DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 021995
NDA 022044
NDA 202270

WRITTEN REQUEST

Merck Sharp & Dohme Corp.
Attention: Lou Ann Eader, Ph.D.
Director, Regulatory Affairs
P. O. Box 1000, UG2C-50
North Wales, PA 19454-1099

Dear Dr. Eader:

Reference is made to your July 30, 2012, Proposed Pediatric Study Request for sitagliptin submitted to NDA 021995.

This study investigates the potential use of sitagliptin in the treatment of pediatric type 2 diabetes mellitus (T2DM) patients, aged 10 to 17 years (inclusive).

The prevalence of T2DM among pediatric patients is increasing, concurrent with the obesity epidemic. However, metformin is the only non-insulin treatment approved for use in children with T2DM, 10 years of age and older. Metformin is limited by gastrointestinal adverse reactions and the need for multiple daily dosing in most cases. In addition, diabetes is a progressive disease such that patients may need additional antidiabetic therapy added to metformin to achieve adequate glycemic control. Sitagliptin would provide a useful additional treatment option for pediatric patients with T2DM based on the low risk of hypoglycemia and oral administration. A single-dose study to assess pharmacokinetics, safety, and tolerability of sitagliptin in adolescents was completed and supports the proposed 100-mg daily dose in adolescents. Efficacy of sitagliptin must be established in the pediatric population because it is unknown whether the effects of sitagliptin are sufficiently similar between adults and the pediatric population. The use of placebo in sitagliptin pediatric clinical studies is ethically justified as the protocols include strict inclusion and hyperglycemic rescue criteria as well as diet, exercise, and diabetic education.

Studies of T2DM patients under 10 years of age, including neonates, are impossible or highly impractical because few of these patients require pharmacologic therapy.

To obtain needed pediatric information on sitagliptin, 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 and the Food and Drug Administration Safety and Innovation Act of 2012, that you submit information from the studies described below.

- *Nonclinical studies*:

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 studies:*

Study 1: A randomized, double-blind, placebo- and active-controlled, safety and efficacy study of the effect of sitagliptin on hemoglobin A1c (HbA1c) in pediatric subjects 10 to 17 years (inclusive) with T2DM who are not on treatment with an antihyperglycemic agent for ≥12 weeks prior to screening and have inadequate glycemic control (HbA1c ≥7.0% and ≤10.0%). The trial must consist of a screening period, a one-week, single-blind, run-in period, a 20-week, placebo- and active-controlled Phase "A," and a, at least, 32-week, active-controlled Phase "B." The protocol must specify glycemic rescue and individual patient discontinuation criteria.

- *Objectives of the study:*
  - To assess the effect of treatment with sitagliptin compared to placebo at 20 weeks on the change from baseline in HbA1c in Phase A
  - To evaluate the long-term safety of sitagliptin in the pediatric population in Phase B

- *Patients to be studied:*
  - Age group in which the study will be performed: Patients ages 10 to 17 years (inclusive)
  - At least 30% of randomized patients must be 10-14 years old
  - At least 30% of randomized patients must be female
  - Number of patients to be randomized: At least 360 total with approximately equal numbers of patients randomized to each of the three treatment groups
  - No patients may have been taking an antihyperglycemic agent (AHA) for at least 12 weeks prior to randomization
  - Inadequate glycemic control (HbA1c ≥7.0% and ≤10.0%)

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.

Study endpoints:

- ☐ *Efficacy Endpoints:*
  - ☐ The primary efficacy endpoint must be the change in HbA1c from baseline to the end of the 20-week, double-blind, treatment period and must be assessed by a centrally analyzed, NGSP-certified hemoglobin A1c assay

- ☐ Important secondary endpoints must include the following:
  - The change in fasting plasma glucose from baseline to week 20 assessed by a centrally analyzed plasma glucose assay
  - The proportion of subjects who achieve HbA1c <7.0% and <6.5% at week 20
- ☐ The protocol must describe how patient compliance will be assessed

☐ *Safety Endpoints:*

- ☐ Safety outcomes must include:
  - Nature, frequency, severity, and relationship to treatment of all adverse events (AEs)
  - Vital signs
  - Laboratory parameters including hematology, biochemistry, and sex hormones
  - 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:
  - Effect on linear growth must be monitored at baseline, endpoint, and every 3 to 6 months by height measurements, Tanner staging, X-ray of left hand and wrist for bone age, and the following laboratories: IGFR-1, IGF-BP3, bone markers, and calcitonin
  - Effect on dentition (including tooth enamel hardness and discoloration) must be monitored at baseline, endpoint, and every 3 to 6 months by dental exams
  - Gastrointestinal AEs
  - Hypoglycemia using the American Diabetes Association definitions
  - Hypersensitivity reactions
  - Infection by AE reporting
  - Renal impairment by serum creatinine monitoring
  - Pancreatitis by AE reporting
  - All adverse events must be monitored until symptom resolution or until the condition stabilizes

The following adverse events must be captured when spontaneously reported: changes in growth or dentition, gastrointestinal events, hypoglycemia, infection, hypersensitivity, acute renal failure, and pancreatitis

A Data Monitoring Committee (DMC) must be included because the study is being performed in children; see the guidance for industry *Establishment and Operation of Clinical Trial Data Monitoring Committees, available at* http://www.fda.gov/downloads/RegulatoryInformation/Guidances/ucm127073.pdf

- *Study 2*: You must submit the complete study report for study 170 conducted under NDA 022044: A phase 3, multicenter, double-blind, randomized, placebo-controlled

clinical trial to evaluate the safety and efficacy of MK-0431A (a fixed-dose combination tablet of sitagliptin and metformin) in pediatric patients with type 2 diabetes mellitus.

- *Study 3*: You must submit the complete study report for study 296 conducted under NDA 202270: A study to assess the pharmacokinetics and ability for pediatric patients with type 2 diabetes to swallow MK-0431A XR tablets.

- *Study 4*: You must submit the complete study report for study 289 conducted under NDA 202270: A phase 3, multicenter, double-blind, randomized, placebo-controlled clinical trial to evaluate the safety and efficacy of MK-0431A XR (a fixed-dose combination tablet of sitagliptin and extended-release metformin) in pediatric subjects with type 2 diabetes mellitus with inadequate glycemic control on metformin monotherapy.

- *Known drug safety concerns and monitoring:* Safety issues that must be addressed include gastrointestinal AEs, hypoglycemia, infection, hypersensitivity AEs, renal impairment, pancreatitis, severe hypoglycemia, effect on linear growth, and effect on dentition.

- *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* *Tablets*
  - *route of administration* *Oral*
  - *regimen* *Once daily*

  The 100-mg daily dose is supported by results of a pediatric clinical pharmacology study, *A single-dose study to assess the PK, safety, and tolerability of sitagliptin in adolescents*. The results of this study were reviewed by the FDA.

  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, 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 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 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:* The primary null hypothesis is that sitagliptin is equal to placebo for the primary efficacy endpoint, HbA1c change from baseline to Week 20. The alternative hypothesis is that sitagliptin and placebo are different with respect to the primary efficacy endpoint.

  One hundred twenty randomized patients (120) per group will provide 94% power to detect a 0.5% difference between the groups in HbA1c change from baseline assuming a standard deviation of 1.1% and a two-sided alpha of 0.05. Assuming 15% of patients drop out prior to Week 26, approximately 102 completed patients per group will provide 90% power to detect a 0.5% difference between the groups in HbA1c change from baseline assuming a standard deviation of 1.1% and a two-sided alpha of 0.05. The trial is also adequately powered assuming, very conservatively, that the average treatment difference for dropouts is zero. In this case, the average effect size for all patients receiving sitagliptin and placebo (including the 15% of patients who drop out) is 0.425%. The trial has 85% power to detect a 0.425% difference between the groups in HbA1c

change from baseline assuming a standard deviation of 1.1% and a two-sided alpha of 0.05.

The primary analysis population must be the Full Analysis Set (FAS) consisting of all randomized patients who take at least one dose of study medication and have HbA1c data at baseline and after randomization. The primary analysis model must be pre-specified in the study protocol. You must conduct at least two sensitivity analyses to investigate the impact of missing data on the primary analysis result.

The treatment comparisons between the active control group and placebo and between sitagliptin and the active control are considered secondary hypotheses. You should provide estimates of the treatment differences and corresponding 95% confidence intervals.

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.

- *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 sitagliptin is safe and effective, or whether such study results are inconclusive in the studied pediatric population or subpopulations, 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/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 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 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:* A report of the above study must be submitted to the Agency on or before **April 25, 2018**. 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 study 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.

The report 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 report, 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 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)(1) 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. 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 is pending)
3. the action taken (i.e., approval, complete response)
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 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.

If you have any questions, call Richard Whitehead, Regulatory Project Manager, at 301-796-4945.

Sincerely,

{See appended electronic signature page}

Curtis J. Rosebraugh, M.D., M.P.H.
Director
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/

CURTIS J ROSEBRAUGH
11/27/2012