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WRITTEN REQUEST – AMENDMENT 6

Janssen Pharmaceuticals, Inc.
C/O: Janssen Research & Development
Attention: Ilona Scott
Senior Director, Global Regulatory Affairs
1125 Trenton-Harbourton Road
Titusville, NJ 08560

Dear Ilona Scott:

Please refer to your correspondence dated December 20, 2023, requesting changes to FDA's March 18, 2014, Written Request for pediatric studies for Invokana (canagliflozin).

We have reviewed your proposed changes and are amending the Written Request. All other terms stated in our Written Request issued on March 18, 2014, and as amended on February 10, 2015, October 15, 2018, July 16, 2020, July 28, 2020, and July 12, 2022, remain the same. (Text added is underlined. Text deleted is strikethrough.)

BACKGROUND

These studies investigate the potential use of canagliflozin (Invokana) in the treatment of type 2 diabetes mellitus in pediatric patients from ≥ 10 to < 18 years of age. Canagliflozin was approved as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus in the US on March 29, 2013.

The prevalence of type 2 diabetes among pediatric patients is increasing, concurrent with the obesity epidemic. Canagliflozin would provide a useful additional treatment option for pediatric patients with type 2 diabetes based on the low risk of hypoglycemia, once-daily oral administration, and the fact that it does not have adverse effects on body weight.

The pharmacokinetics, pharmacodynamics, efficacy, and safety of canagliflozin must be established in the pediatric population because it is unknown whether the effects of canagliflozin are sufficiently similar between adults and the pediatric population with type 2 diabetes mellitus. Studies of canagliflozin are not requested in children less than 10

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years of age including neonates because type 2 diabetes is not a disease expected to affect this younger population.

To obtain needed pediatric information on canagliflozin, 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.

REQUESTS

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 protocols and statistical analysis plan for the following two clinical studies must be submitted and agreed upon with the Agency. Data from Study 1 that supports dose selection for Study 2 must be submitted before the initiation of Study 2.

Study 1: A phase 1 clinical pharmacology study to evaluate the pharmacokinetics (PK), pharmacodynamics (PD), and safety of canagliflozin in subjects ≥ 10 to < 18 years of age with type 2 diabetes mellitus (T2DM) on a background of metformin.

Study 2: A randomized, double-blind, placebo-controlled, phase 3, 52-week study to evaluate the efficacy and safety of canagliflozin in subjects ≥ 10 to < 18 years of age with T2DM who have inadequate glycemic control ($HbA_{1c} \geq 6.5\% \leq 11.0\%$). The study must consist of a screening period, a two-week placebo run-in/stabilization period, a 26-week, double-blind, core treatment period, and an additional 26-week double-blind, extension treatment period. The protocol must specify glycemic rescue and individual subject discontinuation criteria. The study will include at least 33 subjects per group (i.e., canagliflozin vs placebo) who are well-controlled on stable doses of metformin ($\geq 1,000$ mg for at least 8 weeks before screening) with or without insulin to evaluate the safety and efficacy of canagliflozin as add-on to metformin.

Objective of each study

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Study 1: To evaluate the PK of canagliflozin after multiple oral doses of canagliflozin in subjects with T2DM who are ≥ 10 to < 18 years of age and are currently taking a stable dose of metformin.

- Evaluate the pharmacodynamic effects of canagliflozin on plasma glucose levels, urinary glucose excretion, and the renal threshold for glucose after multiple oral doses to establish a dose(s) for Study 2;
- Assess the acceptability (e.g., taste, smell, and swallowability) of the canagliflozin tablets (via a questionnaire);
- Assess safety and tolerability.

Study 2: To assess the efficacy and safety of canagliflozin in subjects ≥ 10 to < 18 years of age with T2DM who have inadequate glycemic control (i.e., HbA_{1c} of $\geq 6.5\%$ to $\leq 11.0\%$), either on diet and exercise only, or on diet and exercise and metformin monotherapy, on diet and exercise and insulin monotherapy, or on diet and exercise and a combination of metformin and insulin therapy.

PRIMARY OBJECTIVES

- To assess the effect of canagliflozin relative to placebo on the change from baseline in HbA_{1c} after 26 weeks of treatment in the overall study population.
- To assess the overall safety and tolerability of canagliflozin.

MAJOR SECONDARY OBJECTIVES

- After 26 weeks of treatment, to assess the effect of canagliflozin relative to placebo for the subset of subjects taking background metformin (with or without insulin) on the change from baseline in HbA_{1c}
- After 26 weeks of treatment, to assess the effect of canagliflozin relative to placebo on:
 - Fasting plasma glucose (FPG)
 - Proportion of subjects with HbA_{1c} $< 7.5\%$, $< 7.0\%$ and $< 6.5\%$
 - Time to rescue therapy and proportion of subjects receiving rescue therapy
 - Body weight
 - Body mass index (BMI)
 - Systolic and diastolic blood pressure

- Fasting plasma lipids (i.e., total cholesterol, low density lipoprotein cholesterol [LDL-C], high density lipoprotein cholesterol [HDL-C], non-HDL-C, ratio of LDL-C/HDL-C, triglycerides)
- After 52 weeks of treatment, to assess the effect of canagliflozin relative to placebo on:
 - HbA1c and FPG
 - Proportion of subjects with HbA1c <7.5%, <7.0% and <6.5%
 - Time to rescue therapy and proportion of subjects receiving rescue therapy
 - Body weight
 - Body Mass Index (BMI)
 - Fasting plasma lipids (i.e., LDL-C, HDL-C, total cholesterol, non-HDL-C, LDL-C to HDL-C ratio, non-HDL-C to LDL-C ratio, and triglycerides)
 - Systolic and diastolic blood pressure
 - Long-term safety and tolerability

ADDITIONAL SECONDARY OBJECTIVES

- After 12 weeks of treatment, to assess the effects of canagliflozin relative to placebo on HbA1c
- After 26 weeks of treatment, to assess the effect of canagliflozin 100 mg relative to placebo on HbA1c
- After 26 weeks of treatment, to assess the effect of canagliflozin 100 mg followed by a dose increase to 300 mg relative to placebo on HbA1c

Patients to be Studied:

- *Age group in which studies will be performed:* subjects (≥ 10 to < 18 years of age) with T2DM
- *Number of patients to be studied:*

Study 1: At least 8 subjects per dose group will be enrolled.

Study 2: Subjects with T2DM ≥ 10 and < 18 years of age who have inadequate glycemic control (ie, HbA1c of $\geq 6.5\%$ to $\leq 11.0\%$) and who meet 1 of the criteria below will be eligible to be screened:

- Are on diet and exercise for at least 4 weeks prior to screening
or
- Are on diet and exercise and a stable dose of metformin monotherapy $\geq 1,000$ mg per day or maximum tolerated dose (MTD) per day (defined by the investigator) for at least 8 weeks prior to screening,
or
- Are on diet and exercise and a stable insulin monotherapy regimen for at least 8 weeks prior to screening (stable dose is defined as no change in the insulin regimen (ie, type[s] of insulin) and $\leq 15\%$ change in the total daily dose of insulin [averaged over 1 week to account for day-to-day variability]),
or
- Are on diet and exercise and a stable combination therapy with metformin and insulin for at least 8 weeks prior to screening as described above.
 - At least 30% of randomized subjects must be 10 to <15 years of age.
 - At least 20% of randomized subjects in both age subsets (10 to <15 years, and ≥ 15 to <18 years) must be male.

Representation of Ethnic and Racial Minorities: Study 2 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:

Pharmacokinetic/Pharmacodynamic Endpoints:

The pharmacokinetic and pharmacodynamic endpoints for Study 1 must include:

- $C_{\max,ss}$ maximum observed plasma concentration during a dosing interval at steady-state
- t_{\max} : time to reach the maximum observed plasma concentration
- AUC_{τ} area under the plasma concentration-time curve during a dosing interval (τ)

- $t_{1/2,\lambda}$: elimination half-life associated with the terminal slope (λ_z) of the semilogarithmic drug concentration-time curve, calculated as $0.693/\lambda_z$
- CL_{ss}/F : total clearance of drug at steady-state after extravascular administration, uncorrected for absolute bioavailability calculated as: $D/AUCT$
- MPG_{0-24h} : mean concentration for plasma glucose during the 0 to 24-hour interval at baseline and following last dose.
- UGE_{0-24h} : cumulative daily urinary glucose excretion over 0 to 24 hours at baseline and following last dose
- RTG ($_{0-12h}$, $_{0-24h}$, and $_{24h}$) mean renal threshold for glucose excretion at baseline and following last dose

Study 2:

EFFICACY ENDPOINTS

- The primary efficacy endpoint must be the change in hemoglobin A1c from baseline to the end of the 26-week double-blind treatment period and must be assessed by a centrally analyzed, NGSP-certified hemoglobin A1c assay.
- Important secondary endpoints must include fasting plasma glucose which must be assessed by a centrally analyzed plasma glucose assay.
- Important secondary endpoints must include the proportion of subjects who achieve HbA1c <7.0% and <6.5% at the end of 26 weeks.

The protocol must describe how patient compliance will be assessed.

SAFETY ENDPOINTS:

The protocol must include the following safety endpoints:

- Nature, frequency, severity, and relationship to treatment of all adverse events;
- Vital signs including heart rate;
- Laboratory parameters including hematology, biochemistry (including pancreatic and liver enzymes), lipid profile, urinalysis, and markers of calcium and phosphate; homeostasis (serum parathyroid hormone, calcium, magnesium, phosphate; urinary excretion of calcium and phosphate; 1,25 dihydroxyvitamin D and calcitonin);
- Bone biomarkers (osteocalcin, C-telopeptide of collagen cross-links);

- Assessment of growth and development using the Tanner scale and by regular collection of standardized measurements of anthropometric parameters (height and body weight) using calibrated and standardized body weight scales and stadiometers;
- Incidence of hypoglycemia;
- Incidence of genital mycotic infections;
- Incidence of urinary tract infections.

The protocol must include a plan for monitoring the following adverse events

- Hypoglycemia using the American Diabetes Association definitions
- Hypersensitivity reactions
- Renal impairment by serum creatinine monitoring

A Data Monitoring Committee (DMC) must be included.

Known Drug Safety concerns and monitoring: Safety issues that must be assessed include genital mycotic infections (including vulvovaginal or balanitis), urinary tract infections, adverse events related to reduced intravascular volume and osmotic diuresis (including symptomatic hypotension), hyperkalemia, all malignancies, fatal pancreatitis, hemorrhagic/necrotizing pancreatitis, severe hypersensitivity reactions (angioedema, anaphylaxis, Stevens-Johnson syndrome), photosensitivity reactions, serious adverse events of hepatic injury, nephrotoxicity/acute kidney injury, venous thromboembolic events, fractures, pregnancy, increases in low-density lipoprotein cholesterol (LDL-C), effect on growth and development, hypoglycemia, urosepsis, pyelonephritis, ketoacidosis, and lower limb amputations.

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, 100 mg and 300 mg
- **route of administration:** Oral
- **regimen:** Once daily; see below for Study 2

Study 2: The results of Study 1 will determine the doses of canagliflozin to be studied in Study 2. All subjects will receive the 100 mg of canagliflozin (or placebo) after initial randomization. After Week 12, eligible subjects ($HbA_{1c} \geq 7\%$ and have an estimated glomerular filtration rate ≥ 60 mL/min/1.73m² and tolerating 100 mg dose) will be re-randomized to either remain on double-blind canagliflozin 100 mg (or matching placebo) or to up-titrate to double-blind canagliflozin 300 mg (or matching placebo).

Subjects requiring additional glycemic control will be rescued during the study.

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(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 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 studies and statistical assessments:

Study 1: The study must be prospectively powered to target a 95% confidence interval within 60% and 140% of the geometric mean estimates of clearance and volume of distribution for canagliflozin in each dose group with at least 80% power.

Study 2: Hypothesis testing must be done for the overall study population and in the subset of subjects on add-on to metformin.

Study 2: The primary efficacy endpoint is the change in HbA_{1c} from baseline at Week 26. The sample size calculation is based on the 2-stage randomization design using a 2-sample, 2-sided t-test with a Type 1 error rate of 0.05, and an updated (based on blinded assessment of the data from the ongoing study) estimate of the standard deviation of 1.69%.

- Overall study: for all subjects who are randomized to canagliflozin or placebo, the planned sample size (based on the initial estimates of the treatment effect of 0.4% to 0.5% and a standard deviation of 0.9%) of 132 subjects (146 accounting for anticipated missing data) may not provide 80% study power in light of the revised estimate of treatment difference of 0.7% and standard deviation of 1.69%. To continue with the current sample size and complete the study as originally planned, if the primary analysis does not result in a statistically significant result (i.e., type 1 error rate of < 0.05), a supplementary analysis using an informative Bayesian prior (using information from a similar subgroup of subjects from adult studies) in the analysis of primary efficacy endpoint ~~will~~ should be performed to offset any potential necessary increase in the sample size.
- Add-on metformin: for the subjects who are on background metformin (with or without insulin), if the secondary analysis of the primary efficacy endpoint does not result in a statistically significant result (ie, type 1 error rate of < 0.05), an informative Bayesian prior (using information from add-on metformin subjects from adult studies) in the analysis of primary efficacy endpoint ~~will~~ should be performed as a supplementary analysis to offset any potential loss of power (to detect 0.7% treatment difference with revised estimate of the standard deviation of 1.69% while maintaining 80% study power) with the currently planned sample size.

AN OUTLINE OF INFORMATIVE BAYESIAN PRIOR ANALYSIS APPROACH:

A Bayesian mixture prior will be used in the analysis of the primary efficacy endpoint of change from baseline at Week 26 in HbA_{1c} if the primary analysis does not demonstrate statistical significance (ie, a type 1 error rate <0.05). If performed, ~~t~~The Bayesian analysis

will borrow information from adult studies as agreed upon with the FDA. This will be done using a mixture prior that includes both an informative and a non-informative component. If the pediatric study on its own yields a non-significant treatment effect, the weight of adult data that is needed to tip to a significant treatment effect will be determined. The maximum amount of adult trial information that can be borrowed for the primary analysis must be no more than the total pediatric sample size enrolled in the study, as determined by the calculated effective sample size (ESS) of the prior distribution using an agreed upon method, unless an additional justification for increased borrowing is provided and agreed upon with the agency prior to unblinding. Sensitivity analyses must also be conducted where the amount of information that is borrowed is varied ranging from no borrowing to borrowing all the available adult information. The main SAP must be agreed upon with the FDA prior to conducting the analysis. The supplemental Bayesian statistical analysis plan must be agreed upon with the FDA prior to conducting the analysis only if the primary analysis does not result in a statistically significant result.

The primary analysis of HbA1c change from baseline at Week 26 will be a test of superiority of canagliflozin compared to placebo, applied to the Full Analysis Set, which consists of data from subjects who were randomized and receive at least one dose of canagliflozin or canagliflozin placebo and have a baseline HbA1c measurement. The estimand of interest is the intention-to-treat (ITT) estimand. The primary analysis will be a pattern mixture model with multiple imputation to account for missing data and will include all post-baseline measurements taken before week 26, regardless of whether the subject was on or off treatment, and regardless of the initiation of glycemic rescue therapy. A corresponding analysis will also be performed in subjects randomized to a background of metformin with or without insulin. Missing data should be kept to a minimum. When addressing missing data in the primary analysis you may want to account for the therapy received and seek further advice from the National Academies of Sciences report on The Prevention and Treatment of Missing Data in Clinical Trials (NAS, 2010). There will be no interim analysis performed.

To control the family-wise type 1 error rate at 0.05, the primary and secondary hypotheses (in terms of change in HbA1c from baseline to week 26) will be tested as a 2-step sequential procedure:

1. Primary hypothesis on the overall study population
2. Secondary hypothesis on the add-on to metformin group with/without insulin

The analysis should include a descriptive summary of the primary and secondary efficacy results by age group, categorized by (10-<15 years) and (\geq 15 years). As stated above, at least 30% of randomized patients must be 10-<15 years old.

Labeling that may result from the studies: You must submit proposed pediatric labeling to incorporate the findings of the studies. Under section 505A(j) of the Act, regardless of whether the studies demonstrate that canagliflozin 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 studies. 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 the studies.

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 studies 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/Latina or Not Hispanic/Latina. 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 or in another format such as the Periodic Benefit-Risk Evaluation Report as described in the draft guidance for Industry *E2C(R2) Periodic Benefit-Risk Evaluation Report and the guidance addendum*¹. You are encouraged to contact the reviewing Division for further guidance.

For studies started after December 17, 2017 , study data must 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 FDA.gov² and referenced in the guidance for industry

¹ We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database <https://www.fda.gov/RegulatoryInformation/Guidances/default.htm>.

² <https://www.fda.gov/media/154109/download>

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Providing Regulatory Submissions in Electronic Format - Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications.

Although not currently required, we request that study data be submitted electronically according to the Study Data Tabulation (SDTM) standard published by the Clinical Data Interchange Standards Consortium (CDISC) provided in the document "Study Data Specifications," which is posted on the http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM19_9759.pdf and referenced in the FDA Guidance for Industry, *Providing Regulatory Submissions in Electronic Format - Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications* at <http://www.fda.gov/Cder/guidance/7087rev.htm>.

Timeframe for submitting reports of the studies: Reports of the above studies must be submitted to the Agency on or before June 30, 2016, for the first study and June 30, 2024, for the second study. 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 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.

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**"

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

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.

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 18, 2014, as amended by this letter and by previous amendments dated February 10, 2015, October 15, 2018, July 16, 2020, July 28, 2020, and July 12, 2022, must be submitted to the Agency on or before June 30, 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**”

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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.

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³ <https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm316937.htm>

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If you have any questions, contact Eric Trachtenberg, Regulatory Project Manager at Eric.Trachtenberg@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Lisa B. Yanoff, MD
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 6

BACKGROUND

These studies investigate the potential use of canagliflozin (Invokana) in the treatment of type 2 diabetes mellitus in pediatric patients from ≥ 10 to < 18 years of age. Canagliflozin was approved as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus in the US on March 29, 2013.

The prevalence of type 2 diabetes among pediatric patients is increasing, concurrent with the obesity epidemic. Canagliflozin would provide a useful additional treatment option for pediatric patients with type 2 diabetes based on the low risk of hypoglycemia, once-daily oral administration, and the fact that it does not have adverse effects on body weight.

The pharmacokinetics, pharmacodynamics, efficacy, and safety of canagliflozin must be established in the pediatric population because it is unknown whether the effects of canagliflozin are sufficiently similar between adults and the pediatric population with type 2 diabetes mellitus. Studies of canagliflozin 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.

To obtain needed pediatric information on canagliflozin, 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.

REQUESTS

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 protocols and statistical analysis plan for the following two clinical studies must be submitted and agreed upon with the Agency. Data from Study 1 that supports dose selection for Study 2 must be submitted before the initiation of Study 2.

Study 1: A phase 1 clinical pharmacology study to evaluate the pharmacokinetics (PK), pharmacodynamics (PD), and safety of canagliflozin in subjects ≥ 10 to < 18 years of age with type 2 diabetes mellitus (T2DM) on a background of metformin.

Study 2: A randomized, double-blind, placebo-controlled, phase 3, 52-week study to evaluate the efficacy and safety of canagliflozin in subjects ≥ 10 to < 18 years of age with T2DM who have inadequate glycemic control ($HbA_{1c} \geq 6.5\% \leq 11.0\%$). The study must consist of a screening period, a two-week placebo run-in/stabilization period, a 26-week, double-blind, core treatment period, and an additional 26-week double-blind, extension treatment period. The protocol must specify glycemic rescue and individual subject discontinuation criteria. The study will include at least 33 subjects per group (i.e., canagliflozin vs placebo) who are well-controlled on stable doses of metformin ($\geq 1,000$ mg for at least 8 weeks before screening) with or without insulin to evaluate the safety and efficacy of canagliflozin as add-on to metformin.

Objective of each study

Study 1: To evaluate the PK of canagliflozin after multiple oral doses of canagliflozin in subjects with T2DM who are ≥ 10 to < 18 years of age and are currently taking a stable dose of metformin.

- Evaluate the pharmacodynamic effects of canagliflozin on plasma glucose levels, urinary glucose excretion, and the renal threshold for glucose after multiple oral doses to establish a dose(s) for Study 2;
- Assess the acceptability (e.g., taste, smell, and swallowability) of the canagliflozin tablets (via a questionnaire);
- Assess safety and tolerability.

Study 2: To assess the efficacy and safety of canagliflozin in subjects ≥ 10 to < 18 years of age with T2DM who have inadequate glycemic control (i.e., HbA_{1c} of $\geq 6.5\%$ to $\leq 11.0\%$), either on diet and exercise only, or on diet and exercise and metformin monotherapy, on diet and exercise and insulin monotherapy, or on diet and exercise and a combination of metformin and insulin therapy.

PRIMARY OBJECTIVES

- To assess the effect of canagliflozin relative to placebo on the change from baseline in HbA_{1c} after 26 weeks of treatment in the overall study population.

- To assess the overall safety and tolerability of canagliflozin.

MAJOR SECONDARY OBJECTIVES

- After 26 weeks of treatment, to assess the effect of canagliflozin relative to placebo for the subset of subjects taking background metformin (with or without insulin) on the change from baseline in HbA_{1c}
- After 26 weeks of treatment, to assess the effect of canagliflozin relative to placebo on:
 - Fasting plasma glucose (FPG)
 - Proportion of subjects with HbA_{1c} <7.5%, <7.0% and <6.5%
 - Time to rescue therapy and proportion of subjects receiving rescue therapy
 - Body weight
 - Body mass index (BMI)
 - Systolic and diastolic blood pressure
 - Fasting plasma lipids (i.e., total cholesterol, low density lipoprotein cholesterol [LDL-C], high density lipoprotein cholesterol [HDL-C], non- HDL-C, ratio of LDL-C/HDL-C, triglycerides)
- After 52 weeks of treatment, to assess the effect of canagliflozin relative to placebo on:
 - HbA_{1c} and FPG
 - Proportion of subjects with HbA_{1c} <7.5%, <7.0% and <6.5%
 - Time to rescue therapy and proportion of subjects receiving rescue therapy
 - Body weight
 - Body Mass Index (BMI)
 - Fasting plasma lipids (i.e., LDL-C, HDL-C, total cholesterol, non-HDL- C, LDL-C to HDL-C ratio, non-HDL-C to LDL-C ratio, and triglycerides)
 - Systolic and diastolic blood pressure
 - Long-term safety and tolerability

ADDITIONAL SECONDARY OBJECTIVES

- After 12 weeks of treatment, to assess the effects of canagliflozin relative to placebo on HbA1c
- After 26 weeks of treatment, to assess the effect of canagliflozin 100 mg relative to placebo on HbA1c
- After 26 weeks of treatment, to assess the effect of canagliflozin 100 mg followed by a dose increase to 300 mg relative to placebo on HbA1c

Patients to be Studied:

- *Age group in which studies will be performed:* subjects (≥ 10 to < 18 years of age) with T2DM
- *Number of patients to be studied:*

Study 1: At least 8 subjects per dose group will be enrolled.

Study 2: Subjects with T2DM ≥ 10 and < 18 years of age who have inadequate glycemic control (ie, HbA1c of $\geq 6.5\%$ to $\leq 11.0\%$) and who meet 1 of the criteria below will be eligible to be screened:

- Are on diet and exercise for at least 4 weeks prior to screening
or
- Are on diet and exercise and a stable dose of metformin monotherapy $\geq 1,000$ mg per day or maximum tolerated dose (MTD) per day (defined by the investigator) for at least 8 weeks prior to screening,
or
- Are on diet and exercise and a stable insulin monotherapy regimen for at least 8 weeks prior to screening (stable dose is defined as no change in the insulin regimen (ie, type[s] of insulin) and $\leq 15\%$ change in the total daily dose of insulin [averaged over 1 week to account for day-to-day variability]),
or
- Are on diet and exercise and a stable combination therapy with metformin and insulin for at least 8 weeks prior to screening as described above.

- At least 30% of randomized subjects must be 10 to <15 years of age.
- At least 20% of randomized subjects in both age subsets (10 to <15 years, and ≥ 15 to <18 years) must be male.

Representation of Ethnic and Racial Minorities: Study 2 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:

Pharmacokinetic/Pharmacodynamic Endpoints:

The pharmacokinetic and pharmacodynamic endpoints for Study 1 must include:

- $C_{\max,ss}$ maximum observed plasma concentration during a dosing interval at steady-state
- t_{\max} : time to reach the maximum observed plasma concentration
- AUC_{τ} area under the plasma concentration-time curve during a dosing interval (τ)
- $t_{1/2,\lambda}$: elimination half-life associated with the terminal slope (λz) of the semilogarithmic drug concentration-time curve, calculated as $0.693/\lambda z$
- CL_{ss}/F : total clearance of drug at steady-state after extravascular administration, uncorrected for absolute bioavailability calculated as: $D/AUCT$
- MPG_{0-24h} : mean concentration for plasma glucose during the 0 to 24-hour interval at baseline and following last dose.
- UGE_{0-24h} : cumulative daily urinary glucose excretion over 0 to 24 hours at baseline and following last dose
- RTG ($_{0-12h}$, $_{0-24h}$, and $_{24h}$) mean renal threshold for glucose excretion at baseline and following last dose

Study 2:

EFFICACY ENDPOINTS

- The primary efficacy endpoint must be the change in hemoglobin A1c from baseline to the end of the 26-week double-blind treatment period and must be assessed by a centrally analyzed, NGSP-certified hemoglobin A1c assay.
- Important secondary endpoints must include fasting plasma glucose which must be assessed by a centrally analyzed plasma glucose assay.
- Important secondary endpoints must include the proportion of subjects who achieve HbA1c <7.0% and <6.5% at the end of 26 weeks.

The protocol must describe how patient compliance will be assessed.

SAFETY ENDPOINTS:

The protocol must include the following safety endpoints:

- Nature, frequency, severity, and relationship to treatment of all adverse events;
- Vital signs including heart rate;
- Laboratory parameters including hematology, biochemistry (including pancreatic and liver enzymes), lipid profile, urinalysis, and markers of calcium and phosphate; homeostasis (serum parathyroid hormone, calcium, magnesium, phosphate; urinary excretion of calcium and phosphate; 1,25 dihydroxyvitamin D and calcitonin);
- Bone biomarkers (osteocalcin, C-telopeptide of collagen cross-links);
- Assessment of growth and development using the Tanner scale and by regular collection of standardized measurements of anthropometric parameters (height and body weight) using calibrated and standardized body weight scales and stadiometers;
- Incidence of hypoglycemia;
- Incidence of genital mycotic infections;
- Incidence of urinary tract infections.

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The protocol must include a plan for monitoring the following adverse events

- Hypoglycemia using the American Diabetes Association definitions
- Hypersensitivity reactions
- Renal impairment by serum creatinine monitoring

A Data Monitoring Committee (DMC) must be included.

Known Drug Safety concerns and monitoring: Safety issues that must be assessed include genital mycotic infections (including vulvovaginal or balanitis), urinary tract infections, adverse events related to reduced intravascular volume and osmotic diuresis (including symptomatic hypotension), hyperkalemia, all malignancies, fatal pancreatitis, hemorrhagic/necrotizing pancreatitis, severe hypersensitivity reactions (angioedema, anaphylaxis, Stevens-Johnson syndrome), photosensitivity reactions, serious adverse events of hepatic injury, nephrotoxicity/acute kidney injury, venous thromboembolic events, fractures, pregnancy, increases in low-density lipoprotein cholesterol (LDL-C), effect on growth and development, hypoglycemia, urosepsis, pyelonephritis, ketoacidosis, and lower limb amputations.

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, 100 mg and 300 mg
- **route of administration:** Oral
- **regimen:** Once daily; see below for Study 2

Study 2: The results of Study 1 will determine the doses of canagliflozin to be studied in Study 2. All subjects will receive the 100 mg of canagliflozin (or placebo) after initial randomization. After Week 12, eligible subjects ($HbA_{1c} \geq 7\%$ and have an estimated glomerular filtration rate ≥ 60 mL/min/1.73m² and tolerating 100 mg dose) will be re-

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randomized to either remain on double-blind canagliflozin 100 mg (or matching placebo) or to up-titrate to double-blind canagliflozin 300 mg (or matching placebo).

Subjects requiring additional glycemic control will be rescued during the study.

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(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 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 studies and statistical assessments:

Study 1: The study must be prospectively powered to target a 95% confidence interval within 60% and 140% of the geometric mean estimates of clearance and volume of distribution for canagliflozin in each dose group with at least 80% power.

Study 2: Hypothesis testing must be done for the overall study population and in the subset of subjects on add-on to metformin.

Study 2: The primary efficacy endpoint is the change in HbA_{1c} from baseline at Week 26. The sample size calculation is based on the 2-stage randomization design using a 2-sample, 2-sided t-test with a Type 1 error rate of 0.05, and an updated (based on blinded assessment of the data from the ongoing study) estimate of the standard deviation of 1.69%.

- Overall study: for all subjects who are randomized to canagliflozin or placebo, the planned sample size (based on the initial estimates of the treatment effect of 0.4% to 0.5% and a standard deviation of 0.9%) of 132 subjects (146 accounting for anticipated missing data) may not provide 80% study power in light of the revised estimate of treatment difference of 0.7% and standard deviation of 1.69%. To continue with the current sample size and complete the study as originally planned, if the primary analysis does not result in a statistically significant result (i.e., type 1 error rate of < 0.05), a supplementary analysis using an informative Bayesian prior (using information from a similar subgroup of subjects from adult studies) in the analysis of primary efficacy endpoint should be performed to offset any potential necessary increase in the sample size.
- Add-on metformin: for the subjects who are on background metformin (with or without insulin), if the secondary analysis of the primary efficacy endpoint does not result in a statistically significant result (ie, type 1 error rate of < 0.05), an informative Bayesian prior (using information from add-on metformin subjects from adult studies) in the analysis of primary efficacy endpoint should be performed as a supplementary analysis to offset any potential loss of power (to detect 0.7% treatment difference with revised estimate of the standard deviation of 1.69% while maintaining 80% study power) with the currently planned sample size.

AN OUTLINE OF INFORMATIVE BAYESIAN PRIOR ANALYSIS APPROACH:

A Bayesian mixture prior will be used in the analysis of the primary efficacy endpoint of change from baseline at Week 26 in HbA_{1c} if the primary analysis does not demonstrate

statistical significance (ie, a type 1 error rate <0.05). If performed, the Bayesian analysis will borrow information from adult studies as agreed upon with the FDA. This will be done using a mixture prior that includes both an informative and a non-informative component. If the pediatric study on its own yields a non-significant treatment effect, the weight of adult data that is needed to be borrowed to tip to a significant treatment effect will be determined. The maximum amount of adult trial information that can be borrowed for the primary analysis must be no more than the total pediatric sample size enrolled in the study, as determined by the calculated effective sample size (ESS) of the prior distribution using an agreed upon method, unless an additional justification for increased borrowing is provided and agreed upon with the agency prior to unblinding. Sensitivity analyses must also be conducted where the amount of information that is borrowed is varied ranging from no borrowing to borrowing all the available adult information. The main SAP must be agreed upon with the FDA prior to conducting the analysis. The supplemental Bayesian statistical analysis plan must be agreed upon with the FDA prior to conducting the analysis only if the primary analysis does not result in a statistically significant result.

The primary analysis of HbA1c change from baseline at Week 26 will be a test of superiority of canagliflozin compared to placebo, applied to the Full Analysis Set, which consists of data from subjects who were randomized and receive at least one dose of canagliflozin or canagliflozin placebo and have a baseline HbA1c measurement. The estimand of interest is the intention-to-treat (ITT) estimand. The primary analysis will be a pattern mixture model with multiple imputation to account for missing data and will include all post-baseline measurements taken before week 26, regardless of whether the subject was on or off treatment, and regardless of the initiation of glycemic rescue therapy. A corresponding analysis will also be performed in subjects randomized to a background of metformin with or without insulin. Missing data should be kept to a minimum. When addressing missing data in the primary analysis you may want to account for the therapy received and seek further advice from the National Academies of Sciences report on The Prevention and Treatment of Missing Data in Clinical Trials (NAS, 2010). There will be no interim analysis performed.

To control the family-wise type 1 error rate at 0.05, the primary and secondary hypotheses (in terms of change in HbA1c from baseline to week 26) will be tested as a 2-step sequential procedure:

1. Primary hypothesis on the overall study population
2. Secondary hypothesis on the add-on to metformin group with/without insulin

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The analysis should include a descriptive summary of the primary and secondary efficacy results by age group, categorized by (10-<15 years) and (\geq 15 years). As stated above, at least 30% of randomized patients must be 10-<15 years old.

Labeling that may result from the studies: You must submit proposed pediatric labeling to incorporate the findings of the studies. Under section 505A(j) of the Act, regardless of whether the studies demonstrate that canagliflozin 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 studies. 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 the studies.

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 studies 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/Latina or Not Hispanic/Latina. 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 or in another format such as the Periodic Benefit-Risk Evaluation Report as described in the draft guidance for Industry E2C(R2) Periodic Benefit-Risk Evaluation Report and the guidance addendum.⁴ You are encouraged to contact the reviewing Division for further guidance.

For studies started after December 17, 2017 , study data must be submitted electronically according to the Study Data Tabulation (SDTM) standard published by the Clinical Data

⁴ We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database <https://www.fda.gov/RegulatoryInformation/Guidances/default.htm>.
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Interchange Standards Consortium (CDISC) provided in the document “Study Data Specifications,” which is posted on FDA.gov⁵ and referenced in the guidance for industry *Providing Regulatory Submissions in Electronic Format - Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications*.

Timeframe for submitting reports of the studies: Reports of the above studies must be submitted to the Agency on or before June 30, 2016, for the first study and June 30, 2024, for the second study. 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 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.

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 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

⁵ <https://www.fda.gov/media/154109/download>

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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.⁶

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.

⁶ <https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm316937.htm>

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
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