DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 212018

ACCELERATED APPROVAL

Janssen Biotech, Inc.
Attention: Hsiao-Ling Hung, PhD
920 US Highway 202, PO Box 300
Raritan, NJ 08869

Dear Dr. Hung:

Please refer to your New Drug Application (NDA) dated September 18, 2018, received September 18, 2018, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Balversa™ (erdafinitib) tablets, 3 mg, 4 mg, and 5 mg.

This new drug application provides for the use of Balversa™ (erdafinitib) for the treatment of adult patients with locally advanced or metastatic urothelial carcinoma (mUC), that has:

- susceptible FGFR3 or FGFR2 genetic alterations, and
- progressed during or following at least one line of prior platinum-containing chemotherapy, including within 12 months of neoadjuvant or adjuvant platinum-containing chemotherapy.

Select patients for therapy based on an FDA-approved companion diagnostic for Balversa.

This indication is approved under accelerated approval based on tumor response rate. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

APPROVAL & LABELING

We have completed our review of this application. It is approved under the provisions of accelerated approval regulations (21 CFR 314.500), effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text. Marketing of this drug product and related activities must adhere to the substance and procedures of the referenced accelerated approval regulations.

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 (prescribing information and patient package insert). Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible via publicly available labeling repositories.

CARTON AND CONTAINER LABELING

Submit final printed carton and container labeling that are identical to the bottle carton and container labeling submitted on September 18, 2018 and the blister cards carton and container labeling submitted on February 12, 2019, as soon as they are available, but no more than 30 days after they are printed. Please submit these labeling electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (April 2018, Revision 5).* For administrative purposes, designate this submission "**Final Printed Carton and Container Labeling for approved NDA 212018**." Approval of this submission by FDA is not required before the labeling is used.

ADVISORY COMMITTEE

Your application for Balversa was not referred to an FDA advisory committee because the safety profile is acceptable for patients with relapsed or refractory advanced urothelial carcinoma. The application did not raise significant safety or efficacy issues that were unexpected for a drug of this class, and outside expertise was not necessary; there were no controversial issues that would benefit from advisory committee discussion.

ACCELERATED APPROVAL REQUIREMENTS

Products approved under the accelerated approval regulations, 21 CFR 314.510, require further adequate and well-controlled studies/clinical trials to verify and describe clinical benefit. You are required to conduct such studies/clinical trials with due diligence. If postmarketing studies/clinical trials fail to verify clinical benefit or are not conducted with due diligence, we may, following a hearing in accordance with 21 CFR 314.530, withdraw this approval. We remind you of your postmarketing requirement specified in your submission dated April 3, 2019. This requirement, along with required completion dates, is listed below.

3561-1 Submit the analysis, and datasets with the final report demonstrating clinical benefit of erdafitinib in patients with locally advanced and metastatic urothelial carcinoma with susceptible FGFR 3 or FGFR 2 genetic alterations from clinical trial BLC3001 entitled; "A Phase 3 Study of Erdafitinib Compared With Vinflunine or Docetaxel or Pembrolizumab in Subjects with Advanced Urothelial Cancer and Selected FGFR Gene Aberrations."

Final Protocol Submission:	10/2017
Trial Completion:	04/2022
Final Report Submission:	10/2022

Submit clinical protocols to your IND 117490 for this product. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii) you should include a status summary of each requirement in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial.

Submit final reports to this NDA as a supplemental application. For administrative purposes, all submissions relating to this postmarketing requirement must be clearly designated "**Subpart H Postmarketing Requirement(s)**."

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), 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 this application because necessary studies are impossible or highly impracticable since urothelial carcinoma occurs rarely in the pediatric population.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (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 a signal of serious risk of toxicity from drug over-exposure of erdafinitib due to impaired hepatic function or the over-exposure of concomitant CYP3A4 substrates due to the impact of erdafinitib on CYP3A4.

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 these serious risks.

Finally, 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 toxicity from drug over-exposure of

erdafinitib due to impaired hepatic function on the pharmacokinetics, or the toxicity from over-exposure of concomitant CYP3A4 substrates due to the impact of erdafinitib on CYP3A4.

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

3561-2 Complete and submit the results of your ongoing hepatic impairment trial EDI1008, entitled; "A Phase 1, Open-Label, Single-Dose Study to Evaluate the Effect of Hepatic Impairment on the Pharmacokinetics of Erdafitinib".

The timetable you submitted on April 3, 2019 states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	02/2019
Trial Completion:	09/2020
Final Report Submission:	03/2021

3561-3 Conduct a clinical pharmacokinetic trial that evaluates the effect of repeated doses of erdafitinib on the single dose pharmacokinetics of a sensitive CYP3A substrate (e.g., midazolam), to address the potential for excessive drug toxicity or decreased drug exposure, and to determine appropriate dosing recommendations when coadministering erdafitinib with a sensitive CYP3A substrate. This trial should be designed and conducted in accordance with FDA Draft Guidance for Industry: *Clinical Drug Interaction Studies – Study Design, Data Analysis, and Clinical Implications*. Submit the analysis and datasets with the final report.

The timetable you submitted on April 3, 2019 states that you will conduct this trial according to the following schedule:

Draft Protocol Submission:	12/2019
Final Protocol Submission:	03/2020
Trial Completion:	06/2022
Final Report Submission:	12/2022

Submit clinical protocol(s) to your IND 117490 with a cross-reference letter to this NDA. Submit nonclinical and chemistry, manufacturing, and controls protocols and all final report(s) 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.

POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

3561-4 Conduct a clinical pharmacokinetic trial that evaluates the effect of repeated doses of a strong inducer (e.g., rifampin) of CYP2C9 and CYP3A on the single dose pharmacokinetics of erdafitinib to assess the magnitude of decreased drug exposure and to determine appropriate dosing recommendations when erdafitinib is coadministered with CYP2C9 and CYP3A inducers. This trial should be designed and conducted in accordance with the FDA Draft Guidance for Industry: *Clinical Drug Interaction Studies – Study Design, Data Analysis, and Clinical Implications*. Submit the analysis and datasets with the final report.

The timetable you submitted on April 5, 2019, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	10/2019
Final Protocol Submission:	01/2020
Trial Completion:	10/2020
Final Report Submission:	04/2021

3561-5 Conduct a clinical pharmacokinetic study that evaluates the effect of repeated doses of erdafitinib (at steady-state) on the single dose pharmacokinetics of a probe substrate of OCT2 to determine appropriate dosing recommendations for OCT2 substrate when it is coadministered with erdafitinib. This study should be designed and conducted in accordance with the FDA Draft Guidance for Industry: *Clinical Drug Interaction Studies – Study Design, Data Analysis, and Clinical Implications*. Submit the analysis and datasets with the final report.

The timetable you submitted on April 3, 2019, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	12/2019

Final Protocol Submission:	03/2020
Study/Trial Completion:	06/2022
Final Report Submission:	12/2022

A final submitted protocol is one that the FDA has reviewed and commented upon, and you have revised as needed to meet the goal of the study or clinical trial.

Submit clinical protocols to your IND 117490 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii) you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled **"Postmarketing Commitment Protocol," "Postmarketing Commitment Final Report," or "Postmarketing Commitment Correspondence."**

PROMOTIONAL MATERIALS

Under 21 CFR 314.550, you are required to submit, during the application pre-approval review period, all promotional materials, including promotional labeling and advertisements, that you intend to use in the first 120 days following marketing approval (i.e., your launch campaign). If you have not already met this requirement, you must immediately contact the Office of Prescription Drug Promotion (OPDP) at (301) 796-1200. Please ask to speak to a regulatory project manager or the appropriate reviewer to discuss this issue.

As further required by 21 CFR 314.550, submit all promotional materials that you intend to use after the 120 days following marketing approval (i.e., your post-launch materials) at least 30 days before the intended time of initial dissemination of labeling or initial publication of the advertisement. We ask that each submission include a detailed cover letter together with three copies each of the promotional materials, annotated references, and approved Prescribing Information (PI)/Medication Guide/Patient Package Insert (as applicable).

Send each submission directly to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotions (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit promotional materials for accelerated approval products electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at:

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf).

REPORTING REQUIREMENTS

We remind you that you must comply with the 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 APPROVAL FEEDBACK MEETING

New molecular entities and new biologics qualify for a post approval 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, contact Clara Lee, Regulatory Project Manager, at (240) 402-4809 or Clara.Lee@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Gideon Blumenthal, MD
Deputy Director – Oncology Center for Excellence
Supervisory Associate Director (Acting)
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

ENCLOSURE(S):
Content of Labeling
Prescribing Information
Patient Package Insert

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/

GIDEON M BLUMENTHAL
04/12/2019 11:53:41 AM