NDA 208712

ACCELERATED APPROVAL

CTI BioPharma Corp
Attention: John Volpone
Sr. Vice President, Strategic Operations
3101 Western Avenue #800
Seattle, WA 98121

Dear Mr. Volpone:

Please refer to your new drug application (NDA) dated and received March 30, 2021, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Vonjo (pacritinib) capsules.

We acknowledge receipt of your major amendment dated November 24, 2021, which extended the goal date by three months.

This NDA provides for the treatment of adults with intermediate or high-risk primary or secondary (post-polycythemia vera or post-essential thrombocythemia) myelofibrosis with a platelet count below 50×10^9/L.

APPROVAL & LABELING

We have completed our review of this application, as amended. 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.

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 FDA.gov.[1] Content of labeling must be identical to the enclosed labeling text for the Prescribing Information and Patient Package Insert. Information on submitting SPL files

[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

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 via publicly available labeling repositories.

CARTON AND CONTAINER LABELING

Submit final printed carton and container labeling that are identical to the enclosed carton and container labeling, as soon as they are available, but no more than 30 days after they are printed. Please submit this 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 208712**." Approval of this submission by FDA is not required before the labeling is used.

DATING PERIOD

Based on the stability data submitted to date, the expiry dating period for Vonjo (pacritinib) capsules shall be 60 months from the date of manufacture when stored at 25°C.

ADVISORY COMMITTEE

Your application for Vonjo was not referred to an FDA advisory committee because the application did not raise efficacy or safety issues requiring input from outside experts.

ACCELERATED APPROVAL REQUIREMENTS

Products approved under the accelerated approval regulations, 21 CFR 314.510, require further adequate and well-controlled clinical trials to verify and describe clinical benefit. You are required to conduct such clinical trial with due diligence. If a postmarketing clinical trial fails to verify clinical benefit or is 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 February 28, 2022. This requirement, along with required completion dates, is listed below.

4154-1 Conduct a randomized, controlled trial to verify and describe the clinical benefit of Vonjo in adults with intermediate-1, intermediate-2 or high-risk myelofibrosis (MF) [as defined by the Dynamic International Prognostic

[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.

Scoring System (DIPSS), including primary MF, post-polycythemia vera and post-essential thrombocythemia MF] with platelet counts of less than 50 x 10^9/L. The co-primary efficacy endpoints are the proportion of patients achieving ≥35% spleen volume reduction as measured by magnetic resonance imaging or computed tomography imaging; and the proportion of patients achieving a ≥50% reduction in modified total symptom score (mTSS) [as defined by the Myeloproliferative Neoplasm Symptom Assessment Form (MPN-SAF TSS 2.0) that excludes the "tiredness" component] from baseline through 24 weeks of therapy. Long-term safety outcomes include the risks for bleeding, thrombosis, infections, major adverse cardiac events, secondary malignancies, and survival.

Final Protocol Submission:	06/2022
Trial Completion:	06/2025
Final Report Submission:	06/2026

Submit clinical protocols to your IND 078406 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.

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 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 a serious risk of a drug-drug interaction between Vonjo and strong and moderate CYP3A inhibitors.

Furthermore, the active post market risk identification and analysis system as available 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 studies:

4154-2 Conduct physiologically based pharmacokinetic (PBPK) modeling analyses using a revised and validated PBPK model to evaluate the effect of repeat doses of strong and moderate CYP3A inhibitors and inducers on the pharmacokinetics of Vonjo 200 mg twice daily dosed to steady state, to support appropriate dosing recommendations. Use data from PMR 4154-3 to update the PBPK model. If the results from the PBPK analyses are inconclusive, conduct a pharmacokinetic study in adult healthy volunteers.

The timetable you submitted on February 28, 2022, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	02/2024
Final Protocol Submission:	04/2024
Study Completion:	08/2024
Final Report Submission:	10/2024

FDA considers the term *final* to mean that the applicant has submitted a protocol, the FDA review team has sent comments to the applicant, and the protocol has been revised as needed to meet the goal of the study or clinical trial.[3]

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 1) an effect of Vonjo on drugs that are substrates of multiple CYPs and transporters; and 2) reduced Vonjo exposures in subjects with hepatic impairment.

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

[3] See the guidance for Industry *Postmarketing Studies and Clinical Trials—Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (October 2019).* https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

4154-3 Conduct a pharmacokinetic drug-drug interaction trial to evaluate the effect of Vonjo 200 twice daily dosed to steady state on a cocktail of substrates for CYP3A4, CYP1A2, CYP2C19, BCRP, and P-gp transporters in adult healthy volunteers. Characterize the pharmacokinetics of Vonjo 200 mg BID on Day 1 and at steady state in this trial.

The timetable you submitted on February 28, 2022, states that you will conduct this trial according to the following schedule:

Draft Protocol Submission:	07/2022
Final Protocol Submission:	09/2022
Trial Completion:	08/2023
Final Report Submission:	12/2023

4154-4 Conduct a dedicated pharmacokinetic trial to evaluate the impact of hepatic impairment on the pharmacokinetics of Vonjo following administration of Vonjo 200 mg twice daily dosed to steady state in adults with moderate (Child-Pugh B) and severe hepatic impairment (Child-Pugh C) compared to matched healthy adult subjects.

The timetable you submitted on February 28, 2022, states that you will conduct this trial according to the following schedule:

Draft Protocol Submission:	07/2022
Final Protocol Submission:	09/2022
Trial Completion:	08/2023
Final Report Submission:	12/2023

FDA considers the term *final* to mean that the applicant has submitted a protocol, the FDA review team has sent comments to the applicant, and the protocol has been revised as needed to meet the goal of the study or clinical trial.[4]

Submit clinical protocol(s) to your IND 078406 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).**

[4] See the guidance for Industry *Postmarketing Studies and Clinical Trials—Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (October 2019).* https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

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

Under 21 CFR 314.55, 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 314.55, 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, Medication Guide, and Patient Package Insert (as applicable).

For information about submitting promotional materials, see the final guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format-Promotional Labeling and Advertising Materials for Human Prescription Drugs*.[5]

[5] For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/media/128163/download.

REPORTING REQUIREMENTS

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

POST APPROVAL FEEDBACK MEETING

New molecular entities 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 Caden Brennen, Regulatory Project Manager, at 301-796-6591 or at Caden.Brennen@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}
Hylton V. Joffe, M.D., M.M.Sc.
Director
Office of Cardiology, Hematology,
Endocrinology, and Nephrology
Center for Drug Evaluation and Research

ENCLOSURES:

- Content of Labeling
  - Prescribing Information
  - Patient Package Insert
- Carton and Container Labeling

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/

HYLTON V JOFFE
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