NDA 202293
NDA 205649
NDA 209091
IND 068652
IND 118840

WRITTEN REQUEST – AMENDMENT 1

AstraZeneca AB
c/o AstraZeneca Pharmaceuticals LP
Attention: Lei Hua, PhD, PMP, RAC
Regulatory Project Manager, Regulatory Affairs
One MedImmune Way
Gaithersburg, MD 20878

Dear Dr. Hua:

Please refer to your correspondence dated July 2, 2021, requesting changes to FDA's March 26, 2019, Written Request for pediatric studies for Farxiga (dapagliflozin).

We have reviewed your proposed changes and are amending the Written Request. All other terms stated in our Written Request issued on March 4, 2019, as clarified on March 26, 2019, remain the same. (Text added is underlined. Text deleted is strikethrough.)

BACKGROUND:

This study investigates the potential use of dapagliflozin in the treatment of pediatric type 2 diabetes mellitus (T2D) patients, aged 10 to 17 years (inclusive).

The prevalence of T2D among pediatric patients is increasing, concurrent with the obesity epidemic. Currently the only approved treatment options for pediatric patients 10 years of age and older diagnosed with type T2D are metformin and insulin either as monotherapy or in combination. 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 antihyperglycemic therapy added to metformin to achieve adequate glycemic control. Dapagliflozin would provide useful additional treatment options for pediatric patients with T2D. Efficacy of dapagliflozin must be established in the pediatric population because it is unknown whether the effects of dapagliflozin are sufficiently similar between adults and the pediatric population. The use of placebo in the proposed dapagliflozin clinical trial is ethically justified as all subjects will be receiving background metformin and/or insulin therapy, and the protocol includes strict inclusion and hyperglycemic rescue criteria, as well as diet, exercise, and diabetic education.

Studies of T2D in 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 dapagliflozin, the Food and Drug Administration (FDA) is hereby making a formal Written Request, pursuant to Section 505A of the 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(ies)*:

  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 26 week, multicenter, randomized, placebo- controlled, double-blind, parallel group, dose ranging (at least two doses) Phase 3 trial with a 26-week safety extension period evaluating the safety, efficacy, and pharmacokinetics of dapagliflozin (and saxagliptin) in pediatric patients 10 to less than 18 years of age diagnosed with T2D who are on diet and exercise and metformin, or insulin, or metformin and insulin.

  Efficacy in children aged 10 to less than 18 years cannot be fully extrapolated and will be determined by the study outlined in the Written Request.

- *Objective of the study:*

  - Efficacy: To compare the mean hemoglobin A1c (HbA1c) change from baseline to week 26 in pediatric T2D subjects: 1) between saxagliptin 2.5 mg (with titration to 5 mg for those who do not achieve the glycemic target of HbA1c <7% at 12 weeks) andplacebo; and 2) between dapagliflozin 5 mg (with titration to 10 mg for those who do not achieve the glycemic target of HbA1c <7% at 12 weeks) and placebo. Saxagliptin, dapagliflozin, or placebo will be added to diet and exercise plus metformin (immediate release [IR] or extended release [XR]) and/or insulin in T2D subjects with inadequate glycemic control (i.e., HbA1c of 6.5 to 10.5%) on diet and exercise and metformin, insulin, or metformin plus insulin.

    ~~The effect of monotherapy of dapagliflozin and saxagliptin will be assessed by a randomized withdrawal of background metformin in a subset of study subjects. The subjects will be receiving background treatment with metformin~~

~~only, have a HbA1c <7.5% at week 26 or week 32 and have not initiated glycemic rescue therapy. Additionally, eligible subjects (HbA1c <7.5% at week 26 or week 32) from the placebo arm will undergo, in addition to randomized withdrawal of metformin background therapy, a randomized switch to active treatment (i.e., high-dose saxagliptin or high-dose dapagliflozin).~~

- Safety: To evaluate the safety (including the incidence of hypoglycemia and diabetic ketoacidosis [DKA]) and tolerability of saxagliptin and dapagliflozin as add-on to diet, exercise and background antihyperglycemic therapy (i.e., metformin, insulin or metformin plus insulin) at 26 and 52 weeks, as well as the effects of these products ongrowth, maturity, Tanner staging, and markers of bone health at ~~up to~~ 104 weeks ~~(i.e., 52 weeks following discontinuation of investigational product)~~. Additionally, the safety and tolerability of dapagliflozin and saxagliptin monotherapy will be evaluated in a subset of subjects who are randomized to withdraw background metformin.

- *Patients to be studied:*

  - *Age group in which study(ies) will be performed*: 10 to less than 18 years of age.

  - *Number of patients to be studied:* Total enrollment in the study will be at least 243 subjects, including the dapagliflozin, saxagliptin and placebo arms (randomized in a 1:1:1 ratio, with approximately 80 subjects in each treatment arm with at least 15% of subjects enrolled from the United States).

  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 (PK)/pharmacodynamic (PD) endpoints:* The pharmacokinetic endpoints for the proposed trial (CV181375) must include assessment of dapagliflozin, saxagliptin, and 5-OH-saxagliptin plasma concentrations as agreed upon in the protocol. ~~pre- and 2- hours postdose at Weeks 6, 12, 20, and 26; and the pharmacodynamic endpoints will include assessment of fasting plasma glucose (FPG) and dipeptidyl peptidase-4 (DPP-4) inhibition on Day 1 (pre-dose) and pre- and 2-hours postdose at Weeks 6, 12, 20, and 26.~~ All PK/PD assessments are to be collected under fasting conditions.

- *Efficacy endpoints;* The primary efficacy endpoint must be the change from baseline in HbA1c at Week 26. HbA1c will be measured at timelines agreed upon in the protocol. ~~randomization, and weeks 6, 12, 20, 26, 32, 40, and 52~~.

- Important secondary efficacy endpoints must include change from baseline in fasting plasma glucose (FPG) at Week 26, and the percentage of subjects with baseline HbA1c ≥7% who achieve an HbA1c level <7.0% at Week 26.

- *Safety endpoints:*

  Safety outcomes must include (and agreed upon with the Agency in the protocol):
  - Nature, frequency, severity, and relationship to treatment of all adverse events(AEs)
  - Physical examination findings
  - Vital sign changes
  - Electrocardiogram findings
  - Laboratory parameters, including hematology, biochemistry, and urinalysis
  - Pubertal development (based on Tanner staging)
  - Growth parameters (based on replicated and standardized measures of height and weight)
  - Measures and biomarkers of growth, maturity and bone health, including: height; weight; thyroid-stimulating hormone (TSH), free thyroxine (FT4), luteinizing hormone (LH), follicle-stimulating hormone (FSH), estradiol, total testosterone, insulin-like growth factor-1 (IGF-1), insulin-like growth factor binding protein-3 (IGFBP-3), calcitonin, 25-hydroxy vitamin D, bone alkaline phosphatase, osteocalcin, parathyroid hormone (PTH), cross-linked telopeptide of Type 1 collagen (CTX-1)
  - Incidence of hypoglycemia

- The protocol must include the following adverse events ~~must be~~that will be actively monitored:
  - Gastrointestinal AEs
  - Hepatic AEs/liver laboratory abnormalities
  - Hypersensitivity reactions
  - Hypoglycemia using the American Diabetes Association (ADA) definitions[1]
  - Infection by AE reporting

[1] American Diabetes Association. 6. Glycemic targets: standards of medical care in diabetes-2019. Diabetes Care 2019;42:S61- S70.

- Pancreatitis by AE reporting
- Renal impairment by serum creatinine/eGFR monitoring
- Volume depletion (including orthostatic changes in blood pressure and heartrate)

The protocol must include a plan for ~~All adverse events must be monitored~~ monitoring all adverse events until symptom resolution or until the condition stabilizes.

A Data Monitoring Committee (DMC) must be included. 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:* The following are possible safety concerns associated with DPP-4 inhibitors and/or SGLT-2 inhibitors, which should be considered adverse events of special interest and must be captured when spontaneously reported:

  Amputations/peripheral revascularizations, changes in growth; drug-induced liver injury/marked hepatic laboratory abnormalities (including liver function test abnormalities accompanied by jaundice or hyperbilirubinemia); hypersensitivity reactions(including anaphylaxis, angioedema, exfoliative skin conditions); severe cutaneous adverse reactions (including bullous pemphigoid); genital mycotic infections; necrotizingfasciitis of the perineum (Fournier's gangrene); urinary tract infections (including urosepsis/pyelonephritis); opportunistic infections; decreased lymphocyte and/or thrombocyte counts; oral soft tissue conditions (e.g., stomatitis); pancreatitis; cardiac failure (including hospitalization for heart failure); acute kidney injury, renal impairment and/or renal failure; volume depletion; bone fractures; hyperlipidemia; hypoglycemic events; hyperglycemic events; ketoacidosis; malignancies (including bladder cancer); andarthralgia.

- *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 (saxagliptin 2.5 and 5 mg; and dapagliflozin 5 and 10 mg)
- *route of administration:* Oral
- *regimen:* Once daily

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 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 theAgency 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: A statistical analysis plan will be submitted and agreed upon with the Agency.* The primary objective for this study is to find if there is a greater mean reduction in HbA1c after 26 weeks of oral double-blind add-on therapy of dapagliflozin 5 mg or saxagliptin 2.5 mg (with titration to the high-dose for those who do not achieve the glycemic target ofHbA1c <7% at 12 weeks) compared to placebo. In order to assess this, there is a second randomization planned at week 12 of the 26-week treatment period (investigational product [IP] administration). This means participants will end up in one of four subgroups based on dose titration at the second randomization. Certain subgroups will be combined and used for hypothesis testing of various primary and secondary objectives.

  The sample size for this study is based on the ability to detect a 0.5% reduction in HbA1c from baseline to Week 26 for dapagliflozin over placebo, and for saxagliptin over placebo, with at least 80 % power for each comparison at a two-sided alpha level of 0.025. No comparison between saxagliptin and dapagliflozin will be performed. Assuming a standard deviation of 0.9% for HbA1c change from baseline at Week 26, and that 50% of subjects will undergo the second randomization, and that 2% of subjects do not have a baseline and at least one post-baseline assessment, a total of 237 pediatric subjects would need to be randomized in a 1:1:1 ratio to receive dapagliflozin 5 mg (79 subjects), saxagliptin 2.5 mg (79 subjects), or placebo (79 subjects) respectively. ~~Assuming that 2%of subjects do not have a baseline and at least one post-baseline assessment, a total of approximately 243 subjects will be randomized (approximately 81 subjects in each treatment arm).~~

  The statistical analysis plan, including randomization strategy, methods to control type 1 error rate, handling of missing data, and methods for multiplicity adjustment must be agreed upon in the statistical analysis plan. The primary efficacy analysis will be performed using a weighted analysis of covariance (ANCOVA). For each drug, the comparison between the low-dose/high-dose regimen and placebo will be tested at a two-sided alpha level of 0.025. The intention-to-treat (ITT) estimand (which will be estimated using all available data regardless of premature treatment discontinuation and regardless of glycemic rescue therapy initiation) will be evaluated as the primary estimand.
  ~~Randomization will be stratified based on the baseline antihyperglycemic treatment regimen (metformin IR or XR, insulin, or metformin plus insulin), gender, and age (10 to below 15 years of age, 15 to below 18 years of age).~~

  ~~The Bonferroni method to control the type 1 error rate across two comparisons with respect to the two groups of research hypotheses (dapagliflozin vs. placebo and saxagliptin vs. placebo) will be used. Within each group of hypotheses,~~

multiplicity adjustment with respect to the comparisons will be made using a hierarchical approach. No comparisons between saxagliptin and dapagliflozin will be performed.

Dapagliflozin and saxagliptin will be summarized separately. A common placebo group will be included in each summary, if applicable.

All efficacy analyses will be performed using the Randomized Subjects Data Set unless otherwise specified. The Randomized Subjects Data Set will consist of all randomized subjects who receive at least one dose of study medication during the treatment period.

The Up-titration Randomized Subjects Data Set will consist of the subset of randomized subjects who are re-randomized because their HbA1c is greater ≥7% at Week 12.

The following treatment regimens are considered for analysis:

- Low-dose/high-dose: Initial treatment of the low-dose followed by up-titrating to the high-dose for those who do not achieve the glycemic target of HbA1c <7% at Week 12 (not responding and re-randomized to high-dose) and continuing treatment with the low-dose for those achieving the glycemic target of HbA1c <7% at Week 12 (responding and not re-randomized; Groups 1 & 3).

- Low-dose: Initial treatment of the low-dose followed by continuing treatment on the low-dose drug for those who do not achieve the glycemic target of HbA1c < 7% at Week 12 (not responding and re-randomized to low-dose) and for those achieving glycemic target of HbA1c <7% at Week 12 (responding and not re- randomized; Groups 1 & 2).

The primary efficacy analysis will be performed using a weighted analysis of covariance (ANCOVA). Each model (saxagliptin and dapagliflozin analyses) will have terms for baseline value, treatment group, and randomization strata (note that strata variable levels may be combined or the variable removed if there is sparseness of data for the imputation and/or analysis models). For each drug, the comparison between the low-dose/high-dose regimen and placebo will be tested at a two-sided alpha level of 0.025. Point estimates and 95% confidence intervals will be calculated based on maximum likelihood for the adjusted mean changes within each treatment group as well as for the differences in adjusted mean changes between treatment groups.

~~For the comparison of the low-dose/high-dose treatment regimen vs. placebo, all saxagliptin and dapagliflozin subjects who had HbA1c <7% at Week 12 and remained on the low-dose will be assigned a weight of one. The saxagliptin and dapagliflozin subjects who had HbA1c ≥7% at Week 12 and continued on the low-dose will be assigned a weight of 0. The saxagliptin and dapagliflozin subjects who had HbA1c ≥7% at Week 12 and received the high-dose will be assigned a weight of 2. All subjects who do not undergo the second randomization and all placebo subjects will get a weight of one.~~

~~The intention-to-treat (ITT) estimand (which will be estimated using all available data regardless of premature treatment discontinuation and regardless of glycemic rescuetherapy initiation) will be evaluated as the primary estimand. Missing values for Week 26will be imputed using a multiple imputation method assuming the data are not missing at random. Multiple imputation using retrieved drop outs will be used if there is sufficient data from 'retrieved drop-outs', defined as subjects who discontinued the treatment (but not the study) and had a Week 26 HbA1c value. Subjects who discontinue study drug before the end of the study treatment period will enter a non-treatment, follow-up phase, in which they will follow their visit schedules with modified assessments until study completion.~~

Secondary analyses ~~and exploratory monotherapy assessments~~ will include separate analyses for saxagliptin and dapagliflozin. ~~This includes four different exploratory comparisons:~~

1. ~~Subjects initially randomized to dapagliflozin: those re-randomized to withdraw metformin compared to those re-randomized to stay on metformin~~
2. ~~Subjects initially randomized to saxagliptin: those re-randomized to withdraw metformin compared to those re-randomized to stay on metformin~~
3. ~~Subjects initially randomized to placebo: those re-randomized to switch to dapagliflozin compared to those re-randomized to stay on placebo with background metformin.~~
4. ~~Subjects initially randomized to placebo: those re-randomized to switch to saxagliptin compared to those re-randomized to stay on placebo with background metformin.~~

~~Comparisons for HbA1c and FPG will use descriptive statistics. Comparisons for those who achieve or maintain HbA1c <7% at the end of the withdrawal period will be described with the number and percentage. Time from baseline withdrawal to initiation of glycemic rescue medication or discontinuation of study medication due to lack of efficacy during the randomized withdrawal period will be summarized using Kaplan-Meier estimates. Information from these analyses will be constrained to a subset of patients with low statistical power to run any exploratory statistical~~

~~comparisons. Such constraints limit the reliability and interpretation of any comparisons.~~

- *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 Act, regardless of whether the study(ies) demonstrate that saxagliptin and dapagliflozin are 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(ies). 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(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 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 electronicallyaccording to the Study Data Tabulation (SDTM) standard published by the Clinical DataInterchange Standards Consortium (CDISC) provided in the document “Study DataSpecifications,” which is posted on the https://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM312964.pdf and referenced in the FDA Guidance for Industry, *Providing RegulatorySubmissions in Electronic Format - Human Pharmaceutical Product Applications andRelated Submissions Using the eCTD Specifications* at

https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidan ces/ucm333969.pdf.

- *Timeframe for submitting reports of the study(ies):* Reports of the above studies must be submitted to the Agency on or before December 31, 2025 to allow for submission of the 104-week safety study data (i.e., 52-week post-study visit data). Please keep in mind that pediatric exclusivity attaches only to existing patent protection or exclusivity that would otherwise expire nine (9) months or more after pediatric exclusivity is granted, and FDA has 180 days from the date that the study reports are submitted to make a pediatric exclusivity determination. Therefore, to ensure that a particular patent or exclusivity is eligible for pediatric exclusivity to attach, you are advised to submit the reports of the studies at least 15 months (9 months plus 6 months/180 days for determination) before such patent or exclusivity is otherwise due to expire.

- *Response to Written Request:* Under section 505A(d)(2)(A)(i), within 180 days of receipt of this Written Request you must notify the Agency whether or not you agree to the Written Request. If you agree to the request, you must indicate when the pediatric studies will be initiated. If you do not agree to the request, you must indicate why you are declining to conduct the study(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.

  Furthermore, if you agree to conduct the study(ies) 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.

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

Reports of the studies that meet the terms of the Written Request dated March 26, 2019, as amended by this letter, must be submitted to the Agency on or before December 31, 2025, in order to possibly qualify for pediatric exclusivity extension under Section 505A of the Act.

Submit reports of the studies as a new drug application (NDA) or 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 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.[2]

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.

[2] https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm316937.htm

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

ENCLOSURE:

- Complete Copy of Written Request as Amended

WRITTEN REQUEST - AMENDMENT 1

BACKGROUND:

This study investigates the potential use of dapagliflozin in the treatment of pediatric type 2 diabetes mellitus (T2D) patients, aged 10 to 17 years (inclusive).

The prevalence of T2D among pediatric patients is increasing, concurrent with the obesity epidemic. Currently the only approved treatment options for pediatric patients 10 years of age and older diagnosed with type T2D are metformin and insulin either as monotherapy or in combination. 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 antihyperglycemic therapy added to metformin to achieve adequate glycemic control. Dapagliflozin would provide useful additional treatment options for pediatric patients with T2D. Efficacy of dapagliflozin must be established in the pediatric population because it is unknown whether the effects of dapagliflozin are sufficiently similar between adults and the pediatric population. The use of placebo in the proposed dapagliflozin clinical trial is ethically justified as all subjects will be receiving background metformin and/or insulin therapy, and the protocol includes strict inclusion and hyperglycemic rescue criteria, as well as diet, exercise, and diabetic education.

Studies of T2D in 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 dapagliflozin, the Food and Drug Administration (FDA) is hereby making a formal Written Request, pursuant to Section 505A of the 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(ies)*:

  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 26 week, multicenter, randomized, placebo- controlled, double-blind, parallel group, dose ranging (at least two doses) Phase 3 trial with a 26-week safety extension period evaluating the safety, efficacy, and pharmacokinetics of dapagliflozin

(and saxagliptin) in pediatric patients 10 to less than 18 years of age diagnosed with T2D who are on diet and exercise and metformin, or insulin, or metformin and insulin.

Efficacy in children aged 10 to less than 18 years cannot be fully extrapolated and will be determined by the study outlined in the Written Request.

- *Objective of the study:*

  - Efficacy: To compare the mean hemoglobin A1c (HbA1c) change from baseline to week 26 in pediatric T2D subjects: 1) between saxagliptin 2.5 mg (with titration to 5 mg for those who do not achieve the glycemic target of HbA1c <7% at 12 weeks) andplacebo; and 2) between dapagliflozin 5 mg (with titration to 10 mg for those who do not achieve the glycemic target of HbA1c <7% at 12 weeks) and placebo. Saxagliptin, dapagliflozin, or placebo will be added to diet and exercise plus metformin (immediate release [IR] or extended release [XR]) and/or insulin in T2D subjects with inadequate glycemic control (i.e., HbA1c of 6.5 to 10.5%) on diet and exercise and metformin, insulin, or metformin plus insulin.

  - Safety: To evaluate the safety (including the incidence of hypoglycemia and diabetic ketoacidosis [DKA]) and tolerability of saxagliptin and dapagliflozin as add-on to diet, exercise and background antihyperglycemic therapy (i.e., metformin, insulin or metformin plus insulin) at 26 and 52 weeks, as well as the effects of these products ongrowth, maturity, Tanner staging, and markers of bone health at 104 weeks. Additionally, the safety and tolerability of dapagliflozin and saxagliptin monotherapy will be evaluated in a subset of subjects who are randomized to withdraw background metformin.

- *Patients to be studied:*

  - *Age group in which study(ies) will be performed*: 10 to less than 18 years of age.

  - *Number of patients to be studied:* Total enrollment in the study will be at least 243 subjects, including the dapagliflozin, saxagliptin and placebo arms (randomized in a 1:1:1 ratio, with approximately 80 subjects in each treatment arm with at least 15% of subjects enrolled from the United States).

  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 (PK)/pharmacodynamic (PD) endpoints:* The pharmacokinetic endpoints for the proposed trial (CV181375) must include assessment of dapagliflozin, saxagliptin, and 5-OH-saxagliptin plasma concentrations as agreed upon in the protocol. All PK/PD assessments are to be collected under fasting conditions.

  - *Efficacy endpoints;* The primary efficacy endpoint must be the change from baseline in HbA1c at Week 26. HbA1c will be measured at timelines agreed upon in the protocol.

  - Important secondary efficacy endpoints must include change from baseline in fasting plasma glucose (FPG) at Week 26, and the percentage of subjects with baseline HbA1c ≥7% who achieve an HbA1c level <7.0% at Week 26.

  - *Safety endpoints:*

    Safety outcomes must include (and agreed upon with the Agency in the protocol):

    - Nature, frequency, severity, and relationship to treatment of all adverse events(AEs)
    - Physical examination findings
    - Vital sign changes
    - Electrocardiogram findings
    - Laboratory parameters, including hematology, biochemistry, and urinalysis
    - Pubertal development (based on Tanner staging)
    - Growth parameters (based on replicated and standardized measures of height and weight)
    - Measures and biomarkers of growth, maturity and bone health, including: height; weight; thyroid-stimulating hormone (TSH), free thyroxine (FT4), luteinizing hormone (LH), follicle-stimulating hormone (FSH), estradiol, total testosterone, insulin-like growth factor-1 (IGF-1), insulin-like growth factor binding protein-3 (IGFBP-3), calcitonin, 25-hydroxy vitamin D, bone alkaline phosphatase, osteocalcin, parathyroid hormone (PTH), cross-linked telopeptide of Type 1 collagen (CTX-1)
    - Incidence of hypoglycemia

  - The protocol must include the following adverse events that will be actively

monitored:

- Gastrointestinal AEs
- Hepatic AEs/liver laboratory abnormalities
- Hypersensitivity reactions
- Hypoglycemia using the American Diabetes Association (ADA) definitions[3]
- Infection by AE reporting
- Pancreatitis by AE reporting
- Renal impairment by serum creatinine/eGFR monitoring
- Volume depletion (including orthostatic changes in blood pressure and heartrate)

The protocol must include a plan for monitoring all adverse events until symptom resolution or until the condition stabilizes.

A Data Monitoring Committee (DMC) must be included. 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:* The following are possible safety concerns associated with DPP-4 inhibitors and/or SGLT-2 inhibitors, which should be considered adverse events of special interest and must be captured when spontaneously reported:

Amputations/peripheral revascularizations, changes in growth; drug-induced liver injury/marked hepatic laboratory abnormalities (including liver function test abnormalities accompanied by jaundice or hyperbilirubinemia); hypersensitivity reactions (including anaphylaxis, angioedema, exfoliative skin conditions); severe cutaneous adverse reactions (including bullous pemphigoid); genital mycotic infections; necrotizing fasciitis of the perineum (Fournier's gangrene); urinary tract infections (including urosepsis/pyelonephritis); opportunistic infections; decreased lymphocyte and/or thrombocyte counts; oral soft tissue conditions (e.g., stomatitis); pancreatitis; cardiac failure (including hospitalization for heart failure); acute kidney injury, renal impairment and/or renal failure; volume depletion; bone fractures; hyperlipidemia; hypoglycemic events; hyperglycemic events; ketoacidosis; malignancies (including bladder cancer); and arthralgia.

[3] American Diabetes Association. 6. Glycemic targets: standards of medical care in diabetes-2019. Diabetes Care 2019;42:S61-S70.

- *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 (saxagliptin 2.5 and 5 mg; and dapagliflozin 5 and 10 mg)
  - *route of administration:* Oral
  - *regimen:* Once daily

  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 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 theAgency 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: A statistical analysis plan will be submitted and agreed upon with the Agency.* The primary objective for this study is to find if there is a greater mean reduction in HbA1c after 26 weeks of oral double-blind add-on therapy of dapagliflozin 5 mg or saxagliptin 2.5 mg (with titration to the high-dose for those who do not achieve the glycemic target of HbA1c <7% at 12 weeks) compared to placebo. In order to assess this, there is a second randomization planned at week 12 of the 26-week treatment period (investigational product [IP] administration). This means participants will end up in one of four subgroups based on dose titration at the second randomization. Certain subgroups will be combined and used for hypothesis testing of various primary and secondary objectives.

  The sample size for this study is based on the ability to detect a 0.5% reduction in HbA1cfrom baseline to Week 26 for dapagliflozin over placebo, and for saxagliptin over placebo, with at least 80% power for each comparison at a two-sided alpha level of 0.025. No comparison between saxagliptin and dapagliflozin will be performed. Assuming a standard deviation of 0.9% for HbA1c change from baseline at Week 26, and that 50% of subjects will undergo the second randomization, and that 2% of subjects do not have a baseline and at least one post-baseline assessment, a total of 237 pediatric subjects would need to be randomized in a 1:1:1 ratio to receive dapagliflozin 5 mg (79 subjects), saxagliptin 2.5 mg (79 subjects), or placebo (79 subjects) respectively.

  The statistical analysis plan, including randomization strategy, methods to control type 1 error rate, handling of missing data, and methods for multiplicity adjustment must be agreed upon in the statistical analysis plan. The primary efficacy analysis will be performed using a weighted analysis of covariance (ANCOVA). For each drug, the comparison between the low-dose/high-dose regimen and placebo will be tested at a two-sided alpha level of 0.025. The intention-to-treat (ITT) estimand (which will be estimated using all available data regardless of premature treatment discontinuation and regardless of glycemic rescue therapy initiation) will be evaluated as the primary estimand.

Secondary analyses will include separate analyses for saxagliptin and dapaglifozin.

- *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 Act, regardless of whether the study(ies) demonstrate that saxagliptin and dapagliflozin are 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(ies). 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(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 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 electronicallyaccording to the Study Data Tabulation (SDTM) standard published by the Clinical DataInterchange Standards Consortium (CDISC) provided in the document “Study DataSpecifications,” which is posted on the https://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM312964.pdf and referenced in the FDA Guidance for Industry, *Providing RegulatorySubmissions in Electronic Format - Human Pharmaceutical Product Applications andRelated Submissions Using the eCTD Specifications* at

https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidan ces/ucm333969.pdf.

- *Timeframe for submitting reports of the study(ies):* Reports of the above studies must be submitted to the Agency on or before December 31, 2025 to allow for submission of the 104-week safety study data (i.e., 52-week post-study visit data). Please keep in mind that pediatric exclusivity attaches only to existing patent protection or exclusivity that would otherwise expire nine (9) months or more after pediatric exclusivity is granted, and FDA has 180 days from the date that the study reports are submitted to make a pediatric exclusivity determination. Therefore, to ensure that a particular patent or exclusivity is eligible for pediatric exclusivity to attach, you are advised to submit the reports of the studies at least 15 months (9 months plus 6 months/180 days for determination) before such patent or exclusivity is otherwise due to expire.

- *Response to Written Request:* Under section 505A(d)(2)(A)(i), within 180 days of receipt of this Written Request you must notify the Agency whether or not you agree to the Written Request. If you agree to the request, you must indicate when the pediatric studies will be initiated. If you do not agree to the request, you must indicate why you are declining to conduct the study(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.

  Furthermore, if you agree to conduct the study(ies) 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. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

LISA B YANOFF
10/29/2021 05:55:03 PM