Dear Mr. Ibrahim:

Please refer to your supplemental new drug application (sNDA) dated and received October 30, 2018 (S-011), February 28, 2019 (S-014), and May 24, 2019 (S-015) and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for VENCLEXTA® (venetoclax); 10, 50, and 100 mg tablets.

These Prior Approval supplemental new drug applications provide for:

S-011: description of the effect of hepatic impairment on the pharmacokinetics and safety of venetoclax compared to subjects with normal hepatic function based on the results of clinical trial M15-342 to fulfill PMR-3068-2

S-014: updated efficacy information for venetoclax monotherapy from clinical trials M14-032 and M12-175, to fulfill two postmarketing commitments (PMC 3426-1 and PMC 3426-2)

S-015: adding section 5.6 to the WARNINGS AND PRECAUTIONS section of the US Prescribing Information for venetoclax to inform prescribers of the risks observed in the study M14-031 (BELLINI).

APPROVAL & LABELING

We have completed our review of these applications, as amended. They are approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling.
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 FDA.gov.¹ Content of labeling must be identical to the enclosed labeling text for the Prescribing Information and Medication Guide, with the addition of any labeling changes in pending “Changes Being Effected” (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

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.²

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in Microsoft Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes. To facilitate review of your submission(s), provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(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.

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

¹ https://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm
² 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.
FULFILLMENT OF POSTMARKETING REQUIREMENT(S)/COMMITMENT(S)

We have received your submission dated October 30, 2018, containing the final reports for the following postmarketing requirement listed in the April 11, 2016, approval letter.

PMR 3068-2: Evaluate the effect of hepatic impairment on the pharmacokinetics and safety of VENCLEXTA (venetoclax) compared to subjects with normal hepatic function. Submit a complete final report with all supporting datasets for trial M15-342 entitled, “A Study to Evaluate the Safety and Pharmacokinetics of a Single Dose of Venetoclax in Female Subjects with Mild, Moderate, or Severe Hepatic Impairment.”

Trial Completion: 03/2017
Final Report Submission: 12/2017

We refer to your March 9, 2017, request for a revised milestone for PMR-3068-2 and the April 4, 2017, FDA letter with your proposed revised milestones as follows:

Trial Completion: 01/2018
Final Report Submission: 10/2018

We have also received your submission dated February 28, 2019, containing the final reports for the following postmarketing commitments listed in the June 8, 2018, approval letter.

PMC 3426-1: Provide updated efficacy information from Study M14-032 to characterize longer-term efficacy of venetoclax monotherapy in patients with previously treated chronic lymphocytic leukemia (CLL). Data will include independent review committee-assessed and investigator-assessed duration of response for all 127 patients with CLL with a shared cut-off date of March 30, 2018. Include a written summary and associated derived and tabulated datasets.

Final Report Submission: 12/2018

PMC 3426-2: Provide updated efficacy information from Study M12-175 to characterize longer-term efficacy of venetoclax monotherapy in patients with previously treated chronic lymphocytic leukemia (CLL) and small lymphocyte lymphoma (SLL). Data will include independent review committee-assessed and investigator-assessed duration of response for all 67 patients with CLL or SLL treated at the 400 mg dose, with a shared cut-off date of March 30,
2018. Include a written summary and associated derived and tabulated datasets.

Final Report Submission: 02/2019

We refer to the agreement with the Applicant via e-mail communication on November 13, 2018 to fulfill PMC-3426-1 and PMC-3426-2 under one prior approval Labeling Supplement containing a single redlined label with target submission in February 2019.

We have reviewed your submissions and conclude that the above requirement and commitments were fulfilled.

This completes all of your postmarketing requirements and postmarketing commitments acknowledged in our April 11, 2016 and June 8, 2018 letters.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the Prescribing Information to:

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

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft guidance for industry Providing Regulatory Submissions in Electronic and Non-Electronic Format-Promotional Labeling and Advertising Materials for Human Prescription Drugs.  

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3 When final, this guidance will represent the FDA’s current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.
You must submit final promotional materials and Prescribing Information, accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at FDA.gov.\textsuperscript{4} Information and Instructions for completing the form can be found at FDA.gov.\textsuperscript{5} For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see FDA.gov.\textsuperscript{6}

**REPORTING REQUIREMENTS**

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

If you have any questions, call Beatrice Kallungal, Regulatory Project Manager, at 301-796-9304.

Sincerely,

\textit{\{See appended electronic signature page\}}

Ann Farrell, MD  
Director  
Division of Hematology Products  
Office of Hematology Oncology Products  
Center for Drug Evaluation and Research

**ENCLOSURE:**
- Content of Labeling

\textsuperscript{4} \url{http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf}  
\textsuperscript{5} \url{http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf}  
\textsuperscript{6} \url{http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.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/

ANN T FARRELL
07/25/2019 05:12:01 PM