IND 102145, IND 131597, IND 134810, IND 147385, NDA 204629, NDA 206073, NDA 206111, NDA 208658, NDA 212614

WRITTEN REQUEST – AMENDMENT 1

Boehringer Ingelheim Pharmaceuticals, Inc.
Attention: Addison Nguyen, Pharm.D.
Post Doctoral Medical Fellow, Regulatory Affairs
900 Ridgebury Road, PO Box 368
Ridgefield, CT 06877

Dear Dr. Nguyen:

Please refer to your correspondence dated April 15, 2022, requesting changes to FDA's July 30, 2019, Written Request for pediatric studies for Jardiance (empagliflozin).

We have reviewed your proposed changes and are amending the Written Request. All other terms stated in our Written Request issued on July 30, 2019, and as amended on August 5, 2019, remain the same. (Text added is underlined. Text deleted is strikethrough.)

BACKGROUND:

These studies will investigate the potential use of empagliflozin in the treatment of pediatric patients ages 10 to 17 inclusive with type 2 diabetes mellitus, to be used as an adjunct to diet and exercise to improve glycemic control. Studies of empagliflozin are not requested in children less than 10 years of age including neonates because type 2 diabetes is not a disease expected to affect this younger population.

The prevalence of type 2 diabetes in children and adolescents is increasing, concurrent with the obesity epidemic. Prevention and reversal of disease progression with diet and exercise is presently the preferred therapeutic approach but is rarely sufficient. Treatment with metformin is limited by gastrointestinal adverse reactions and the need for multiple daily dosing in some cases. ~~Therefore, study of empagliflozin as monotherapy is needed in pediatric patients with type 2 diabetes, as some pediatric patients may be intolerant of metformin.~~ In addition, diabetes is a progressive disease such that patients may need additional anti-diabetic therapy added to metformin to achieve adequate glycemic control. For this reason, empagliflozin should be studied in children and adolescents to determine if it can be a treatment option for pediatric patients with type 2 diabetes mellitus, ages 10 to 17 inclusive who need additional therapy beyond metformin.

To obtain needed pediatric information on empagliflozin, the Food and Drug Administration (FDA) is hereby making a formal Written Request, pursuant to Section

505A of the Federal Food, Drug, and Cosmetic Act (the Act), as amended by the Food and Drug Administration Amendments Act of 2007, that you submit information from the studies described below.

- *Nonclinical study(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 ~~studi~~studyes~~*:*

  Study 1 (DINAMO): A phase 3, double-blind, randomized, placebo-controlled, parallel group study to evaluate the efficacy and safety of empagliflozin as an add-on to metformin and/or insulin therapy over 26 weeks, with double-blind active treatment safety extension period up to 52 weeks, in children and adolescents with type 2 diabetes mellitus.

  ~~Study 2 (DINAMO Mono): A double-blind, randomized, placebo-controlled, parallel group study that will evaluate the efficacy and safety of empagliflozin as a monotherapy over 26 weeks, with a double-blind active treatment safety extension period up to 52 weeks, in children and adolescents with type 2 diabetes mellitus.~~

  ~~Study 1 and Study 2 may be conducted under a single protocol.~~The protocol for DINAMO (Study 1 mentioned above) also included an ancillary study named "DINAMO Mono" to evaluate the effect of empagliflozin as monotherapy in children and adolescents with type 2 diabetes mellitus. The recruitment into DINAMO Mono was stopped due to challenges in recruiting pediatric patients with type 2 diabetes mellitus who were treatment-naïve and currently available information suggests that there would be no clinically meaningful difference in the efficacy of linagliptin between monotherapy and add-on to metformin and/or insulin. The safety and efficacy of pediatric patients that have enrolled into DINAMO Mono before it was stopped should be summarized separately.

- *Objective of DINAMO~~of each study~~:*

  ~~Study 1 (DINAMO):~~ To assess the efficacy and safety of empagliflozin (10 or 25 mg) once daily as add-on to metformin and/or insulin therapy versus placebo after 26 weeks of treatment in children and adolescents with type 2 diabetes mellitus. In addition, this study will assess the safety of empagliflozin after 52 weeks of treatment.

  ~~*Study 2 (DINAMO Mono):* To assess the efficacy and safety of empagliflozin (10 or 25 mg) once daily as monotherapy versus placebo after 26 weeks of treatment in~~

~~children and adolescents with type 2 diabetes mellitus. In addition, this study will assess the safety of empagliflozin after 52 weeks of treatment.~~

- *Patients to be Studied:*

  - *Age group in which study~~(ies)~~ will be performed*: Patients aged~~s~~ 10 to 17 inclusive.

  - *Number of patients to be studied:*

  ~~Study 1 (DINAMO) will have a~~At least 50 patients treated with empagliflozin and at least 50 patients treated with placebo for evaluation of the primary endpoint after 26 weeks of treatment. At Week 26, patients initially randomized to the placebo group will be re-randomized to receive empagliflozin 10 or empagliflozin 25 mg or linagliptin 5 mg.

  ~~Study 2 (DINAMO Mono) will have at least 12 patients treated with empagliflozin and at least 12 patients treated with placebo for evaluation of the primary endpoint after 26 weeks of treatment. At Week 26, patients initially randomized to the placebo group will be re-randomized to receive empagliflozin 10 or 25 mg.~~

  The re-randomization approach must be specified in the protocol.

Representation of Ethnic and Racial Minorities:

The study~~ies~~ 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:*

~~*Study 1 (DINAMO):*~~

- ☐ *Efficacy Endpoints;*
  - ☐ The primary efficacy endpoint will be the change in HbA1c (%) from baseline to the end of the 26 week, double-blind treatment period and must be assessed by a centrally analyzed, National Glycohemoglobin Standardization Program (N~~S~~GSP)-certified hemoglobin A1c assay. If a centrally analyzed, NGSP-certified hemoglobin A1c assay is unavailable, an A1c assay performed at a local laboratory is acceptable.

  - ☐ Important secondary endpoints must include:

- Change in fasting plasma glucose (FPG, mg/dL) from baseline to the end of the 26 week, double-blind treatment period ~~and must be assessed by a centrally analyzed plasma glucose assay~~
- Change in body weight (kg) from baseline to the end of 26 week, double-blind treatment period
- Change in systolic blood pressure (SBP, mmHg) from baseline to ~~at~~the end of 26 week, double-blind treatment period
- Change in diastolic blood pressure (DBP, mmHg) from baseline to ~~at~~ the end of 26 week, double-blind treatment period
- Proportion of patients achieving glycemic goals (i.e., HbA1c <7% and <6.5%) at the end of 26 weeks.

☐ The protocol must describe how patient compliance will be assessed.

~~*Study 2 (DINAMO Mono):*~~

~~☐~~ ~~*Efficacy Endpoints;*~~

~~☐ The primary efficacy endpoint will be the occurrence of treatment failure up to or at Week 26 as a binary endpoint, defined as meeting at least one of the following criteria:~~

- ~~Use of rescue medication~~
- ~~Increase from baseline in HbA1c by 0.5% at Week 26~~
- ~~Increase from baseline in HbA1c to above 7.0% at Week 26 in patients with baseline HbA1c <7.0%~~

~~☐ Important secondary endpoints must include:~~

- ~~Time to treatment failure~~
- ~~Change in HbA1c (%) from baseline to the end of the 26 week, double- blind treatment period and must be assessed by a centrally analyzed, National Glycohemoglobin Standardization Program (NSGP) certified hemoglobin A1c assay~~
- ~~Change in fasting plasma glucose (FPG, mg/dL) from baseline to the end of the 26 week, double-blind treatment period and must be assessed by a centrally analyzed plasma glucose assay~~
- ~~Change in body weight (kg) from baseline to the end of 26 week, double blind treatment period~~
- ~~Change in systolic blood pressure (SBP, mmHg) from at the end of 26 week, double-blind treatment period~~
- ~~Change in diastolic blood pressure (DBP, mmHg) from at the end of 26 week, double-blind treatment period~~
- ~~Proportion of patients achieving glycemic goals (i.e., HbA1c <7% and <6.5%) at the end of 26 weeks.~~

~~☐ The protocol must describe how patient compliance will be assessed~~

~~*Study 1 and 2:*~~

☐ *Safety Endpoints:*

☐ Safety outcomes must include:

- Nature, frequency, severity, and relationship to treatment of all adverse events, including genital infections, urinary tract infections and ketone measurements reported as adverse event after 26 and 52 weeks;
- Vital signs including heart rate after 26 and 52 weeks;
- Laboratory parameters including hematology, biochemistry, renal function, lipid profile, urinalysis after 26 and 52 weeks;
- Assessment of growth and development using the Tanner scale and by regular collection of standardized measurements of anthropometric parameters (height and body weight and BMI) using calibrated and standardized body weight scales and stadiometers after 26 and 52 weeks;
- IGF-1 and IGF-BP3 and markers of mineral and bone metabolism after 26 and 52 weeks;
- Growth velocity (cm/year) after 26 and 52 weeks;
- Incidence and rate of hypoglycemia after 26 and 52 weeks.

☐ The protocol must include plans for monitoring the following adverse events~~must be actively monitored~~:

- Hypoglycemia using the American Diabetes Association definitions
- Genital infections
- Urinary tract infections
- Ketoacidosis
- Hypersensitivity reactions
- Decreased renal function and renal failure
- ~~All adverse events must be monitored until symptom resolution or until the condition stabilizes.~~

☐ The protocol must include a plan for capturing ~~A~~all adverse events ~~must be captured~~ when spontaneously reported.

☐ A Data Monitoring Committee (DMC) must be included. See Guidance: Establishment and Operation of Clinical Trial Data Monitoring Committees http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM1265 78.pdf

- *Known Drug Safety concerns and monitoring:* Safety issues that must be assessed include ketoacidosis, genital mycotic infections (including vulvovaginal or balanitis), urinary tract infections (including urosepsis or pyelonephritis), adverse events related to reduced intravascular volume and osmotic diuresis (including symptomatic hypotension)~~,~~, potential effects on growth and development, and hypoglycemia (see above).

- *Extraordinary results:* In the course of conducting thisese study~~ies~~, 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:* 10 or 25 mg tablet
  - *route of administration:* oral
  - *regimen:* 1 tablet, once daily

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

  - ~~*Study 1 (DINAMO):*~~

  The primary analysis population must be all randomized patients who are treated with at least one dose of study drug. With respect to the primary efficacy analysis, we are interested in estimating the treatment effect based on the treatment policy estimand, i.e., the difference in mean HbA1c change in all randomized patients regardless of adherence to treatment or use of rescue. We recommend continued collection of efficacy data even after study treatment discontinuation, and these post-treatment data should be included in the primary analysis. The analysis methods for the primary and key secondary endpoints should account for missing data in a fashion consistent with what the measurements would have been, had they been measured.

  ~~Simultaneous testing of empagliflozin and linagliptin versus placebo must be accounted for. A strategy must be pre-specified to control the overall Type I error across the analyses of the primary and key secondary endpoints.~~

  A detailed statistical analysis plan, including randomization strategy, methods to control type 1 error rate, handling of missing data, and methods for multiplicity adjustment must be submitted to and agreed upon by the Agency prior to the unblinding of the study.

  The sample size of 50 patients per treatment group at the first randomization is designed~~required~~ to have 85% power at the 2-sided alpha-level of 0.05 to detect a treatment difference of 0.55% assuming a covariate adjusted standard deviation of 0.9% in the primary effective analysis.~~,~~ ~~and a power of 78% at the 2-sided alpha-level of 0.025 for the stricter test within the Hochberg procedure in case the primary effectiveness analysis for linagliptin fails.~~ However, a sample size of 50 per group may not provide 80% study power with a standard deviation of 1.65%. To continue with the current sample size and complete the study as originally planned, a supplementary analysis using an informative Bayesian prior (using information from a model based on the adult and pediatric studies) in the analysis of the primary efficacy endpoint will be used to offset any potential necessary increase in the sample size. Sensitivity analyses must be performed to

assess the sensitivity of the conclusion to the choice of prior. For the primary analysis the maximum number of effective borrowed patients as determined by the calculated effective sample size (ESS) of the prior distribution (calculated using the expected local information ratio [https://onlinelibrary.wiley.com/doi/abs/10.1111/biom.13252]) must be no more than the total pediatric sample size enrolled in the study, unless an additional justification for increased borrowing is provided and agreed upon with the agency prior to unblinding.

It is expected that this sample size will also provide a reasonable safety database.

- ~~*Study 2 (DINAMO Mono):* The primary efficacy endpoint will be the occurrence of treatment failure up to or at Week 26 as a binary endpoint. It will be analyzed using descriptive statistical methods with a minimum sample size of 12 patients per group.~~

- *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 empagliflozin is safe and effective, or whether such study results are inconclusive in the studied pediatric population(s) or subpopulation(s), the labeling must include information about the results of the study(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 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 https://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM31 2964.pdf and referenced in the FDA Guidance for Industry, *Providing Regulatory Submissions in Electronic Format - Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications* at 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 February 1, 2024. 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 July 30, 2019, as amended by this letter and by previous amendment~~(s)~~ dated August 5, 2019, must be submitted to the Agency on or before February 1, 2024, 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 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 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.[1]

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.

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

If you have any questions, call 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

BACKGROUND:

These studies will investigate the potential use of empagliflozin in the treatment of pediatric patients ages 10 to 17 inclusive with type 2 diabetes mellitus, to be used as an adjunct to diet and exercise to improve glycemic control. Studies of empagliflozin are not requested in children less than 10 years of age including neonates because type 2 diabetes is not a disease expected to affect this younger population.

The prevalence of type 2 diabetes in children and adolescents is increasing, concurrent with the obesity epidemic. Prevention and reversal of disease progression with diet and exercise is presently the preferred therapeutic approach but is rarely sufficient. Treatment with metformin is limited by gastrointestinal adverse reactions and the need for multiple daily dosing in some cases. In addition, diabetes is a progressive disease such that patients may need additional anti-diabetic therapy added to metformin to achieve adequate glycemic control. For this reason, empagliflozin should be studied in children and adolescents to determine if it can be a treatment option for pediatric patients with type 2 diabetes mellitus, ages 10 to 17 inclusive who need additional therapy beyond metformin.

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

- *Nonclinical study(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 study:*

  Study 1 (DINAMO): A phase 3, double-blind, randomized, placebo-controlled, parallel group study to evaluate the efficacy and safety of empagliflozin as an add-on to metformin and/or insulin therapy over 26 weeks, with double-blind active treatment safety extension period up to 52 weeks, in children and adolescents with type 2 diabetes mellitus.

  The protocol for DINAMO (Study 1 mentioned above) also included an ancillary study named “DINAMO Mono to evaluate the effect of empagliflozin as monotherapy in children and adolescents with type 2 diabetes mellitus. The recruitment into DINAMO Mono was stopped due to challenges in recruiting pediatric patients with type 2 diabetes mellitus who were treatment-naïve and currently available information suggests that there would be no clinically meaningful difference in the

efficacy of linagliptin between monotherapy and add-on to metformin and/or insulin. The safety and efficacy of pediatric patients that have enrolled into DINAMO Mono before it was stopped should be summarized separately.

- *Objective of DINAMO:*

To assess the efficacy and safety of empagliflozin (10 or 25 mg) once daily as add-on to metformin and/or insulin therapy versus placebo after 26 weeks of treatment in children and adolescents with type 2 diabetes mellitus. In addition, this study will assess the safety of empagliflozin after 52 weeks of treatment.

- *Patients to be Studied:*

  - *Age group in which study will be performed*: Patients aged 10 to 17 inclusive.

  - *Number of patients to be studied:*

At least 50 patients treated with empagliflozin and at least 50 patients treated with placebo for evaluation of the primary endpoint after 26 weeks of treatment. At Week 26, patients initially randomized to the placebo group will be re-randomized to receive empagliflozin 10 or empagliflozin 25 mg or linagliptin 5 mg.

The re-randomization approach must be specified in the protocol.

Representation of Ethnic and Racial Minorities:

The study 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:*

  ☐ *Efficacy Endpoints;*
    ☐ The primary efficacy endpoint will be the change in HbA1c (%) from baseline to the end of the 26 week, double-blind treatment period and must be assessed by a centrally analyzed, National Glycohemoglobin Standardization Program (NGSP)-certified hemoglobin A1c assay. If a centrally analyzed, NGSP-certified hemoglobin A1c assay is unavailable, an A1c assay performed at a local laboratory is acceptable.

    ☐ Important secondary endpoints must include:

- Change in fasting plasma glucose (FPG, mg/dL) from baseline to the end of the 26 week, double-blind treatment period
- Change in body weight (kg) from baseline to the end of 26 week, double-blind treatment period
- Change in systolic blood pressure (SBP, mmHg) from baseline to the end of 26 week, double-blind treatment period
- Change in diastolic blood pressure (DBP, mmHg) from baseline to the end of 26 week, double-blind treatment period
- Proportion of patients achieving glycemic goals (i.e., HbA1c <7% and <6.5%) at the end of 26 weeks.

☐ 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, including genital infections, urinary tract infections and ketone measurements reported as adverse event after 26 and 52 weeks;
- Vital signs including heart rate after 26 and 52 weeks;
- Laboratory parameters including hematology, biochemistry, renal function, lipid profile, urinalysis after 26 and 52 weeks;
- Assessment of growth and development using the Tanner scale and by regular collection of standardized measurements of anthropometric parameters (height and body weight and BMI) using calibrated and standardized body weight scales and stadiometers after 26 and 52 weeks;
- IGF-1 and IGF-BP3 and markers of mineral and bone metabolism after 26 and 52 weeks;
- Growth velocity (cm/year) after 26 and 52 weeks;
- Incidence and rate of hypoglycemia after 26 and 52 weeks.

☐ The protocol must include plans for monitoring the following adverse events:

- Hypoglycemia using the American Diabetes Association definitions
- Genital infections
- Urinary tract infections
- Ketoacidosis
- Hypersensitivity reactions
- Decreased renal function and renal failure

☐ The protocol must include a plan for capturing all adverse events when spontaneously reported.

☐ A Data Monitoring Committee (DMC) must be included. See Guidance: Establishment and Operation of Clinical Trial Data Monitoring Committees

http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM1265 78.pdf

- *Known Drug Safety concerns and monitoring:* Safety issues that must be assessed include ketoacidosis, genital mycotic infections (including vulvovaginal or balanitis), urinary tract infections (including urosepsis or pyelonephritis), adverse events related to reduced intravascular volume and osmotic diuresis (including symptomatic hypotension), potential effects on growth and development, and hypoglycemia (see above).

- *Extraordinary results:* In the course of conducting this study, 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:* 10 or 25 mg tablet
  - *route of administration:* oral
  - *regimen:* 1 tablet, once daily

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

The primary analysis population must be all randomized patients who are treated with at least one dose of study drug. With respect to the primary efficacy analysis, we are interested in estimating the treatment effect based on the treatment policy estimand, i.e., the difference in mean HbA1c change in all randomized patients regardless of adherence to treatment or use of rescue. We recommend continued collection of efficacy data even after study treatment discontinuation, and these post-treatment data should be included in the primary analysis. The analysis methods for the primary and key secondary endpoints should account for missing data in a fashion consistent with what the measurements would have been, had they been measured.

A detailed statistical analysis plan, including randomization strategy, methods to control type 1 error rate, handling of missing data, and methods for multiplicity adjustment must be submitted to and agreed upon by the Agency prior to the unblinding of the study.

The sample size of 50 patients per treatment group at the first randomization is designed to have 85% power at the 2-sided alpha-level of 0.05 to detect a treatment difference of 0.55% assuming a covariate adjusted standard deviation of 0.9% in the primary effective analysis. However, a sample size of 50 per group may not provide

80% study power with a standard deviation of 1.65%. To continue with the current sample size and complete the study as originally planned, a supplementary analysis using an informative Bayesian prior (using information from a model based on the adult and pediatric studies) in the analysis of the primary efficacy endpoint will be used to offset any potential necessary increase in the sample size. Sensitivity analyses must be performed to assess the sensitivity of the conclusion to the choice of prior. For the primary analysis the maximum number of effective borrowed patients as determined by the calculated effective sample size (ESS) of the prior distribution (calculated using the expected local information ratio [https://onlinelibrary.wiley.com/doi/abs/10.1111/biom.13252]) must be no more than the total pediatric sample size enrolled in the study, unless an additional justification for increased borrowing is provided and agreed upon with the agency prior to unblinding.

It is expected that this sample size will also provide a reasonable safety database.

- *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 empagliflozin is safe and effective, or whether such study results are inconclusive in the studied pediatric population(s) or subpopulation(s), the labeling must include information about the results of the study(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 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 https://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM31 2964.pdf and referenced in the FDA Guidance for Industry, *Providing Regulatory Submissions in Electronic Format - Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications* at 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 February 1, 2024. 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
08/11/2022 07:57:32 PM