NDA 219616

ACCELERATED APPROVAL

Verastem, Inc.
Attention: Bao Le
Regulatory Affairs Scientist
117 Kendrick Street, Suite 500
Needham, MA 02494

Dear Bao Le:

Please refer to your new drug application (NDA) dated October 31, 2024, received October 31, 2024, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for AVMAPKI™ FAKZYNJA™ CO-PACK (avutometinib capsules and defactinib tablets).

This NDA provides for the use of AVMAPKI™ FAKZYNJA™ CO-PACK (avutometinib [capsules]; defactinib [tablets]) for the treatment of adult patients with *KRAS*-mutated recurrent low-grade serous ovarian cancer (LGSOC) who have received prior systemic therapy.

APPROVAL & LABELING

We have completed our review of this application. It is approved under accelerated approval pursuant to section 506(c) of the Federal Food, Drug, and Cosmetic Act (FDCA) and 21 CFR 314.510, 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 accelerated approval statutory provisions and 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 text for the Patient Package Insert). Information on submitting SPL files using eLIST may be found in the guidance for industry

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

SPLStandard 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 these 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 219616**." Approval of this submission by the FDA is not required before the labeling is used.

DATING PERIOD

Based on the stability data submitted to date, the expiry dating period for AVMAPKI™ FAKZYNJA™ CO-PACK [avutometinib (capsules); defactinib (tablets)] shall be the earliest expiration date of either of the component products used in the co-package, with a maximum of 30 months from the date of manufacture when stored refrigerated at 2-8ºC (36-46ºF) in their original bottles.

ADVISORY COMMITTEE

Your application for AVMAPKI™ FAKZYNJA™ CO-PACK was not referred to an FDA advisory committee because outside expertise was not necessary; there were no controversial issues that would benefit from advisory committee discussion.

ACCELERATED APPROVAL REQUIREMENTS

Pursuant to section 506(c) of the FDCA and 21 CFR 314.510 you are required to conduct further adequate and well-controlled clinical trials intended to verify and describe clinical benefit. You are required to conduct such clinical trials with due diligence. If required postmarketing clinical trials fail to verify clinical benefit or are not conducted with due diligence, including with respect to the conditions set forth below, we may withdraw this approval. We remind you of your postmarketing requirement specified in your submission dated May 2, 2025. This requirement is listed below.

[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.

4835-1 Complete the ongoing trial titled, “RAMP 301: A Phase 3, Randomized, Open-Label Study of Combination Therapy with Avutometinib plus Defactinib Versus Investigator’s Choice of Treatment in Patients with Recurrent Low-Grade Serous Ovarian Cancer (LGSOC)”, and provide the progression-free survival and the final overall survival analyses, intended to describe and verify the clinical benefit of avutometinib and defactinib in combination in adult patients with recurrent, *KRAS*-mutated low grade serous ovarian cancer. Include central *KRAS* testing results for all patients.

The timetable you submitted on May 2, 2025, states that you will conduct this trial according to the following schedule:

Trial Completion:	12/2027
Final Report Submission:	06/2028

Submit clinical protocols to your IND 151352 for this product. The 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.

You must submit status reports of the progress of each clinical trial required under section 506(c) (listed above) to the NDA 180 days after the date of approval of this NDA and approximately every 180 days thereafter (see section 506B(a)(2) of the FDCA) (hereinafter “180-day reports”).

You are required to submit two 180-day reports per year for each open study or clinical trial required under section 506(c). The initial report will be a standalone submission and the subsequent report will be combined with your application’s annual status report (ASR) required under section 506B(a)(1) of the FDCA and 21 CFR 314.81(b)(2). The standalone 180-day report will be due 180 days after the date of approval (with a 60-day grace period). Submit the subsequent 180-day report with your application’s ASR. Submit both of these 180-day reports each year until the final report for the corresponding study or clinical trial is submitted[3].

Your 180-day reports must include the information listed in 21 CFR 314.81(b)(2)(vii)(a). Ensure that enrollment status updates include enrollment status for the *KRAS* mutation-positive cohort specifically. The FDA recommends that you use FORM FDA 3989, *PMR/PMC Annual Status Report for Drugs and Biologics,* to submit your 180-day reports.[4]

[3] You are required to submit information related to your confirmatory trial as part of your annual reporting requirement under section 506B(a)(1) until the FDA notifies you, in writing, that the FDA concurs that the study requirement has been fulfilled or that the study either is no longer feasible or would no longer provide useful information.

[4] FORM FDA 3989, along with instructions for completing this form, is available on the FDA Forms web page at https://www.fda.gov/about-fda/reports-manuals-forms/forms.

180-day reports must be clearly designated "**NDA 219616 180-Day AA PMR Progress Report**."

The FDA will consider the submission of your application's ASR under section 506B(a)(1) and 21 CFR 314.81(b)(2), in addition to the submission of reports 180 days after the date of approval each year (subject to a 60-day grace period), to satisfy the periodic reporting requirement under section 506B(a)(2).

Submit final reports to this NDA as a supplemental application. For administrative purposes, the cover page of 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.

We are waiving the pediatric study requirement for ages 0 to <2 years of age because necessary studies are impossible or highly impracticable. This is because the number of pediatric patients is so small in the recurrent treatment setting for the tumor types to be evaluated.

We are deferring submission of your pediatric studies for ages 2 to <17 years of age for this application because this product is ready for approval for use in adults and the pediatric studies have not been completed.

Your deferred pediatric studies required by section 505B(a) of the Federal Food, Drug, and Cosmetic Act 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 the FDCA. These required studies are listed below.

4835-2 Conduct a molecularly targeted pediatric investigation of avutometinib as a single agent and in combination with defactinib to evaluate preliminary efficacy**,** and characterize dosing, pharmacokinetics/pharmacodynamics and preliminary safety in a sufficient number of pediatric patients ages 2 to <17 years of age with relapsed or refractory unresectable or metastatic RAS/MAPK pathway-driven pediatric cancers.

Draft Protocol Submission:	11/2027
Final Protocol Submission:	04/2028
Study Completion:	03/2034
Final Report Submission:	09/2034

The 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 the protocol(s) to your IND 151352, 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 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 the FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if the 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 of serious adverse reactions when defactinib is taken concomitantly with moderate CYP3A4 inhibitors.

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 this serious risk.

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

4835-3 Conduct a clinical pharmacokinetic trial or conduct a physiologically-based PK (PBPK) modeling assessing the effect of multiple doses of a moderate CYP3A4 inhibitor on the single dose PK of defactinib and its active metabolite M4 to evaluate the potential serious risk of increased serious adverse reactions and identify a proposed dosage of defactinib in patients taking defactinib concomitant with moderate CYP3A4 inhibitors. Design

[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.

and conduct the trial or PBPK analysis in accordance with the ICH Harmonized Guidance entitled “M12 Drug Interaction Studies.”

The timetable you submitted on May 2, 2025, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	10/2025
Final Protocol Submission:	01/2026
Study/Trial Completion:	06/2026
Final Report Submission:	12/2026

The 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.[6]

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 cardiotoxicity; to identify an unexpected serious risk of serious adverse reactions with use of avutometinib and defactinib in patients with moderate and severe hepatic impairment; to identify an unexpected serious risk of serious adverse reactions when avutometinib is used in patients with severe renal impairment; to identify an unexpected serious risk of serious adverse reactions when defactinib is used concomitantly with CYP2C9, BCRP, and P-gp inhibitors; to identify an unexpected serious risk of serious adverse reactions when defactinib is used concomitantly with CYP3A4, CYP2C9, P-gp, BCPR, OATP1B1, and OATP1B3 substrates; and to identify an unexpected serious risk of serious adverse reactions when defactinib is used concomitantly with MATE2-K substrates.

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

4835-4 Conduct a clinical trial to characterize and evaluate the potential serious risk of cardiomyopathy related to the use of the combination of avutometinib and defactinib in adult patients with recurrent, low grade serous ovarian cancer. The trial should include serial monitoring of blood pressure, left ventricular ejection fraction (LVEF), high-sensitivity troponin, and N-terminal brain natriuretic peptide. The cardiac assessments must include a sufficient number of patients, over a sufficient time period, to systematically determine the incidence of LVEF reductions ≥10% from baseline. A randomized trial design is preferred given the unknown population risk. Include an analysis of the risk, and monitoring and mitigation measures.

[6] 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.

The timetable you submitted on May 2, 2025, states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	07/2025
Trial Completion:	10/2028
Final Report Submission:	04/2029

4835-5 Conduct a clinical trial enrolling an adequate number of patients with moderate hepatic impairment (i.e., at least 15 evaluable patients), using the NCI-ODWG criteria, to evaluate the potential serious risk of increased serious adverse reactions in patients with moderate hepatic impairment who receive the treatment of avutometinib in combination with defactinib. The evaluation should be 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.”

The timetable you submitted on May 2, 2025, states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	07/2025
Trial Completion:	10/2028
Final Report Submission:	04/2029

4835-6 Conduct a clinical pharmacokinetic trial assessing the effect of severe hepatic impairment on the pharmacokinetics of defactinib and its active metabolite M4 to evaluate the potential serious risk of increased serious adverse reactions in patients with severe hepatic impairment who receive treatment with defactinib. 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.”

The timetable you submitted on May 2, 2025, states that you will conduct this trial according to the following schedule:

Draft Protocol Submission:	09/2025
Final Protocol Submission:	12/2025
Trial Completion:	12/2027
Final Report Submission:	06/2028

4835-7 Conduct a clinical pharmacokinetic trial assessing the effect of severe hepatic impairment, using the NCI-ODWG criteria, on the pharmacokinetics of avutometinib to evaluate the potential serious risk of increased serious adverse reactions in patients with severe hepatic impairment who receive treatment with avutometinib. 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."

The timetable you submitted on May 2, 2025, states that you will conduct this trial according to the following schedule:

Draft Protocol Submission:	10/2025
Final Protocol Submission:	01/2026
Trial Completion:	01/2028
Final Report Submission:	07/2028

4835-8 Conduct a clinical pharmacokinetic trial assessing the effect of severe renal impairment, as estimated by the Cockcroft-Gault equation, on the pharmacokinetics of avutometinib to evaluate the potential serious risk of increased serious adverse reactions in patients with severe renal impairment who receive treatment with avutometinib. Design and conduct the trial in accordance with the FDA Guidance for Industry entitled "Pharmacokinetics in Patients with Impaired Renal Function: Study Design, Data Analysis, and Impact on Dosing and Labeling."

The timetable you submitted on May 2, 2025, states that you will conduct this trial according to the following schedule:

Draft Protocol Submission:	11/2025
Final Protocol Submission:	02/2026
Trial Completion:	02/2028
Final Report Submission:	08/2028

4835-9 Complete the clinical trial, Study VS-6063-108, assessing the effect of multiple doses of a BCRP inhibitor, a P-gp Inhibitor, and a moderate CYP2C9 inhibitor on the pharmacokinetics of defactinib and its active metabolite M4 to evaluate the potential serious risk of increased serious adverse reactions from increased levels of defactinib when defactinib is used concomitantly with a BCRP inhibitor, a P-gp Inhibitor, and a moderate CYP2C9 inhibitor, respectively. Design and conduct the trial in accordance with ICH Harmonized Guidance entitled "M12 Drug Interaction Studies."

The timetable you submitted on May 2, 2025, states that you will conduct this trial according to the following schedule:

Final Report Submission:	06/2025

4835-10 Conduct a clinical pharmacokinetic trial assessing the effects of multiple doses of defactinib on single dose pharmacokinetics of substrates of

CYP3A4, CYP2C9, P-gp, BCPR, OATP1B1, and OATP1B3 to evaluate the potential serious risks of increased serious adverse reactions from elevated levels of CYP3A4, CYP2C9, P-gp, BCPR, OATP1B1, and OATP1B3 substrates, respectively, when they are used concomitantly with defactinib. Design and conduct the trial in accordance with the ICH Harmonized Guidance entitled "M12 Drug Interaction Studies."

The timetable you submitted on May 2, 2025, states that you will conduct this trial according to the following schedule:

Draft Protocol Submission:	09/2025
Final Protocol Submission:	11/2025
Trial Completion:	03/2026
Final Report Submission:	09/2026

4835-11 Conduct a clinical pharmacokinetic trial assessing the effect of multiple doses of defactinib on single dose pharmacokinetics of a substrate of MATE2-K to evaluate the potential serious risk of increased serious adverse reactions from elevated levels of MATE2-K substrates when used concomitantly with defactinib. Alternatively, evaluate the change in exposure of a well-characterized endogenous substrate of MATE2-K to assess the impact of defactinib on the inhibition of MATE2-K. Design and conduct the trial in accordance with the ICH Harmonized Guidance entitled "M12 Drug Interaction Studies."

The timetable you submitted on May 2, 2025, states that you will conduct this trial according to the following schedule:

Draft Protocol Submission:	09/2025
Final Protocol Submission:	11/2025
Trial Completion:	03/2026
Final Report Submission:	09/2026

The 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.[7]

Submit clinical protocol(s) to your IND 151352 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**

[7] 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.

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 the 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.

The 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:

4835-12 Conduct an in vitro study to assess the potential for CYP1A2, CYP2B6, CYP2C8, CYP2C19, and CYP2D6 inhibitors to impact the pharmacokinetics of defactinib metabolite M4 to determine for the need of additional clinical drug-drug interaction studies between M4 and inhibitors of these CYP enzymes. Design and conduct the in vitro study in accordance with the ICH Harmonized Guidance entitled “M12 Drug Interaction Studies.”

The timetable you submitted on May 2, 2025, states that you will conduct this study according to the following schedule:

Study Completion: 09/2025
Final Report Submission: 11/2025

4835-13 Conduct an appropriate analytical and clinical validation study to support the development of a diagnostic device that is essential to the safe and effective use of the combination of avutometinib and defactinib in *KRAS*-mutated, recurrent low grade serous ovarian cancer.

The timetable you submitted on May 2, 2025, states that you will conduct this study according to the following schedule:

Final Report Submission: 05/2026

Submit clinical protocols to your IND 151352 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

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 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*.[8]

REPORTING REQUIREMENTS

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

[8] https://www.fda.gov/media/128163/download.

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)). The 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 official USP monographs. More information on the USP-NF is available on USP's website[9].

If you have any questions, email Benjamin Chukwurah at benjamin.chukwurah@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Richard Pazdur, MD
Office Director
Office of Oncologic Diseases
Center for Drug Evaluation and Research

ENCLOSURE:

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

[9] 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/

RICHARD PAZDUR
05/08/2025 10:09:03 AM