



NDA 218197

NDA APPROVAL

AstraZeneca Pharmaceuticals LP
Attention: Bhargavi Pandit, BPharm, MS, RAC
Director, Regulatory Affairs
1 MedImmune Way
Gaithersburg, MD 20878

Dear Bhargavi Pandit:

Please refer to your new drug application (NDA) dated and received March 28, 2023, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Truqap (capiwasertib) tablets.

This NDA provides for the use of Truqap (capiwasertib) tablets in combination with fulvestrant, for the treatment of adult patients with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, locally advanced or metastatic breast cancer with one or more PIK3CA/AKT1/PTEN-alteration as detected by an FDA-approved test following progression on at least one endocrine-based regimen in the metastatic setting or recurrence on or within 12 months of completing adjuvant therapy.

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.

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 eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*.²

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>.

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 *SPL Standard for Content of Labeling Technical Qs & As*. For administrative purposes, designate this submission “**Final Printed Carton and Container Labeling for approved NDA 218197.**” 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 Truqap (capivasertib) tablets shall be 36 months from the date of manufacture when stored at controlled room temperature: 20°– 25° (68°– 77°F). Excursions permitted to 15°C to 30°C (59°F to 86°F).

ADVISORY COMMITTEE

Your application for capivasertib was not referred to an FDA advisory committee because the clinical trial design is acceptable and outside expertise was not necessary. 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 waiving the pediatric study requirement for ages birth to less than 6 months of age because necessary studies are impossible or highly impracticable. This is due to the rarity of patients in this age group.

We are deferring submission of your pediatric studies for ages 6 months to <17 years for this application due to the fact that 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.

- 4548-1 Conduct a clinical study of capivasertib in combination with one or more active drugs to evaluate dosing, pharmacokinetics, safety, and preliminary efficacy of capivasertib in combination with other active agents in a sufficient number of pediatric patients 2 years of age and older with relapsed or refractory cancer harboring AKT pathway gene alterations.

Draft Protocol Submission : 02/2024
Final Protocol Submission: 07/2024
Study Completion: 01/2028
Final Report Submission: 07/2028

- 4548-2 Develop an age appropriate pediatric formulation of capivasertib and conduct a clinical study of this pediatric formulation in combination with one or more active drugs to evaluate dosing, pharmacokinetics, safety, and preliminary efficacy in a sufficient number of pediatric patients 6 months of age and older with relapsed or refractory cancer harboring AKT pathway gene alterations.

Draft Protocol Submission: 07/2025
Final Protocol Submission: 12/2025
Study Completion: 12/2028
Final Report Submission: 06/2029

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.³

Submit the protocols to your IND 118046, 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 Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require holders of approved drug and biological product applications to conduct

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>.

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 of increased serious adverse reactions in patients with moderate hepatic impairment, and when capivasertib is used concomitantly with OATP1B and/or 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 identify these unexpected serious risks.

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

- 4548-3 Conduct a hepatic impairment clinical trial to evaluate the pharmacokinetics and safety of capivasertib in patients with moderate hepatic impairment to assess for potential increase in capivasertib exposure and serious risk of increased adverse reactions. Design and conduct the trial in accordance with the FDA Guidance for Industry titled: "Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling."

The timetable you submitted on November 15, 2023, states that you will conduct this trial according to the following schedule:

Draft Protocol Submission:	09/2024
Final Protocol Submission:	12/2024
Trial Completion:	12/2026
Final Report Submission:	06/2027

- 4548-4 Conduct a clinical drug interaction study to evaluate the effect of repeat doses of capivasertib on the pharmacokinetics and safety of transporter substrates of BCRP, OATP1B1 and OATP1B3, to assess for potential serious risk associated with the magnitude of exposure change and inform appropriate drug interaction management strategy for coadministration of capivasertib with these transporter substrates. This trial should be designed and conducted 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 15, 2023, states that you will conduct this trial according to the following schedule:

Draft Protocol Submission:	09/2024
Final Protocol Submission:	12/2024
Trial Completion:	12/2026
Final Report Submission:	06/2027

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.⁴

Submit clinical protocol(s) to your IND 118046 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:

- 4548-5 Conduct an integrated analysis of data from clinical trials and other data sources such as post-marketing reports, real-world evidence and other

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>.

sources to further characterize the safety and efficacy of capivasertib in combination with fulvestrant in patients of underrepresented racial and ethnic minority groups with hormone receptor positive, HER2 negative metastatic breast cancer with one or more PIK3CA/AKT1/PTEN-alterations. The analyses should include safety and efficacy outcome analyses by race and ethnicity.

The timetable you submitted on November 15, 2023, states that you will conduct this study according to the following schedule:

Draft Protocol Submission (Analysis Plan):	12/2024
Final Protocol Submission (Analysis Plan):	06/2025
Study Completion:	01/2029
Final Report Submission:	07/2029

- 4548-6 Complete the ongoing CAPItello-291 study entitled “A Phase III Double-blind Randomised Study Assessing the Efficacy and Safety of Capivasertib + Fulvestrant Versus Placebo + Fulvestrant as Treatment for Locally Advanced (Inoperable) or Metastatic Hormone Receptor Positive, Human Epidermal Growth Factor Receptor 2 Negative (HR+/HER2-) Breast Cancer Following Recurrence or Progression On or After Treatment with an Aromatase Inhibitor”, to obtain the final overall survival (OS) analysis, to further describe the clinical benefit of capivasertib.

The timetable you submitted on November 15, 2023, states that you will conduct this study according to the following schedule:

Trial Completion:	04/2025
Final Report Submission:	10/2025

Submit the datasets with the final report submission.

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 118046 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

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, contact 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 official USP monographs. More information on the USP-NF is available on USP's website⁸.

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>

⁸ <https://www.uspnf.com/>

If you have any questions, contact Rashida Redd, Regulatory Project Manager, at 301-796-5489 or Rashida.Redd@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Paul G. Kluetz, MD
Supervisory Associate Director (acting)
Office of Oncologic Diseases
Center for Drug Evaluation and Research

ENCLOSURE(S):

- 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/

PAUL G KLUETZ
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