each of the clinical trials. The purpose of submission of site-specific PDF listings and clinical trial-specific information is so that FDA can efficiently initiate and conduct inspections of clinical sites and additional CRO or sponsor sites as indicated. We are also requesting submission of a single new dataset as outlined in the document, "Summary Level Clinical Site Data for Data Integrity Review and Inspection Planning in NDA and BLA Submissions." The purpose of an electronic submission of a single new clinical site dataset is to facilitate the timely evaluation of data integrity and selection of appropriate clinical sites for FDA inspection as part of the application review process. Please refer to the attached documents concerning our requests.

Discussion: Novo Nordisk stated that they may require clarifications on some items in the OSI request. If this is the case, we stated that they should provide specific questions together with any needed background information and that we would respond in writing. Novo Nordisk also stated that they may not be able to comply with the requests for the line listings by the time of planned NDA submission on September 30, 2011, because the amount of data is large and would require extra effort on their part to compile and submit. OSI stated that the .xpt files are requested at the time of NDA submission in order to choose clinical sites for inspection. The line listings could be submitted within one month following submission of the NDA.

Post-Meeting Comment: Novo Nordisk has submitted clarifying questions on some items in the OSI request. We will send written responses to these questions in a separate letter.

Question 33: Does the Agency agree with this proposal for Case Reports Forms and Narratives?

FDA Response: No we do not agree. Please also provide narratives for all withdrawals coded to "other" that could potentially be due to adverse events (e.g., patient withdrawal of consent, investigator decision, etc.).

Ensure that all narratives are sorted by category (e.g., deaths, serious adverse events, withdrawals due to adverse events, etc.) and are easily identified/accessible via hyperlinks without the reviewers having to manually search for a narrative in individual study reports.

You are proposing (b) (4) **. Instead, you should include all narratives for these events, regardless of investigator assessment of causality.**

Post Meeting Comment: On June 29, 2011, Novo Nordisk provided additional information detailing how they plan to handle submission of narratives for patients whose reason for withdrawal is categorized as "Other". For these cases Novo Nordisk will review the reason(s) entered in the free-text field of the case report form to assess for a potential safety concern that may have resulted in withdrawal. Narratives will be provided for cases where an immediate or proximal adverse event that could have resulted in withdrawal is identified. Narratives will not be provided for withdrawals labeled as "others" where, for example, the listed reason is "withdrawal of consent" but where no adverse event is identified on the review of the free-text field. This approach for handling withdrawals coded to "Other" is acceptable

Novo Nordisk also provided a description detailing where narratives will be located and how these naratives will be organized and bookmarked in the integrated summary of safety. The description is consistent with recommendations listed in our pre-meeting response to Question 33 and this approach is acceptable.

Question 34: Does the Agency agree with this proposal for transmission of the ECG data?

FDA Response: Yes, we agree.

Discussion: No discussion occurred.

Question 35: At this time, does the Agency have any additional comments to the cross-reference strategy?

FDA Response: Your cross-reference strategy is acceptable.

Discussion: No discussion occurred.

Question 36: Does the Agency agree that it would be helpful for Novo Nordisk to include a Reviewer's Guide in Module 1 of each NDA?

FDA Response: We do not feel that this is needed.

Discussion: No discussion occurred.

Question 37: Novo Nordisk intends to submit the IDeg and IDegAsp NDAs so that both are received on the same day. In order to ensure this, is the Agency able to provide any guidance as to whether the NDAs should be submitted in parallel or should they be submitted one after the other?

FDA Response: The IDeg NDA should be submitted first, then the IDegAsp NDA should be submitted.

Discussion: No discussion occurred.

Question 38: As the Agency has extensive experience with insulin products, does the Agency agree that an Advisory Committee Meeting would not be needed?

FDA Response: This decision will be made after filing.

Discussion: No discussion occurred.

Question 39: If the Agency determines an Advisory Committee Meeting is necessary, can the Agency provide an idea of the timing for this meeting relative to their expectations for PDUFA review/action timelines as well as to when the decision would be communicated to Novo Nordisk?

FDA Response: For a standard review with a 10-month review clock, advisory committee meetings are typically scheduled during months 7 or 8 of the review process. If it is determined by the filing date that an Advisory Committee meeting will be necessary, you will be informed of this decision shortly after the filing meeting. Please note that the date of such a meeting may not be known at that time.

Discussion: No discussion occurred.

Question 40: Does the Agency agree that a Risk Evaluation and Mitigation Strategy would not be required for filing or approval of the NDAs?

FDA Response: Based on the limited data included in your briefing document, you do not require a Risk Evaluation and Mitigation Strategy (REMS) to file. Whether or not a REMS will be required at the time of approval will be a review issue. We will inform you in a timely manner if we identify the need for postmarketing commitments or postmarketing required studies during our review of the NDAs.

Discussion: No discussion occurred.

ADDITIONAL FDA COMMENTS

Biostatistics

a. Page 160 of the meeting package states that both baseline and postbaseline values were used for the last-observation-carried-forward (LOCF) analyses. We have interpreted this to mean that, in the absence of post-baseline data, you intend to carry forward baseline values. If baseline is carried forward, change from baseline in HbA1c at endpoint would be zero which, in a non-inferiority trial, could reduce the standard error and also bias the treatment difference towards the alternative hypothesis. For this reason, we suggest you apply LOCF to patients who have one or more post-baseline measurements.

Discussion: It was agreed that Novo Nordisk would keep their currently designated primary analysis. As requested, Novo Nordisk also will submit an LOCF analysis applied to patients who had at least one post-baseline measurement. Novo Nordisk will also include, for both 26- and 52-week studies, an analysis of patients completing 12 weeks irrespective of protocol violations. This is acceptable to FDA. Most patients who withdrew prematurely did so prior to

the 12-week timepoint; therefore this analysis is similar to an analysis of completers that we typically request as a sensitivity analysis in non-inferiority studies.

b. Include the following in your safety analyses:
   i. A search of your entire degludec and degludec/aspart database for biochemical cases of Hy's Law (serum ALT ≥3x ULN with serum total bilirubin ≥2x ULN). Include narratives for all cases identified.
   ii. Liver analyses based on all pooled phase 2/3 data that show the incidence of serum alanine aminotransferase (ALT) elevations ≥3x ULN, ≥5x ULN, ≥10x ULN, and ≥20x ULN for degludec and degludec/aspart vs. comparator

Discussion: Novo Nordisk agreed to include these analyses in the NDAs.

c. We recommend that you submit for review your proposed Standardised MedDRA Queries (SMQs) and Preferred Terms that will be used to search your database for adverse events of interest. If you submit this information within 1 week of the PreNDA meeting, we will aim to include feedback as a post-meeting note in the finalized meeting minutes.

Post Meeting Comment: On June 29, 2011, Novo Nordisk provided the proposed SMQs and Preferred Terms that will be used in MedDRA version 13.1 to search the database for potential adverse events of allergic reactions, injection site reactions, lipodystrophy, peripheral edema, neoplasms, medication error, diabetic retinopathy, peripheral neuropathy, hyperglycemia, and rare events in the degludec and degludec/aspart programs. The outlined strategy is acceptable and results from these search strategies should constitute the main analyses in the study report. With regard to allergic reactions we note that you have restricted your search to narrow scope terms and have excluded less specific but easily recognized symptoms and signs coded by such terms as throat tightness, stridor, wheezing, swelling, etc. We request that you perform an additional analysis for allergic reactions that includes these types of broader terms and that you include this analysis in the form of an appended table.

Novo Nordisk also described how they will be handling the conversion from Système Internationale (SI) units to United States units for laboratory parameters. Novo Nordisk's proposal is acceptable. However, to facilitate our review we request that all figures and text embedded in the main safety reports use U.S. units, particularly for the Integrated Summary of Efficacy and Integrated Summary of Safety. Provide laboratory parameters and reference ranges in U.S. units for all laboratory datasets.

Clinical Pharmacology

d. Since IDeg is highly bound to albumin, you should address the drug-drug interaction potential of IDeg with fatty acids and other protein bound drugs.

Discussion: No discussion occurred.

e. At the time of NDA submission, provide a Table that clearly lists the Trial number, Phase, type of population, formulation used, and an indicator column that clarifies whether the formulation was exploratory or the intended commercial formulation.

Discussion: Novo Nordisk agreed to include such a table in the Appendix under Module 2 Section 2.7.2. This is acceptable.

f. Please consider providing analysis-ready, raw concentration and PK/PD parameter data sets (preferably, as SAS transport files) for the clinical pharmacology/biopharmaceutics studies.

i. The concentration data set(s) should at minimum have the following columns, as applicable: ID, Trial Number, Nominal Time, Actual Time, Concentration, Unit, Comments (if any), Treatment, Period, and Sequence.
ii. The PK/PD parameter data set(s) should at minimum have the following columns, as applicable: ID, Trial Number, Parameter Name, Unit, Comments (if any), Treatment, Period, and Sequence.

Post-Meeting Comment: After the industry meeting Novo Nordisk submitted a sample dataset from a Phase 1 PK/PD trial. The format of this dataset seems reasonable. Also see Post-Meeting Comment under Question 11.

Required Pediatric Assessments

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.

Prescribing Information

Proposed prescribing information (PI) submitted with your application must conform to the content and format regulations found at 21 CFR 201.56 and 201.57.

Summary of the Final Rule on the Requirements for Prescribing Information for Drug and Biological Products, labeling guidances, sample tool illustrating Highlights and Table of Contents, an educational module concerning prescription drug labeling, and fictitious prototypes of prescribing information are available at: http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm. We encourage you to review the information at this website and use it as you draft prescribing information for your application.

Manufacturing Facilities

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

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

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

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

Corresponding names and titles of onsite contact:

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

3. ISSUES REQUIRING FURTHER DISCUSSION

None.

4. ATTACHMENTS AND HANDOUTS

1- OSI data and clinical trial information request
2- Summary Level Clinical Site Data for Data Integrity Review and Inspection Planning in NDA and BLA Submissions
3- Novo Nordisk Response to FDA's June 13, 2011, Request for Information

OSI Data and Clinical Trial Information Request

I. Request for general study related information and specific 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 Phase 3 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. Current Location of Principle Investigator (if no longer at Site): Address (e.g. Street, City, State, Country) and contact information (i.e., phone, fax, email)

2. Please include the following information in a tabular format by site in the original NDA for each of the completed Phase 3 clinical trials:

    a. Number of subjects screened for each site by site
    b. Number of subjects randomized for each site by 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 Phase 3 clinical trials:

    a. Location of Trial Master File [actual physical site(s) where documents are maintained and would be available for inspection]
    b. Name, address and contact information of all CROs used in the conduct of the clinical trials
    c. The location (actual physical site where documents are maintained and would be available for inspection) for all source data generated by the CROs with respect to their roles and responsibilities in conduct of respective studies
    d. The location (actual physical site where documents are maintained and would be available for inspection) of sponsor/monitor files (e.g. monitoring master files, drug accountability files, SAE files, etc.)

4. For each pivotal trial, please state the location and format of the source documents containing the primary efficacy endpoint. Specifically, are the data available at the clinical site and in what format? If not at the clinical site, please describe the location and format for the primary efficacy data.

5. For each pivotal trial provide a sample annotated Case Report Form.

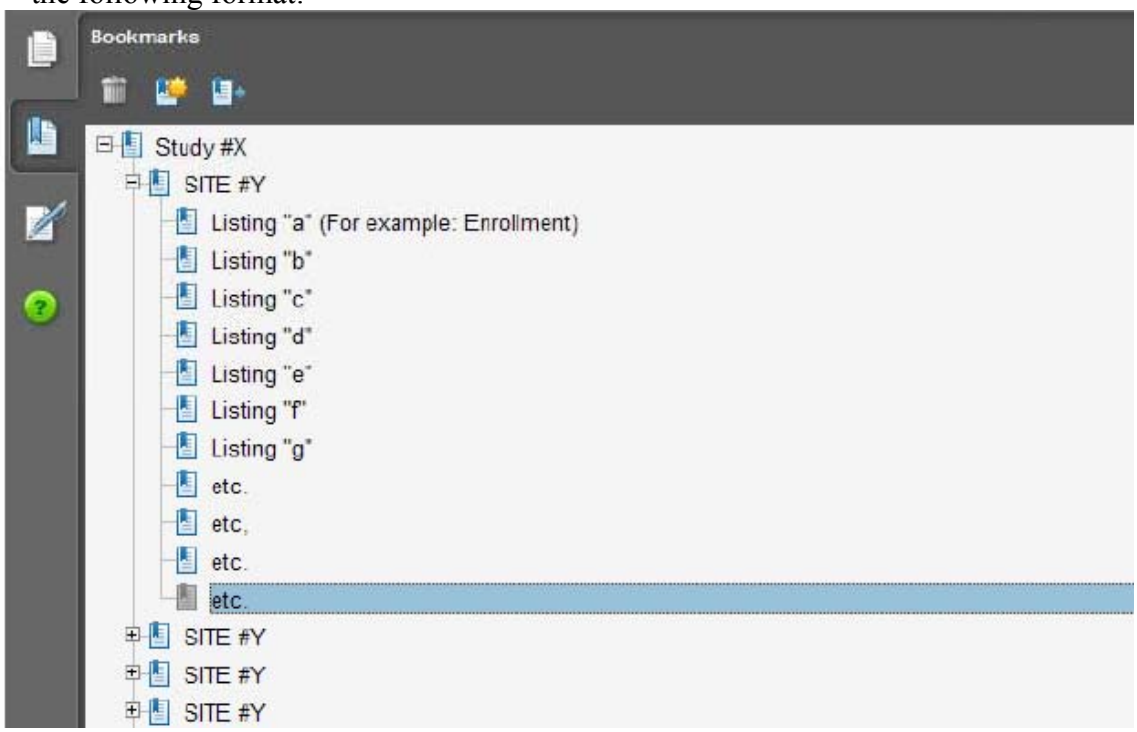
6. For each pivotal trial provide original protocol and all amendments.

II. Request for Subject Level Data Listings by Site

1. For each pivotal trial: Site-specific individual subject data ("line") listings. For each site provide line listings for:

    a. Listing for each subject/number screened and reason for subjects who did not meet eligibility requirements
    b. Subject listing for treatment assignment (randomization)
    c. Subject listing of drop-outs and subjects that discontinued with date and reason
    d. Evaluable subjects/ non-evaluable subjects and reason not evaluable
    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, 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 laboratory tests performed for safety monitoring
    k. By subject listing of exposure to test article.

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:

DSI is piloting a risk based model for site selection. Electronic submission of site level datasets will facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. Please refer to the attached document, "Summary Level Clinical Site Data for Data Integrity Review and Inspection Planning in NDA and BLA Submissions" for further information. We request that you provide a dataset, as outlined that includes requested data for each pivotal study submitted in your application.

Summary Level Clinical Site Data for Data Integrity Review and Inspection Planning in NDA and BLA Submissions

I. INTRODUCTION

The purpose of this electronic submission of a single new clinical site dataset is to facilitate the timely evaluation of data integrity and selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process.

II. DESCRIPTION OF THE SUMMARY LEVEL CLINICAL SITE DATASET

The summary level clinical site data are intended (1) to clearly identify individual clinical investigator sites within an application or supplement, (2) to specifically reference the studies to which those clinical sites are associated, and (3) to present the characteristics and outcomes of the study at the site level.

For each study used to support efficacy, data should be submitted by clinical site and treatment arm for the population used in the primary analysis to support efficacy. As a result, a single clinical site may contain multiple records depending on the number of studies and treatment arms supported by that clinical site.

The site-level efficacy results will be used to support site selection and are not intended to support evaluation of efficacy. To this end, for each study used to support efficacy, the summary level clinical site dataset submission should include site-specific efficacy results by treatment arm and the submission of site-specific effect sizes.

The following paragraphs provide additional details on the format and structure of the efficacy related data elements.

Site-Specific Efficacy Results

For each study and investigator site, the variables associated with efficacy and their variable names are:

- Treatment Efficacy Result (TRTEFFR) – the efficacy result for each primary endpoint, by treatment arm (see below for a description of endpoint types and a discussion on how to report this result)

- Treatment Efficacy Result Standard Deviation (TRTEFFS) – the standard deviation of the efficacy result (treatEffR) for each primary endpoint, by treatment arm

- Site-specific Efficacy Effect Size (SITEEFFE) – the effect size should be the same representation as reported for the primary efficacy analysis

- Site-specific Efficacy Effect Size Standard Deviation (SITEEFFS) – the standard deviation of the site-specific efficacy effect size (SITEEFFE)

- Endpoint (endpoint) – a plain text label that describes the primary endpoint as described in the Define file data dictionary included with each application.

- Treatment Arm (ARM) – a plain text label for the treatment arm that is used in the Clinical Study Report

In addition, for studies whose primary endpoint is a time-to-event endpoint, include the following data element:

- Censored Observations (CENSOR) –the number of censored observations for the given site and treatment.

If a study does not contain a time-to-event endpoint, record this data element as a missing value.

To accommodate the variety of endpoint types that can be used in analyses please reference the below endpoint type definitions when tabulating the site-specific efficacy result variable by treatment arm, "TRTEFFR".

- Discrete Endpoints – endpoints consisting of efficacy observations that can take on a discrete number of values (e.g., binary, categorical). Summarize discrete endpoints by an event frequency (i.e., number of events), proportion of events, or similar method at the site for the given treatment.

- Continuous Endpoints – endpoints consisting of efficacy observations that can take on an infinite number of values. Summarize continuous endpoints by the mean of the observations at the site for the given treatment.

- Time-to-Event Endpoints – endpoints where the time to occurrence of an event is the primary efficacy measurement. Summarize time-to-event endpoints by two data elements: the number of events that occurred (TRTEFFR) and the number of censored observations (CENSOR).

- Other – if the primary efficacy endpoint cannot be summarized in terms of the previous guidelines, a single or multiple values with precisely defined variable interpretations should be submitted as part of the dataset.

In all cases, the endpoint description provided in the "endpoint" plain text label should be expressed clearly to interpret the value provided in the (TRTEFFR) variable.

The site efficacy effect size (SITEEFFE) should be summarized in terms of the primary efficacy analysis (e.g., difference of means, odds ratio) and should be defined identically for all records in the dataset regardless of treatment.

The Define file for the dataset is presented in Exhibit 1.

III. CREATING AND SUBMITTING THE DATA FILE (SUBMISSION TEMPLATE AND STRUCTURE)

A sample data submission for the variables identified in Exhibit 1 is provided in Exhibit 2. The summary level clinical site data can be submitted in SAS transport file format (*.xpt). The file may be submitted electronically through the FDA Electronic Submission Gateway (ESG) referencing the active IND number or via secure CD addressed to the Division of Scientific Investigations point of contact.

Exhibit 1: Table 1 Clinical Site Data Elements Summary Listing (DE)

Variable Index	Variable Name	Variable Label	Type	Controlled Terms or Format	Notes or Description	Sample Value
1	STUDY	Study Number	Char	String	Study or trial identification number.	ABC-123
2	STUDYTL	Study Title	Char	String	Title of the study as listed in the clinical study report (limit 200 characters)	Double blind, randomized placebo controlled clinical study on the influence of drug X on indication Y
3	DOMAIN	Domain Abbreviation	Char	String	Two-character identification for the domain most relevant to the observation. The Domain abbreviation is also used as a prefix for the variables to ensure uniqueness when datasets are merged.	DE
4	SPONNO	Sponsor Number	Num	Integer	Total number of sponsors throughout the study. If there was a change in the sponsor while the study was ongoing, enter an integer indicating the total number of sponsors. If there was no change in the sponsor while the study was ongoing, enter “1”.	1
5	SPONNAME	Sponsor Name	Char	String	Full name of the sponsor organization conducting the study at the time of study completion, as defined in 21 CFR 312.3(a).	DrugCo, Inc.
6	IND	IND Number	Num	6 digit identifier	Investigational New Drug (IND) application number. If study not performed under IND, enter -1.	010010
7	UNDERIND	Under IND	Char	String	Value should equal "Y" if study at the site was conducted under an IND and "N" if study was not conducted under an IND (i.e., 21 CFR 312.120 studies).	Y
8	NDA	NDA Number	Num	6 digit identifier	FDA new drug application (NDA) number, if available/applicable. If not applicable, enter -1.	021212

Variable Index	Variable Name	Variable Label	Type	Controlled Terms or Format	Notes or Description	Sample Value
9	BLA	BLA Number	Num	6 digit identifier	FDA identification number for biologics license application, if available/applicable. If not applicable, enter -1.	123456
10	SUPPNUM	Supplement Number	Num	Integer	Serial number for supplemental application, if applicable. If not applicable, enter -1.	4
11	SITEID	Site ID	Char	String	Investigator site identification number assigned by the sponsor.	50
12	ARM	Treatment Arm	Char	String	Plain text label for the treatment arm as referenced in the clinical study report (limit 200 characters).	Active (e.g., 25mg), Comparator drug product name (e.g., Drug x), or Placebo
13	ENROLL	Number of Subjects Enrolled	Num	Integer	Total number of subjects enrolled at a given site by treatment arm.	20
14	SCREEN	Number of Subjects Screened	Num	Integer	Total number of subjects screened at a given site.	100
15	DISCONT	Number of Subject Discontinuations	Num	Integer	Number of subjects discontinuing from the study after being enrolled at a site by treatment arm as defined in the clinical study report.	5
16	ENDPOINT	Endpoint	Char	String	Plain text label used to describe the primary endpoint as described in the Define file included with each application (limit 200 characters).	Average increase in blood pressure
17	ENDPTYPE	Endpoint Type	Char	String	Variable type of the primary endpoint (i.e., continuous, discrete, time to event, or other).	Continuous
18	TRTEFFR	Treatment Efficacy Result	Num	Floating Point	Efficacy result for each primary endpoint by treatment arm at a given site.	0, 0.25, 1, 100
19	TRTEFFS	Treatment Efficacy Result Standard Deviation	Num	Floating Point	Standard deviation of the efficacy result (TRTEFFR) for each primary endpoint by treatment arm at a given site.	0.065
20	SITEEFFE	Site-Specific Efficacy Effect Size	Num	Floating Point	Site effect size with the same representation as reported for the primary efficacy analysis.	0, 0.25, 1, 100
21	SITEEFFS	Site-Specific Efficacy Effect Size Standard Deviation	Num	Floating Point	Standard deviation of the site-specific efficacy effect size (SITEEFFE).	0.065
22	CENSOR	Censored Observations	Num	Integer	Number of censored observations at a given site by treatment arm. If not applicable, enter -1.	5
23	NSAE	Number of Non-Serious Adverse Events	Num	Integer	Total number of non-serious adverse events at a given site by treatment arm. This value should include multiple events per subject and all event types (i.e., not limited to only those that are deemed related to study drug or treatment emergent events).	10
24	SAE	Number of Serious Adverse Events	Num	Integer	Total number of serious adverse events excluding deaths at a given site by treatment arm. This value should include multiple events per subject.	5
25	DEATH	Number of Deaths	Num	Integer	Total number of deaths at a given site by treatment arm.	1

Variable Index	Variable Name	Variable Label	Type	Controlled Terms or Format	Notes or Description	Sample Value
26	PROTVIOL	Number of Protocol Violations	Num	Integer	Number of protocol violations at a given site by treatment arm as defined in the clinical study report. This value should include multiple violations per subject and all violation type (i.e., not limited to only significant deviations).	20
27	FINLMAX	Maximum Financial Disclosure Amount	Num	Floating Point	Maximum financial disclosure amount ($USD) by any single investigator by site. Under the applicable regulations (21 CFR Parts 54, 312, 314, 320, 330, 601, 807, 812, 814, and 860). If unable to obtain the information required to the corresponding statements, enter -1.	20000.00
28	FINLDISC	Financial Disclosure Amount	Num	Floating Point	Total financial disclosure amount ($USD) by site calculated as the sum of disclosures for the principal investigator and all sub-investigators to include all required parities. Under the applicable regulations (21 CFR Parts 54, 312, 314, 320, 330, 601, 807, 812, 814, and 860). If unable to obtain the information required to the corresponding statements, enter -1.	25000.00
29	LASTNAME	Investigator Last Name	Char	String	Last name of the investigator as it appears on the FDA 1572.	Doe
30	FRSTNAME	Investigator First Name	Char	String	First name of the investigator as it appears on the FDA 1572.	John
31	MINITIAL	Investigator Middle Initial	Char	String	Middle initial of the investigator, if any, as it appears on the FDA 1572.	M
32	PHONE	Investigator Phone Number	Char	String	Phone number of the primary investigator. Include country code for non-US numbers.	44-555-555-5555
33	FAX	Investigator Fax Number	Char	String	Fax number of the primary investigator. Include country code for non-US numbers.	44-555-555-5555
34	EMAIL	Investigator Email Address	Char	String	Email address of the primary investigator.	john.doe@mail.com
35	COUNTRY	Country	Char	ISO 3166-1-alpha-2	2 letter ISO 3166 country code in which the site is located.	US
36	STATE	State	Char	String	Unabbreviated state or province in which the site is located. If not applicable, enter NA.	Maryland
37	CITY	City	Char	String	Unabbreviated city, county, or village in which the site is located.	Silver Spring
38	POSTAL	Postal Code	Char	String	Postal code in which site is located. If not applicable, enter NA.	20850
39	STREET	Street Address	Char	String	Street address and office number at which the site is located.	1 Main St, Suite 100

The following is a fictional example of a data set for a placebo-controlled trial. Four international sites enrolled a total of 205 subjects who were randomized in a 1:1 ratio to active or placebo. The primary endpoint was the percent of responders. The site-specific efficacy effect size (SITEEFFE) is the difference between the active and the placebo treatment efficacy result. Note that since there were two treatment arms, each site contains 2 rows in the following example data set and a total of 8 rows for the entire data set.

Exhibit 2: Example for Clinical Site Data Elements Summary Listing (Table 1)

STUDY	STUDYTL	DOMAIN	SPONNO	SPONNAME	IND	UNDERIND	NDA	BLA	SUPPNUM	SITEID	ARM	ENROLL	SCREEN	DISCONT
ABC-123	Double blind…	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	001	Active	26	61	3
ABC-123	Double blind…	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	001	Placebo	25	61	4
ABC-123	Double blind…	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	002	Active	23	54	2
ABC-123	Double blind…	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	002	Placebo	25	54	4
ABC-123	Double blind…	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	003	Active	27	62	3
ABC-123	Double blind…	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	003	Placebo	26	62	5
ABC-123	Double blind…	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	004	Active	26	60	2
ABC-123	Double blind…	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	004	Placebo	27	60	1

ENDPOINT	ENDTYPE	TRTEFFR	TRTEFFS	SITEEFFE	SITEEFFS	CENSOR	NSAE	SAE	DEATH	PROTVIOL	FINLMAX	FINLDISC	LASTNAME	FRSTNAME
Percent Responders	Binary	0.48	0.0096	0.34	0.0198	-1	0	2	0	1	-1	-1	Doe	John
Percent Responders	Binary	0.14	0.0049	0.34	0.0198	-1	2	2	0	1	-1	-1	Doe	John
Percent Responders	Binary	0.48	0.0108	0.33	0.0204	-1	3	2	1	0	45000.00	45000.00	Washington	George
Percent Responders	Binary	0.14	0.0049	0.33	0.0204	-1	0	2	0	3	20000.00	45000.00	Washington	George
Percent Responders	Binary	0.54	0.0092	0.35	0.0210	-1	2	2	0	1	15000.00	25000.00	Jefferson	Thomas
Percent Responders	Binary	0.19	0.0059	0.35	0.0210	-1	3	6	0	0	22000.00	25000.00	Jefferson	Thomas
Percent Responders	Binary	0.46	0.0095	0.34	0.0161	-1	4	1	0	0	0.00	0.00	Lincoln	Abraham
Percent Responders	Binary	0.12	0.0038	0.34	0.0161	-1	1	2	0	1	0.00	0.00	Lincoln	Abraham

MINITIAL	PHONE	FAX	EMAIL	COUNTRY	STATE	CITY	POSTAL	STREET
M	555-123-4567	555-123-4560	John@mail.com	RU	Moscow	Moscow	103009	Kremlin Road 1
M	555-123-4567	555-123-4560	John@mail.com	RU	Moscow	Moscow	103009	Kremlin Road 1
	020-3456-7891	020-3456-7890	george@mail.com	GB	Westminster	London	SW1A 2	10 Downing St
	020-3456-7891	020-3456-7890	george@mail.com	GB	Westminster	London	SW1A 2	10 Downing St
	01-89-12-34-56	01-89-12-34-51	tom@mail.com	FR	N/A	Paris	75002	1, Rue Road
	01-89-12-34-56	01-89-12-34-51	tom@mail.com	FR	N/A	Paris	75002	1, Rue Road
	555-987-6543	555-987-6540	abe@mail.com	US	Maryland	Rockville	20852	1 Rockville Pk.
	555-987-6543	555-987-6540	abe@mail.com	US	Maryland	Rockville	20852	1 Rockville Pk.

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/s/

RACHEL E HARTFORD
07/15/2011

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

IND 76,496
IND 73,198

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 Investigational New Drug Applications (INDs) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for NN 1250, Soluble Insulin Basal Analogue (SIBA), injection and NN 5401, Soluble Insulin Analogue Combination (SIAC), injection.

We also refer to the Combined End-of-Phase 2 meeting between representatives of your firm and the FDA on February 24, 2009.

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) 796-0331.

Sincerely,

{See appended electronic signature page}

Rachel Hartford
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 DATE:	**February 24, 2009**
TIME:	**1:30 – 3:30pm**
LOCATION:	**FDA - Federal Research Facility** **White Oak Building 22, Rm 1313** **10903 New Hampshire Avenue** **Silver Spring, MD**
APPLICATION:	**IND 76,496 SIBA** **IND 73,198 SIAC**
TYPE OF MEETING:	**End-of-Phase 2**
MEETING CHAIR:	**Mary H. Parks, M.D.**
MEETING RECORDER:	**Rachel Hartford**

FDA ATTENDEES (alphabetic): (Title and Office/Division)

Karen Davis Bruno, Ph.D.
Supervisor, Pharmacology/Toxicology, Division of Metabolism and Endocrinology Products (DMEP)

Lee Elmore, Ph.D.
Pharmacology/Toxicology Reviewer, DMEP

Enid Galliers
Chief, Project Management Staff, DMEP

Jean-Marc Guettier, M.D.
Medical Officer, DMEP

Rachel Hartford
Regulatory Project Manager, DMEP

Hylton Joffe, M.D., M.M.Sc.
Clinical Diabetes Team Leader, DMEP

Cynthia Liu, Ph.D.
Statistician, Division of Biometrics II

Robert Misbin, M.D.
Medical Officer, DMEP

Mary H. Parks, M.D.
Director, DMEP

Wei Qiu, Ph.D.
Team Leader, Division of Clinical Pharmacology II

Katrina Rhodes, M.D.
Medical Officer, DMEP

Todd Sahlroot, Ph.D.
Statistics Team Leader, Deputy Director, Division of Biometrics II

Millie Wright, RN, MSN
Safety Regulatory Project Manager, Office of Surveillance and Epidemiology

Xavier Ysern, Ph.D.
Chemistry Reviewer, Division of Pre-Marketing Assessment I

Immo Zdrojewski, Ph.D.
Clinical Pharmacology Reviewer, Division of Clinical Pharmacology II

EXTERNAL CONSTITUENT ATTENDEES (alphabetic):

Jan Vanggaard Anderson, Senior Preclinical Project Manager
Lars Endahl, International Project Statistician
Mari-Anne Gall, VP Medical & Science – Insulin Management
Hanne L. Haahr, Head of Insulin Clinical Pharmacology, Principal Clinical Pharmacologist
Dorrit Espersen Juul, Global RA Project Director
Peter Kristensen, Senior VP Global Development Management
Mary Ann McElligott, Associate VP Regulatory Affairs
Henriette Mersebach, International Medical Director
Inger Mollerup, VP Regulatory Affairs
Jane Moll Pederson, Senior Regulatory Project Manager
Lewis Pollack, Senior Director Regulatory Affairs
Henrik Rasmussen, VP Clinical Medical Regulatory Affairs
Susanne Rugh, Corporate Project VP – Insulin Management
Fannie Smith, Director Clinical Development & Medical Affairs, Diabetes & Metabolism
Elizabeth L. Tan, Associate Director Regulatory Affairs

BACKGROUND:

IND 76,496 for NN 1250, Soluble Insulin Basal Analogue (SIBA), injection was submitted on September 5, 2007. SIBA is composed of insulin 454 (a long acting soluble insulin analogue). IND 73,198 for NN 5401, Soluble Insulin Analogue Combination (SIAC), injection was submitted on March 20, 2008. SIAC is a combination of insulin 454 and insulin aspart (a rapid acting insulin analogue). Both are for the treatment of diabetes mellitus.

The combined End-of-Phase 2 meeting for SIBA and SIAC was requested on November 21, 2008, and granted on December 12, 2008.

DISCUSSION:

Preliminary responses to the questions enclosed in the January 27, 2009, meeting package were sent to Novo Nordisk via email on February 20, 2009. The background and questions appear below, followed by the FDA responses in bold. For questions where no additional discussion is indicated, neither Novo Nordisk nor FDA raised any additional issues pertaining to the questions.

SIBA (Soluble Insulin Basal Analogue)

CMC

Drug Substance Bioactivity Correlation Studies
With reference to the Investigational New Drug Application (IND) submitted under section 505 (i) of the Federal Food, Drug, and Cosmetic Act for NN1250 SIBA injection FDA submitted the recommendation:

"We recommend establishing as part of the insulin 454 characterization studies, the correlation between the potency values determined by the proposed bioassay, KIRA-TRIFMA (318G-04.152), and by the current compendial U.S. pharmacopeia (USP) bioassay <121> Rabbit Blood Sugar Method."

Our experience with the pharmacopoeia (USP) bioassay <121> Rabbit Blood Sugar Method is that it is not suitable for testing basal insulin analogue. The KIRA-TRIFMA assay has been established as the bioactivity assay for insulin 454; however the KIRA-TRIFMA assay is used only to confirm that the drug substance is biologically active and it is not used to define the dosing unit.

In a study investigating comparability between KIRA-TRIFMA and a Mouse Blood Glucose Assay, forced degraded samples of human insulin were used. It was demonstrated that the KIRA-TRIFMA method correlates with the Mouse Blood Glucose Assay and is suitable for detecting the decrease in insulin potency due to extremes in acid, base, light, heat, changed redox, or mechanical stress.

Question 1: Given the above, Novo Nordisk believes that the existing correlation data obtained on human insulin is sufficient to justify the KIRA-TRIFMA assay and therefore proposes that a separate comparability study with the USP Rabbit Blood Sugar Method should not be necessary. Does the Agency agree with the proposal?

FDA Response: Yes.

Revised Drug Product Specifications

Stability studies have been performed on various formulation versions of SIBA as part of product development efforts. Based on data from the large number of development batches as well as information obtained from ongoing stability studies of clinical trial supplies, four parameters of interest (pH, freezing point depression, zinc, and bacterial endotoxin) are not anticipated to be stability-indicating. In addition, filled containers (pen cartridges) are tested for closure integrity (b) (4). Sterility is also tested at release and end of shelf-life.

The four parameters of interest are part of the SIBA specifications which have been used from IND up to Phase 2. Novo Nordisk proposes decreasing their level of testing as presented in Table 1.

Table 1 Release and shelf life specifications for phase 2, phase 3, and NDA

Test	**Phase 2**		**Phase 3**		**NDA filing and Post Approval**	
	Release	**Shelf life**	**Release**	**Shelf life**	**Release**	**Shelf life**
pH	Test	Test	Test	Test	Test	No Test
Freezing Point Depression	Test	Test	Test	No Test	No Test	No Test
Zinc	Test	Test	Test	Test	Test	No Test
Bacterial Endotoxins	Test	Test	Test	No Test	Test	No Test

Question 2:

a) Does the Agency agree that it is not necessary to include pH as a testing parameter in the stability studies initiated after the NDA approval and can therefore be omitted from NDA shelf life specifications?

FDA Response: Yes

b) Does the Agency agree that it is not necessary to include Freezing Point Depression as a testing parameter in the stability studies initiated during phase 3 and after the NDA approval and can therefore be omitted from NDA shelf life specifications?

FDA Response: Yes.

c) Does the Agency agree that Freezing Point Depression can be omitted from post approval release specification?

FDA Response: Yes.

d) Does the Agency agree that it is not necessary to include Zinc as a testing parameter in the stability studies initiated after the NDA approval and can therefore be omitted from NDA shelf life specifications?

FDA Response: Yes.

e) Does the Agency agree that it is not necessary to include Bacterial Endotoxins as a testing parameter in the stability studies initiated during phase 3 and after the NDA approval and can therefore be omitted from NDA shelf life specifications?

FDA Response: Yes.

NON-CLINICAL

Carcinogenicity

The in vivo carcinogenicity assessment of insulin 454 will be based on a 12-month toxicity study in Sprague-Dawley rats with group sizes of 40-50 per group per sex and Neutral Protamine Hagedorn (NPH) insulin as comparator. The study will include full histopathology on all animals and additionally will include proliferation markers (BrdU) to study the proliferation index in female mammary tissue. Prior to initiation the study design has been discussed with EMEA and FDA.

Question 3: Does the Agency agree that the conducted carcinogenicity assessment program of insulin 454 is sufficient to support NDA approval?

FDA Response: The sponsor should remain aware that approval of an NDA depends upon review of all data submitted as part of that NDA. The study design of the 12-month toxicity study with insulin 454 and the NPH comparator appears reasonable.

CLINICAL PHARMACOLOGY & CLINICAL

Clinical Pharmacology Program

The pharmacokinetic and pharmacodynamic properties of SIBA have been investigated in four clinical pharmacology trials conducted in healthy subjects and in subjects with type 1 or type 2

diabetes. In addition, SIBA has been investigated in an insulin combination with insulin aspart, known as SIAC, in five clinical pharmacology trials.

Planned clinical pharmacology trials with SIBA include investigation of dose-response in a multiple dose setting and investigation in special populations such as subjects with renal or hepatic impairment, children and elderly. In addition, the effect of different injection sites, intra-subject variability in glucose-lowering effect at steady-state, as well as the counter-regulatory hormone responses during hypoglycemia episodes will be investigated in subjects with type 1 diabetes. Use of subjects with type 1 rather than type 2 diabetes facilitates the achievement of clinically relevant pharmacodynamic responses at therapeutic dose levels in steady state without introducing the confounding factor of endogenous insulin production.

Question 4: Does the Agency agree that the proposed clinical pharmacology program is adequate to support NDA approval?

FDA Response: Your proposed clinical pharmacology program seems acceptable. However we would like to advise you that in case your clinical program indicates ethnic differences in efficacy/safety, an additional pharmacokinetic study might be useful to explore these differences.

Please clarify if the formulation used in your phase 3a program is the same as the one to be used in your proposed clinical pharmacology studies.

Please clarify whether your phase 3a formulation is the same as the to-be-marketed formulation.

Additional Discussion:
Novo Nordisk will consider an additional pharmacokinetic study if there is a signal for ethnic differences. The formulation used in the Phase 3a program is the same as the one to be used in the proposed clinical pharmacology studies and the to-be-marketed formulation.

ECG-QT/QTc Measurements
Long term clinical experience with insulin administration in humans utilizing animal insulins, human insulins and insulin analogue, all acting through the same insulin receptor has not demonstrated any direct adverse effects of insulins on prolongation of the electrocardiogram-QT interval.

Four non-clinical studies have been performed to clarify the effect of insulin 454 on the QT/QTc interval:

- hERG receptor binding, tested up to 1000 nmol/l
- Action potential in isolated rabbit pukinje fibers, tested up to 1000 nmol/l
- QT interval in conscious dogs (tested up to 24 nmol/kg (s.c.))
- QT and QTc interval in anaesthetized dogs (tested up to 12 nmol/kg (i.v.)) – corresponding to a plasma concentration of approximately 100 nmol/l insulin 454

No effect was observed in any of the four studies, where insulin 454 has been tested up to 50x human exposure in vitro and 5x human exposure in vivo, assuming a maximal plasma human exposure of 20 nmol/l.

As with other insulin products, standard assessment of ECGs in healthy volunteers and in subjects with type 1 and type 2 diabetes during the phase 1-2 trials of SIBA have not shown any clinically meaningful changes. For the phase 3 development program, standard 12-lead ECG measurements will be performed at baseline and end of study and data on QT/QTc changes will be evaluated.

Question 5: Given the levels of drug investigated in animals and ECG results in phase 1 and 2, does the Agency agree that there is no need to perform a thorough QTc clinical pharmacology study in humans investigating potential effects on QT intervals?

FDA Response: Yes.

Additional Discussion:
Novo Nordisk proposed standard electrocardiogram (ECG) measurements at baseline and at the end of treatment in phase 3 clinical trials and asked if this would be acceptable without additional QTc evaluation. The proposal was not acceptable to DMEP. The Division suggested a sub-study with ECGs at expected Cmax read by a cardiologist blinded to treatment. The sponsor agreed to submit a proposal for more rigorously assessing QT intervals in phase 3. This proposal will include pharmacokinetic information showing when Cmax is expected to occur.

ADME Studies
The in vivo distribution, metabolism and excretion of 3H-insulin 454 (labeled in the fatty acid moiety) have been studied intensively in rats and dogs following s.c. and i.v. administration. The in vitro degradation has been investigated in hepatocytes and following incubation with catepsin D.

The uptake of systemic insulin 454 was low in the majority of tissue as expected for a 6kD protein with a high affinity to serum albumin. Insulin 454 was distributed like human insulin, i.e. through a large uptake in kidney and liver. Insulin 454 is mainly circulating as intact insulin 454 in plasma. It stimulates insulin action by binding to the human insulin receptor and undergoes extensive degradation before elimination. Insulin 454, like human insulin, is eliminated through both renal and hepatic routes.

The plasma radioactivity was mainly related to unchanged insulin 454 and a very polar component (tritiated water) whereas the level of circulating metabolites was low compared to insulin 454. Radioactivity was excreted in the form of numerous metabolites. The high number of components and low concentration of each individual component suggest an extensive degradation of insulin 454, which is further supported by the formation of tritiated water formed

following total metabolism of the fatty acid moiety. This slow excretion rate and a possible recycling of radioactivity (as fatty acid metabolites into non-drug related endogenous components) resulted in a low excretion recovery.

In vitro degradation with catepsin D showed the same initial degradation of insulin 454 and human insulin (B24-B25 and B25-B26 cleavage). Studies in human hepatocytes did not show any unique degradation products when compared to data from studies in animal hepatocytes. Following review of the non-clinical ADME data summarized above Novo Nordisk does not foresee safety concerns for circulating metabolites as the levels compared to intact insulin 454 are expected to be low and the likelihood of formation of human-specific metabolites (disproportionate drug metabolite) is considered to be low.

Major objectives for human ADME studies like excretion pathways and metabolite profile may be difficult to investigate due to recycling of radioactivity and formation of tritiated water. Based on above considerations, Novo Nordisk does not plan to perform a human ADME study.

Question 6: Does the Agency agree that there is no need to perform a human ADME study with radiolabeled insulin 454 to obtain NDA Approval?

FDA Response: Yes.

Proposed Phase 3a Development Program

The proposed clinical phase 3a program for SIBA will include seven global confirmatory trials. Six of these trials (2 trials of 12 months duration; 4 trials of 6 months duration) will be conducted in subjects with type 2 diabetes. One trial (12 months duration) will be carried out in subjects with type 1 diabetes, another in subjects with type 2 diabetes, both provide a possibility to continue treatment in an extension study (12 months duration). Insulin glargine, insulin detemir and dipeptidyl peptidase 4 (DPP-4) inhibitor will be used as active comparators in the phase 3a trials.

Novo Nordisk plans to submit with 12 months data at time of NDA submission. The goal of the clinical phase 3a program is to demonstrate that SIBA is safe and efficacious for the treatment of diabetes mellitus, including exposure to elderly and obese patients. We anticipate that our recruitment strategy (and selection of trial sites with all trials being global trials) will allow sufficient exposure of the main racial and ethnic groups to SIBA.

Question 7:

a) Does the Agency agree that the proposed phase 3a development program for SIBA is adequate to support the following indication?
SIBA is a soluble insulin product indicated to improve glycemic control in patients with diabetes mellitus

FDA Response: The initial indication will be for adults with diabetes mellitus. Please see our response to Question 19 pertaining to your proposed pediatric development program.

b) Does the Agency agree with the choice of comparators in the proposed development program for SIBA?

FDA Response: The Division does not understand the purpose of performing a non-inferiority trial (Study 3580) comparing your titratable insulin to the modest efficacy of a dipeptidyl peptidase (DPP) 4 inhibitor. Use of a non-inferiority margin of 0.4% in this setting is too liberal. Instead, we recommend that you compare SIBA to a glucagon-like peptide (GLP)-1 analog. Such a study will provide much more relevant data for a patient who has failed oral anti-diabetic medications and is deciding between the use of a basal insulin, like SIBA, or another injectable medication like a GLP-1 analog.

The Division also does not understand the purpose of Study 3581, because both treatment groups will have received liraglutide starting 12 weeks prior to randomization, essentially comparing SIBA to no additional therapy. A more meaningful study would initiate liraglutide with or without SIBA at randomization.

Detemir should be dosed twice daily (not once daily) in Study 3718 to ensure that SIBA is compared to an optimal detemir regimen.

Additional Discussion:
Novo Nordisk asked if a non-inferiority margin of 0.2% instead of 0.4% would be acceptable in study 3580. The Division responded that a margin of 0.3% might be a possibility but stressed that study 3580 is viewed as a marketing study. Little, if any data from this trial may be allowed into the label. A DDP-4 inhibitor with fair to modest efficacy is not a good comparator for a pivotal trial for a new insulin that is titratable. Pivotal trials for a new insulin should compare the new insulin to a previously approved insulin. The overall design of Study 3580 is not optimal and the Division strongly urged the sponsor several times during the discussion that the design be modified to yield more meaningful data.

Novo Nordisk stated that the liraglutide studies would be initiated after liraglutide approval and that the run-in period ensures all patients are optimized prior to starting insulin, as is expected in clinical practice. Novo Nordisk stated that the purpose was to obtain data on the combination of SIBA with a GLP-1 analog. However, little, if any data from this trial may be allowed into the label because SIBA is essentially being compared to no additional therapy. Again, the Division strongly urged the sponsor during the discussion that the design be modified to yield more meaningful data. The Division suggested comparing liraglutide plus another approved insulin versus liraglutide plus SIBA. Novo Nordisk agreed to consider the design.

Novo Nordisk stated that the correct study number is 3672 (not 3718) and that Detemir is currently labeled for once or twice daily injections. The Division responded that in non-

inferiority studies the comparator dosing regimen should be optimized. Novo Nordisk has data comparing once and twice a day dosing of Levemir and agreed to submit these data for FDA review in order to support the proposed once daily Levemir dosing in Study 3672.

c) Does the Agency agree that the proposed trials investigating SIBA in combination with metformin, sulfonyureas, thiazolidinediones, DPP-4 inhibitors and GLP-1 receptor agonists are sufficient for obtaining a general indication for the use of SIBA in combination with antidiabetic agents?

FDA Response: Yes.

d) Can the Agency confirm the acceptability of the broad inclusion/exclusion criteria for the proposed phase 3 trials?

FDA Response: Your broad inclusion and exclusion criteria for your phase 3 trials are acceptable.

Duration of Exposure and Number of Subjects Exposed
Overall, approximately 2873 subjects (466 and 2407 subjects with type 1 and type 2 diabetes, respectively) will be exposed to SIBA in the phase 3a development program, of which an estimated 2443 subjects will be exposed for 6 months and 1500 subjects for 12 months. In addition, 474 subjects will be treated for 18 months in an extension trial.

Eighty years of experience has demonstrated that insulin has a restricted range of biologic effects all mediated through the insulin receptor. Novo Nordisk has demonstrated that acylation of the insulin molecule can produce a biologically active and clinically safe basal insulin analogue (insulin detemir, Levemir®). Insulin 454 has a similar molecular structure to insulin detemir (both products are attached to a fatty acid ligand at position B29 of the B-chain), has a higher relative affinity for the insulin receptor than for the IGF receptor, and is expected to have a low immunologic response. The mode of action of insulin 454 is identical to that of human insulin and other insulin analogue as they all act through the same insulin receptor.

Based on these characteristics and given the nature of the pharmacological effects of insulin 454, Novo Nordisk plans to file for marketing approval based on 12-month exposure data. The safety profiles of injectable insulins and insulin analogues are well established and therefore Novo Nordisk supports the 12-month exposure requirements of the ICH E1 guidance and that any additional exposure information be provided as a post-approval commitment.

The FDA and other international regulatory authorities have significant experience with insulin and insulin analogue, and it is expected that additional pre-approval exposure required by the recently published FDA Draft Guidance on treatment and prevention of diabetes mellitus would not provide additional safety and efficacy data above what is known about this class of products.

Question 8: Does the Agency agree that the proposed number of exposed subjects and the duration of exposure in the proposed phase 3a program at the time of NDA filing are sufficient to support marketing authorization approval?

FDA Response: Yes.

Direct Switch from other Insulin Products

The basis for the proposed unit-to-unit transfer is the results from the clinical pharmacology and phases 2 trials, which support a potency of insulin 454 very close to 100% of that of insulin glargine. Further, for type 1 patients in NN1250-1835 none of those who were switched in a 1:1 manner from existing OD basal insulins to SIBA had any severe hypos within the first two weeks and the frequency of minor hypos was comparable between treatment arms indicating the safety of 1:1 switch.

In two phase 3a trials (NN1250-3582 for type 2 diabetes and -3583 for type 1 diabetes), subjects who are already using basal insulins (NPH, glargine, detemir) will be included and transferred to SIBA on a unit-to-unit basis with respect to the basal insulin dose, followed by individual dose optimization. It is expected that the phase 3a program will provide evidence of a safe and effective unit to unit switch, which takes into account that SIBA, as with all other insulins, requires close monitoring and dose adjustments.

Question 9: Is the proposed program sufficient to generate recommendations in the Dosage and Administration section of the SIBA labeling for switching subjects from other insulin products to SIBA on a unit-to-unit basis?

FDA Response: The labeling in the Dosage and Administration section should be consistent with how SIBA was studied in your phase 3 program. If you use a 1:1 switch in the phase 3 programs and there is sufficient efficacy and safety information from that approach, then the Dosage and Administration section will incorporate that recommendation for a 1:1 switch. If there are no data or inadequate data to support the proposed labeling language or if the 1:1 switch results in efficacy/safety concerns, it is unlikely that a 1:1 switch will be recommended.

Additional Discussion:

Novo Nordisk stated that all trial participants will have HbA1c levels ≥ 7%. The Division agreed that the comments under Question 9 will also apply to patients switched to SIBA (once approved) who have HbA1c <7%.

Secondary Confirmatory Endpoints

The trials in the SIBA phase 3a program are designed to compare SIBA and comparator products with respect to the primary endpoint (HbA1c). Provided that non-inferiority is established for HbA1c for a particular trial, a small number of confirmatory secondary endpoints also will be tested in different trials such as fasting plasma glucose and proportion of responders.

For the analyses of the confirmatory secondary efficacy endpoints the one-sided type 1 errors will be preserved at a 2.5% level through a hierarchical test strategy. Novo Nordisk believes that the program is sufficient to support statements in the clinical studies section of the labeling regarding the proposed confirmatory secondary endpoints should significant differences be found between SIBA and other basal insulin treatments.

The confirmatory secondary endpoints will be individually defined in each protocol depending on the trial design and comparator used. The statistical details of the sequential testing can be found in the abbreviated statistical analysis plan in the briefing document.

One of the confirmatory secondary endpoints is 'responders without hypoglycemia' defined as subjects with at least 12 weeks of exposure achieving an HbA1c value of ≤7% at the end of treatment in the absence of any confirmed hypoglycemic events in the 12-weeks period prior to the end of treatment.

Question 10:
a) Does the Agency agree (b) (4)

FDA Response: (b) (4) **The Division cannot commit to this at the present time. We recommend that you control the type 1 error rate for key secondary endpoints** (b) (4) **, you will need to show that the data are reliable. For example, for the proposed endpoint of "responders without hypoglycemia", how will you ensure that there is capturing of all hypoglycemic events that occur? How will you ensure that the open-label designs of your trials do not bias reporting of hypoglycemia? If there are differences between treatment groups in the distribution of patients with HbA1c ≤7%, how would you account for the expected slightly higher incidence of hypoglycemia in patients with HbA1c several tenths of a percentage point below 7% at endpoint compared to patients who have HbA1c just below or at 7% at endpoint? How would you account for patients who have a short-period of more intensive glycemic control that is not reflected much in HbA1c but which accounts for a short-period of more frequent hypoglycemia?**

We note that the order of your proposed key secondary endpoints differs across your SIBA and SIAC trials. Please provide an explanation of how you decided to prioritize these secondary endpoints. Also, please clarify whether you will be using a superiority test or non-inferiority test for each of the key proposed secondary endpoints.

Additional Discussion:
Novo Nordisk explained that priority of secondary endpoints is based on clinical relevance and statistical chance of superiority; all secondary endpoints will use a superiority test.

b) Does the Agency agree that inclusion of information regarding the number of type 2 patients achieving a value of HbA1c < 7% at the end of treatment in the absence of any confirmed hypoglycemic events in the 3-month period prior to end of treatment ('responders without hypoglycaemia') can be used as a confirmatory secondary endpoint?

FDA Response: Please see our response to Question 10(a). Reporting of hypoglycemia is somewhat observer-dependent. Because the trials are unblinded, there may be bias in reporting of hypoglycemia events.

Additional Discussion:
The Division explained that (b) (4) **as requested above, will be a review issue.**

Due to the long half-life of SIBA, the Division recommended extending the adverse event collection time frame to seven days (instead of 5 days) after the last dose of study medication.

Definition of Hypoglycemia
Novo Nordisk intends to collect information on hypoglycemia using the ADA definition as well as the Novo Nordisk definition previously used in the applications for marketing authorization approval of other insulin analogues (insulin detemir, insulin aspart, and biphasic insulin aspart). Major hypoglycemia being defined as a hypoglycemic event where the subject is not able to treat him/herself, whereas minor hypoglycemia is defined as a hypoglycemic event where a plasma glucose measurement of less than 56 mg/dL (3.1mM) has been assessed.

Moreover, for defining the confirmatory secondary endpoints on hypoglycemic event rates and responders without hypoglycemia, Novo Nordisk proposes to use "confirmed hypoglycaemic events" as the combination term of major and minor hypoglycemic events, both classified according to the Novo Nordisk definition. Hence a confirmed hypoglycemic event is defined as an event where the subject is not able to treat him/herself and/or a plasma glucose measurement of less than 56 mg/dL (3.1mM) has been assessed.

Question 11:
a) Does the Agency agree with the use of the Novo Nordisk definition for hypoglycemia for reporting in clinical studies section of the label?

FDA Response: The definitions are acceptable; but we are concerned that ascertainment of hypoglycemia may be biased. Please see our responses to Question 10.

b) Does the Agency agree with the use of confirmed hypoglycaemic events for defining confirmatory secondary endpoints?

FDA Response: Please see the caveats described above relating to hypoglycemic endpoints.

Meta-analysis of Hypoglycemic Events

From previous development programs it is known that even substantial differences in rates of hypoglycemia between treatments can fail to reach statistical significance due to the limited power in the statistical model for analyzing hypoglycemic events. In order to confirm potential differences in rates of hypoglycemia between SIBA and the comparator, data from all insulin phase 3a trials, except trials utilizing the SIBA 200U, will be analyzed individually and also in a combined meta-analysis. The strategy to be used will be described in a meta-analysis plan that will be finalized before the first database lock in the phase 3a development program.

Question 12: Does the Agency agree that a (b) (4)

FDA Response: See the response to Questions 10 and 11 above. A detailed meta-analysis plan with a pre-specified statistical analysis model should be submitted well in advance to allow sufficient time for review.

Additional Discussion:

The meta-analysis plan will be submitted 30-60 days prior to database lock.

Blood Glucose Fluctuation

For all phase 3a trials, glucose fluctuation (defined as the average excursion from the mean of any glucose profile) will be assessed in all subjects by means of standard 9-point self-measured plasma glucose profiles recorded over 24-hour periods at designated stages of the trial, including baseline.

In addition, two of these trials (NN1250-3579 and NN1250-3583), Novo Nordisk plans to more closely evaluate glucose fluctuation via continuous glucose measurement (CGM), whereby 72-hour interstitial glucose profiles will be measured in a representative subgroup of subjects. The number of subjects undergoing CGM will be calculated to provide sufficient statistical power to detect differences in interstitial glucose fluctuation between SIBA and the comparator.

Question 13: (b) (4)

FDA Response: The Division cannot commit to this at the present time. We recommend that you control the type 1 error rate for key secondary endpoints (b) (4) **s part of this justification, you will need to show that the data derived from CGM and 9-point glucose profiles are reliable and**

standardized across patients, [redacted] (b) (4) **.**

Additional Discussion:
The Division stated that continuous glucose monitors are currently only approved for tracking and trending of blood glucoses because of technological limitations of the devices. [redacted] (b) (4) **.**
The other proposed endpoints in Question 13 are also novel. [redacted] (b) (4) **The rationale should include a description of the reliability of the data measures. The type 1 error rate must be controlled for all efficacy parameters** [redacted] (b) (4) **.**

Evaluation of Antibody Development
Antibody development to exogenous insulin usually peaks after 3-6 months after which antibody levels plateau or decline depending on the insulin product and the subjects exposed. Samples for antibody measurement will be taken in certain phase 3a trials at start of treatment, during trial, at end of treatment, and at follow-up. Determination of antibodies specific for insulin 454, antibodies specific for insulin aspart, antibodies specific for comparator and antibodies cross-reacting to human insulin will be done using a validated subtraction Radio Immuno Assay (RIA), modified from Lindholm et al. 2002. (ref. 1)

Insulin 454 interferes with anti-insulin 454 antibody measurement causing the resulting antibody binding to be lower than in a sample with no insulin 454 present. Treatment pauses to allow insulin 454 wash-out during trials will not be introduced because the potential safety and ethical implications are considered significant. Therefore, the main analyses of antibody development will be based on antibody levels before and after treatment (1 week after drug is discontinued) analyses.

Antibody development will be monitored in selected phase 3 trials. In a 12-month trial in subjects with type 1 diabetes (NN1250-3583) an estimated 466 subjects will be exposed (and subjects are offered to participate in a 12-month extension of this trial). In addition, a 12-month trial in subjects with type 2 diabetes (NN1250-3579) an estimated 736 subjects will be exposed.

Testing for correlations between antibody titres and relevant efficacy and safety parameters (e.g. levels of glycemic control, insulin dose) is well established in detecting any clinically relevant effects of antibody induction by exogenous insulin. Assessment of neutralizing antibodies do not add to the interpretation of the potential impact of antibody development on glucose control. Therefore assays for detection of neutralizing antibodies will not be developed.

Question 14:

a) Does the Agency agree to the proposed strategy in the phase 3a program for evaluating insulin antibody development?

FDA Response: Yes. At the present time, you do not need to develop an assay for neutralizing antibodies (see our response to Question 14b). Testing of correlations between antibody titer and relevant clinical parameters is acceptable. It is not clear why there must be a washout period prior to measurement of antibodies to Insulin 454, because a washout period is not needed when measuring antibodies to other insulins. Please clarify.

Additional Discussion:
The sponsor stated that all insulins (even endogeneous insulin) in plasma interfere with antibody measurement. The sponsor clarified that Insulin 454 has a longer half-life which exacerbates interference and necessitates the wash-out period for better assay sensitivity and noted that the Detemir trials also utilized a wash-out period. The Division agreed that a wash-out period is acceptable and inquired about the antibody half-life. Novo Nordisk responded that the antibody half-life is weeks.

b) Does the agency agree to the analysis strategy whereby the development in antibody titres will be described and correlations between antibody titres and relevant efficacy and safety parameter will be estimated?

FDA Response: Yes. However, we advise you to bank blood samples in case additional antibody testing is needed to assess for neutralizing antibody if there are significant efficacy and safety differences associated with the production of antibodies to Insulin 454.

Cardiovascular Risk Profile
Insulin 454 has a similar molecular structure to insulin detemir (Levemir®) and shares the same molecular mechanism of action as human insulin and insulin detemir. In approximately 2 million patient years of exposure with insulin detemir, only 90 adverse reaction reports (serious as well as non-serious) were reported from unsolicited sources within the MedDRA System Organ Class "Cardiac Disorders" and "Vascular Disorders" (according to the Levemir® PSUR of Oct. 8, 2008). There is no reason to believe that the cardiovascular profile of insulin 454 should be any different from insulin detemir or any other analogue of human insulin.

To evaluate the CV profile of insulin 454, Novo Nordisk will allow for inclusion of patients at higher risk of cardiovascular events such as patients with relatively advanced disease, elderly patients and patients with some degree of renal impairment. This is done by allowing for inclusion of subjects with a prior cardiovascular event (stroke, myocardial infarction, unstable angina pectoris, coronary arterial by-pass graft or angioplasty) occurring up to 6 months before inclusion into the trial as opposed to 12 months for previous insulin development programs (NovoLog®, NovoLogMix®, Levemir®), and more liberal serum-creatinine limits (serum-creatinine up to 125 µmol/L for men and 110 µmol/L for females) will be used to allow for patients with some degree of renal impairment. In addition, there will be no limitations on age, diabetes duration, or micro- or macro-albuminuria. However, as all the phase 3a trials implement a tight titration schedule to bring the patients toward euglycemia, severely ill patients with regard to cardiovascular disease will not be included in the trials, since the titration schedule might pose

a safety risk for these patients (Skyler J S et al, Circulation 2009;119). A list of inclusion and exclusion criteria is given in section E3.3.

Novo Nordisk intends to monitor all CV treatment emergent adverse events closely. This will be done by recording all major adverse CV events, including myocardial infarction, stroke or CV related death, as Medical Events of Special Interest (MESI) in the phase 3a trials, enabling immediate and consistent collection of data. A list of Preferred Terms covering CV events (Acute Coronary Syndrome, Stroke and Cardiac Death) to be defined as MESIs in the phase 3a program is included in Appendix E.

All collected CV events will be evaluated by an internal Novo Nordisk Safety Committee for the product. A Safety Committee of internal Novo Nordisk employees from the product safety and medical departments is constituted and chaired by a Safety Surveillance Adviser, Novo Nordisk A/S Head Quarters (NNHQ). The safety surveillance department from International Product Safety belong to a different part of the Novo Nordisk A/S organisation than the Global Development departments in order to be independent. The internal SIBA SIAC Safety Committee (SC) is established to review the ongoing safety surveillance conducted on data from clinical trials and pre-clinical findings in relation to SIBA and SIAC. The SC works according to written guidelines and has scheduled meetings every 2-3 months to discuss and evaluate the overall safety of SIBA SIAC in the phase 3a clinical trials. The SC works under blinded conditions. If the SC recommends unblinding of any data for further analysis, an ad hoc group will be established consisting of NN employees with no relationship to the SIBA SIAC clinical trials. This is to maintain the blinding of the employees working with the trial.

All CV treatment emergent adverse events will be tabulated by preferred terms, by the classification suggested in (FDA guidance DEC2008). The tabulation will be done across all phase 3a trials in total and by subgroup (age, sex, race and age). In trials with the patient populations normally included in treat to target trials, as required for approval of new insulins, the number of events observed in previous development programs is very low making a tabulation more relevant for insulin 454 than a formal statistical evaluation and conclusion across trials based on an estimated risk ratio.

Question 15:
a) Considering that insulin 454 is an analogue of human insulin, does the Agency agree that the proposed clinical program, with inclusion criteria as described, tabulations and surveillance of CV events sufficiently investigates the cardiovascular risk profile of SIBA?

FDA Response: At the present time, we are not holding inhaled or injectable insulins to the 95% confidence interval upper bound values of 1.8 and 1.3 described in the December 2008 guidance document. Nonetheless, you should still collect and analyze the cardiovascular data from your clinical trials as outlined in that guidance document, perform statistical testing on your cardiovascular data, and report the values in your NDA submission. We recommend that you submit with your phase 3 protocols, a detailed plan describing how you will capture and analyze cardiovascular adverse events of interest in each trial and across your development programs.

You mention that all collected cardiovascular events will be evaluated by an internal committee of Novo Nordisk employees. Please clarify how this committee's make-up and responsibilities will differ from those of an external adjudication committee.

Additional Discussion:
Novo Nordisk presented slide three.

b) Does the Agency agree to the inclusion and exclusion criteria for including patients at higher risk of cardiovascular events?

FDA Response: These inclusion and exclusion criteria appear reasonable. In some trials, you could consider enrolling patients who have had a prior cardiovascular event up to 3 months prior to your screening visit.

Having more liberal inclusion and exclusion criteria will not guarantee that higher risk patients will be enrolled. Therefore, you should also actively encourage investigators to enroll higher risk patients.

Additional Discussion:
Novo Nordisk prefers to enroll patients with a prior cardiovascular event up to six months prior to the screening visit because patients may still be medically unstable at three months. It will be emphasized to investigators not to exclude higher risk patients. There is not an upper age limit; the Sponsor will encourage inclusion of elderly patients.

The Division agreed to review the cardiovascular meta–analysis proposal in a one to two month time frame from the date of submission.

Post-Meeting Note: The types of patients studied in your clinical trials should be representative of patients who will take SIBA and SIAC, if approved.

c) Does the Agency agree that the list of MedDRA Preferred Terms covers all relevant major CV events. (ref Appendix E)

FDA Response: We are still determining the acceptability of this list of MedDRA preferred terms. A response will be included in the final meeting minutes.

Post Meeting Note: The sponsor should use the following Standardised MedDRA Queries (SMQs) to identify potential cardiovascular adverse events of interest.

- **Myocardial Infarction**
- **Ischaemic Heart Disease**
- **Cardiac Arrhythmias**
- **Cardiac Failure**
- **Embolic and Thrombotic Events**
- **Shock**

- **Torsade de pointes/QT prolongation**
- **Cerebrovascular Disorders**
- **Central Nervous System Haemorrhages and Cerebrovascular Accidents**

The sponsor should also search for potential cardiovascular events of interest using the following System-Organ-Classes (SOCs), Lowest Level Terms (LLTs) and Preferred Terms (PTs):

- **SOC: Cardiac Disorders**
- **SOC: General Disorders and Administration Site Conditions**
- **SOC: Injury, Poisoning, and Procedural Complications**
- **SOC: Investigations**
- **SOC: Musculoskeletal and Connective Tissue Disorders**
- **SOC: Respiratory, Thoracic, and Mediastinal Disorders**
- **SOC: Surgical and Medical Procedures**
- **SOC: Vascular Disorders**
- **LLT: Cerebral Revascularization Synangiosis**
- **LLT: Coronary Revascularization**
- **LLT: Peripheral Revascularization**
- **LLT: Renal Revascularization**
- **LLT: Transmyocardial Revascularization**
- **PT: Acute Myocardial Infarction**
- **PT: Myocardial Infarction**
- **PT: Post Procedural Myocardial Infarction**
- **PT: Silent Myocardial Infarction**

Please note that the Division is in the process of standardizing definitions for major cardiovascular events (e.g., myocardial infarction) and other aspects regarding cardiovascular assessment, including the use of checkbox forms for ensuring adequate capturing of cardiovascular events of interest. We will communicate this information within the next few months and will request that you incorporate these recommendations in your phase 3 trials.

d) Does the Agency agree that formal non-inferiority assessments of the CV risk ratio such as those recommended in FDA guidance DEC2008 are not needed for SIBA?

FDA Response: As explained above, at the present time, we are not holding inhaled or injectable insulins to the upper bound values of 1.8 and 1.3 described in the December 2008 guidance document. Nonetheless, you should still perform statistical testing on your data as described in that guidance document and report the values in your NDA submission.

Proposed 200U Formulation Clinical Program

SIBA is being developed as two formulation strengths, 100U and 200U. Novo Nordisk intends to file both product strengths for approval in the initial NDA with the objective of having them on the market at the same time.

Studies have shown that 25-30% of patients with diabetes in US have a daily average consumption of more than 50 units long acting insulin. The 200U strength is intended for insulin-resistant patients who normally require high insulin doses which result in large injection volumes. Availability of the 200U product would enable such patients to receive the same doses using smaller injection volumes and would conveniently allow dosing with fewer injections. One PK/PD and two phase 3a studies are planned to support approval of the 200U strength.

A clinical pharmacology study is planned with the objective of characterizing the pharmacodynamic and pharmacokinetic properties after administration of the two different SIBA concentrations at steady state. The PK/PD properties of a basal insulin at steady state conditions are considered to be clinically more relevant than those obtained after a single dose. The AUC□GIR, 0-24h and AUC□,I454,0-24h of both 100U and 200U formulations will be determined under steady state conditions following multiple dosing. It has been previously determined that steady state levels of SIBA are achieved after two to four days.

One six month safety and efficacy trial will investigate dosing SIBA 200U once daily. In addition to a once daily administration, Novo Nordisk is also interested in a new paradigm of dosing SIBA at a frequency rate lower than a once-daily administration. To achieve the latter, a second Phase 3a study will involve injecting patients with SIBA 200U for only three days out of a week.

The 200U product will only be marketed in a pre-filled pen clearly distinguishable from other pre-filled pens with 100U formulations in order to ensure the safe use.

Question 16: Given insulin 454's PK/PD profile and assuming that an acceptable risk/benefit ratio is proven in the safety/efficacy studies, does the Agency agree that the three proposed trials are adequate to support approval of the 200U formulation?

FDA Response: Please justify why you are not testing U200 three times per week in patients with type 1 diabetes. These patients could potentially be at risk for initial hypoglycemia from the larger dose of insulin administered on alternate days and could also potentially be at risk for later hyperglycemia and diabetic ketoacidosis if there is insufficient residual insulin prior to the next dose of Insulin 454.

Additional Discussion:
Novo Nordisk is pursuing U200 because many patients with type 2 diabetes need more insulin in one day than any U100 device can deliver. U200 is not being tested in type 1 diabetes mellitus patients three times per week because of the increased risks for hypo- and hyperglycemia.

The Division is concerned that patients with type 1 diabetes mellitus may use three times a week dosing off-label and there would be no efficacy or safety data for this regimen in this patient population if only studied in patients with type 2 diabetes. The Division strongly urged that the three times per week regimen also be tested in patients with type 1 diabetes.

In addition, there is great potential for confusion and medication errors between SIBA U200, SIBA U100, and SIAC U100. As a result labeling will be critical and Risk Evaluation and Mitigation Strategies (REMS) may be needed to ensure safe use.

Novo Nordisk acknowledged the medication error potential and has been working on product differentiation to include color coding.

100U and 200U Injection Time (Flexible Dosing)
Insulin 454 has a flat and stable action profile with long half-life, both of which extend beyond 24 hours. The clinical pharmacology data indicates that the exact time of injecting the daily dose is not anticipated to affect the insulin's overall efficacy and safety.

As stated in Question 16, a study is planned wherein the pharmacokinetic and pharmacodynamic properties of SIBA 100U and 200U will be investigated at steady state.

Novo Nordisk is interested in having patients be allowed to dose at any time of the day when utilizing the once-daily use dosing regimen.

Question 17: Does the Agency agree that the PK/PD profile of insulin 454 combined with the PK/PD profiles of the two formulation strengths of SIBA are sufficient to support labeling text stating that dosing for SIBA (100U and 200U) is once a day at any time of day?

FDA Response: This will be a review issue. As discussed in our response to Question 9, the labeling should be consistent with how SIBA was studied in your phase 3 program. You could consider a substudy testing morning vs. evening administration of Insulin 454 to obtain data showing that dosing at different times of the day does not affect efficacy or safety.

Additional Discussion:
Novo Nordisk's goal is for the patient to decide when to dose; it might be in the morning one day and in the afternoon another day. The sponsor will submit a protocol for the proposed study of SIBA once daily at the same time of day, SIBA once daily with forced changes to timing of injections (the same patient would inject at different times of day), and glargine dosed according to label with non-inferiority tests for each SIBA arm versus glargine. Evidence for the efficacy and safety of flexible dosing will need to be obtained in patients with type 1 diabetes and in patients with type 2 diabetes.

100U and 200U Dosing Schedules

As evidenced by preclinical and clinical data generated to date, insulin 454 has potential for allowing more convenient and flexible dosing schedules to accommodate different patient needs. Novo Nordisk plans to prove feasibility of the modified dosing schedule with the Phase 3 program (see tabulation of trials and trial synopses in meeting package).

Based on the fact that, at similar dose levels, insulin-naïve subjects with type 2 diabetes treated for 16 weeks with SIBA (D, 900 nmol/ml)) three times weekly (Monday, Wednesday, Friday) in combination with OAD, resulted in comparable glycaemic control to that observed for insulin glargine given once daily, it is believed that a dosing frequency of 3 times weekly will be sufficiently effective.

It is anticipated that the PKPD (NN1250-3678) will confirm the flat profile and stable action profile beyond 24 hours for both strengths supporting a dosing frequency rate lower than a once-daily administration relevant for SIBA 100U and SIBA 200U.

Novo Nordisk envisions the following text for SIBA 100U and 200U in the Dosage and Administration section of the product label:

SIBA doses should be individually based on the physician's advice and in accordance with the convenience and needs of the patient. SIBA can be administered either once daily every day or less frequently; e.g., three time a week:
- For patients treated once daily every day, SIBA injections can be given at any time of the day
- For patients treated three times a week, SIBA can be given once a day on three alternate days of the week; e.g. Monday, Wednesday and Friday or a similar schedule.

Question 18: Given the outlined Phase 3 clinical program, does the Agency agree that the proposed dosing regimens listed above (b) (4)

FDA Response: See responses to Questions 16 and 17.

Pediatric Clinical Development Program

(b) (4)

(b) (4)

(b) (4)

FDA Response: (b) (4) **Your NDA should include a proposed pediatric plan (including an overview of your proposed pediatric studies and a timeline that lists dates when each pediatric protocol will be submitted, when each pediatric study will be initiated, and when complete study reports from each pediatric study will be submitted to FDA). In addition, the NDA should contain a request for waiver and/or deferral in children with type 1 diabetes and in children with type 2 diabetes together with justification for the proposed waiver/deferral. The proposed pediatric plan included in your NDA will be discussed with the Pediatric Review Committee (PeRC).**

Additional Discussion: (b) (4)

SIAC (Soluble Insulin Analogue Combination)

CMC

Drug Substance Bioactivity Correlation Studies

With reference to the Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for NN1250 SIBA injection FDA submitted the recommendation:

"We recommend establishing as part of the insulin 454 characterization studies, the correlation between the potency values determined by the proposed bioassay, KIRA-TRIFMA (318G-04.152), and by the current compendial U.S. pharmacopeia (USP) bioassay <121> Rabbit Blood Sugar Method."

Our experience with the pharmacopoeia (USP) bioassay <121> Rabbit Blood Sugar Method is that it is not suitable for testing basal insulin analogues. The KIRA-TRIFMA assay has been established as the bioactivity assay for insulin 454; however the KIRA-TRIFMA assay is used only to confirm that the drug substance is biologically active and it is not used to define the dosing unit.

In a study investigating comparability between KIRA-TRIFMA and a Mouse Blood Glucose Assay, forced degraded samples of human insulin were used. It was demonstrated that the KIRA-TRIFMA method correlates with the Mouse Blood Glucose Assay and is suitable for detecting the decrease in insulin potency due to extremes in acid, base, light, heat, changed redox, or mechanical stress.

Question 1: Given the above, Novo Nordisk believes that the existing correlation data obtained on human insulin is sufficient to justify the KIRA-TRIFMA assay and therefore proposes that a separate comparability study with the USP Rabbit Blood Sugar Method should not be necessary. Does the Agency agree with the proposal?

FDA Response: Yes.

Revised Drug Product Specifications

Stability studies have been performed on various formulation versions of SIAC as part of product development efforts. Based on data from the large number of development batches as well as information obtained from ongoing stability studies of clinical trial supplies, four parameters of interest (pH, freezing point depression, zinc, and bacterial endotoxin) are not anticipated to be stability-indicating. In addition, filled containers (pen cartridges) are tested for closure integrity as an in-process control. Sterility is also tested at release and end of shelf-life.

The four parameters of interest are part of the SIAC specifications which have been used from IND up to Phase 2. Novo Nordisk proposes decreasing their level of testing as presented in Table 3.

Table 3 Release and shelf life specifications for phase 2, phase 3, and NDA

Test	**Phase 2**		**Phase 3**		**NDA filing and Post Approval**	
	Release	Shelf life	Release	Shelf life	Release	Shelf life
pH	Test	Test	Test	Test	Test	No Test
Freezing Point Depression	Test	Test	Test	No Test	No Test	No Test
Zinc	Test	Test	Test	Test	Test	No Test

	Phase 2		**Phase 3**		**NDA filing and Post Approval**	
Bacterial Endotoxins	Test	Test	Test	No Test	Test	No Test

Question 2:
a) Does the Agency agree that it is not necessary to include pH as a testing parameter in the stability studies initiated after the NDA approval and can therefore be omitted from NDA shelf life specifications?

FDA Response: Yes.

b) Does the Agency agree that it is not necessary to include Freezing Point Depression as a testing parameter in the stability studies initiated during phase 3 and after the NDA approval and can therefore be omitted from NDA shelf life specifications?

FDA Response: Yes.

c) Does the Agency agree that Freezing Point Depression can be omitted from post approval release specification?

FDA Response: Yes.

d) Does the Agency agree that it is not necessary to include Zinc as a testing parameter in the stability studies initiated after the NDA approval and can therefore be omitted from NDA shelf life specifications?

FDA Response: Yes.

e) Does the Agency agree that it is not necessary to include Bacterial Endotoxins as a testing parameter in the stability studies initiated during phase 3 and after the NDA approval and can therefore be omitted from NDA shelf life specifications?

FDA Response: Yes.

NON-CLINICAL

Carcinogenicity
The in vivo carcinogenicity assessment of insulin 454 will be based on a 12-month toxicity study in Sprague-Dawley rats with group sizes of 40-50 per group per sex and Neutral Protamine Hagedorn (NPH) insulin as comparator. The study will include full histopathology on all animals and additionally will include proliferation markers (BrdU) to study the proliferation index in female mammary tissue. Prior to initiation the study design has been discussed with EMEA and FDA.

Based on the in vitro and in vivo testing, the carcinogenic potential of insulin 454 is considered low, and no further studies are planned.

Question 3: Does the Agency agree that the conducted carcinogenicity assessment program of insulin 454 is sufficient for to support NDA approval?

FDA Response: The sponsor should remain aware that approval of an NDA depends upon review of all data submitted as part of that NDA. The study design of the 12-month toxicity study with insulin 454 and the NPH comparator appears reasonable.

CLINICAL PHARMACOLOGY & CLINICAL

Clinical Pharmacology Program

SIAC is an insulin combination product of insulin 454 (drug substance in SIBA) and insulin aspart (marketed by Novo Nordisk as NovoLog®). The pharmacokinetic and pharmacodynamic properties of SIAC have been investigated in five clinical pharmacology trials conducted in healthy subjects and in subjects with type 1 or type 2 diabetes. In addition, SIBA has been investigated in four clinical pharmacology trials.

Five planned clinical pharmacology trials with SIAC include investigation of dose-response in a single dose setting, comparison to SIBA and insulin aspart, and investigation in special populations such as children and the elderly. Pharmacokinetic properties of SIAC in subjects with renal or hepatic impairment as well as the effect of different injection sites will be bridged from trials performed with SIBA, since insulin aspart is already well characterized. Planned clinical pharmacology trials with SIBA include investigation of dose-response in a multiple dose setting in subjects with type 1 diabetes, intra-subject variability in glucose-lowering effect at steady-state in subjects with type 1, as well as the counter-regulatory hormone responses during hypoglycaemic episodes will be investigated in subjects with type 1 diabetes. These studies will be used for SIAC to represent the basal insulin 454 component during steady state.

Novo Nordisk plans to conduct a trial with SIBA in subjects with renal impairment (NN1250-1990) and hepatic impairment (NN1250-1989) and additionally refer to a previous trials with insulin aspart in subjects with renal impairment and hepatic impairment. These trials are considered sufficient to document the safety of SIAC in subjects with renal and hepatic impairment.

Question 4:

a) Does the Agency agree that the proposed clinical pharmacology program together with the confirmatory clinical program is sufficient for obtaining marketing authorization approval?

FDA Response: Your proposed clinical pharmacology program seems acceptable.

b) Does the Agency agree that it is sufficient to investigate the pharmacokinetic and safety profiles of SIAC in patients with renal and hepatic impairment by conducting studies with SIBA and by referring to previously submitted data on insulin aspart?

FDA Response: Yes.

c) Does the Agency agree that the suggested design of NN5401-1977 is appropriate to investigate the pharmacokinetic (PK) and pharmacodynamic (PD) properties of SIAC versus SIBA and insulin aspart?

FDA Response: Please clarify the rationale used to choose the time intervals of 0-6 hours (for SIAC and SIBA) and 4-24 hours (for SIAC and insulin aspart) for your AUC_{GIR} primary endpoint.

Additional Discussion:
Novo Nordisk chose 0-6 to account for the whole course of mealtime. Slide 4 was shown. The possibility of replacing study NN5401-1977 with biomodeling was discussed. The Division believes Study NN5401-1997 will be necessary and cannot comment on the model without seeing it and the validation.

d) From TPP: Does the Agency agree that the target difference of at least 20 percent of the pharmacokinetic and pharmacodynamic profiles for a pre-mixed product (a combination of a short- and a long-acting insulin of the same active drug substance) is not a requirement for the SIAC insulin combination product?

FDA Response: You propose that the target difference of at least 20% of the pharmacokinetic and pharmacodynamic profiles for a pre-mixed product is not a requirement for your product. Please provide your rationale.

Do you already have preliminary data for the PD profiles of SIAC compared to SIBA and insulin aspart? If yes, based on these preliminary data is there at least a 20% difference in PD between SIAC and its individual components?

Additional Discussion:
Novo Nordisk still views SIAC as a combination product. The sponsor does not have data for SIAC compared to SIBA and insulin aspart, but based on biomodeling expects at least a 20% difference in PK and PD. Regardless of how SIAC is ultimately classified (insulin mix or combination product), its PK and PD profiles must be sufficiently different from those of SIBA to justify marketing.

ECG-QT/QTc Measurements
Long term clinical experience with insulin administration in humans utilizing animal insulins, human insulins and insulin analogues, all acting through the same insulin receptor has not

demonstrated any direct adverse effects of insulins on prolongation of the electrocardiogram-QT interval.

Four non-clinical studies have been performed to clarify the effect of insulin 454 on the QT/QTc interval:

- hERG receptor binding, tested up to 1000 nmol/l
- Action potential in isolated rabbit pukinje fibers, tested up to 1000 nmol/l
- QT interval in conscious dogs (tested up to 24 nmol/kg (s.c.))
- QT and QTc interval in anaesthetized dogs (tested up to 12 nmol/kg (i.v.)) – corresponding to a plasma concentration of approximately 100 nmol/l insulin 454

No effect was observed in any of the four studies, where insulin 454 has been tested up to 50x human exposure in vitro and 5x human exposure in vivo, assuming a maximal plasma human exposure of 20 nmol/l.

As with other insulin products, standard assessment of ECGs in healthy volunteers and in subjects with type 1 and type 2 diabetes during the phase 1 and phase 2 trials of SIAC have not shown any clinically meaningful changes. For the phase 3 development program, standard 12 lead ECG measurements will be performed at baseline and end of study and data on QT/QTc changes will be evaluated.

Question 5: Given the levels of drug investigated in animals and ECG results in phase 1 and 2, does the Agency agree that there is no need to perform a thorough QTc clinical pharmacology study in humans investigating potential effects on QT intervals?

FDA Response: Yes.

Proposed Phase 3a Development Program

SIAC offers the advantage that it is the first soluble ready-to-use insulin combination product for subcutaneous (s.c.) injection. The combination of the two drug substances provides SIAC with an action profile with rapid onset of action due the bolus insulin component (insulin aspart) combined with a flat action profile due to the basal insulin component (insulin 454). It is expected that SIAC will provide main meal coverage as well as at least 24 hours basal coverage for all patients when used once daily.

The goal of the clinical phase 3a program is to demonstrate that SIAC is safe and efficacious for the treatment of diabetes mellitus. Since SIAC is an insulin combination of insulin 454 and insulin aspart, the development program for SIAC will link with SIBA data, including a pre-clinical package, clinical pharmacology studies, overall safety exposure, exposure to elderly and obese patients. In order to establish the distinctiveness of SIAC compared with SIBA and insulin aspart, the pharmacokinetic exposure and the pharmacodynamic response will be compared between SIAC and SIBA and between SIAC and insulin aspart.

The key comparator for SIAC once daily as insulin initiation, as well as insulin intensification, is insulin glargine. Insulin glargine is an insulin analogue with a longer duration of action and a relatively flat time-action profile compared to human insulin thus making it a more appropriate standard.

For investigation of switch and intensification from twice daily premix or self mix regimens, the key comparator for SIAC twice daily is NovoLog® Mix 70/30. NovoLog® Mix 70/30 is the most widely used insulin preparation that has both a rapid acting and a basal component.

In subjects with type 1 diabetes, the comparator to SIAC OD with additional insulin aspart boluses at the meals not covered by the SIAC prandial component will be insulin detemir OD with insulin aspart boluses at each meal. Insulin detemir is a long-acting insulin analogue established for daily insulin use, while insulin aspart is an established bolus insulin.

The SIAC development program contains combination treatment with OADs of the three classes: biguanides, dipeptidyl peptidase (DPP-4) inhibitors, and thiazolidinediones. Subjects will be exposed to SIAC plus OAD combination therapy for up to 6 months. In the majority of cases subjects will continue their prescribed (pre-trial) class of OAD treatment upon trial inclusion; hence trials are anticipated to approximate OAD use in clinical practice.

Question 6:
a) Does the Agency agree that the proposed phase 3a development program for SIAC is adequate to support the following indication?
SIAC is a soluble insulin combination product indicated to improve glycemic control in patients with diabetes mellitus.

FDA Response: The initial indication will be for adults with diabetes mellitus. Please see our response to Question 14 pertaining to your proposed pediatric development program.

b) Does the Agency agree with the choice of comparators in the proposed phase 3a development program for SIAC?

FDA Response: Yes, except Study 3589. The Division does not understand the purpose of Study 3589, because both treatment groups will have received liraglutide starting 12 weeks prior to randomization, essentially comparing SIAC to no additional therapy. A more meaningful study would initiate liraglutide with or without SIAC at randomization.

Detemir should be dosed twice daily (not once daily) in Study 3594 to ensure that SIAC is compared to an optimal detemir regimen.

c) (b) (4)

oes the Agency agree?

FDA Response: (b) (4)

d) Does the Agency agree that the proposed trials investigating SIAC in combination with metformin, thiazolidinediones, DPP-4 inhibitors and GLP-1 receptor agonists are sufficient for obtaining a general indication for the use of SIAC in combination with antidiabetic agents?

FDA Response: Yes.

e) Can the agency confirm the acceptability of the broad inclusion/exclusion and withdrawal criteria for the proposed phase 3 studies?

FDA Response: Your proposed broad inclusion/exclusion criteria are acceptable. With regard to the withdrawal criteria, we do not recommend that you discontinue patients with inadequate glycemic control. Instead, these patients should be kept in the trials and glycemic rescue therapy should be added. This will increase your safety database. For the primary efficacy analysis, any data after rescue can be treated as missing. Safety data can be presented with and without rescue. This comment regarding glycemic rescue also applies to your SIBA development program.

Additional Discussion:
Novo Nordisk stated that the European Medicines Agency (EMEA) does not support continued participation of patients with inadequate glycemic control. The Division stated that these patients would already be obtaining maximal antidiabetic therapy (i.e., insulin) and that they would not be expected to have further improvements in glycemic control upon discontinuation from the trials. The Division's main concern is that there be sufficient long-term safety data beyond 6 months of therapy, which could be jeopardized if there is substantial dropout due to inadequate glycemic control. The sponsor stated that it expects low rates of withdrawal due to inadequate efficacy based on experiences with other insulin trials and agreed to submit these data (with a focus on those trials >6 months in duration) for review.

Duration of Exposure and Number of Subjects Exposed
The efficacy assessment of SIAC will be based on an estimated 1288 subjects (352 and 936 subjects type 1 and type 2 diabetes, respectively) of which an estimated 1093 subjects will be exposed for 6 months. The safety evaluation for SIAC will be based on data from the above mentioned subjects combined with data from the SIBA development program and the documented safety profile of insulin aspart.

For the SIBA phase 3a program, approximately 2873 subjects (466 and 2407 subjects with type 1 and type 2 diabetes, respectively) will be exposed to SIBA in the phase 3a development program, of which an estimated 2443 subjects will be exposed for 6 months and 1500 subjects for 12

months. The safety profiles of injectable insulin and insulin analogues are well established and therefore Novo Nordisk supports the 12-month exposure requirements of the ICH E1 guidance and suggests that any additional exposure information be provided as a post-approval commitment.

Based on these characteristics and given the nature of the pharmacological effects of insulin aspart and insulin 454, Novo Nordisk plans to file for marketing approval based on 6-month exposure data for SIAC and 12-month exposure data for SIBA.

Eighty years of experience has demonstrated that insulin has a restricted range of biologic effects all mediated through the insulin receptor. Novo Nordisk has demonstrated that acylation of the insulin molecule can produce a biologically active and clinically safe basal insulin analogue (insulin detemir, Levemir®). Insulin 454 has a similar molecular structure to insulin detemir (both products are attached to a fatty acid ligand at position B 29 of the B-chain), has a higher relative affinity for the insulin receptor than for the IGF receptor, and is expected to have a low immunologic response. The mode of action of insulin 454 is identical to that of human insulin and other insulin analogues as they all act through the same insulin receptor.

The FDA and other international regulatory authorities have significant experience with these diabetes treatments, and it is expected that additional pre-approval exposure required by the recently published FDA Draft Guidance on treatment and prevention of diabetes mellitus would not provide additional safety and efficacy data above what is known about these classes of products.

Question 7: Does the Agency agree that the proposed number of exposed subjects and the duration of exposure in the proposed phase 3a program at the time of NDA filing are sufficient to support NDA approval?

FDA Response: Yes.

Dosing Regimen

Overall, the proposed phase 3a program is planned to provide documentation on the safety and efficacy of dosing SIAC once daily with any main meal.

The rationale behind this flexible strategy is based on a SIAC pharmacodynamic profile that shows a clear separation of the rapid-acting and basal components where, the action profile of the insulin aspart component of SIAC is anticipated to be comparable to that of insulin aspart (NovoRapid®, NovoLog®) at therapeutic dose levels. Moreover, pharmacokinetic and pharmacodynamic simulations indicate that, due to the flat and stable activity profile and long half life, the action profile of SIAC is largely unaffected by the timing of the dose given over the course of a day.

Insulin initiation with SIAC OD in insulin-naïve subjects with type 2 diabetes will be confirmed in two trials in the phase 3a programme (NN5401-3589 and NN5401-3590). Insulin

intensification from basal insulin to SIAC OD will be documented in one trial (NN5401-3593). Trial NN5401-3590 is planned to dose SIAC OD with the breakfast meal. In trials NN5401-3589 and NN5401-3593 subjects will be instructed to dose SIAC with the evening meal or largest meal. In trial NN5401-3594 in subjects with type 1 diabetes, subjects will be instructed to dose SIAC at the meal where the basal-bolus ratio fits best with the previous treatment. In addition, subjects will be allowed to move the SIAC injection to another meal in case a limitation for optimal titration of the basal or bolus component arises. The time of day (and at which meal) SIAC is administered will be recorded through use of a patient diary.

Based on the above considerations, Novo Nordisk believes that variations in the timing of dosing will be safe and efficacious, giving the patient the possibility to vary the timing of dosing (according to individual needs).

Question 8: Does the Agency agree that the proposed studies will support labelling in the "Dosage and Administration" section stating that SIAC is used once daily with any main meal?

FDA Response: Yes, provided that there are adequate data with dosing at different times of the day and our review of the NDA does not identify unique efficacy or safety issues related to the timing of dosing.

Direct Switch from other Insulin Products to SIAC

Overall in the SIAC phase 3a program, an estimated 450 subjects with type 2 diabetes and 352 subjects with type 1 diabetes will be transferred to SIAC from basal insulin and premixed insulin preparations.

Transferring subjects from once daily (OD) human or analogue basal insulin to SIAC OD will be investigated in NN5401-3593. The switch will be done on a unit-to-unit basis and insulin dose will be further titrated to reach predefined glycaemic targets.

Transferring subjects from OD or BID human or analogue premixed insulin (including self mix) to SIAC BID will be investigated in NN5401-3592. The switch will be done on a unit-to-unit basis and the insulin dose will be further titrated to reach predefined glycaemic targets.

When switching from a basal-bolus regimen in type 1 diabetes (NN5401-3594), the basal dose provided by SIAC should be as close to the previous basal dose and will be injected at the meal where the basal-bolus ratio fits best with the previous treatment.

The basis for the proposed unit-to-unit transfer is the results from the clinical pharmacology and phase 2 trials, which support a potency of insulin 454 very close to 100% of that of insulin glargine and a potency of SIAC very close to insulin glargine as well as NovoLogMix® 70/30.

In the two SIBA 16-week treat-to-target clinical studies, NN1250-1835 in subjects with type 1 diabetes and NN1250-1836 in subjects with type 2 diabetes, insulin 454 were compared with

insulin glargine during once-daily dosing. Treatment with the SIBA E (600 nmol/ml) formulation resulted in similar HbA1c compared to insulin glargine in both type 1 and type 2 subjects. The doses at the end of trial were comparable to that of insulin glargine.

The SIAC phase 2 trials (NN5401-1791, NN5401-1792) investigating effects of SIAC 30 formulation (600 nmol/ml) in type 2 subjects resulted in similar HbA1c at a dose 14 or 16 % lower than insulin glargine when given once daily and NovoMix® 30 when given twice daily, respectively.

Further, a dose-response trial (NN1250-1876) was performed in subjects with type 1 diabetes to investigate the steady state clinical potency of insulin 454 relative to insulin glargine. Subjects received insulin 454 or insulin glargine once-daily for 8 days, at one out of three dose levels. The steady state pharmacodynamic response was evaluated during a 42-hour euglycaemic glucose clamp that was initiated after the last dosing (on Day 8). Based on AUCGIR,0-24h at steady state, insulin 454 was estimated to have a molar dose ratio (potency) of 0.81 [0.72, 0.93] relative to insulin glargine. The dataset altogether supports the conclusion that 600 nmol/ml of insulin 454 corresponds to 100 U.

Question 9: Is the proposed program sufficient to generate recommendations in the Dosage and Administration section of the SIAC labeling for switching subjects with type 2 diabetes from other insulin products to SIAC on a one-to-one unit basis?

FDA Response: The labeling in the Dosage and Administration section should be consistent with how SIAC was studied in your phase 3 program. If you use a 1:1 switch in the phase 3 programs and there is sufficient efficacy and safety information from that approach, then the Dosage and Administration section will incorporate that recommendation for a 1:1 switch. If there are no data or inadequate data to support the proposed labeling language or if the 1:1 switch results in efficacy/safety concerns, it is unlikely that a 1:1 switch will be recommended.

Secondary Confirmatory Endpoints

The trials in the SIAC phase 3a program are designed to compare SIAC and comparator products with respect to the primary endpoint (HbA1c). Provided that non-inferiority is established for HbA1c for a particular trial, a small number of confirmatory secondary endpoints also will be tested in different trials such as fasting plasma glucose and proportion of responders..
For the analyses of the confirmatory secondary efficacy endpoints the one-sided type 1 errors will be preserved at a 2.5% level through a hierarchical test strategy. (b) (4)

regarding the proposed confirmatory endpoints should significant differences be found between SIAC and other basal insulin treatments.

The confirmatory secondary endpoints will be individually defined in each protocol depending on the trial design and comparator used. The statistical details of the sequential testing can be found in the abbreviated statistical analyzed plan in the briefing document.

One of the confirmatory secondary endpoints is 'responders without hypoglycemia' defined as subjects with at least 12 weeks of exposure achieving an HbA1c value of ≤7% at the end of treatment in the absence of any confirmed hypoglycemic events in the 12-weeks period prior to the end of treatment..

Question 10:
a) Does the Agency agree (b) (4)

FDA Response: Please see our response to SIBA Question 10(a).

b) Does the Agency agree that inclusion of information regarding the number of type 2 patients achieving a value of HbA1c < 7% at the end of treatment in the absence of any confirmed hypoglycemic events in the 3-month period prior to end of treatment ('responders without hypoglycaemia') can be used as a confirmatory secondary endpoint?

FDA Response: Please see our response to SIBA Question 10(b).

Blood Glucose Fluctuation
For all phase 3a trials, glucose fluctuation (defined as the average excursion from the mean of any glucose profile) will be assessed in all subjects by means of standard 9-point self-measured plasma glucose profiles recorded over 24-hour periods at designated stages of the trial.

In addition, for two of these trials, Novo Nordisk plans to more closely evaluate glucose fluctuation via continuous glucose measurement (CGM), whereby 72-hour interstitial glucose profiles will be measured in a representative subgroup of subjects. The number of subjects undergoing CGM will be calculated to provide sufficient statistical power to detect differences in interstitial glucose fluctuation between SIAC and the comparator.

Question 11: (b) (4)

FDA Response: Please see our response to SIBA Question 13.

Evaluation of Antibody Development (Overall Strategy)
Antibody development to exogenous insulin usually peaks after 3-6 months after which antibody levels plateau or decline depending on the insulin product and the subjects exposed. Samples for antibody measurement will be taken in certain phase 3a trials at start of treatment, during trial, at end of treatment, and at follow-up. Determination of antibodies specific for insulin 454, antibodies specific for insulin aspart, antibodies specific for comparator and antibodies cross-

reacting to human insulin will be done using a validated subtraction Radio Immuno Assay (RIA), modified from Lindholm et al. 2002. (ref. 1)

Insulin 454 interferes with anti-insulin 454 antibody measurement causing the resulting binding to be lower than in a sample with no insulin 454 present. Treatment pauses to allow insulin 454 wash-out during trials will not be introduced because the potential safety and ethical implications are considered significant. Therefore, the main analyses of antibody development will be based on antibody levels before and after treatment (1 week after drug is discontinued) analyses.

Novo Nordisk already has data for antibody development for insulin aspart and in the clinical phase 3a program for SIBA antibodies will be measured in two 12-months trials; one trial in an estimated 621 (466 SIBA exposed) subjects with type 1 diabetes (NN1250-3583) (where subjects are offered to participate in a 12-month extension of the trial) and one trial in an estimated 981 (736 SIBA exposed) insulin naïve subjects with type 2 diabetes (NN1250-3579).

In the clinical phase 3a program for SIAC, antibodies will be measured in one trial of 6-month duration in an estimated 528 (298 SIAC exposed) subjects with type 1 diabetes (NN5401-3594) and in one trial of 6-month duration in an estimated 525 (223 SIAC exposed) insulin naïve subjects with type 2 diabetes (NN5401-3590). Altogether the SIBA and SIAC studies are anticipated to confirm no unexpected increase in antibody formation and no effect of antibodies on HbA1c and dose.

Testing for correlations between antibody titres and relevant efficacy and safety parameters (e.g. levels of glycemic control, insulin dose) is well established in detecting any clinically relevant effects of antibody induction by insulin 454. In-vitro assays for neutralizing antibodies do not add to the interpretation of antibody measurements and will therefore not be developed.

Question 12:
a) Does the Agency agree to the proposed strategy in the phase 3a program for evaluating insulin antibody development?

FDA Response: Please see our response to SIBA Question 14(a).

b) Does the agency agree to the analysis strategy whereby the development in antibody titres will be described and correlations between antibody titres and relevant efficacy and safety parameter will be estimated?

FDA Response: Please see our response to SIBA Question 14(b).

Cardiovascular Risk Profile
SIAC is an insulin combination product consisting of insulin aspart and insulin 454. Insulin aspart is an analogue of human insulin and is the active substance in NovoLog® and NovoLogMix®, whereas insulin 454 has a similar molecular structure to insulin detemir (Levemir®) and shares the same molecular mechanism of action as human insulin and insulin

detemir. Both insulin detemir and insulin aspart have a well-established CV safety profile. In approximately 16.5 million patient years of exposure with insulin aspart (NovoLog® and NovoLogMix®), only 220 adverse reaction reports (serious as well as non-serious) were reported (according to the NovoLog®/NovoLogMix® PSUR of Nov 11, 2008), whereas in approximately 2 million patient years of exposure with insulin detemir, only 90 adverse drug reaction reports (serious as well as non-serious) were reported (according to the Levemir® PSUR of Oct. 8, 2008) from unsolicited sources within the MedDRA System Organ Class "Cardiac Disorders" and "Vascular Disorders". There is no reason to believe that the cardiovascular profile of insulin 454 should be any different from insulin detemir or any other analogue of human insulin.

To evaluate the CV profile of SIAC, Novo Nordisk will allow for inclusion of patients at higher risk of cardiovascular events such as patients with relatively advanced disease, elderly patients and patients with some degree of renal impairment. This is done by allowing for inclusion of subjects with a prior cardiovascular event (stroke, myocardial infarction, unstable angina pectoris, coronary arterial by-pass graft or angioplasty) occurring up to 6 months before inclusion into the trial as opposed to 12 months for previous insulin development programs (NovoLog®, NovoLogMix®, Levemir®), and more liberal serum-creatinine limits (serum-creatinine up to 125 µmol/L for men and 110 µmol/L for females) will be used to allow for patients with some degree of renal impairment. In addition, there will be no limitations on age, diabetes duration, or micro- or macro-albuminuria. However, as all the phase 3a trials implement a tight titration schedule to bring the patients toward euglycemia, severely ill patients with regard to cardiovascular disease will not be included in the trials, since the titration schedule might pose a safety risk for these patients (Skyler J S et al, Circulation 2009;119). A list of inclusion and exclusion criteria is given in section F.3.3.

Novo Nordisk intends to monitor all CV treatment emergent adverse events closely. This will be done by recording all major adverse CV events, including myocardial infarction, stroke or CV related death, as Medical Events of Special Interest (MESI) in the phase 3a trials, enabling immediate and consistent collection of data. A list of Preferred Terms covering CV events (Acute Coronary Syndrome, Stroke and Cardiac Death) to be defined as MESIs in the phase 3a program is included in Appendix E.

All collected CV events will be evaluated by an internal Novo Nordisk Safety Committee for the product. A Safety Committee of internal Novo Nordisk employees from the product safety and medical departments is constituted and chaired by a Safety Surveillance Adviser, Novo Nordisk A/S Head Quarters (NNHQ). The safety surveillance department from International Product Safety belong to a different part of the Novo Nordisk A/S organisation than the Global Development departments in order to be independent. The internal SIBA SIAC Safety Committee (SC) is established to review the ongoing safety surveillance conducted on data from clinical trials and pre-clinical findings in relation to SIBA and SIAC. The SC works according to written guidelines and has scheduled meetings every 2-3 months to discuss and evaluate the overall safety of SIBA SIAC in the phase 3a clinical trials. The SC works under blinded conditions. If the SC recommends unblinding of any data for further analysis, an ad hoc group will be established consisting of NN employees with no relationship to the SIBA SIAC clinical trials. This is to maintain the blinding of the employees working with the trial.

All CV treatment emergent adverse events will be tabulated by preferred terms, by the classification suggested in (FDA guidance DEC2008). The tabulation will be done across all phase 3a trials in total and by subgroup (age, sex, race and age). In trials with the patient populations normally included in treat to target trials, as required for approval of new insulins, the number of events observed in previous development programs is very low making a tabulation more relevant for insulin 454 than a formal statistical evaluation and conclusion across trials based on an estimated risk ratio.

Question 13:
a) Considering that SIAC is an insulin combination of insulin 454 and insulin aspart, does the Agency agree that the proposed clinical program, with inclusion criteria as described, tabulations and surveillance of CV events sufficiently investigates the cardiovascular risk profile of SIAC?

FDA Response: Please see our response to SIBA Question 15(a). The same response applies to SIAC.

b) Does the Agency agree to the inclusion and exclusion criteria for including patients at higher risk of cardiovascular events?

FDA Response: Please see our response to SIBA Question 15(b).

c) Does the Agency agree that the list of MedDRA Preferred Terms covers all relevant major CV events. (ref Appendix E)

FDA Response: Please see our response to SIBA Question 15(c).

d) Does the Agency agree that formal non-inferiority assessments of the CV risk ratio such as those recommended in FDA guidance DEC2008 are not needed for SIAC?

FDA Response: Please see our response to SIBA Question 15(d). The same response applies to SIAC.

Pediatric Development Program

(b) (4)

(b) (4)

(b) (4)

FDA Response: (b) (4) **Your NDA should include a proposed pediatric plan (including an overview of your proposed pediatric studies and a timeline that lists dates when each pediatric protocol will be submitted, when each pediatric study will be initiated, and when complete study reports from each pediatric study will be submitted to FDA). In addition, the NDA should contain a request for waiver and/or deferral in children with type 1 diabetes and in children with type 2 diabetes together with justification for the proposed waiver/deferral. The proposed pediatric plan included in your NDA will be discussed with the Pediatric Review Committee (PeRC).**

Additional Comments:

Non-Clinical:

1. **We would like to request information concerning the pen delivery device to be utilized for administration of the drug products. Is the pen an already approved medical device? If not, safety assessment of any novel drug delivery device may be required (specifically, biocompatibility studies to qualify leachables).**

   Additional Discussion:
   Novo Nordisk showed slide 5 and explained that the cartridge and needle are the only parts of PDS290 to come into contact with the drug product.

2. **The reproductive toxicology studies required to proceed to Phase 3 in the clinic appear complete, however a sufficiently powered GLP study for effects on prenatal and postnatal development, including maternal function (Segment III) in a single species (preferably rats) should be submitted for marketing approval.**

Clinical:

3. **You should ensure that patients enrolled in your multinational trials are representative of patients in the United States who will be treated with your insulins, if approved.**

4. **You may need to perform studies with your pen delivery device, such as a Human Factor Study. You should submit your proposal for the pen device soon so that FDA can provide comments on your proposal early during phase 3 development.**

5. **Comments provided were based on protocol synopses. We may have additional comments after we have reviewed the full protocols.**

6. **The design of your extension trials was not described in the briefing package. These trials should remain controlled. Uncontrolled extensions have limited utility when attempting to interpret efficacy and safety.**

   Additional Discussion:
   Novo Nordisk confirmed that extension trials will be controlled.

   Post-Meeting Note: The Division strongly recommends that extension trials also be non-voluntary (i.e., all patients who complete the core studies should participate).

7. **Please clarify if insulin will be titrated throughout the treatment periods of your phase 3 trials. If insulin doses will not be kept stable for the latter part of the trials, the endpoint HbA1c measurement may not accurately reflect glycemic control. Please clarify your approach.**

   Additional Discussion:
   Insulin will be titrated throughout the trial for all products. Novo Nordisk expects most titration will take place in the early part of the trials. The Division expressed concern about the reliability of the HbA1c data if there is substantial titration at the end of the trials.

8. **You mention that patients may be carefully eliminated from your FAS statistical population. All patients who meet the definition for inclusion in the FAS population should be maintained.**

9. **Because of the long-half life of Insulin 454, is there any concern for accumulation with once daily dosing, particularly in patients with renal impairment?**

Additional Discussion:
Based on current available data Novo Nordisk is not concerned but plans to study.

UNRESOLVED ISSUES OR ISSUES REQUIRING FURTHER DISCUSSION:

1. The FDA will determine the acceptability of the list of MedDRA preferred terms and respond in the final meeting minutes.

ACTION ITEMS:

1. Novo Nordisk to submit data comparing once and twice a day dosing of Levemir for review. FDA agreed to review.
2. Novo Nordisk to submit efficacy withdrawal rate data from Novo Nordisk's other insulin trials for review. FDA agreed to review.
3. Novo Nordisk to submit a protocol for the proposed study of SIBA once daily, SIBA forced flex, and glargine dosed according to label. FDA agreed to review.
4. Novo Nordisk to submit the meta-analysis plan 30-60 days prior to database lock. FDA agreed to review.

ATTACHMENTS/HANDOUTS:

1. Novo Nordisk slide handout
2. Novo Nordisk prioritization of SIBA and SIAC EOP2 Questions

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Linked Applications	Sponsor Name	Drug Name / Subject
IND 73198	NOVO NORDISK INC	NN5401 SIAC [(NN1250 SIBA [insulin 454]) + insulin aspart] Injection
IND 76496	NOVO NORDISK INC	NN 1250 SIBA INSULIN ANALOG INJ.

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/s/

RACHEL E HARTFORD
05/05/2009