IND 137406

WRITTEN REQUEST

Novo Nordisk Inc.
Attention: Helen Chen, MSc, RAC
Director, Regulatory Affairs
800 Scudders Mill Road
Plainsboro, NJ 08536

Dear Ms. Chen:

Reference is made to your December 16, 2021, Proposed Pediatric Study Request for NNC0148-0287.

This study investigates the potential use of NNC0148-0287 for the treatment of type 2 diabetes mellitus in children and adolescents (age 10 to <18 years).

BACKGROUND:

Type 2 diabetes (T2D) is a complex metabolic disorder, a result of environmental and genetic risk factors. In the pediatric population, T2D is more common among patients ages 10 and older with the mean age for disease diagnosis of 13.5 years, generally coinciding with the peak of pubertal insulin resistance. There has been an increase of T2D in adolescents and children in recent years. In the United States (US), the total number of adolescents with T2D is estimated to be between 20,000-25,000. Unlike adults with T2D, children and adolescents with the disease have few approved options for glycemic control. Metformin, liraglutide, exenatide extended release, and certain insulin products are the only antihyperglycemics approved in the US for treatment of children and adolescents with T2D, and there is an important need for additional approved medications to treat children and adolescents with T2D that are safe and effective. Type 2 diabetes in this age group may be associated with a more rapid decline in ß-cell function and accelerated development of diabetes complications.

Although there are available basal insulin products for pediatric patients, increased convenience through less frequent injections with a once-weekly basal insulin, such as NNC0148-0287, could potentially offer meaningful public health benefits by improving treatment adherence and quality of life for pediatric T2D patients, with its requirement of only 52 weekly injections compared to 365 daily injections per year for available basal insulin therapy, while achieving similar glycemic control. Data from the TODAY trial indicate that adolescents with T2D may have a relatively high rate of nonadherence

over time (44% of participants randomized to metformin) and also have high treatment failure rates with metformin (~50%).

The overall pharmacokinetic (PK) properties of NNC0148-0287 are expected to be similar in pediatrics aged 10 to <18 and adults. Therefore, the Agency supports extrapolation of efficacy and safety for NNC0148-0287 from the adult population by demonstrating comparable PK properties in children and adolescents aged 10 to <18 years with T2D. A single dose PK study in the children and adolescents with T2D aged 10 to <18 years, is expected to provide PK data to model the steady state PK properties of NNC0148-0287 in this pediatric subpopulation. This information will be used to compare the PK in adults and pediatric T2D patients aged 10 to <18 and support evidence of effectiveness and safety in pediatric T2D patients aged 10 to <18.

Children with T2D less than 10 years of age (including neonates) are not included in this Written Request because the prevalence of T2D in this age group is low and studies in this age group would be impossible or highly impracticable. Additionally, there is a lack of meaningful benefit for the use of NNC0148-0287 in pediatric type 1 diabetes (T1D) because this once weekly dosed insulin product does not allow for frequently changing insulin dose requirements. Pediatric T1D patients have insulin dose requirements that are variable and require constant monitoring and adjustment.

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.

To obtain needed pediatric information on NNC0148-0287, the Food and Drug Administration (FDA) is hereby making a formal Written Request, pursuant to Section 505A of the Federal Food, Drug, and Cosmetic Act (the Act), as amended by the Food and Drug Administration Amendments Act of 2007, that you submit information from the studies described below.

- *Nonclinical study*:

  Based on review of the available nonclinical toxicology, no additional animal studies are required at this time to support the clinical studies described in this Written Request.

- *Clinical study:*

  Study 1: A Study Investigating the Pharmacokinetic Properties of NNC0148-0287 *in Children and Adolescents with Type 2 Diabetes*

- *Study Objectives:*

  Primary: To investigate pharmacokinetic properties of a single dose of subcutaneously administered NNC0148-0287 in children and adolescents with T2D.

  Secondary: To predict steady state pharmacokinetic properties of subcutaneously administered NNC0148-0287 across one dosing interval using modelling in children and adolescents with T2D.

- *Patients to be Studied:*

  - *Age groups to be studied:* 10 to <18 years of age

  - *Number of patients to be studied:* A minimum of 16 patients must complete the study, of which at least 5 patients must be 10 to <14 years of age

- *Study endpoints:*

  - Pharmacokinetic endpoints:

    Primary pharmacokinetic endpoint(s) must include:

    1. Area under the serum NNC0148-0287 concentration-time curve from 0 hours until infinity after a single dose ($AUC_{0\text{-}inf}$)
    2. Maximum observed serum NNC0148-0287 concentration after a single dose (C_{max})
    3. Time to maximum observed serum NNC0148-0287 concentration after a single dose (t_{max})

    Secondary pharmacokinetic endpoints must include:

    1. Model-based area under the serum NNC0148-0287 concentration-time curve during one dosing interval at steady state ($AUC_{tau,SS,model}$)
    2. Model-based maximum serum NNC0148-0287 concentration during one dosing interval at steady state ($C_{max,SS,model}$)

- *Safety Endpoints/Monitoring:*

  The protocol must include monitoring for adverse events (AEs) including the following: serious adverse events (SAEs) and adverse events of special interest (severe or serious events of hypoglycemia, hyperglycemia, hypersensitivity, and

injection site reactions). The protocol must also include monitoring for laboratory assessments including anti-NNC0148-0287 antibodies and additional immunogenicity assessments if warranted in case of systemic hypersensitivity reactions. The safety endpoints/monitoring in the protocol must be agreed upon with the FDA prior to study initiation.

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

  The number of subjects to be exposed to a single dose of NNC0148-0287 for the primary analysis is a minimum of 16 patients who must complete the study.

  PK modelling must be performed to predict the steady state PK properties of NNC0148-0287 in patients enrolled in this study. Based on the serum NNC0148-0287 concentration data, a population PK model for NNC0148-0287 must be developed.

  The primary and secondary PK endpoints should be summarized using descriptive statistics.

  The protocol and modelling approach must be agreed upon with the FDA.

The following information pertains to all clinical studies in the Written Request:

- *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.

- *Biological product information:*

  - *dosage form:* Solution for injection
  - *route of administration:* Subcutaneous (SC)
  - *regimen:* Single NNC0148-0287 dose as specified in the protocol

  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)(1) 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 prepared 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 preparing an age-appropriate formulation from commercially available ingredients that are acceptable to the Agency. If you conduct the requested studies using such a formulation, the following information must be provided for inclusion in the product labeling upon approval: active ingredients, diluents, suspending and sweetening agents; detailed step-by-step preparation 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.

- *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 FD&C Act, regardless of whether the study demonstrate that NNC0148-0287 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 FD&C 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/Latino or Not Hispanic/Latino. If you choose to use other categories, you should obtain agency agreement.

  Under section 505A(d)(2)(B) of the FD&C 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 CFR 600.80 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.[1] You are encouraged to contact the reviewing Division for further guidance.

  For studies started after December 17, 2017 , study data must 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 FDA.gov[2] and referenced in the guidance for industry *Providing Regulatory Submissions in Electronic Format - Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications*.

- *Timeframe for submitting reports of the study:* Reports of the above studies must be submitted to the Agency on or before June 30, 2026. Please keep in mind that pediatric exclusivity attaches only to existing exclusivity, 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

[1] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.
[2] https://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM312964.pdf

otherwise due to expire.

If FDA has not determined whether NNC0148-0287 is eligible for reference product exclusivity under section 351(k)(7) of the PHS Act, you may submit a request for reference product exclusivity with supporting data and information to the Agency. Note that neither the issuance of this formal pediatric Written Request, nor any request for exclusivity made by you confers or otherwise implies that you are eligible for reference product exclusivity under section 351(k)(7) of the PHS Act.

- *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 biologics license application (BLA) or as a supplement to your approved BLA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, please 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 accordance with section 505A(k)(1) of the FD&C 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.[3]

If you wish to discuss any amendments to this Written Request, submit your proposed changes using strikethrough and underline (Text added is underlined. Text deleted is strikethrough.) 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)(1)(A)(i) of the 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 on the Clinical Trials website.[4]

If you have any questions, contact Michael Oyewole, Regulatory Project Manager, at (301) 796-3897.

Sincerely,

{See appended electronic signature page}

Lisa B. Yanoff, M.D.
Deputy Director
Office of Cardiology, Hematology, Endocrinology, and Nephrology
Office of New Drugs
Center for Drug Evaluation and Research

[3] https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm316937.htm
[4] www.ClinicalTrials.gov

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

/s/

LISA B YANOFF
04/15/2022 09:26:39 AM