DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 204042

NDA APPROVAL

Janssen Research & Development, LLC
Attention: Sukhdev K. Saran
Associate Director, Regulatory Affairs
920 U.S. Highway; P.O. Box 300
Raritan, New Jersey 08869

Dear Ms. Saran:

Please refer to your New Drug Application (NDA) dated May 31, 2012, received May 31, 2012, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Invokana (canagliflozin) Tablets, 100 mg and 300 mg.

We acknowledge receipt of your amendments dated June 29, July 5 and 27 (2), August 10, September 7 and 17, October 1 and 23, November 15, 28, 29, and 30 (2), December 3, 4, 12, 18, 19, 21 (2), and 27, 2012, and January 8 (2), 18, 21, 30, February 8, 11, 12, 22, and 28, and March 6, 8, 13, 18, 24, and 27, 2013. We also acknowledge receipt of your email dated March 29, 2013, that includes the agreed-upon package insert and Medication Guide.

This NDA provides for the use of Invokana (canagliflozin) Tablets as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

We have completed our review of this application, as amended. It is **approved**, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

WAIVER OF HIGHLIGHTS SECTION

We acknowledge your request to waive the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of prescribing information. As previously discussed with you, we are denying your request.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the package insert and Medication Guide).

Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*, available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible via publicly available labeling repositories.

CARTON AND IMMEDIATE-CONTAINER LABELS

Submit final printed carton and immediate-container labels that are identical to the enclosed carton and immediate container labels submitted on March 24, 2013, as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry *Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008)*. Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission "**Final Printed Carton and Container Labels for approved NDA 204042**." Approval of this submission by FDA is not required before the labeling is used.

Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for ages 0 through 9 years because the product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this age group **and** is not likely to be used in a substantial number of pediatric patients in this group.

We are deferring submission of your pediatric studies for ages 10 to 17 years for this application because this product is ready for approval for use in adults and the pediatric studies have not been completed.

Your deferred pediatric studies required by section 505B(a) of the FDCA are required postmarketing studies. The status of these postmarketing studies must be reported annually according to 21 CFR 314.81 and section 505B(a)(3)(B) of the FDCA. These required studies are listed below.

2027-1 A clinical pharmacology study to evaluate the pharmacokinetics, pharmacodynamics, and safety of canagliflozin in pediatric patients ages 10 to <18 years with type 2 diabetes mellitus on metformin monotherapy.

Final Protocol Submission:	October 2013
Study Completion:	December 2014
Final Report Submission:	June 2015

2027-2 A 26-week, randomized double-blind, placebo-controlled study, followed by a 26-week double-blind, placebo- or active-controlled extension, to evaluate the efficacy and safety of canagliflozin compared to placebo in pediatric patients ages 10 to <18 years with type 2 diabetes mellitus, as add-on to metformin and as monotherapy.

Final Protocol Submission:	December 2015
Study Completion:	June 2020
Final Report Submission:	December 2020

Submit the protocols to your IND 076479, with a cross-reference letter to this NDA.

Reports of these required pediatric postmarketing studies must be submitted as a 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 REQUIRED PEDIATRIC ASSESSMENTS**" in large font, bolded type at the beginning of the cover letter of the submission.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess signals of serious risks of malignancy (pheochromocytoma, Leydig cell tumor, renal cell carcinoma), pancreatitis, hypersensitivity reactions, photosensitivity reactions, hepatotoxicity, bone fractures, nephrotoxicity, and adverse pregnancy outcomes in patients treated with Invokana (canagliflozin).

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess this serious risk.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

2027-3 An assessment and analysis of all foreign and domestic spontaneous reports of malignancy (pheochromocytoma, Leydig cell tumor, and renal cell carcinoma), fatal pancreatitis, hemorrhagic/necrotizing pancreatitis, severe hypersensitivity reactions (angioedema, anaphylaxis, Stevens-Johnson syndrome), photosensitivity reactions, serious hepatic abnormalities, and pregnancy in patients treated with canagliflozin. The enhanced pharmacovigilance should continue for 10 years from the date of approval for malignancies and 5 years for all other events.

The timetable you submitted on March 27, 2013, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	December 2013
Interim Report Submissions:	May 2014
	May 2015
	May 2016
	May 2017
	May 2018
	May 2019
	May 2020
	May 2021
	May 2022
Study Completion:	March 2023
Final Report Submission:	November 2023

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess a signal of an increased risk of bone fractures in patients treated with Invokana (canagliflozin). Furthermore, there have been signals of a serious risk of cardiovascular events with some medications developed for the treatment of type 2 diabetes mellitus, and available data have not definitively excluded the potential for this serious risk with Invokana (canagliflozin). We have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess a signal of a serious risk of major adverse cardiovascular events with antidiabetic medications, including Invokana (canagliflozin). Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

2027-4 Completion and submission of the final report for the 78-week double-blind extension phase of DIA3010, a clinical trial to assess the long-term safety of canagliflozin, including, but not limited to, the effect of the addition of canagliflozin to the addition of placebo on bone mineral density and markers of bone turnover.

The timetable you submitted on March 27, 2013, states that you will complete this trial according to the following schedule:

Final Report Submission:	December 2013

2027-5 A randomized, double-blind, placebo-controlled trial evaluating the effect of canagliflozin on the incidence of major adverse cardiovascular events (MACE) in patients with type 2 diabetes mellitus. The primary objective of the trial should be to demonstrate that the upper bound of the 2-sided 95% confidence interval for the estimated risk ratio comparing the incidence of MACE (non-fatal myocardial infarction, non-fatal stroke, cardiovascular death) observed with canagliflozin to that observed in the placebo group is less than 1.3.

The timetable you submitted on March 27, 2013, states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	September 2013
Trial Completion:	June 2017
Final Report Submission:	September 2017

Submit the protocols to your IND 076479, with a cross-reference letter to this NDA. Submit all final reports to your NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **"Required Postmarketing Protocol Under 505(o)", "Required Postmarketing Final Report Under 505(o)", "Required Postmarketing Correspondence Under 505(o)"**.

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii).

We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
5901-B Ammendale Road
Beltsville, MD 20705-1266

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

MEDWATCH-TO-MANUFACTURER PROGRAM

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.htm.

POST-ACTION FEEDBACK MEETING

New molecular entities and new biologics qualify for a post-action feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, call the Regulatory Project Manager for this application.

If you have any questions, please call Ms. Jena Weber, Regulatory Project Manager, at 301-796-1306.

Curtis J. Rosebraugh, M.D., M.P.H.
Director
Office of Drug Evaluation II
Office of New Drugs
Center for Drug Evaluation and Research

Enclosures: Package Insert
Medication Guide
Carton and Container Labeling

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

/s/

CURTIS J ROSEBRAUGH
03/29/2013