DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 204042

WRITTEN REQUEST – AMENDMENT 1

Janssen Pharmaceuticals, Inc.
Attention: Sukhdev K. Saran
Director, Global Regulatory Affairs
920 U.S. Highway 202
P.O. Box 300
Raritan, NJ 08869-0602

Dear Ms. Saran:

Please refer to your correspondence dated September 12, 2014, requesting changes to FDA's March 18, 2014, Written Request for pediatric studies for canagliflozin.

We have reviewed your proposed changes and are amending the below-listed sections of the Written Request. All other terms stated in our Written Request issued on March 18, 2014, remain the same. (Text added is underlined. Text deleted is strikethrough.)

Under *Timeframe for submitting reports of the studies*:

Reports of the above studies must be submitted to the Agency on or before June 30, ~~2015~~ 2016, for the first study, December 31, ~~2020~~ 2021, for the second study, and December 31, ~~2025~~ 2026, for the third 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.

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 must be submitted to the Agency on or before June 30, 2016, for the first study, December 31, 2021, for the second study, and December 31, 2026, for the third study, in order to possibly qualify for pediatric exclusivity extension under Section 505A of the Act.

Submit reports of the studies as a supplement to an approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, clearly mark your submission **"SUBMISSION OF PEDIATRIC STUDY REPORTS – PEDIATRIC EXCLUSIVITY DETERMINATION REQUESTED"** in large font, bolded type at the beginning of the cover letter of the submission and include a copy of this letter. In addition, send a copy of the cover letter of your submission, via fax (240-276-9327) or messenger, to the Director, Office of Generic Drugs, HFD-600, Metro Park North IV, 7519 Standish Place, Rockville, MD 20855-2773.

In accordance with section 505A(k)(1) of the Act, FDA must make available to the public the medical, statistical, and clinical pharmacology reviews of the pediatric studies conducted in response to this Written Request within 210 days of submission of your study report(s). These reviews will be posted regardless of the following:

- the type of response to the Written Request (i.e., complete or partial response);
- the status of the application (i.e., withdrawn after the supplement has been filed or pending);
- the action taken (i.e., approval, complete response); or
- the exclusivity determination (i.e., granted or denied).

FDA will post the medical, statistical, and clinical pharmacology reviews on the FDA website at http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM049872.

If you wish to discuss any amendments to this Written Request, submit proposed changes and the reasons for the proposed changes to your application. Clearly mark submissions of proposed changes to this request **"PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES"** in large font, bolded type at the beginning of the cover letter of the submission. We will notify you in writing if we agree to any changes to this Written Request.

If you have any questions, call Elizabeth Chen, Regulatory Project Manager, at (240) 402-3729.

Sincerely,

{See appended electronic signature page}

Mary H. Parks M.D
Deputy Director
Office of Drug Evaluation II
Office of New Drugs
Center for Drug Evaluation and Research

ENCLOSURE:
Complete Copy of Written Request as Amended

REVISED WRITTEN REQUEST, AMENDMENT 1

- *Nonclinical studies:*

Based on review of the available non-clinical 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 three clinical studies must be submitted and agreed upon with the Agency. Study 1 must be completed before Study 2 to determine doses to be studied in Studies 2 and 3. The results of Study 1 must be completed and submitted before initiating Studies 2 and 3. Study 3 must be completed after both safety and efficacy of canagliflozin as add-on to metformin have been established in Study 2 and the safety of canagliflozin as monotherapy in the open-label cohort of Study 2 has been established.

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 when added on to metformin in subjects ≥ 10 to < 18 years of age with T2DM who have been treated with a stable dose of metformin (≥1000 mg for at least 3 months before screening) and are experiencing inadequate glycemic control (HbA1c ≥7% and ≤10%). The trial must consist of a screening period, a four-week placebo run-in/stabilization period, a 24-week, double-blind, primary endpoint treatment period, and an additional 28-week double-blind, safety endpoint treatment period. The protocol must specify glycemic rescue and individual subject discontinuation criteria. The study will include an open-label cohort to investigate the safety and tolerability of canagliflozin as monotherapy in subjects ≥ 10 to < 18 years of age with T2DM who have either inadequate glycemic control (HbA1c ≥7% and ≤10%) without any antidiabetic medications, or well-controlled on stable doses of metformin (≥1000 mg for at least 3 months before screening).

Study 3: 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 been treated with diet and exercise, have received less than seven days of any antidiabetic medications within eight weeks before screening, and are experiencing inadequate glycemic control (HbA1c ≥7% and ≤10%). The trial must consist of a screening period, a four-week placebo run-in/stabilization period, a 24-week, double-blind, primary endpoint treatment period, and an additional 28-week double-blind, safety endpoint treatment period. The protocol must specify glycemic rescue and individual subject discontinuation criteria.

- *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 in subjects ≥ 10 to < 18 years of age with T2DM failing diet and exercise therapy:

- The efficacy and safety and tolerability of canagliflozin as add-on therapy to metformin;
- The safety of canagliflozin as monotherapy.

Add-on to Metformin Cohort:

- Primary: To assess the effect of treatment with canagliflozin compared to placebo when added on to metformin on the change from baseline in HbA1c after 24 weeks, and the safety and tolerability of canagliflozin;
- Secondary: To assess the effect of treatment with canagliflozin compared to placebo when added on to metformin after 24 weeks on:
  - fasting plasma glucose (FPG)
  - body weight
  - body mass index (BMI)
  - blood pressure
  - proportion of subjects achieving glycemic goals (i.e., HbA1c <7%, HbA1c <6.5%)
  - fasting plasma lipids (i.e., total cholesterol, low-density lipoprotein cholesterol [LDLC], high-density lipoprotein cholesterol [HDL-C], non-HDL-C, ratio of LDL-C/HDL-C, triglycerides);
- Additional: To assess the effect of treatment with canagliflozin compared to placebo when added on to metformin on HbA1c and all assessments listed above for the secondary objectives after 52 weeks.

Monotherapy Cohort:

- Primary: To assess the safety and tolerability of canagliflozin

Study 3: To evaluate the efficacy and safety/tolerability of canagliflozin as monotherapy in subjects ≥ 10 to < 18 years of age with T2DM:

- To assess the effect of treatment with canagliflozin compared to placebo after 24 weeks on the change from baseline in HbA1c;
- To evaluate the long-term safety of canagliflozin

- *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:
  For the add-on to metformin cohort in Study 2:
  - Age group in which the study will be performed: Patients ages 10 to <18 years
  - At least 30% of randomized subjects must be 10-14 years of age
  - At least 30% of randomized subjects and not more than two-thirds of subjects in both age subsets (10 to 14 years, and 15 to <18 years) must be female
  - Number of subjects to be randomized: The study must include a sufficient number of subjects to provide 90% power to detect a between-group difference of 0.5% in the mean HbA1c change from baseline to week 24
  - Subjects must have received stable doses of metformin for at least 3 months with a dose of at least 1000 mg per day
  - Inadequate glycemic control (HbA1c ≥7% and ≤10%)

  The open-label monotherapy group in Study 2 must include at least 30% of the total subjects in the add-on to metformin cohort, and they should undergo an adequate washout and run-in period if they were previously well-controlled on stable doses of metformin therapy (≥1000 mg for at least 3 months).

  Study 3:
  - Age group in which the study will be performed: Patients ages 10 to <18 years
  - At least 30% of randomized subjects must be 10-14 years of age
  - At least 30% of randomized subjects and not more than two-thirds of subjects in both age subsets (10 to 14 years, and 15 to <18 years) must be female
  - Number of subjects to be randomized: The study must include a sufficient number of subjects to provide 90% power to detect a between-group difference of 0.5% in the mean HbA1c change from baseline to week 24
  - Subjects must have received less than seven days of any antidiabetic medications within eight weeks before screening
  - Inadequate glycemic control (HbA1c ≥7% and ≤10%)

  Representation of Ethnic and Racial Minorities: Study 2 and Study 3 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/AUC_τ
- $MPG_{0\text{-}24h}$: mean concentration for plasma glucose during the 0 to 24 hour interval at baseline and following last dose.
- $UGE_{0\text{-}24h}$: cumulative daily urinary glucose excretion over 0 to 24 hours at baseline and following last dose
- $RT_{G(0\text{-}12h,\ 0\text{-}24h,\ and\ 24h)}$: mean renal threshold for glucose excretion at baseline and following last dose

Study 2 and Study 3:
Efficacy Endpoints

- The primary efficacy endpoint must be the change in hemoglobin A1c from baseline to the end of the 24-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 24 weeks.

The protocol must describe how patient compliance will be assessed.

Safety Endpoints:

Safety endpoints must include:

- 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.

The following adverse events must be actively monitored:

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

All adverse events must be monitored until symptom resolution or until the condition stabilizes.

All adverse events must be captured when spontaneously reported.

A Data Monitoring Committee (DMC) must be included because the study is being performed in children, a vulnerable population. See Guidance: Establishment and Operation of Clinical Trial Data Monitoring Committees http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126578.pdf

- *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, and hypoglycemia.

- *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 either 50 mg or 300 mg
  - *route of administration*: Oral
  - *regimen*: Once daily; see below for Study 2 and Study 3

Study 2 and Study 3: The results of Study 1 will determine two doses of canagliflozin to be studied in Study 2 and Study 3, a low dose and a high dose; this can be either 50 mg (low dose) and 100 mg (high dose), or 100 mg (low dose) and 300 mg (high dose). All subjects will receive the low dose of canagliflozin (or placebo) after randomization, and the dose will be up-titrated to the high dose based on their need for additional glycemic control. Subjects with estimated glomerular filtration rate ≥60 mL/min/1.73m^2 requiring additional glycemic control will up-titrate from the low dose to the high dose of canagliflozin (or placebo) if they meet the following criteria:

- After randomization through Week 6: FPG >240 mg/dL;
- After Week 6 through Week 12: FPG >200 mg/dL;
- After Week 12 through Week 24: FPG >160 mg/dL;
- After Week 24 through Week 52: HbA1c ≥7%.

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 add-on to metformin cohort in Study 2.

Study 2 and Study 3: The primary efficacy endpoint is the change in HbA1c from baseline at Week 24. The sample size must provide at least 90% power to detect 0.5% difference between two treatment arms in HbA1c change from baseline using two-sided alpha of 0.05, taking into account of anticipated missing data.

The primary analysis of HbA1c change from baseline at Week 24 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 full or partial dose of canagliflozin or canagliflozin placebo. The exact method of analysis will be provided in the protocol and agreed upon with the medical division. 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. The protocol should also contain how the testing of secondary endpoints will be performed to control the study-wise type 1 error rate at (two-sided) 0.05.

The analysis should include a descriptive summary of the primary and secondary efficacy results by age group, categorized by (10-14 years) and (>14 years). As stated above, at least 30% of randomized patients must be 10-14 years old.

- *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 of 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/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 http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM199759.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, December 31, 2021, for the second study, and December 31, 2026, for the third 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 protocols for the above studies to an investigational new drug application (IND) and clearly mark your submission "**PEDIATRIC PROTOCOL SUBMITTED FOR PEDIATRIC EXCLUSIVITY STUDY**" in large font, bolded type at the beginning of the cover letter of the submission.

Reports of the studies must be submitted as a new drug application (NDA) or as a supplement to your approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission "**SUBMISSION OF PEDIATRIC STUDY REPORTS - PEDIATRIC EXCLUSIVITY DETERMINATION REQUESTED**" in large font, bolded type at the beginning of the cover letter of the submission and include a copy of this letter. Please also send a copy of the cover letter of your submission to the Director, Office of Generic Drugs, HFD-600, Metro Park North IV, 7519 Standish Place, Rockville, MD 20855-2773. If you wish to fax it, the fax number is 240-276-9327.

In accordance with section 505A(k)(1) of the Act, *Dissemination of Pediatric Information*, FDA must make available to the public the medical, statistical, and clinical pharmacology reviews of the pediatric studies conducted in response to this Written Request within 210 days of submission of your study report(s). These reviews will be posted regardless of the following circumstances:

1. the type of response to the Written Request (i.e. complete or partial response);
2. the status of the application (i.e. withdrawn after the supplement has been filed or pending);
3. the action taken (i.e. approval, complete response); or
4. the exclusivity determination (i.e. granted or denied).

FDA will post the medical, statistical, and clinical pharmacology reviews on the FDA website at http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM049872

If you wish to discuss any amendments to this Written Request, please submit proposed changes and the reasons for the proposed changes to your application. Submissions of proposed changes to this request should be clearly marked "**PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES**" in large font, bolded type at the beginning of the cover letter of the submission. You will be notified in writing if any changes to this Written Request are agreed upon by the Agency.

Please note that, if your trial is considered an "applicable clinical trial" under section 402(j)(1)(A)(i) of the Public Health Service Act (PHS Act), you are required to comply with the provisions of section 402(j) of the PHS Act with regard to registration of your trial and submission of trial results. Additional information on submission of such information can be found at www.ClinicalTrials.gov.

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

/s/

MARY H PARKS
02/10/2015