NDA 214801

CORRECTED APPROVAL

Taiho Oncology, Inc.
Attention: Angela Hu, Ph.D.
Senior Director, Regulatory Affairs
101 Carnegie Center, Suite 10
Princeton, NJ 08540

Dear Dr. Hu:

Please refer to your new drug application (NDA) dated and received January 31, 2022, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Lytgobi (futibatinib), tablets.

We also refer to our approval letter dated September 30, 2022, which contained the following error: the 'Initial U.S. Approval' date in the Highlights section of the Prescribing Information (PI) was incomplete. The date was listed as 'XXXX', and should have been "2022".

This corrected action letter incorporates the correction of the error. The effective action date will remain September 30, 2022, the date of the original letter.

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 text for the Patient Package Insert). 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

We acknowledge your July 8, 2022, submission containing final printed 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 214801**." 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 Lytgobi (futibatinib) 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 to 86°F).

Results of ongoing stability should be submitted throughout the dating period in your annual report, as they become available.

ADVISORY COMMITTEE

Your application for Lytgobi (futibatinib) 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

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 trials with due diligence. If postmarketing clinical trials fail to verify clinical benefit or are 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 September 29, 2022. This requirement, along with required completion dates, is listed below.

4345-1 Conduct a randomized clinical trial comparing dosages of futibatinib 16 mg and 20 mg once daily to verify and describe the clinical benefit of futibatinib in patients with advanced or metastatic cholangiocarcinoma harboring an FGFR2 gene fusion or other rearrangement. The overall response rate and duration of response should be assessed by a blinded independent review. The study should also evaluate other clinical outcomes that denote clinical benefit, such as patient reported outcomes. This study should enroll a minimum of 120 patients and all responders should have a minimum of 6 months from the date of initial response (or until disease progression, whichever comes first). Ensure that racial and ethnic minorities are adequately represented in the trial population, at a minimum, proportional to the prevalence of FGFR2 alterations in these subgroups in the US population.

Draft Protocol Submission:	10/2022
Final Protocol Submission:	12/2022
Trial Completion:	02/2027
Final Report Submission:	10/2027

Submit clinical protocols to your IND 121062 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 subjects 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.

We are waiving the pediatric studies requirement for ages less than one year because necessary studies are impossible or highly impracticable. This is because the incidence of tumors that harbor FGFR alterations in this age group is extremely low.

We are deferring submission of your pediatric studies for ages 1 to 17 years for this application because pediatric studies should be delayed until additional safety or effectiveness data have been collected.

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 the FDCA. These required studies are listed below.

4345-2 Conduct a clinical trial of futibatinib in pediatric patients to further characterize the safety, pharmacokinetics, and anti-tumor activity of futibatinib for pediatric patients 1 year of age or older with advanced or metastatic solid tumors harboring FGFR gene alterations, deferred until the results of the non-clinical in vitro and in vivo efficacy studies in human cell line-derived mouse xenografts of rhabdomyosarcoma, submitted to and reviewed by FDA, have been found to support a clinical investigation in the pediatric population. In addition, include the results of Arm O of the eSMART trial, which will also be used to support the decision for the pediatric investigation.

Draft Protocol Submission:	03/2023
Final Protocol Submission:	06/2023
Trial Completion:	12/2029
Final Report Submission:	12/2030

With the final report(s) submission, submit the datasets from the study(ies).

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 121062 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.

[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 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 assess a known serious risk of ophthalmologic toxicity, and rates of Grade ≥3 adverse reactions including Grade ≥3 hyperphosphatemia, and serious adverse reactions, in patients receiving futibatinib.

Additionally, 505(k)(1) of the FDCA will not be sufficient to identify an unexpected serious risk of increased futibatinib exposure in the presence of moderate or severe hepatic impairment, and when futibatinib is used concomitantly with P-gp 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 these serious risk(s).

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess the known serious risks and identify the unexpected serious risks.

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

4345-3 Conduct a clinical trial of futibatinib 20 mg once daily in a sufficient number of patients with cholangiocarcinoma harboring a FGFR2 fusion or other rearrangement, that incorporates prospectively specified, scheduled ophthalmologic assessments that include optic coherence tomography (OCT), for all patients (symptomatic or asymptomatic), at baseline and during treatment with futibatinib, to further characterize the incidence and severity of futibatinib-related ocular adverse events.

The timetable you submitted on September 29, 2022, states that you will conduct this trial according to the following schedule:

Draft Protocol Submission:	10/2022
Final Protocol Submission:	12/2022
Trial Completion:	02/2027
Final Report Submission:	10/2027

With the final report submission, submit the datasets from the study.

4345-4 Conduct a randomized study that compares the recommended dosage of 20 mg daily to a lower dosage (e.g., 16 mg) to provide a comparative analysis of dose- and exposure-response relationships for safety including further characterization of the rates of Grade ≥3 adverse reactions, Grade ≥3 hyperphosphatemia, serious adverse reactions, and dose reductions, interruptions, and discontinuations due to adverse reactions. Incorporate systematically assessed patient-reported outcome assessments to evaluate tolerability. Core outcomes should include patient-reported symptomatic adverse event data, overall side effect bother, physical function, and role function. The study should also provide a comparative analysis of dose- and exposure-response relationships for efficacy, including overall response rate and duration of response.

The timetable you submitted on September 29, 2022, states that you will conduct this trial according to the following schedule:

Draft Protocol Submission:	10/2022
Final Protocol Submission:	12/2022
Trial Completion:	02/2027
Final Report Submission:	10/2027

With the final report submission, submit the datasets from the study.

4345-5 Conduct a clinical pharmacokinetic trial to determine an appropriate dosage of futibatinib to minimize toxicity in subjects with moderate and severe hepatic impairment. 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 September 29, 2022, states that you will conduct this trial according to the following schedule:

Final Report Submission:	10/2022

4345-6 Conduct a drug interaction study to evaluate the effect of a P-gp inhibitor on the pharmacokinetics of futibatinib to assess the magnitude of increased drug exposure and determine appropriate dosage recommendations when futibatinib is administered concomitantly with P-gp inhibitors. Design and conduct the study in accordance with the FDA Guidance for Industry titled *Clinical Drug Interaction Studies — Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions*.

The timetable you submitted on September 29, 2022, states that you will conduct this trial according to the following schedule:

Draft Protocol Submission:	12/2022
Final Protocol Submission:	03/2023
Study Completion:	03/2024
Final Report Submission:	09/2024

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.[4]

Submit clinical protocol(s) to your IND 121062 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 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.

[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.

POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

4345-7 Establish, through the use of clinical trial data, an in-vitro diagnostic device that is essential to the safe and effective use of futibatinib for patients with advanced unresectable or metastatic cholangiocarcinoma harboring an FGFR2 gene fusions or other alterations.

The timetable you submitted on September 29, 2022, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	10/2022
Final Protocol Submission:	12/2022
Trial Completion:	02/2027
Final Report Submission:	10/2027

4345-8 Conduct exploratory analyses aimed at identifying potential mechanisms of primary and acquired resistance to futibatinib using longitudinal ctDNA samples collected at baseline and at the end of treatment or time of progression from patients treated with futibatinib in TAS-120-101 and in the randomized clinical trial to verify and describe the clinical benefit of futibatinib in patients with advanced or metastatic cholangiocarcinoma harboring an FGFR2 gene fusion or other rearrangement. Include a discussion of the results in the context of the available published literature.

The timetable you submitted on September 29, 2022, states that you will conduct this study according to the following schedule:

Study Completion:	02/2027
Final Report Submission:	10/2027

4345-9 Conduct Study TAS-120-301 (FOENIX-CCA3), investigating futibatinib for the first line treatment of patients with locally advanced or metastatic cholangiocarcinoma harboring an FGFR2 fusion or other rearrangement, and submit the final progression-free survival results.

The timetable you submitted on September 29, 2022, states that you will conduct this study according to the following schedule:

Study Completion:	12/2026
Final Report Submission:	06/2027

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 121062 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, call the Regulatory Project Manager for this application.

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[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

If you have any questions, call your Regulatory Health Project Manager, Kristin Jarrell, Pharm.D., at 301-796-0137.

Sincerely,

{See appended electronic signature page}

Paul G Kluetz, M.D.
Acting Supervisory Associate Director
Office of Oncologic Diseases
Division of Oncology 3
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/

PAUL G KLUETZ
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