NDA 214958

NDA APPROVAL

Bristol-Myers Squibb Company
Attention: Shih-Yi Kim, PharmD
Senior Director, Regulatory Affairs
86 Morris Avenue
Summit, NJ 07901

Dear Dr. Kim:

Please refer to your new drug application (NDA) dated and received September 10, 2021 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Sotyktu (deucravacitinib) tablets, for oral use.

This NDA provides for the use of Sotyktu (deucravacitinib) tablets for the treatment of adults with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy.

APPROVAL & LABELING

We have completed our review of this application. It is 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) 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 via publicly available labeling repositories.

[1] http://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.

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 these labeling electronically according to the guidance for industry *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications*. For administrative purposes, designate this submission "**Final Printed Carton and Container Labeling for approved NDA 214958** 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 Sotyktu (deucravacitinib) tablets shall be 36 months from the date of manufacture when stored at 20°C to 25°C (68°F to 77°F), excursions permitted between 15°C and 30°C (59°F and 86°F) [see USP Controlled Room Temperature].

ADVISORY COMMITTEE

Your application for Sotyktu 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.

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 ages <4 years because necessary studies are impossible or highly impracticable due to insufficient numbers of pediatric patients with moderate to severe psoriasis who are candidates for systemic therapy and phototherapy in this age group.

We are deferring submission of your pediatric study for ages 4 to 18 years for this application because pediatric studies should be delayed until additional safety or effectiveness data have been collected and because adult studies are completed and ready for approval.

Your deferred pediatric studies required by section 505B(a) of the FDCA are required postmarketing studies. The status of these postmarketing studies must be reported

annually according to 21 CFR 314.81 and section 505B(a)(4)(C) of FDCA. These required studies are listed below.

4336-1 **PREA PMR 1**

Conduct a randomized, controlled trial to evaluate the safety, efficacy, and pharmacokinetics of deucravacitinib in the adolescent population (12 years to less than 18 years) with moderate to severe psoriasis who are candidates for systemic therapy or phototherapy. Evaluate at least 300 subjects exposed to deucravacitinib at the highest proposed dosage for a minimum of 52 weeks.

Final Protocol Submission: May 2023
Study Completion: June 2029
Final Report Submission: December 2029

4336-2 **PREA PMR 2**

Conduct a trial to evaluate the safety, efficacy, and pharmacokinetics of deucravacitinib in pediatric subjects 4 years to less than 12 years of age with moderate to severe psoriasis who are candidates for systemic therapy or phototherapy. Evaluate at least 150 subjects exposed to deucravacitinib at the highest proposed dosage for a minimum of 52 weeks.

The trial should not be initiated until results from PMR 4336-1 for pediatric subjects 12 to less than 18 years of age are reviewed by the Agency. Based on the review, the Agency will determine the type of data and the trial design that would be required to evaluate the pediatric population age 4 years to less than 12 years.

Final Protocol Submission: September 2030
Study Completion: September 2035
Final Report Submission: March 2036

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 131993 with a cross-reference letter to this NDA. Reports of these required pediatric postmarketing studies 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 these studies. When submitting the reports, please clearly mark your submission "**SUBMISSION OF REQUIRED**

[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.

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 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 identify an unexpected serious risk for adverse pregnancy, fetal, or infant outcomes from the use of Sotyktu (deucravacitinib) tablets during pregnancy.

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.

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

4336-3 **Pregnancy PMR 1**

Conduct a prospective, registry based observational exposure cohort study that compares the maternal, fetal, and infant outcomes of women exposed to deucravacitinib during pregnancy to an unexposed control population. The registry should be designed to detect and record major and minor congenital malformations, spontaneous abortions, stillbirths, elective terminations, small for gestational age, preterm birth, and any other adverse pregnancy outcomes. These outcomes will be assessed throughout pregnancy. Infant outcomes, including effects on postnatal growth and development, will be assessed through at least the first year of life.

For more information, see the May 2019 FDA draft guidance for Industry *Post approval Pregnancy Safety Studies* available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/postapprovalpregnancy-safetystudies-guidance-industry

The timetable you submitted on August 31, 2022, states that you will conduct this study according to the following schedule:

Draft Protocol Submission: February 2023
Final Protocol Submission: October 2023
Interim Report: July 2026
Study Completion: July 2028
Final Report Submission: February 2029

4336-4 **Pregnancy PMR 2**

Conduct a pregnancy study that uses a different design from the pregnancy registry (for example a retrospective cohort study using claims or electronic medical record data or a case control study) to assess major congenital malformations, spontaneous abortions, stillbirths, and small for gestational age and preterm birth in women exposed to deucravacitinib during pregnancy compared to an unexposed control population.

The timetable you submitted on August 31, 2022, states that you will conduct this study according to the following schedule:

Draft Protocol Submission: February 2023
Final Protocol Submission: October 2023
Study Completion: July 2028
Final Report Submission: February 2029

4336-5 **Lactation PMR**

Perform a lactation study (milk only) in lactating women who have received deucravacitinib to assess concentrations of deucravacitinib in breastmilk using a validated assay.

The timetable you submitted on August 31, 2022, states that you will conduct this study according to the following schedule:

Draft Protocol Submission: February 2023
Final Protocol Submission: September 2023
Study Completion: March 2025
Final Report Submission: September 2025

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]

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 major adverse cardiovascular events (MACE), thrombosis, opportunistic infections and malignancy.

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

[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.

4336-6 **Long-Term Safety PMR**

Conduct a randomized, active-controlled clinical trial to evaluate the long-term safety of deucravacitinib in patients with moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy. The trial should be of sufficient size and duration to characterize safety events of interest, including cardiovascular adverse events, opportunistic infections, and malignancy.

The timetable you submitted on September 8, 2022, states that you will conduct the trial according to the following schedule:

Draft Protocol Submission: February 2023
Final Protocol Submission: May 2023
Trial Completion: June 2028
Final Report Submission: December 2028

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.[5]

Submit clinical protocol(s) to your IND 131993 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).**

Submission of the protocol(s) for required postmarketing observational studies to your IND is for purposes of administrative tracking only. These studies do not constitute clinical investigations pursuant to 21 CFR 312.3(b) and therefore are not subject to the IND requirements under 21 CFR part 312.

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

[5] 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.

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

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.*[6]

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.[7] Information and Instructions for completing the form can be found at FDA.gov.[8]

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.

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

If you have any questions, call Jennifer Harmon, Regulatory Project Manager, at 240-402-4880.

Sincerely,

{See appended electronic signature page}

Julie Beitz, MD
Director
Office of Immunology and Inflammation
Office of New Drugs
Center for Drug Evaluation and Research

ENCLOSURE(S):

- Content of Labeling
  - Prescribing Information
  - Medication Guide
- 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/

JULIE G BEITZ
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