NDA 218213

NDA APPROVAL

Bristol-Myers Squibb Company
Attention: He Wang, Ph.D., RAC
Director, Global Regulatory Strategy and Policy
PO Box 5326
Princeton, NJ 08543

Dear Dr. Wang:

Please refer to your new drug application (NDA) dated and received March 27, 2023, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Augtyro (repotrectinib) capsules.

This NDA provides for the use of Augtyro (repotrectinib) capsules for the treatment of adult patients with locally advanced or metastatic ROS1-positive non-small cell lung cancer (NSCLC).

APPROVAL & LABELING

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.

WAIVER OF ½ PAGE LENGTH REQUIREMENT FOR HIGHLIGHTS

We are waiving the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of Prescribing Information. This waiver applies to all future supplements containing revised labeling unless we notify you otherwise.

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) as well as annual reportable changes not included in the enclosed labeling. Information on submitting SPL files using

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

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 carton and container labeling submitted on November 2, 2023, 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 *SPL Standard for Content of Labeling Technical Qs & As.* For administrative purposes, designate this submission "**Final Printed Carton and Container Labeling for approved NDA 218213**." 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 Augtyro (repotrectinib) shall be 36 months from the date of manufacture when stored at 20° to 25°C (68° to 77°F); excursions permitted between 15°–30°C (59°–86°F).

ADVISORY COMMITTEE

Your application for Augtyro was not referred to an FDA advisory committee because the application did not raise significant safety or efficacy issues that were unexpected for a drug of this class; the application did not raise significant public health questions on the role of the drug in the diagnosis, cure, mitigation, treatment, or prevention of a disease; and outside expertise was not necessary, and there were no controversial issues that would benefit from advisory committee discussion.

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 deferring submission of your pediatric study until March 2027, because this product is ready for approval for use in adults and the pediatric study has not been completed.

[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.

Your deferred pediatric study required under section 505B(a) of the Federal Food, Drug, and Cosmetic Act (FDCA) is a required postmarketing study. The status of this postmarketing study must be reported annually according to 21 CFR 314.81 and section 505B(a)(4)(C) of the FDCA. This required study is listed below.

4547-1 Conduct a clinical study (ongoing CARE study) to assess the appropriate dose of repotrectinib and to assess safety, tolerability, pharmacokinetics (PK), and efficacy of repotrectinib, in pediatric and young adult patients with advanced or metastatic solid tumors, primary central nervous system (CNS) tumors, or anaplastic large cell lymphoma (ALCL), with ALK, ROS1, or NTRK alterations. At least 3 patients 6 years of age or younger will be evaluated in the dose-finding phase.

Study Completion: 09/2026
Final Report Submission: 03/2027

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]

Submit the protocol(s) to your IND (b) (4) with a cross-reference letter to this NDA. Reports of this required pediatric postmarketing study must be submitted as an NDA or as a supplement to your approved NDA with the proposed labeling changes you believe are warranted based on the data derived from this study. 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 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 ocular toxicity and to identify unexpected serious risks of drug toxicity in patients with moderate or severe hepatic impairment; drug toxicity when repotrectinib is used concomitantly with strong CYP3A and P-gp inhibitors or dual P-gp and moderate CYP3A inhibitors; and increased serious adverse reactions when

[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.

repotrectinib is used concomitantly with MATE2-K, P-gp, OATP1B1, and BCRP substrates.

Furthermore, the active postmarket risk identification and analysis system as available 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 this signal of serious risk and to identify the unexpected serious risks.

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

4547-2 Conduct a prospective study to evaluate risk factors, manifestations, and outcomes associated with the signal of serious ocular toxicity with repotrectinib in patients with ROS1 positive NSCLC or other solid tumors. The study will include collection, grading, classification, and analysis of data on ocular toxicity in patients exposed to repotrectinib. Evaluate a sufficient number of patients treated at the recommended phase 2 dose (160 mg daily for the first 14 days, then increase to 160 mg twice daily) who receive repotrectinib as a single agent. Include baseline ophthalmologic exam with vision test, scheduled follow-up, and symptom-driven ocular assessments to include visual acuity assessments, ophthalmologic evaluations including slit lamp examination, and elicitation for visual symptoms.

The timetable you submitted on November 9, 2023, states that you will conduct this trial according to the following schedule:

Draft Protocol Submission:	02/2024
Final Protocol Submission:	05/2024
Study Completion:	02/2028
Final Report Submission:	08/2028

4547-3 Conduct a clinical pharmacokinetic trial in non-cancer hepatically impaired subjects to evaluate the effect of moderate and severe hepatic impairment on the single dose pharmacokinetics and safety of repotrectinib. Design and conduct the trial in accordance with the FDA Guidance for Industry entitled “Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling.” In addition, conduct a physiologically based pharmacokinetic (PBPK) modeling study, using data from the clinical trial, to evaluate the effect of hepatic impairment on multiple dose pharmacokinetics of repotrectinib, to determine an appropriate dosage of repotrectinib, and to identify and assess the potential serious risk of increased drug toxicity, in patients with moderate and severe hepatic impairment. Design and conduct the

modeling study in accordance with FDA Guidance for industry entitled "Physiologically Based Pharmacokinetic Analyses - Format and Content."

The timetable you submitted on November 9, 2023, states that you will conduct this trial according to the following schedule:

Draft Protocol Submission:	01/2024
Final Protocol Submission:	04/2024
Trial Completion:	10/2025
Final Report Submission:	06/2026

4547-4 Conduct a clinical pharmacokinetic trial to evaluate the effects of multiple doses of a specific strong CYP3A inhibitor and a specific P-gp inhibitor, respectively on the single-dose pharmacokinetics and safety of repotrectinib. Design and conduct the trial in accordance with the FDA Guidance for Industry entitled "Clinical Drug Interaction Studies — Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions." In addition, conduct a physiologically based pharmacokinetic (PBPK) modeling study, using data from the clinical trial, to evaluate the effects of a specific strong CYP3A inhibitor, a specific moderate CYP3A inhibitor, a specific P-gp inhibitor, and a dual P-gp and moderate CYP3A inhibitor, respectively on the multiple-dose pharmacokinetics of repotrectinib to identify and assess the potential serious risk of increased drug toxicity and to identify appropriate dosage recommendations for repotrectinib when used concomitantly with these inhibitors. Design and conduct the modeling study in accordance with FDA Guidance for industry entitled, "In Vitro Metabolism- and Transporter-Mediated Drug-Drug Interaction Studies" and "Physiologically Based Pharmacokinetic Analyses - Format and Content."

The timetable you submitted on November 9, 2023, states that you will conduct this trial according to the following schedule:

Draft Protocol Submission:	04/2024
Final Protocol Submission:	07/2024
Trial Completion:	10/2025
Final Report Submission:	06/2026

4547-5 Conduct a clinical pharmacokinetic trial to evaluate the effect of multiple doses of repotrectinib on the single dose pharmacokinetics of a substrate of MATE2-K, P-gp, OATP1B1, and BCRP, respectively to identify and assess the potential serious risk of increased drug toxicity with repotrectinib. Design and conduct the trial in accordance with the FDA

Guidance for Industry entitled "Clinical Drug Interaction Studies — Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions".

The timetable you submitted on November 9, 2023, states that you will conduct this trial according to the following schedule:

Trial Completion:	10/2028
Final Report Submission:	07/2029

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 130465 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(a)(1) 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(a)(1) 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:

[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.

4547-6 Complete a clinical study (TRIDENT-1) to further characterize the clinical benefit of repotrectinib for the treatment of adult patients with ROS1 fusion-positive metastatic NSCLC by providing a more precise estimation of the BICR-assessed overall response rate (ORR) and duration of response (DOR) in the 71 ROS1 TKI-naive patients with ROS1-positive NSCLC and 56 ROS1 TKI-pretreated patients with measurable disease enrolled on TRIDENT-1. Provide updated DOR results for the 56 responders in the efficacy evaluable population of 71 ROS1 TKI-naïve patients (primary analysis population) and for the 21 responders in the efficacy evaluable population of 56 ROS1 TKI-pretreated patients, after all responders have been followed for at least 18 months from the date of initial response.

The timetable you submitted on November 9, 2023, states that you will conduct this study according to the following schedule:

Study Completion:	10/2023
Final Report Submission:	07/2024

Submit the datasets with the final report submission.

4547-7 Conduct a physiologically based pharmacokinetic (PBPK) modeling study, using data from the clinical trials with specific CYP3A and P-gp inhibitors, to evaluate the effect of multiple doses of a moderate CYP3A inducer on the multiple-dose pharmacokinetics of repotrectinib to assess the magnitude of decreased drug exposure with appropriate dosage recommendations of repotrectinib when concomitantly used with moderate CYP3A inducers. Design and conduct the modeling study in accordance with FDA Guidance for industry entitled, “In Vitro Metabolism- and Transporter-Mediated Drug-Drug Interaction Studies” and “Physiologically Based Pharmacokinetic Analyses - Format and Content.”

The timetable you submitted on November 9, 2023, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	06/2024
Final Protocol Submission:	09/2024
Study Completion:	10/2025
Final Report Submission:	06/2026

4547-8 Conduct a clinical pharmacokinetic trial with repeat doses of repotrectinib on the single dose pharmacokinetics of a substrate of CYP2B6, CYP2C9, and CYP2C19, respectively to assess the magnitude of decreased drug exposure. Design and conduct the trial in accordance with the FDA Guidance for Industry entitled “Clinical Drug Interaction Studies —

Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions". In addition, conduct a physiologically based pharmacokinetic (PBPK) modeling study to predict impact of repotrectinib on the magnitude of decreased drug exposure of CYP2C8 substrates. Design and conduct the modeling study in accordance with FDA Guidance for industry entitled, "In Vitro Metabolism- and Transporter-Mediated Drug-Drug Interaction Studies" and "Physiologically Based Pharmacokinetic Analyses - Format and Content."

The timetable you submitted on November 9, 2023, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	01/2024
Final Protocol Submission:	04/2024
Trial Completion:	10/2028
Final Report Submission:	07/2029

4547-9 Commitment to support the availability of an in vitro diagnostic device, through an appropriate analytical and clinical validation study using clinical trial data that demonstrates the device is essential to the safe and effective use of repotrectinib for the treatment of adult patients with locally advanced or metastatic ROS1 positive non-small cell lung cancer.

The timetable you submitted on November 9, 2023, states that you will conduct this study according to the following schedule:

Final Report Submission: 12/2024

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 130465 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/subjects 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

You may request advisory comments on proposed introductory advertising and promotional labeling. 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]

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the Prescribing Information, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. Form FDA 2253 is available at FDA.gov.[6] Information and Instructions for completing the form can be found at FDA.gov.[7]

METHODS VALIDATION

We have not completed validation of the regulatory methods. However, we expect your continued cooperation to resolve any problems that may be identified.

REPORTING REQUIREMENTS

We remind you that you must comply with 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.

COMPENDIAL STANDARDS

A drug with a name recognized in the official United States Pharmacopeia or official National Formulary (USP-NF) generally must comply with the compendial standards for strength, quality, and purity, unless the difference in strength, quality, or purity is plainly stated on its label (see FD&C Act § 501(b), 21 USC 351(b)). FDA typically cannot share application-specific information contained in submitted regulatory filings with third parties, which includes USP-NF. To help ensure that a drug continues to comply with compendial standards, application holders may work directly with USP-NF to revise

[5] For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/media/128163/download.
[6] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf
[7] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf

official USP monographs. More information on the USP-NF is available on USP's website[8].

If you have any questions, call Opeyemi Udoka, DPT, CSM, Senior Regulatory Health Project Manager, at 240-402-4558.

Sincerely,

{See appended electronic signature page}

Paul Kluetz, M.D.
Deputy Director
Oncology Center of Excellence
Supervisory Associate Director (acting)
Office of Oncologic Diseases
Center for Drug Evaluation and Research

ENCLOSURE(S):

- Content of Labeling
  - Prescribing Information
  - Patient Package Insert

[8] https://www.uspnf.com/

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/

PAUL G KLUETZ
11/15/2023 11:58:01 AM