DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 204384

ACCELERATED APPROVAL

Janssen Research and Development, LLC
Attention: Gary Lewis
Associate Director, Global Regulatory Affairs
920 Route 202 South
Raritan, NJ 08869

Dear Mr. Lewis:

Please refer to your New Drug Application (NDA) dated June 28, 2012, received June 29, 2012, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for SIRTURO (bedaquiline) 100 mg tablets.

We acknowledge receipt of your amendment(s) dated July 20, 24, 25, and 31, August 14, 24, and 31, September 12, 19, and 27, October, 02, 12, 25, and 26, November 13 (3), 15, and 20, December 04, 07, 10, 12, 20 (2), 21 (4) , 26 and 28 (2), 2012.

This new drug application provides for the use of SIRTURO (bedaquiline) 100 mg tablets as part of combination therapy in adults (≥ 18 years) with pulmonary multi-drug resistant tuberculosis (MDR-TB).

We have completed our review of this application, as amended. It is approved under the provisions of the 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.

We note that your December 28, 2012, submission includes final printed labeling (FPL) for your package insert and Medication Guide. We have not reviewed this FPL. You are responsible for assuring that the wording in this printed labeling is identical to that of the approved content of labeling in the structured product labeling (SPL) format.

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 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 IMMEDIATE CONTAINER LABELS

We acknowledge your December 20, 2012, submission containing final printed carton and container labels.

TROPICAL DISEASE PRIORITY REVIEW VOUCHER

We also inform you that you have been granted a tropical disease priority review voucher, as provided under section 524 of the FDCA. This voucher entitles you to designate a single human drug application submitted under section 505(b)(l) of the Federal Food, Drug, and Cosmetic Act (FDCA) or a single biologic application submitted under section 351 of the Public Health Service Act as qualifying for a priority review. Such an application would not have to meet any other requirements for a priority review. This priority review voucher may be transferred by you to another sponsor of a human drug or biologic application. When redeeming this priority review voucher, you should refer to this letter as an official record of the voucher. If the voucher is transferred, the sponsor to whom the voucher has been transferred should include a copy of this letter (which will be posted on our Web site as are all approval letters) and proof that the voucher was transferred. In addition, this priority review voucher has been assigned a tracking number, PRV 204384. All correspondences related to this voucher should refer to this tracking number. For additional information regarding the priority review voucher, see FDA's guidance, *Tropical Disease Priority Review Vouchers,* at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM080599.pdf.

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 December 26, 2012. This requirement, along with required completion dates, is listed below.

1988-001: Conduct a confirmatory randomized double blind placebo controlled multicenter Phase 3 trial in subjects with sputum smear-positive pulmonary multidrug resistant tuberculosis (MDR-TB). This trial should assess long term outcomes of failure or relapse or death at least 6 months after all MDR-TB treatment is completed.

Final Protocol Submission:	06/2013
Trial Completion:	08/2021
Final Report Submission:	03/2022

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, 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(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because this drug product for this indication has an orphan drug designation, you are exempt from this requirement.

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 a signal of a serious risk of increased mortality, assess a signal of development of decreased bedaquiline susceptibility in MDR-TB isolates , and identify an unexpected serious risk of increased drug levels of SIRTURO (bedaquiline) in HIV patients co-infected with MDR-TB.

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.

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

1988-002: Develop a patient registry for bedaquiline-treated patients to assess incidence rates of serious adverse events, including death. The registry should capture the information listed below:

a. indication for use, including utilization of expert medical consultation
b. Minimum Inhibitory Concentration (MIC) data for baseline and any subsequent MDR-TB isolate (in patients who have relapsed/at end of treatment)
c. drug utilization data
d. information on the drug distribution mechanisms used
e. information on how the drug was actually distributed to patients
f. patient outcomes (clinical and microbiologic)
g. safety assessments in bedaquiline-treated patients, including deaths
h. concomitant medications

The timetable you submitted on December 26, 2012, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	06/2013
Interim Report Submission:	06/2014
	06/2015
	06/2016
	06/2017
	06/2018
Study Completion:	12/2018
Final Report Submission:	08/2019

1988-003: In order to inform PMR 1988-005, conduct a study to define the Quality Control ranges of bedaquiline for MDR-TB isolates using standard proportion methods.

The timetable you submitted on December 26, 2012, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	03/31/2013
Study Completion:	09/30/2014
Final Report Submission:	12/31/2014

1988-004: In order to inform PMR 1988-005, conduct a study to define the Quality Control ranges of bedaquiline for MDR-TB isolates using MIC methods.

The timetable you submitted on December 26, 2012, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	03/31/2013
Study Completion:	09/30/2014
Final Report Submission:	12/31/2014

1988-005: Conduct a prospective in vitro study over a five-year period after introduction of SIRTURO (bedaquiline) to the market to determine MICs of MDR-TB isolates to bedaquiline for the first 5 years from marketing. Report interpretation of these MICs once additional quality control testing methods are developed as noted in the required postmarketing studies PMR 1988-03 and PMR 1988-04. Provide a detailed protocol describing the study to the Agency for review and comment before commencing the study.

The timetable you submitted on December 26, 2012, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	04/30/2015
Interim Report Submission:	12/31/2016
	12/31/2017
	12/31/2018
Study Completion:	09/30/2019
Final Report Submission:	12/31/2019

1988-006: Conduct an in vitro study to characterize the potential of bedaquiline and M2 as a substrate, inhibitor or inducer of the OATP1B1 and OATP1B3 drug transporters.

The timetable you submitted on December 26, 2012, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	04/2013
Study Completion:	10/2013
Final Report Submission:	12/2013

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to identify an unexpected serious risk of increased drug levels of SIRTURO (bedaquiline) in HIV patients co-infected with MDR-TB.

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

1988-007: Conduct a drug interaction trial of bedaquiline and efavirenz to determine a safe and effective dose regimen of both drugs when they are co-administered in HIV co-infected MDR-TB patients. Alternatively, adequate data from a previously conducted drug interaction trial may be submitted.

The timetable you submitted on December 26, 2012, states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	03/30/2013
Final Report Submission:	09/30/2013

Submit the protocol(s) to your IND 69600, with a cross-reference letter to this NDA. Submit 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:

1988-008: Submit final study report and electronic data for Study C208 Stage II.

The timetable you submitted on December 26, 2012, states that you will conduct this trial according to the following schedule:

Final Report Submission:	11/2013

1988-009: Submit final study report and electronic data for Study C209.

The timetable you submitted on December 26, 2012, states that you will conduct this trial according to the following schedule:

Trial Completion:	01/2013
Final Report Submission:	11/2013

Submit clinical protocols to your IND 69600 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 package insert (PI)/Medication Guide/patient PI (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

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-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, call Fariba Izadi, Pharm.D, Regulatory Project Manager, at (301) 796-0563.

Sincerely,

{See appended electronic signature page}

Edward M. Cox, M.D., M.P.H.
Director
Office of Antimicrobial Products
Center for Drug Evaluation and Research

ENCLOSURE(S):
Content of Labeling
Carton and Container Labeling
MedGuide

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

/s/

EDWARD M COX
12/28/2012