DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 125469

WRITTEN REQUEST

Eli Lilly and Company
Attention: John J. Kaiser, PharmD, RPh
Consultant, Global Regulatory Affairs – U.S.
Lily Corporate Center, DC 2543
Indianapolis, IN 46285

Dear Dr. Kaiser:

Reference is made to your May 4, 2016, Proposed Pediatric Study Request for dulaglutide.

This study will investigate the potential use of dulaglutide in the treatment of pediatric patients age 10 to 17 years (inclusive) with type 2 diabetes mellitus (T2DM). Children less than 10 years of age (including neonates) are not included as the prevalence of T2DM in this age group is low and studies in this age group would not be practical or feasible. Study of dulaglutide in pediatric patients with type 1 diabetes mellitus is not included as dulaglutide would not be expected to be of benefit in this population and would come with increased concerns for hypoglycemia, hyperglycemia and ketosis/ketoacidosis.[1]

There has been a significant relative increase of T2DM in adolescents and children in recent years. [2] In the United States (US), children and adolescents at highest risk for T2DM are minority youths who are pubertal or post-pubertal living in urban environments.[3] Unlike adults with T2DM, children and adolescents with the disease have few approved options for glycemic control. Metformin and insulin are the only agents approved in the US for treatment of children and adolescents with T2DM and there is an important need for additional approved agents to treat children and adolescents with T2DM that are safe and effective in this population.

Recent data have shown that glycemic response in adults does not reliably predict response in pediatric patients.[4] Physiological or pathophysiological differences between children and adults with T2DM exist and indirect methods to establish efficacy in children may not be reliable and pharmacokinetic and pharmacodynamic data are not sufficient. As a result, the Agency requires an adequate and well-controlled trial.

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[1] Mathieu C, Zinman B, et al. "Efficacy and Safety of Liraglutide Added to Insulin Treatment in Type 1 Diabetes: The ADJUNCT ONE Treat-To-Target Randomized Trial". *Diabetes Care*, epub August 9, 2016.
[2] Dabelea D, Mayer-Davis EJ, et al. "SEARCH for Diabetes in Youth Study. Prevalence of type 1 and type 2 diabetes among children and adolescents from 2001 to 2009". *JAMA* 2014; 311(17):1778-1786.
[3] Copeland KC, Zeitler P, et al. "TODAY Study Group. Characteristics of adolescents and youth with recent-onset type 2 diabetes: the TODAY cohort at baseline". *J Clin Endocrinol Metab* 2011; 96(1):159-167.
[4] *Journal of Pharmaceutical Sciences* 2012 May; 101(5): 1659–71

To obtain needed pediatric information on dulaglutide, 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 FD&C Act), as amended by the Food and Drug Administration Amendments Act of 2007, and pursuant to section 351(m) of the Public Health Service Act (the PHS Act), as amended by the Biologics Price Competition and Innovation Act of 2009, that you submit information from the studies described below.

- *Nonclinical study(ies)*:

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

- *Clinical studies:*

Study 1: A 26-week randomized, double-blind, placebo-controlled study of the safety, efficacy, and pharmacokinetics (PK) of dulaglutide for the treatment of T2DM in pediatric patients ages 10 to 17 years (inclusive), followed by a 26-week, open-label extension. As part of this study, sparse blood samples for population PK and exposure-response analysis will be collected.

- ☐ Efficacy in pediatric patients with T2DM aged 10-17 years (inclusive) cannot be extrapolated and will be determined by the studies outlined in the Written Request.

- *Objective of the study:*

The primary objective of this study is to test the hypothesis that dulaglutide (0.75 mg and 1.5 mg, pooled) given subcutaneously (SC) once a week for 26 weeks to children and adolescents with T2DM who have inadequate glycemic control, despite diet and exercise, with or without metformin and/or basal insulin is superior to placebo in the treatment of T2DM, as measured by baseline to Week 26 change in HbA1c.

The secondary objectives of the study are to assess the efficacy, safety, PK and pharmacodynamics (PD) in patients.

The key secondary efficacy objectives are to compare dulaglutide 0.75 mg and dulaglutide 1.5 mg arms (individually and pooled) to placebo with respect to the following parameters:

- Change in HbA1c between baseline and Week 26 (individual doses only)
- Change in fasting blood glucose (FBG) between baseline and Week 26
- Percentage of patients with HbA1c ≤6.5% at Week 26

- *Patients to be studied:*

Male and female children and adolescents aged 10 to 17 years (inclusive) at randomization who have T2DM as diagnosed by Global International Diabetes Foundation/International Society for Pediatric and Adolescent Diabetes (IDF-ISPAD) criteria

- *Age group in which study(ies) will be performed*: Patients 10 to 17 years (inclusive)

- at least 30% and not more than two-thirds of the study subjects should be female
- at least 30% and not more than two-thirds of the study subjects should be in the younger age range (i.e., 10-14 years old)

- *Number of patients to be studied:* Enroll at least 150 patients and randomize them in 1: 1: 1 ratio (placebo: dulaglutide 0.75 mg/week: dulaglutide 1.5 mg/week).

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:*

☐ *Pharmacokinetic/Pharmacodynamic Endpoints:*
The pharmacokinetic and pharmacodynamic endpoints of exposure-response analysis for this study must include adequate endpoints for efficacy (e.g., HbA1c, glucose) and safety (e.g., blood pressure, heart rate).

The pharmacokinetic endpoints for this study must include conventional population PK analysis parameters such as CL/F and Vd/F.

The secondary pharmacodynamic endpoints must include metabolic characteristics (e.g., insulin sensitivity, insulinogenic index, C-peptide index, and others) following a standard oral glucose tolerance test conducted in all subjects at baseline and on treatment.

☐ *Efficacy Endpoints:*
- ☐ The primary efficacy endpoint will be change in HbA1c between baseline and week 26 for the combined dulaglutide treatment arms versus placebo and must be assessed by an analysis that properly accounts for missing data.
- ☐ Important secondary endpoints must include change in HbA1c between baseline and Week 26 for the individual doses (dulaglutide 0.75 mg and 1.5 mg). A graphical approach for multiple comparisons will be used to control the overall type I error.
- ☐ Measures of compliance must include direct questioning and assessment of remaining study drug at each study visit.

☐ *Safety Endpoints:*
- ☐ Safety outcomes must include:
  - Nature, frequency, severity, and relationship to treatment of all adverse events,
  - Vital signs (BP, heart rate, body weight, height, body mass index, Tanner staging at baseline, week 26, week 52),
  - Laboratory parameters (serum lipase, amylase, calcitonin, liver function tests, renal function, dulaglutide anti-drug antibodies, morning hormone

levels of estradiol, testosterone in males, luteinizing hormone (LH), Insulin-like growth factor 1 (IGF-1), cortisol, and prolactin).
- The following adverse events should be captured as adverse events of interest: nausea and vomiting, pancreatic adverse events confirmed by adjudication and the effect on pancreatic enzymes, thyroid-related adverse events, hypersensitivity reactions, injection site reactions, and hypoglycemic episodes

☐ The following adverse events must be actively monitored:
- Hypoglycemia based on American Diabetes Association definitions
- Renal impairment by monitoring measures of renal function
- Pancreatitis by serum lipase and amylase monitoring
- Effects on thyroid C-cells by serum calcitonin monitoring

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;
See Guidance: *Establishment and Operation of Clinical Trial Data Monitoring Committees,*
http://www.fda.gov/downloads/RegulatoryInformation/Guidances/ucm127073.pdf

- *Known safety concerns and monitoring:*

Known safety concerns with dulaglutide include potential risk for thyroid-C-cell tumors, pancreatitis, gastrointestinal adverse reactions (i.e., nausea/vomiting), hypersensitivity, injection site reactions, hypoglycemia, and acute renal failure.

These events should be monitored as Adverse Events of Special interest with appropriate exclusion criteria for at-risk subjects, rescue and discontinuation criteria.

- *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:* Dulaglutide
- *Dosage form:* Solution for subcutaneous injection, 0.75mg/0.5 ml or 1.5mg/0.5ml
- *Route of administration:* Subcutaneous injection
- *Regimen:* Once weekly

- Subjects randomized to dulaglutide 0.75 mg will initiate and continue this dose for the entirety of the study; subjects randomized to dulaglutide 1.5 mg will initiate with dulaglutide 0.75 mg for 4 weeks then increase the dose to dulaglutide 1.5 mg for the remainder of the study.

Use an age-appropriate formulation in the study(ies) 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, pure, and potent 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, pure, and potent in the pediatric population(s) studied (i.e., receives approval);
2) you have unexpired reference product exclusivity or orphan exclusivity to which pediatric exclusivity can attach and the Agency grants pediatric exclusivity, including publishing the exclusivity determination notice required under section 505A(e)(1) of the FD&C 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 indication 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.

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

The primary null hypothesis is that dulaglutide (0.75 mg and 1.5 mg, pooled) is equal to placebo for the primary efficacy endpoint, HbA1c change from baseline to Week 26. The alternative hypothesis is that dulaglutide (0.75 mg and 1.5 mg, pooled) and placebo are different with respect to the primary efficacy endpoint.

The primary analysis population must be all patients randomized who have received at least 1 dose of the study drug. With respect to the primary efficacy analysis, we are interested in estimating the treatment effect based on the de facto (intent-to-treat) estimand, i.e., the difference in HbA1c change in all randomized patients regardless of adherence to treatment or use of rescue. You should include provisions to limit missing data through study design and education of investigators and patients, and pre-specify analysis methods to account for missing data for the primary and key secondary efficacy analyses in a fashion consistent with what the measurements would have been, had they been. We recommend designs that encourage continued collection of efficacy data even after study treatment discontinuation, and these post-treatment data should be included in the primary analysis. Statistical methods to quantify this estimand should be specified in the protocol.

The key secondary efficacy objectives are to compare dulaglutide 0.75 mg and dulaglutide 1.5 mg arms (individually and pooled) to placebo with respect to the following parameters:

- Change in HbA1c between baseline and Week 26 (individual doses only)
- Change in fasting blood glucose (FBG) between baseline and Week 26
- Percentage of patients with HbA1c ≤6.5% at Week 26
- Change in body mass index (BMI) between baseline and Week 26

A strategy must be pre-specified to control the overall type I error across the analyses of the primary and key secondary endpoints.

Under the assumption of treatment difference=-0.65%, standard deviation=1%, dropout rate of 20%, the proposed sample size (50 per arm) provides at least 90% power for the primary objective (pooled dose arms) and at least 80% for each of the individual dose arms. The sample size may be increased according to an interim estimate of variance in order to achieve at least 80% power for the primary objective. The sponsor should not be made aware of any interim estimate of the treatment effect.

The analysis must 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. Descriptive data must be provided for clinically important safety endpoints.

The protocol and statistical analysis plan must be submitted to the Division for comment. You must obtain agreement on the final protocol and statistical analysis plan prior to initiation of the study.

- *Labeling that may result from the study(ies)*: You must submit proposed pediatric labeling to incorporate the findings of the study(ies). Under section 505A(j) of the FD&C Act, regardless of whether the study(ies) demonstrate that dulaglutide is safe, pure, and potent, 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(ies). 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(ies).

- *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(ies) 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. 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 http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM199759.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* at http://www.fda.gov/Cder/guidance/7087rev.htm.

- *Timeframe for submitting reports of the study(ies):* Reports of the above studies must be submitted to the Agency on or before January 31, 2023. Please keep in mind that pediatric exclusivity can attach only to existing exclusivity, if any, 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, if there is unexpired exclusivity that 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 exclusivity is otherwise due to expire.

  If FDA has not determined whether Trulicity 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(ies). 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.

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

Reports of the study(ies) 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. Please also send a copy of the cover letter of your submission to the Office of New Drugs, Immediate Office, Therapeutic Biologics and Biosimilars Team, 10903 New Hampshire Ave, Building 22, Mail Stop 6411, Silver Spring, MD 20993. If you wish to fax it, the fax number is 301-796-9855.

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

If you wish to discuss any amendments to this Written Request, please 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)(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 at www.ClinicalTrials.gov.

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

Sincerely,

{See appended electronic signature page}

Mary Thanh Hai Parks, MD
Deputy Director
Office of Drug Evaluation II
Office of New Drugs
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/

MARY H PARKS
08/31/2016