DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 021995

WRITTEN REQUEST – AMENDMENT 2

Merck Sharp & Dohme Corp.
Attention: Lou Ann Eader, PhD
Director, Worldwide Regulatory Affairs
351 N. Sumneytown Pike
P.O. Box 1000, UG2C-50
North Wales, PA 19454-1099

Dear Dr. Eader:

Please refer to your correspondence dated August 7, 2017, requesting changes to FDA's November 27, 2012, and amended May 7, 2013, (Amendment #1) Written Request for pediatric studies for sitagliptin tablets.

We have reviewed your proposed changes and amended sections of the Written Request are listed below. (Text added is underlined. Text deleted is ~~strikethrough~~.)

All other terms stated in our Written Request issued on November 27, 2012, and as amended on May 7, 2013, remain the same. For ease of reference, a complete copy of the Written Request, as amended, is attached to this letter.

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

Efficacy of sitagliptin must be ~~established~~ evaluated in the pediatric population because it is unknown whether the effects of sitagliptin are sufficiently similar between adults and the pediatric population. Sitagliptin would provide a useful additional treatment option for pediatric patients with T2DM based on the low risk of hypoglycemia and oral administration. 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. 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.

Study 1:
You must submit the complete study report for study 083 conducted under IND 065495 (NDA 021995), 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 oral antihyperglycemic agent (AHA) or are on a stable dose of insulin for ≥12 weeks prior to screening and have inadequate glycemic control (HbA1c ≥~~7.0~~ 6.5% and ≤10.0% for drug-naïve patients, and ≥7.0% and ≤10.0% for patients on insulin). 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 a 32-week, active-controlled Phase "B." The protocol must specify glycemic rescue and individual patient discontinuation criteria.

Study 2:
You must submit the complete study report for study 170 conducted under IND 070934 (NDA 022044), a randomized, double-blind, placebo-controlled, safety and efficacy study of the effect of sitagliptin (administered as a fixed-dose combination tablet of sitagliptin and metformin) on hemoglobin A1c (HbA1c) in pediatric subjects 10 to 17 years (inclusive) with T2DM who are being treated with metformin alone or in combination with a stable dose of insulin for ≥12 weeks prior to screening and have inadequate glycemic control (HbA1c ≥6.5% and ≤10.0% patients on metformin, and ≥7.0% and ≤10.0% for patients on metformin and insulin). The trial must consist of a screening period, a one-week, single-blind, run-in period, a 20-week, placebo-controlled "base study", and at least a 32-week, active-controlled "extension study". The protocol must specify glycemic rescue and individual patient discontinuation criteria.

Study 3:
A Phase I PK study of JANUMET XR is also specified in the Written Request. You must submit the complete study report for study 296 conducted under IND 101964 (NDA 202270), a Phase I PK study of JANUMET XR 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 IND 101964 (NDA 202270), a randomized, double-blind, placebo controlled, safety and efficacy study of the effect of sitagliptin (administered as a fixed-dose combination tablet of sitagliptin and metformin extended release) on hemoglobin A1c (HbA1c) in pediatric subjects 10 to 17 years (inclusive) with T2DM who are being treated with metformin alone or in combination with a stable dose of insulin for ≥12 weeks prior to screening and have inadequate glycemic control (HbA1c ≥6.5% and ≤10.0% for metformin-treated patients, and ≥7.0% and ≤10.0% for patients treated with metformin and insulin). The trial must consist of a screening period, a one-week, single-blind, run-in period, a 20-week, placebo- controlled Phase "A", and at least a 32-week, active-

controlled Phase "B". The protocol must specify glycemic rescue and individual patient discontinuation criteria.

- *Objectives of each study:*

Phase III studies:

- *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 through at least 52 weeks.*

- *Patients to be studied:*

Phase III studies

- *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 Approximately 350 patients pooled across Studies 1, 2 and 4 will be randomized to sitagliptin or placebo*
- *No patients may have received more than 10 cumulative days of treatment with an oral antihyperglycemic agent (AHA) (i.e., metformin, SU, meglitinides, or alpha-glucosidase inhibitors) or 3 days of treatment with insulin in the 12 weeks prior to Visit 1.*
- *Inadequate glycemic control (HbA1c ≥7.0 6.5% and ≤10.0% for patients not on insulin and ≥7.0% and ≤10.0% for patients on insulin) at Visit 1. with insulin in the 12 weeks prior to Visit 1.*
- *In Study 1, no patients may have received more than 10 cumulative days of treatment with an oral antihyperglycemic agent (AHA) (i.e., metformin, SU, meglitinides, or alpha-glucosidase inhibitors) or 3 days of treatment with insulin in the 12 weeks prior to Visit 1.*

- *The following adverse events must be actively monitored:*
  - *Status of linear growth must be documented at baseline, 20 weeks (primary endpoint) and 54 weeks by height measurements, Tanner staging, and, in Study 1, by X-ray of left hand and wrist for bone age, and the following laboratories: IGFR-1,IGF-BP3, bone markers (urinary N-telopeptide and creatinine ratio, and bone-specific alkaline phosphatase), and calcitonin*
  - *In the monotherapy study (Study 1), baseline status of dentition must be documented, and effect on dentition (including discoloration) must be documented at 20 weeks (primary endpoint) and at the 54- week endpoint by visual oral exams by a qualified dentist or dental technician.*
  - *Hypoglycemia using the 2016 American Diabetes Association definitions*

- ~~*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 with inadequate glycemic control on metformin therapy (alone or in combination with insulin).*~~
- ~~*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 (alone or in combination with insulin).*~~

Use an age-appropriate formulation in the studies~~y~~ 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.

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

Analysis for study 1 (study p083) alone:

You must conduct a formal analysis for study 1 (study 083) followed by the pooled analysis for studies 1, 2, and 4. The null hypothesis is that there is no difference between sitagliptin and placebo in HbA1c change from baseline to week 20. The alternative hypothesis is that sitagliptin and placebo are different with respect to HbA1c change from baseline to Week 20.

A total sample size of 180 subjects (90 subjects per arm) in study 1 will provide 80% power to detect a treatment difference in HbA1C of 0.5% at week 20 (alpha=0.05, two-sided test), assuming a patient-level residual standard deviation of 1.1%, standard deviation of 1.5%, and 15% dropouts.

A one-sided familywise type I error rate of 2.5% should be maintained when conducting the tests of all endpoints of interest. The assessment of the effectiveness will be based on the totality of the data (i.e., evaluation of sitagliptin effect in the individual trials as well as the pool).

Pooled analysis for studies 1, 2, and 4:

The primary null hypothesis is that there is no difference between sitagliptin ~~is equal to placebo~~ and placebo for the primary efficacy endpoint, HbA1c change from baseline to Week 20 for the pooled patient population for Studies 1, 2 and 4. The alternative hypothesis is that sitagliptin and placebo are different with respect to the primary efficacy endpoint. Your pooled analysis should be stratified by studies and doses under the condition that the study designs and patient characteristics (e.g. disease characteristics) are consistent across the studies.

Given the 1:1 randomization ratio between sitagliptin and placebo in each study, there will be approximately one hundred seventy-five (175) ~~One hundred twenty (120) 350~~ randomized patients per group in the pooled population of Studies 1, 2 and 4 ~~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~~. It is assum~~inged~~ that 15% of patients drop out prior to Week ~~26~~ 20. ~~approximately 102 149 completed patients per group in the combined studies will provide 90~~ A total sample size of 350 subjects will provide 82% power to detect a -0.5% difference between the groups in HbA1c change from baseline assuming a standard deviation of ~~1.1~~ 1.5% 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 pooled trial has 85 75% power to detect a 0.425% difference between the groups in HbA1c change from baseline assuming a standard deviation of 1.1 1.5% and a two-sided alpha of 0.05.~~

The primary analysis population must be the ~~Full Analysis Set (FAS)~~ intention- to-treat (ITT) population consisting of all randomized patients who take at least one dose of study medication. This ITT population should be used in both individual and pooled analyses. ~~consisting of all randomized patients who take at least one dose of study medication and have HbA1c data at baseline and after randomization.~~ Analyses in the ITT population will include all available data, including data obtained after the initiation of pre-specified rescue therapy as well as data after the last dose of study medication taken by patients who remain in the study after discontinuing study medication. The primary analysis model must be pre-specified in the ~~study protocol~~ integrated Statistical Analysis Plan (iSAP). You must conduct at least two sensitivity analyses by varying the assumptions on missing data to investigate the impact of missing data on the primary analysis result.

~~The treatment comparison between the active control group and placebo and is considered a secondary objective. You should provide an estimate of the treatment differences and corresponding 95% confidence interval.~~

Timeframe for submitting reports of the studies~~y~~: A report of the Phase I PK study and the three Phase III studies ~~above study~~ must be submitted to the Agency on or before ~~April 25, 2018~~ April 25, 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 study will be initiated. If you do not agree to the request, you must indicate why you are declining to conduct the studies~~y~~. 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 studies~~y~~, 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.

Reports of the studies that meet the terms of the Written Request dated November 27, 2012, as amended by this letter and by previous amendments dated on May 7, 2013, must be submitted to

the Agency on or before **April 25, 2021**, 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, CDER, FDA, Document Control Room, Metro Park North VII, 7620 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 Richard Whitehead, M.S., 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
Office of New Drugs
Center for Drug Evaluation and Research

ENCLOSURE:
Complete Copy of Written Request as Amended

WRITTEN REQUEST

These studies investigate 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.

Efficacy of sitagliptin must be evaluated in the pediatric population because it is unknown whether the effects of sitagliptin are sufficiently similar between adults and the pediatric population. Sitagliptin would provide a useful additional treatment option for pediatric patients with T2DM based on the low risk of hypoglycemia and oral administration. 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. 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.

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:

The efficacy and safety of sitagliptin in the pediatric population will be evaluated in three Phase III studies (Study 1, Study 2, and Study 4). A Phase I PK study of JANUMET XR (Study 3) is also specified in the Written Request.

Study 1:

You must submit the complete study report for study 083 conducted under IND 065495 (NDA 021995), a randomized, double-blind, placebo-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 oral antihyperglycemic agent (AHA) or are on a stable dose of insulin for ≥12 weeks prior to screening and have inadequate glycemic control (HbA1c ≥6.5% and ≤10.0% for drug-naïve patients, and ≥7.0% and ≤10.0% for patients on insulin). The trial must consist of a screening period, a one-week, single-blind, run-in period, a 20-week, placebo-controlled Phase "A," and a, at least a 32-week, active-controlled Phase "B." The protocol must specify glycemic rescue and individual patient discontinuation criteria.

Study 2:

You must submit the complete study report for study 170 conducted under IND 070934 (NDA 022044), a randomized, double-blind, placebo-controlled, safety and efficacy study of the effect of sitagliptin (administered as a fixed-dose combination tablet of sitagliptin and metformin) on hemoglobin A1c (HbA1c) in pediatric subjects 10 to 17 years (inclusive) with T2DM who are being treated with metformin alone or in combination with a stable dose of insulin for ≥12 weeks prior to screening and have inadequate glycemic control (HbA1c ≥6.5% and ≤10.0% patients on metformin, and ≥7.0% and ≤10.0% for patients on metformin and insulin). The trial must consist of a screening period, a one-week, single-blind, run-in period, a 20-week, placebo-controlled "base study", and at least a 32-week, active-controlled "extension study". The protocol must specify glycemic rescue and individual patient discontinuation criteria.

Study 3:

A Phase I PK study of JANUMET XR is also specified in the Written Request. You must submit the complete study report for study 296 conducted under IND 101964 (NDA 202270), a Phase I PK study of JANUMET XR 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 IND 101964 (NDA 202270), a randomized, double-blind, placebo controlled, safety and efficacy study of the effect of sitagliptin (administered as a fixed-dose combination tablet of sitagliptin and metformin extended release) on hemoglobin A1c (HbA1c) in pediatric subjects 10 to 17 years (inclusive) with T2DM who are being treated with metformin alone or in combination with a stable dose of

insulin for ≥12 weeks prior to screening and have inadequate glycemic control (HbA1c ≥6.5% and ≤10.0% for metformin-treated patients, and ≥7.0% and ≤10.0% for patients treated with metformin and insulin). The trial must consist of a screening period, a one-week, single-blind, run-in period, a 20-week, placebo- controlled Phase "A", and at least a 32-week, active-controlled Phase "B". The protocol must specify glycemic rescue and individual patient discontinuation criteria.

- Objectives of each study:

Phase III studies:

- To assess the effect of treatment with sitagliptin compared to placebo at 20 weeks on the change from baseline in HbA1c
- To evaluate the long-term safety of sitagliptin in the pediatric population through at least 52 weeks.

- Patients to be studied:

Phase III studies

- 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: Approximately 350 patients pooled across Studies 1, 2 and 4 will be randomized to sitagliptin or placebo
- Inadequate glycemic control (HbA1c ≥ 6.5% and ≤10.0% for patients not on insulin and ≥7.0% and ≤10.0% for patients on insulin) at Visit 1.
- In Study 1, no patients may have received more than 10 cumulative days of treatment with an oral antihyperglycemic agent (AHA) (i.e., metformin, SU, meglitinides, or alpha-glucosidase inhibitors) in the 12 weeks prior to Visit 1.

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:

Phase III studies:

- 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 and biochemistry
  - 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:
  - Status of linear growth must be documented at baseline, 20 weeks (primary endpoint) and 54 weeks by height measurements, Tanner staging, and, in Study 1, by X-ray of left hand and wrist for bone age, and the following laboratories: IGF-1,IGF-BP3, bone markers (urinary N-telopeptide and creatinine ratio, and bone-specific alkaline phosphatase), and calcitonin
  - In the monotherapy study (Study 1), baseline status of dentition must be documented, and effect on dentition (including discoloration) must be documented at 20 weeks (primary endpoint) and at the 54- week endpoint.
  - Gastrointestinal AEs
  - Hypoglycemia using the 2016 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 (Study 1 only), 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

- *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 studies 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:*

Analysis for study 1 (study p083) alone:

You must conduct a formal analysis for study 1 (study 083) followed by the pooled analysis for studies 1, 2, and 4. The null hypothesis is that there is no difference between sitagliptin and placebo in HbA1c change from baseline to week 20. The alternative hypothesis is that sitagliptin and placebo are different with respect to HbA1c change from baseline to Week 20.

A total sample size of 180 subjects (90 subjects per arm) in study 1 will provide 80% power to detect a treatment difference in HbA1C of 0.5% at week 20 (alpha=0.05, two-sided test), assuming a patient-level residual standard deviation of 1.1%, standard deviation of 1.5%, and 15% dropouts.

A one-sided familywise type I error rate of 2.5% should be maintained when conducting the tests of all endpoints of interest. The assessment of the effectiveness will be based on the totality of the data (i.e., evaluation of sitagliptin effect in the individual trials as well as the pool).

Pooled analysis for studies 1, 2, and 4:

The primary null hypothesis is that there is no difference between sitagliptin and placebo for the primary efficacy endpoint, HbA1c change from baseline to Week 20 for the pooled patient

population for Studies 1, 2 and 4. The alternative hypothesis is that sitagliptin and placebo are different with respect to the primary efficacy endpoint. Your pooled analysis should be stratified by studies and doses under the condition that the study designs and patient characteristics (e.g. disease characteristics) are consistent across the studies.
Given the 1:1 randomization ratio between sitagliptin and placebo in each study, there will be approximately one hundred seventy-five (175) randomized patients per group in the pooled population of Studies 1, 2 and 4. It is assumed that 15% of patients drop out prior to Week 20. A total sample size of 350 subjects will provide82% power to detect a -0.5% difference between the groups in HbA1c change from baseline assuming a standard deviation of 1.5% and a two-sided alpha of 0.05.

The primary analysis population must be the intention- to-treat (ITT) population consisting of all randomized patients who take at least one dose of study medication. This ITT population should be used in both individual and pooled analyses. Analyses in the ITT population will include all available data, including data obtained after the initiation of pre-specified rescue therapy as well as data after the last dose of study medication taken by patients who remain in the study after discontinuing study medication. The primary analysis model must be pre-specified in the integrated Statistical Analysis Plan (iSAP). You must conduct at least two sensitivity analyses by varying the assumptions on missing data to investigate the impact of missing data on the primary analysis result.

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 studies: A report of the Phase I PK study and the three Phase III studies must be submitted to the Agency on or before April 25, 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 study will be initiated. If you do not agree to the request, you must indicate why you are declining to conduct the studies. 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 studies, 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.

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

/s/

MARY T THANH HAI
12/07/2017