DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022341

WRITTEN REQUEST – AMENDMENT #1

Novo Nordisk, Inc.
Attention: Robert B. Clark
Vice President, Regulatory Affairs
100 College Road West
Princeton, NJ 08540

Dear Mr. Clark:

Please refer to your correspondence dated October 10, 2014, requesting changes to FDA's September 19, 2012, Written Request for pediatric studies for liraglutide (rDNA origin) injection.

We have reviewed your proposed changes and are amending the below-listed sections of the Written Request. All other terms stated in our Written Request issued on September 19, 2012, remain the same. (Text added is underlined. Text deleted is strikethrough.)

Safety Endpoints must include:
Nature, frequency, severity, and relationship to treatment of all adverse events
Vital signs including heart rate
Laboratory parameters including hematology, biochemistry, sex hormones, serum calcitonin and anti-liraglutide antibodies
Pubertal development based on Tanner staging
Growth parameters based on height standard deviation score
~~**Bone age assessments**~~
Incidence of hypoglycemia

The primary statistical evaluation of the active product arm compared to the comparator arm must control for Type I error at a two-tailed α of 0.05. The superiority test must be a two-sided test of the null hypothesis of no difference in the primary endpoint between the liraglutide + metformin arm and the liraglutide placebo + metformin arm. The alternative hypothesis is that there is a difference between the two treatment arms. Superiority of liraglutide over liraglutide placebo will be concluded if the 95% confidence interval for the mean treatment difference for the primary endpoint lies entirely below 0%, implying that the corresponding two-sided p-value is less than 5%. A sufficient number of patients will be randomized to provide approximately ~~**86**~~ **75** patients in each of the two treatment arms with at least one valid post-baseline measurement of HbA1c. The sample size of ~~**86**~~ **75** patients in each of the two treatment arms (a total of ~~**172**~~ **150** patients) will provide at least 80% power

to detect a 0.~~6~~**7**% difference between the two treatment arms in HbAlc change from baseline, assuming a standard deviation of 1.~~3~~**2**% and a two-tailed α of 0.05.

Timeframe for submitting reports of the study: Reports of the above study must be submitted to the Agency on or before ~~**March 30, 2016**~~, **May 21, 2021.** Please keep in mind that pediatric exclusivity attaches only to existing patent protection or exclusivity that would otherwise expire nine (9) months or more after pediatric exclusivity is granted, and FDA has 180 days from the date that the study reports are submitted to make a pediatric exclusivity determination. Therefore, to ensure that a particular patent or exclusivity is eligible for pediatric exclusivity to attach, you are advised to submit the reports of the studies at least 15 months (9 months plus 6 months/180 days for determination) before such patent or exclusivity is otherwise due to expire.

For ease of reference, a complete copy of the Written Request, as amended, is attached to this letter.

Reports of the studies that meet the terms of the Written Request dated September 19, 2012, as amended by this letter must be submitted to the Agency on or before **May 21, 2021**, in order to possibly qualify for pediatric exclusivity extension under Section 505A of the Act.

Submit reports of the studies as a supplement to an approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, clearly mark your submission **"SUBMISSION OF PEDIATRIC STUDY REPORTS – PEDIATRIC EXCLUSIVITY DETERMINATION REQUESTED"** in large font, bolded type at the beginning of the cover letter of the submission and include a copy of this letter. In addition, send a copy of the cover letter of your submission via fax (240-276-9327) or messenger, to the Director, Office of Generic Drugs, HFD-600, Metro Park North IV, 7519 Standish Place, Rockville, MD 20855-2773.

In accordance with section 505A(k)(1) of the Act, FDA must make available to the public the medical, statistical, and clinical pharmacology reviews of the pediatric studies conducted in response to this Written Request within 210 days of submission of your study report(s). These reviews will be posted regardless of the following:

- the type of response to the Written Request (i.e., complete or partial response);
- the status of the application (i.e., withdrawn after the supplement has been filed or pending);
- the action taken (i.e., approval, complete response); or
- the exclusivity determination (i.e., granted or denied).

FDA will post the medical, statistical, and clinical pharmacology reviews on the FDA website at http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM049872.

If you wish to discuss any amendments to this Written Request, submit proposed changes and the reasons for the proposed changes to your application. Clearly mark submissions of proposed changes to this request **"PROPOSED CHANGES IN WRITTEN REQUEST FOR**

PEDIATRIC STUDIES" in large font, bolded type at the beginning of the cover letter of the submission. We will notify you in writing if we agree to any changes to this Written Request.

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

Sincerely,

{See appended electronic signature page}

Curtis Rosebraugh, M.D., M.P.H.
Director
Office of Drug Evaluation II
Office of New Drugs
Center for Drug Evaluation and Research

ENCLOSURE:
Complete Copy of Written Request as Amended

REVISED WRITTEN REQUEST, AMENDMENT #1

- *Nonclinical study:*

  Repeat-dose studies of long-acting glucagon-like peptide (GLP)-l receptor agonists in monkeys suggest that these drugs may accelerate the onset of puberty or the rate of maturation of males. In 52-week and 87-week studies of liraglutide in monkeys, most males were sexually immature at study initiation. In these studies, testes weight trended higher in liraglutide-treated male monkeys at clinically relevant exposures over the study duration. Transient exposure of immature rodents to GLP-1 receptor agonists can cause behavioral and endocrine changes that persist into adulthood. To assess the potential for liraglutide to cause accelerated development, a juvenile rat toxicity study with liraglutide treatment from pre-puberty through reproductive maturity is required (e.g., postnatal day 21-90). Endpoints for development in the study of liraglutide toxicity in juvenile rats must include assessment of effects on cognition (memory and learning), behavior (aggression and anxiety), age of onset of puberty, rate of sexual maturation, rate of overall growth, and reproductive organ maturation. The timing of this study can be concurrent with the proposed pediatric clinical study.

- *Clinical study:*

  Study 1: A randomized and controlled study to evaluate the efficacy and safety of liraglutide for the treatment of type 2 diabetes mellitus in pediatric patients ages 10 to 17 years. The study must contain a 26-week, double-blind, controlled period up until the primary efficacy endpoint. The study must have a 26-week controlled period after the primary efficacy endpoint, which, together with the double-blind period, totals at least 52 weeks in duration.

- *Objective of each study:*

  Study 1:

  - To establish the superiority of liraglutide at the maximum tolerated dose (0.6mg, 1.2 mg, or 1.8 mg) in combination with metformin controlling glycemia versus metformin and liraglutide placebo in children and adolescents (ages 10 to 17 years) with type 2 diabetes to support an indication for the treatment of type 2 diabetes in the pediatric population.

  - To evaluate the long-term safety of liraglutide in the pediatric population.

- *Patients to be studied:*

The study must randomize at least 172 male and female adolescents age 10 years to 17 years. At least 30% of randomized patients must be 10-14 years old so that the effects of liraglutide on early puberty can be assessed. At least 30% of the randomized patients must be female.

All patients who receive run-in treatment with metformin must have at least 8 weeks of stable metformin therapy prior to randomization.

Representation of Ethnic and Racial Minorities: The studies must take into account adequate (e.g., proportionate to disease population) representation of children of ethnic and racial minorities. If you are not able to enroll an adequate number of these patients, provide a description of your efforts to do so and an explanation for why they were unsuccessful.

- *Study Endpoints:*

  Efficacy Endpoints:

  The primary efficacy endpoint must be the change in hemoglobin A1c from baseline to the end of the 26-week double-blind treatment period and must be assessed by a centrally analyzed, NGSP-certified hemoglobin A1c assay.

  Important secondary endpoints must include fasting plasma glucose assessed by a centrally analyzed plasma glucose assay as well as body weight.

  The protocol must describe how patient compliance will be assessed.

  Safety Endpoints must include:

  Nature, frequency, severity, and relationship to treatment of all adverse events
  Vital signs including heart rate
  Laboratory parameters including hematology, biochemistry, sex hormones, serum calcitonin and anti-liraglutide antibodies
  Pubertal development based on Tanner staging
  Growth parameters based on height standard deviation score
  Incidence of hypoglycemia

- The following adverse events must be actively monitored:

  Pancreatitis by adverse event reporting, serum amylase and lipase
  Gastrointestinal adverse events
  Thyroid adverse events, including serum calcitonin
  Hypoglycemia using the American Diabetes Association definitions

Renal impairment by serum creatinine monitoring
Immune/hypersensitivity reactions
Acceleration of puberty

All adverse events must be monitored until symptom resolution or until the condition stabilizes.

All adverse events must be captured when spontaneously reported.

A Data Monitoring Committee (DMC) must be included because the study is being performed in children, a potentially fragile population.

- *Known drug safety concerns and monitoring:* Safety issues that must be assessed include gastrointestinal tolerability, pancreatitis, hypersensitivity, dehydration and renal impairment, anti-liraglutide antibodies (and their impact on efficacy and safety), severe hypoglycemia, calcitonin and thyroid cancers, and acceleration of sexual maturation.

- *Extraordinary results:* In the course of conducting these studies, you may discover evidence to indicate that there are unexpected safety concerns, unexpected findings of benefit in a smaller sample size, or other unexpected results. In the event of such findings, there may be a need to deviate from the requirements of this Written Request.
  If you believe this is the case, you must contact the Agency to seek an amendment. It is solely within the Agency's discretion to decide whether it is appropriate to issue an amendment.

- *Drug information:*

  Dosage form - Solution for subcutaneous injection, pre-filled, multi-dose pen that delivers doses of 0.6 mg, 1.2 mg, or 1.8 mg (6 mg/mL, 3 mL)
  Route of administration- Subcutaneous injection
  Regimen- See below

  Depending on the tolerance level and efficacious dose in the participating individual, a dose of 0.6 mg, 1.2 mg, or 1.8 mg will be administered. Liraglutide and liraglutide placebo will be administered once daily by subcutaneous injection in the abdomen, thigh, or upper arm. After randomization, liraglutide or liraglutide placebo will be escalated weekly, starting at 0.6 mg and increasing with 0.6 mg increments. The starting and maintenance doses were determined based on FDA review of the results of the pediatric clinical pharmacology trial titled *A Phase 1 Randomized, Double-blind, Placebo- Controlled Trial to Assess Safety/Tolerability, Pharmacokinetics and Pharmacodynamics of Liraglutide in Pediatric Subjects (10 - 16 years and 11 month old) with Type 2 Diabetes.*

Use an age-appropriate formulation in the study described above. If an age appropriate formulation is not currently available, you must develop and test an age-appropriate formulation and, if it is found safe and effective in the studied pediatric population(s), you must seek marketing approval for that age-appropriate formulation.

In accordance with section 505A(e)(2), if

1) you develop an age-appropriate formulation that is found to be safe and effective in the pediatric population(s) studied (i.e., receives approval);
2) the Agency grants pediatric exclusivity, including publishing the exclusivity determination notice required under section 505A(e)(l) of the Act; and
3) you have not marketed the formulation within one year after the Agency publishes such notice,

the Agency will publish a second notice indicating you have not marketed the new pediatric formulation.

If you demonstrate that reasonable attempts to develop a commercially marketable formulation have failed, you must develop and test an age-appropriate formulation that can be compounded by a licensed pharmacist, in a licensed pharmacy, from commercially available ingredients. Under these circumstances, you must provide the Agency with documentation of your attempts to develop such a formulation and the reasons such attempts failed. If we agree that you have valid reasons for not developing a commercially marketable, age-appropriate formulation, then you must submit instructions for compounding an age-appropriate formulation from commercially available ingredients that are acceptable to the Agency. If you conduct the requested studies using a compounded formulation, the following information must be provided and will appear in the product labeling upon approval: active ingredients, diluents, suspending and sweetening agents; detailed step-by-step compounding instructions; packaging and storage requirements; and formulation stability information.

Bioavailability of any formulation used in the studies must be characterized, and as needed, a relative bioavailability study comparing the approved drug to the age appropriate formulation may be conducted in adults.

- *Statistical information, including power of study and statistical assessments:*

Patients must be allocated to the treatment arms of the study by a valid randomization procedure, in a 1:1 allocation. The treatment assignments from the time of randomization to the week at which the primary endpoint is determined must be double-blind.

The primary statistical evaluation of the active product arm compared to the comparator arm must control for Type I error at a two-tailed α of 0.05. The superiority test must be a two-sided test of the null hypothesis of no difference in the primary endpoint between the liraglutide + metformin arm and the liraglutide placebo + metformin arm. The alternative hypothesis is that there is a difference between the two treatment arms. Superiority of liraglutide over liraglutide placebo will be concluded if the 95% confidence interval for the mean treatment difference for the primary endpoint lies entirely below 0%, implying that the corresponding two-sided p-value is less than 5%. A sufficient number of patients will be randomized to provide approximately 75 patients in each of the two treatment arms with at least one valid post-baseline measurement of HbA1c. The sample size of 75 patients in each of the two treatment arms (a total of 150 patients) will provide at least 80% power to detect a 0.7% difference between the two treatment arms in HbA1c change from baseline, assuming a standard deviation of 1.2% and a two-tailed α of 0.05.

The primary statistical analysis model should be a repeated measures analysis with HbA1c change from baseline as the dependent variable. Treatment arm and stratification variables should be factors in the model, and baseline level ofHbA1c should be a covariate. The model will be used to compare liraglutide and liraglutide placebo at week 26.

The primary analysis population to analyze the primary efficacy endpoint should be the Full Analysis Set. The Full Analysis Set consists of data from patients who were randomized and who provided at least one post-baseline measurement of the primary efficacy endpoint.

The study protocol should provide a detailed description of the primary analysis model. The protocol should also describe the additional sensitivity analyses of the comparison between liraglutide and liraglutide placebo in the primary HbA1c endpoint.

The analysis should include a descriptive summary of the primary and secondary efficacy results by age group, categorized by (10 -14 years) and (> 14 years). As stated above, at least 30% of randomized patients must be 10-14 years old.

- *Labeling that may result from the study:* You must submit proposed pediatric labeling to incorporate the findings of the study. Under section 505A(j) of the Act, regardless of whether the study demonstrate that liraglutide is safe and effective, or whether such study results are inconclusive in the studied pediatric population(s) or subpopulation(s), the labeling must include information about the results of the study. Under section 505A(k)(2) of the Act, you must distribute to physicians and other

health care providers at least annually (or more frequently if FDA determines that it would be beneficial to the public health), information regarding such labeling changes that are approved as a result of the study.

- *Format and types of reports to be submitted:* You must submit full study reports (which have not been previously submitted to the Agency) that address the issues outlined in this request, with full analysis, assessment, and interpretation. In addition, the reports must include information on the representation of pediatric patients of ethnic and racial minorities. All pediatric patients enrolled in the study should be categorized using one of the following designations for race: American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander, or White. For ethnicity, you should use one of the following designations: Hispanic/Latina or Not Hispanic/Latina. If you choose to use other categories, you should obtain agency agreement.

  Under section 505A(d)(2)(B) of the Act, when you submit the study reports, you must submit all postmarketing adverse event reports regarding this drug that are available to you at that time. All post-market reports that would be reportable under section 21 CPR 314.80 should include adverse events occurring in an adult or a pediatric patient. In general, the format of the post-market adverse event report should follow the model for a periodic safety update report described in the Guidance for Industry *E2C Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs* and the Guidance addendum. You are encouraged to contact the reviewing Division for further guidance.

  Although not currently required, we request that study data be submitted electronically according to the Study Data Tabulation (SDTM) standard published by the Clinical Data Interchange Standards Consortium (CDISC) provided in the document "Study Data Specifications," which is posted on the FDA website at http://www.fda.gov/CDER/REGULATORY/ersr/Studydata.pdf and referenced in the FDA Guidance for Industry, *Providing Regulatory Submissions in Electronic Format- Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications* available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072349.pdf

- *Timeframe for submitting reports of the study:* Reports of the above study must be submitted to the Agency on or before **May 21, 2021.** Please keep in mind that pediatric exclusivity attaches only to existing patent protection or exclusivity that would otherwise expire nine (9) months or more after pediatric exclusivity is granted, and FDA has 180 days from the date that the study reports are submitted to make a pediatric exclusivity determination. Therefore, to ensure that a particular patent or exclusivity is eligible for pediatric exclusivity to attach, you are advised to

submit the reports of the studies at least 15 months (9 months plus 6 months/180 days for determination) before such patent or exclusivity is otherwise due to expire.

- *Response to Written Request:* Under section 505A(d)(2)(A)(i), within 180 days of receipt of this Written Request you must notify the Agency whether or not you agree to the Written Request. If you agree to the request, you must indicate when the pediatric studies will be initiated. If you do not agree to the request, you must indicate why you are declining to conduct the study. If you decline on the grounds that it is not possible to develop the appropriate pediatric formulation, you must submit to us the reasons it cannot be developed.

  Furthermore, if you agree to conduct the study, but have not submitted the study reports on or before the date specified in the Written Request, the Agency may utilize the process discussed in section 505A(n) of the Act.

Submit protocols for the above study to an investigational new drug application (IND) and clearly mark your submission **"PEDIATRIC PROTOCOL SUBMITTED FOR PEDIATRIC EXCLUSIVITY STUDY"** in large font, bolded type at the beginning of the cover letter of the submission.

Reports of the study must be submitted as a new drug application (NDA) or as a supplement to your approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, clearly mark your submission **"SUBMISSION OF PEDIATRIC STUDY REPORTS-PEDIATRIC EXCLUSIVITY DETERMINATION REQUESTED"** in large font, bolded type at the beginning of the cover letter of the submission and include a copy of this letter. Please also send a copy of the cover letter of your submission to the Director, Office of Generic Drugs, HFD-600, Metro Park North IV, 7519 Standish Place, Rockville, MD 20855-2773. If you wish to fax it, the fax number is 240-276-9327.

In accordance with section 505A(k)(l) of the Act, *Dissemination of Pediatric Information,* FDA must make available to the public the medical, statistical, and clinical pharmacology reviews of the pediatric studies conducted in response to this Written Request within 210 days of submission of your study report(s). These reviews will be posted regardless of the following circumstances:

1. the type of response to the Written Request (i.e., complete or partial response);
2. the status of the application (i.e., withdrawn after the supplement has been filed or pending);
3. the action taken (i.e., approval, complete response); or
4. the exclusivity determination (i.e., granted or denied).

FDA will post the medical, statistical, and clinical pharmacology reviews on the FDA website at

http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM049872

If you wish to discuss any amendments to this Written Request, submit proposed changes and the reasons for the proposed changes to your application. Submissions of proposed changes to this request should be clearly marked **"PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES"** in large font, bolded type at the beginning of the cover letter of the submission. You will be notified in writing if any changes to this Written Request are agreed upon by the Agency.

Please note that, if your trial is considered an "applicable clinical trial" under section 402(j)(l)(A)(i) of the Public Health Service Act (PHS Act), you are required to comply with the provisions of section 402(j) of the PHS Act with regard to registration of your trial and submission of trial results. Additional information on submission of such information can be found at www.ClinicalTrials.gov.

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/s/

CURTIS J ROSEBRAUGH
01/15/2015