

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

214801Orig1s000

OTHER REVIEW(S)

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	July 22, 2022
Requesting Office or Division:	Division of Oncology 3 (DO3)
Application Type and Number:	NDA 214801
Product Name and Strength:	Lytgobi (futibatinib) tablets, 4 mg
Applicant/Sponsor Name:	Taiho Oncology, Inc.
OSE RCM #:	2021-1536-1
DMEPA 2 Safety Evaluator:	Sarah Thomas, PharmD
DMEPA 2 Team Leader:	Ashleigh Lowery, PharmD, BCCCP

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container labels and carton labeling received on July 8, 2022 for Lytgobi. The Division of Oncology 3 (DO3) requested that we review the revised container labels and carton labeling for Lytgobi (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.^a

2 CONCLUSION

The Applicant implemented most of our recommendations and provided an explanation for the following two exceptions:

- Container Labels Comment #3: We are concerned the numbering on the blister cells (for example, (b) (4) may cause confusion to the end-user. We recommend removing the numbers from the blister cells and replacing the numbers on the blister cells with the strength per tablet of "4 mg". Alternatively, you may provide justification for the use of the current numbering system on the blister cells for our consideration.

^a Thomas, S. Label and Labeling Review for Lytgobi (NDA 214801). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2022 APRIL 21. RCM No.: 2021-1536.

Taiho's Response: Taiho removed the numbers from the blister cells but didn't replace the numbers on the blister cells with the strength per tablet of "4 mg" because the print will be too small to be readable.

We find their alternative proposal acceptable.

- Carton Labeling Comment #7: We recommend separating the year, month, and day in the proposed expiration date format with hyphens or forward slashes (e.g., 2023-SEP-30 or 2023/SEP/30).

Taiho's Response: Taiho was not able to make this change as the

(b) (4)

(b) (4)

We find their explanation reasonable.

In addition, Taiho revised the storage instructions on the carton labeling to the following:

"(b) (4) in order to align with the stability data and recommended storage condition. We find this edit acceptable from a medication error perspective and note the storage instructions align with that provided in the proposed prescribing information (PI).

We reviewed the revised container labels and carton labeling and find the labels and labeling acceptable, and we have no additional recommendations at this time.

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/s/

SARAH E THOMAS
07/21/2022 05:38:26 PM

ASHLEIGH V LOWERY
07/22/2022 03:17:43 PM

MEMORANDUM

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Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
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**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy**

PATIENT LABELING REVIEW

Date: July 22, 2022

To: Kristin Jarrell, PharmD
Regulatory Project Manager
Division of Oncology III (DO3)

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Shawna Hutchins, MPH, BSN, RN
Senior Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Rebecca Falter, PharmD
Regulator Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: Review of Patient Labeling: Patient Package Insert (PPI)

Drug Name (established name): LYTGobi (futibatinib)

Dosage Form and Route: tablets, for oral use

Application Type/Number: NDA 214801

Applicant: Taiho Oncology, Inc.

1 INTRODUCTION

On January 31, 2022, Taiho Oncology, Inc., submitted for the Agency's review the final unit of their rolling submission (Reviewable Unit #5), for their original New Drug Application (NDA) for LYTGOBI (futibatinib) tablets, for oral use, for the proposed indication of treatment of patients with previously treated locally advanced or metastatic cholangiocarcinoma harboring FGFR2 gene rearrangements, including gene fusions. Reviewable Unit #1 of this NDA was submitted on August 2, 2021.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Oncology III (DO3) on July 14, 2022 and February 11, 2022, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI), for LYTGOBI (futibatinib) tablets, for oral use.

2 MATERIAL REVIEWED

- Draft LYTGOBI (futibatinib) PPI received on January 31, 2022 and received by DMPP on July 14, 2022 and OPDP on July 13, 2022.
- Draft LYTGOBI (futibatinib) Prescribing Information (PI) received on January 31, 2022, revised by the Review Division throughout the review cycle, and received by DMPP on July 14, 2022 and OPDP on July 13, 2022.
- Approved PEMAZYRE (pemigatinib) comparator labeling dated February 23, 2021.

3 REVIEW METHODS

In our collaborative review of the PPI we:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the PPI is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the PPI is consistent with the approved comparator labeling where applicable

4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.

- Our collaborative review of the PPI is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI.

Please let us know if you have any questions.

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REBECCA A FALTER
07/22/2022 07:12:54 AM

LASHAWN M GRIFFITHS
07/22/2022 07:34:48 AM

Clinical Inspection Summary

Date	5/23/2022
From	Michele Fedowitz, MD Karen Bleich, MD Kassa Ayalew, MD, MPH Good Clinical Practice Assessment Branch (GCPAB) Division of Clinical Compliance Evaluation (DCCE) Office of Scientific Investigations (OSI)
To	Shruti Gandhi, Clinical Reviewer Sandra Casek MD, Clinical Team Leader Kristin Jarrell, Regulatory Project Manager Division of Oncology 3 (DO3)
NDA #	214801
Applicant	Taiho Oncology, Inc.
Drug	Futibatinib
NME (Yes/No)	Yes
Therapeutic Classification	Kinase inhibitor
Proposed Indication	Treatment of patients with previously treated locally advanced or metastatic cholangiocarcinoma harboring FGFR2 gene rearrangements, including gene fusions
Consultation Request Date	02/18/2022
Summary Goal Date	06/30/2022
Action Goal Date	08/30/2022
PDUFA Date	09/30/2022

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Clinical data from Study TAS 120-101-b (NCT02052778) were submitted to the Agency in support of a New Drug Application (NDA 214801) for futibatinib (also known as TAS-120) for the treatment of patients with previously treated locally advanced or metastatic cholangiocarcinoma harboring FGFR2 gene rearrangements, including gene fusions.

Two clinical investigators, Drs Goyal (Site 001) and Mahipal (Site 021) were selected for clinical inspections, with Dr Goyal's site as the top enrolling site and Dr. Mahipal's site having a high treatment effect. The CRO Syneos Health which was responsible for multiple regulatory obligations regarding trial conduct was inspected because the application is for a new molecular entity.

The conducted inspections of Drs. Goyal, Mahipal, and the CRO did not find significant concerns regarding the management of the clinical trial, GCP compliance, or the data generated.

II. BACKGROUND

Taiho Oncology, Inc., seeks approval of futibatinib for the proposed indication. In support of the NDA, the Applicant submitted clinical data from Study TAS 120-101-b, an open-label, nonrandomized study with two phases. Phase 1 of the study was a 2-part dose-escalation/dose-expansion study to determine the maximum tolerated dose (MTD) for phase 2 and to evaluate the efficacy and safety of the MTD in subjects with advanced solid tumors harboring FGF/FGFR mutations who had progressed on prior standard therapy or for whom standard therapy did not exist. Phase 2 portion was a single arm study to evaluate the efficacy of futibatinib in intrahepatic cholangiocarcinoma (iCCA) patients with an FGFR2 gene fusion or other FGFR2 rearrangements. The focus of the inspections was the evaluation of the Phase 2 portion of the study.

The primary efficacy endpoint of Phase 2 is objective response rate (ORR) based on independent central radiology review. The key secondary endpoint was the duration of response (DOR) and overall survival (OS).

Screening was to take place within 28 days prior to Day 1 of Cycle 1. At Screening, archived or fresh tumor tissue biopsy samples were to be tested for FGFR2 gene fusions or other FGFR2 rearrangements prior to enrolling patients to the Phase 2 part of the study. Futibatinib was to be administered at a starting dose of 20 mg daily (five 4-mg tablets), continuously on a 21-day treatment cycle until disease progression, unacceptable toxicity, or any other discontinuation criterion was met. Tumor assessments/imaging were to be obtained for all patients with solid tumors at screening and at the end of every 2 cycles through cycle 4. Following Cycle 4, assessments were to be obtained every 3 cycles ($\pm$ 7 days) or as clinically indicated, until documented progression. If the patient discontinued for reasons other than radiological disease progression, tumor assessments were to be continued every 3 cycles as well. At the end of treatment, imaging was to be performed if the prior scan was performed $\geq$ 9 weeks prior to the discontinuation of futibatinib. If a patient had a response, confirmation was to be obtained through tumor assessments/scans 4 to 6 weeks after the first documentation of response. Patients would then return to their original schedule of assessments (i.e., every 2 cycles [or every 3 cycles after Cycle 4]).

As of the data cut off, 103 subjects were enrolled Phase 2 of the study was conducted at 48 sites including Australia, Canada, Germany, Spain, France, Great Britain, Hong Kong, Italy, Japan, Korea, the Netherlands, Taiwan, and the United States. The data cutoff for the current submission was October 1, 2020.

III. RESULTS

1. Dr. Lipka Goyal, (Site 001)

55 Fruit Street

Boston, MA 02114

Inspection Dates: March 10-18, 2022

This investigator was inspected as an onsite surveillance inspection for Study TPU-TAS-120-101-b. This was the first FDA inspection for this investigator. The study was initiated as a Phase 1 study under Dr. Sequist of the Mass General Hospital (MGH) Thoracic Cancers group. On 3/28/2016, it was transitioned to the Gastrointestinal Cancers group and Dr. Goyal took over as the principal investigator for the study; prior to that, she was a subinvestigator on the study.

At the time of data cutoff, there were 12 subjects screened and 8 subjects enrolled and treated at the site. All enrolled subjects discontinued the study due to progressive disease. Three subjects died before the data cut-off (Subjects (b) (6)), one died after the data cutoff date (Subject (b) (6)) on (b) (6). The remaining 4 subjects were still alive in follow up (Subjects (b) (6)) at the time of the inspection.

The source documents for eligibility were reviewed for all 12 screened subjects. All 8 enrolled subjects' records were reviewed. The reviewed records included both internal and external medical records such as radiology reports, scans, laboratory reports, and progress notes, study specific documents such as questionnaires and study visit forms, serious adverse event forms, informed consent, and eligibility criteria. Study related documents were also reviewed including Form FDA 1572s, financial disclosures, delegation of authority log, screening and enrollment log, training records, monitoring records, IRB communications/approvals, protocol deviations, investigational test article accountability records, site protocol with amendments, radiographic scan submission documents, survival follow up and electronic case report forms.

Imaging records were reviewed for all eight subjects enrolled. All protocol required scans were taken and sent to the imaging Contract Research Organization (CRO) (b) (4). All scans taken at the study site had matching scans and dates within the data listings (up to the data cutoff date of 10/30/20) for the central reader. The tumor assessment data for all subjects were reviewed. The central imaging source data from the Sponsor's imaging vendor, (b) (4) was obtained through the Sponsor and submitted to the NDA. At (b) (4) each independent radiologist reviews imaging studies of assigned subjects and records the tumor measurements and assessments in the electronic Imaging Case Record Forms (eICRFs) for each timepoint. The eICRF source data was compared to the data listings and there were no discrepancies.

The source records for survival follow-up and subject disposition used to generate the key secondary endpoint of OS were reviewed and compared with the data listings. There were no discrepancies.

2. Dr. Mahipal (Site 021)

Mayo Clinic – Rochester
200 First St SW
Rochester, MN 55905

Inspection dates: March 14 – 22, 2022.

This investigator was inspected as an onsite surveillance inspection for Study TPU-TAS-120-101-b. This was the second FDA inspection for this investigator. The previous inspection of this CI concluded on May 21, 2019, at H. Lee Moffit Cancer Center & Research Institute in Tampa, Florida, and had a regulatory classification of No Action Indicated.

At the time of data cutoff, there were 3 subjects screened and 3 subjects enrolled and treated at the site. At the time of data cutoff, Subject (b) (6) was still on treatment, Subject (b) (6) had been discontinued due to investigator decision and Subject (b) (6) was discontinued due to disease progression and died on (b) (6). There were no discrepancies between the source records and the data listings. Since data cutoff, Subject (b) (6) died on (b) (6).

The source documents for all 3 enrolled subjects were reviewed. The reviewed records included subject medical histories, subject visits, laboratory assessments, vital signs, physical examinations findings, informed consent, eligibility, treatment, subject pill diaries, study assessments, concomitant medications, protocol deviations, and adverse events. Study related documents were also reviewed including Form FDA 1572s, investigator's agreement, financial disclosures, delegation of authority log, screening and enrollment log, training records, monitoring records, institutional review board (IRB) approvals and communications, sponsor correspondence, investigational test article accountability records, site protocol with amendments, and survival follow up.

Imaging records were reviewed for all three subjects enrolled. All protocol required scans were taken and sent to the imaging Contract Research Organization (CRO) (b) (4). All scans were performed according to the protocol and had matching and dates within the data listings for the central reader. The tumor assessment data for all subjects were reviewed. The central imaging source data from the Sponsor's imaging vendor, (b) (4) was obtained through the Sponsor and submitted to the NDA. At (b) (4) each independent radiologist reviews imaging studies of assigned subjects and records the tumor measurements and assessments in the electronic Imaging Case Record Forms (eICRFs) for each timepoint. The eICRF source data was compared to the data listings and there were no discrepancies.

The source records for survival follow-up and subject disposition used to generate the key secondary endpoint of OS, were reviewed and compared with the data listings. There were no discrepancies.

There was an unreported protocol deviation for Subject (b) (6) who missed an end of treatment ocular exam. The exam was missed due to an emergency room visit for covid symptoms and related findings. The protocol deviation was filed during the inspection.

3. Syneos Health

1030 Sync St.
Morrisville, NC 27560

Inspection dates: March 28 – April 1, 2022

The clinical research organization (CRO), Syneos Health, was inspected as a surveillance inspection for Study TAS120-101b. In 2017, INC Research and inVentiv Health merged and in 2018 the company was rebranded as Syneos Health. They were inspected in 2021 as INC Research with a regulatory classification of no action indicated.

Syneos was the responsible for the following tasks: site start-up, grant management, clinical monitoring, biostatistics, and the data safety monitoring board (DSMB). Syneos had some tasks that were shared with the sponsor, Taiho. These included: project feasibility and site ID, project management, data management, investigator meeting, SAE reporting, trial master file and quality assurance.

Records reviewed included organizational charts; standard operating procedures (SOPs) for TMF management, site management and monitoring activities, project quality and risk management; the safety reporting plan; the clinical monitoring plan; the project management and communication plan; and trial documents such as IRB approvals and continuing reviews FDA 1572s, financial disclosures, and monitoring documents (monitoring visit reports and visit log), focusing on sites 100, 152, 200, 252, and 400.

There was no evidence of inadequate monitoring or oversight of the trial. There were no regulatory violations regarding Syneos' responsibilities for the trial.

None of the inspected sites appear to have had investigators with significant non-compliance. No significant issues were noted during monitoring visits and protocol deviations were addressed, documented, and reported adequately. In general, monitors performed study visits as per the SOPs and monitoring plan.

{See appended electronic signature page}

Michele Fedowitz, M.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

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Kassa Ayalew, M.D., M.P.H
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Review Division /Division Director/"Lola Fashoyin-Aje, MD
Review Division /Project Manager/ Kristin Jarrell
Review Division/Cross Discipline Team Lead/Sandra Casek, MD
Review Division/Clinical Reviewer/ Shruti Gandhi, MD
OSI/Office Director/Dave Burrow
OSI/ GCP Program Analysts/ Joseph Peacock/Yolanda Patague
OSI/Database PM/Dana Walters

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/s/

MICHELE B FEDOWITZ
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KAREN B BLEICH
05/23/2022 02:29:55 PM

KASSA AYALEW
05/23/2022 05:51:09 PM

Medical Officer's Review of NDA 214801
Ophthalmology Consult Review

Consult Request Date: February 9, 2022
Submission Dates: Rolling submission
Review completed: February 22, 2022

Name: Lytgobi (futibatinib) (TAS-120 film-coated tablets)

Pharmacologic Class: Selective kinase inhibitor of fibroblast growth factor receptor (FGFR) 1-4, that blocks FGF/FGFR signaling by its covalent mechanism of binding

Applicant: Taiho, Oncology

Requested: Review of NDA.

The proposed labeling is including in Section 6 “dry eye”; however, several related terms were not grouped (keratitis, punctate keratitis, lacrimation increased, etc.) Section 11.2.4.3.1.2. Retinal Disorders

The summary of safety in Module 2 offers a comprehensive analyses across cohorts (but also appears not grouping terms of similar pathophysiology) 4.2. Ophthalmologic Examination Findings

1. Is the characterization of the [ophthalmologic events](#) adequate?
2. Do you agree with the Applicant’s analysis of ophthalmologic events?
3. Regarding the Sponsor’s [proposed revision of labeling](#) –information and recommendations for dose modifications (Sections 2, 5, and 6) adequate?

Reviewer's Comments: *Comments/recommendations in this review are limited to areas of ophthalmologic interest.*

Submitted: NDA Rolling Submission. TAS-120-101 Clinical Study Report. Phase 2, Uncontrolled study.

Proposed Indication: Futibatinib is indicated for the treatment of patients with previously treated locally advanced or metastatic cholangiocarcinoma harboring FGFR2 gene rearrangements, including gene fusions.

Proposed Dosing Regimen: The recommended dosage of futibatinib is 20 mg (five 4-mg tablets) taken orally once daily (QD) until disease progression or unacceptable toxicity occurs. Take futibatinib with or without food at approximately the same time each day.

Development Plan:

As of 23 January 2021, a total of 715 subjects (526 patients with cancer, 10 subjects in the hepatic impairment study, and 179 healthy subjects in clinical pharmacology studies) have been exposed to futibatinib across 7 completed and 10 ongoing studies at various stages of development. The futibatinib clinical development program focuses on tumors driven by genomic alterations of FGFR signaling and overcoming FGFR-mediated resistance mechanisms.

Futibatinib as a single agent has been studied in a Phase 1 study in Japanese patients with advanced solid tumors (Study 10059010) to evaluate safety, pharmacokinetics (PK), and preliminary activity of futibatinib. In parallel, the Phase 1/2 study TAS-120-101 was evaluating the safety, tolerability, PK, pharmacodynamic, and antitumor activity of futibatinib in patients with advanced solid tumors with FGF/FGFR-related abnormalities. Based on observed PK/pharmacodynamic and preliminary efficacy results, a dose of 20 mg QD futibatinib was selected as the recommended Phase 2 dose (RP2D) for further futibatinib monotherapy studies in the global development program.

The Phase 2 portion of Study TAS-120-101, focusing on iCCA patients with FGFR2 gene rearrangements, was initiated. The Phase 2 portion was an open-label, global, single-arm Phase 2 study to assess the single-agent efficacy of futibatinib in patients with locally advanced or metastatic iCCA with FGFR2 gene rearrangements (including fusions), and disease progression after ≥ 1 line of systemic therapy. The primary endpoint was ORR as assessed by an independent review committee (IRC) according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1.

Ongoing or Planned Studies

For patients with CCA, there is an ongoing confirmatory, randomized-controlled, open-label Phase 3 study (Study TAS-120-301) in previously untreated patients with advanced iCCA harboring FGFR2 rearrangement, including gene fusions (Figure 1). The first patient visit occurred in December 2020. The study is designed to randomize a total of 216 patients in a 1:1 ratio to receive either futibatinib or gemcitabine/cisplatin chemotherapy as current standard of care. The primary objective is to compare PFS between the 2 groups by independent central review. Randomization will be stratified by stage of disease (locally advanced vs metastatic), prior surgery of primary tumor (yes vs no), and region (Asia vs rest of world). Treatment with 20 mg QD futibatinib will continue until progressive disease, intolerable toxicity or any other discontinuation criteria are met. Patients in the control arm will receive gemcitabine-cisplatin chemotherapy for up to 8 cycles. Patients who discontinue gemcitabine-cisplatin due to documented disease progression are allowed to receive treatment with futibatinib (“crossover”).

Abbreviations: EOT=end of treatment; FGFR2=fibroblast growth factor receptor 2; iCCA=intrahepatic cholangiocarcinoma; ICR=independent central review; PD=progressive disease.

Ophthalmology Testing

Study Schedule for Phase 1 Expansion

	Screening Period (Within 28 Days Prior to First Dose)	Treatment Period (1 cycle=21 days)				Safety Follow-up		Survival Follow-up Period	Notes
		Cycle 1				Cycles ≥2			
		Day 1	4 (±1d)	8 (±3d)	15 (±3d)	Day 1 (±3d)	End of Tx (+0-7 days) 30 (±3) days After Last Dose		
Demographics/medical history	X								
Physical examination	X	X				X	X X		
Review of pre-existing signs and symptoms	X	X							
Ophthalmological examination	X					(X)	X X		At screening and 4-6 weeks after first dose; additional on-study evaluation as needed due to local requirements, physician judgment, and/or symptoms or signs of mineral deposits.

9.8. Ophthalmological Examination

Ophthalmological examination will be performed at the following time points:

- Screening within 28 days prior to TAS-120 administration on Day 1 of Cycle 1.
- 4-6 weeks after starting treatment with TAS-120
- Any other time due to local requirements, physician judgement and/or symptoms or signs of mineral deposits.
- At end of treatment (+0-7 days)
- 30-day safety follow-up visit.

The cornea and conjunctiva are readily visible tissues, and therefore, abnormalities of the cornea and conjunctiva can usually be recognized via external ocular examination and routine slit lamp biomicroscopy. The ophthalmologic examination will encompass the following:

- External ocular examination.
- Routine slit lamp biomicroscopy of anterior ocular structures (Fluorescein or rose Bengal or other dyes used to evaluate the ocular surface can be used according to institutional guidelines and local clinical practice).
- Retinal exam to evaluate the anterior and posterior chamber

The examination will be repeated, if clinically indicated, and the repeat examination will include the same testing employed at Screening in addition to any other clinically indicated examination.

Reviewer's Comments:

1. Fluorescein and Rose Bengal stain different structures. They cannot be used interchangeably.
2. The retina is not located in either the anterior or posterior chamber of the eye.
3. Optical coherence tomography should have been included to evaluate the retina.
4. The schedule of examinations is too infrequent to evaluation ophthalmic adverse events.
5. Based on the development of an ulcerative keratitis in a patient noted to have developed dry eyes, the ophthalmic monitoring was not adequate.
6. There was no visual function monitoring.

Case Report Forms:

Project Name: TAS120_101_P1_P2 **Form:** Ophthalmologic Exam **Generated On:** 07 Dec 2020 18:35:54

Was Ophthalmologic Exam Done: Yes No

Date of Examination (DD MMM YYYY)

Were the ophthalmologic exam findings all within normal range? Yes No
If, No, then provide abnormal description below.

External ocular examination:

External ocular examination right eye Check if not done

Description of abnormal findings right eye:

Were any of the findings clinically significant right eye? Yes No

External ocular examination left eye Check if not done

Description of abnormal findings left eye:

Were any of the findings clinically significant left eye? Yes No

Comment: If yes, record abnormal, clinically significant findings on Medical History eCRF (screening) or Adverse Event eCRF (after start of study treatment).

Routine Slit lamp biomicroscopy of anterior ocular structures:

Routine Slit lamp biomicroscopy of anterior ocular structures right eye Check if not done

Description of abnormal findings right eye:

Were any of the findings clinically significant right eye? Yes No

Routine Slit lamp biomicroscopy of anterior ocular structures left eye Check if not done

Description of abnormal findings left eye:

Were any of the findings clinically significant left eye? Yes No

Comment: If yes, record abnormal, clinically significant findings on Medical History eCRF (screening) or Adverse Event eCRF (after start of study treatment).

Was Corneal Staining Performed Right Eye? Yes No

NDA 214801 Lytgobi (futibatinib) Ophthalmology Consult

If yes, specify dye used right eye:

Was Corneal Staining Performed Left Eye?

Yes No

If yes, specify dye used left eye:

Corneal Stain Results (check all that apply):

Corneal Stain Results Right Eye

Check if not done

Stain depth right eye (check all that apply):

Epithelium Right Eye

Stroma Right Eye

Epithelium and Stroma Right Eye

Other Right Eye (If Other, specify Right Eye)

Corneal Stain Results Left Eye

Check if not done

Stain depth left eye (check all that apply):

Epithelium Left Eye

Stroma Left Eye

Epithelium and Stroma Left Eye

Other Left Eye (If Other, specify Left Eye)

Stain extent Right Eye (check all that apply):

Micropunctuate Right Eye

Macropunctuate Right Eye

Coalescent Right Eye

Other Right Eye (If Other, specify Right Eye)

Stain extent Left Eye (check all that apply):

Micropunctuate Left Eye

Macropunctuate Left Eye

Coalescent Left Eye

Other Left Eye (If Other, specify Left Eye)

Negative Staining Right Eye:

Negative Staining Right Eye

Yes No

If yes, specify Right Eye

Negative Staining Left Eye:

Negative Staining Left Eye

Yes No

If yes, specify Left Eye

Retinal Exam:

Retinal Exam Right Eye Anterior Chamber

Check if not done

NDA 214801

Lytgobi (futibatinib)

Ophthalmology Consult

Description of abnormal findings right eye:

Were any of the findings clinically significant right eye? Yes No

Retinal Exam Left Eye Anterior Chamber Check if not done

Description of abnormal findings left eye:

Were any of the findings clinically significant left eye? Yes No

Comment: If yes, record abnormal, clinically significant findings on Medical History eCRF (screening) or Adverse Event eCRF (after start of study treatment).

Retinal Exam Right Eye Posterior Chamber Check if not done

Description of abnormal findings right eye:

Were any of the findings clinically significant right eye? Yes No

Retinal Exam Left Eye Posterior Chamber Check if not done

Description of abnormal findings left eye:

Were any of the findings clinically significant left eye? Yes No

Check this box when all data entry has been completed for this page.

Reviewer's Comments: *The ophthalmic case report forms contains confusing questions for the investigator, raising questions about the interpretation of the reported results.*

- 1. The corneal epithelium is exterior to the stroma; it would not be possible to have stroma staining without epithelial staining.*
- 2. Negative corneal staining is no staining. How can it be specified?*
- 3. The retina is not in the anterior chamber of the eye. What was to be evaluated in the Retinal Exam Anterior Chamber?*
- 4. The retina is not in the posterior chamber of the eye. What was to be evaluated in the Retinal Exam Posterior Chamber?*
- 5. No measure of visual function was evaluated.*
- 6. Optical coherence tomography of the retina was not performed.*

Reported Ocular Results:

5.2.5.1. Retinal Disorders

Retinal disorders are an AESI for futibatinib and have also been reported for other FGFR inhibitors (Alekseev 2021; Goyal 2021; Morales-Barrera 2020). In the Phase 2 portion of TAS-120-101, AESIs in the category of retinal disorders were infrequent, with 8 patients (7.8%) experiencing retinal disorder, including 3 patients (2.9%) with subretinal fluid, 2 patients (1.9%) with chorioretinopathy, and one patient (1.0%) each with detachment of retinal pigment epithelium, maculopathy, and serous retinal detachment. There were no Grade ≥ 3 events of retinal disorders. Median time to onset of retinal disorder was 42 days. In the 3 patients (2.9%) with Grade 2 retinal disorders, all events resolved to Grade < 2 following dose reduction and/or interruption (TAS-120-101 Part 2 CSR Listing 16b.2.7.7). There were no SAEs reported, and no AEs led to discontinuation of futibatinib, although 3 patients (2.9%) experienced AEs leading to dose interruption and/or reduction (TAS-120-101 Part 2 CSR, Section 11.2.4.3.1.2).

Reviewer's Comments: *The retinal pigment detachments have described under multiple different terms. Subretinal fluid, chorioretinopathy, detachment of the retinal pigment epithelium, maculopathy and serious retinal detachment are all likely to be the same adverse event in different patients. The use of the Common Terminology Criteria for Adverse Events (CTCAE) grading system for ophthalmic events is misleading and should be actively discouraged.*

11.2.4.3.1.2. Retinal Disorders

Retinal disorders included the preferred terms retinal detachment, retinal disorder, chorioretinopathy, detachment of retinal pigment epithelium, detachment of macular retinal pigment epithelium, maculopathy, serous retinal detachment, macular oedema, retinal edema, retinopathy, retinal thickening, and subretinal fluid.

Eight (7.8%) patients had AESIs in the category of retinal disorders. Preferred terms were subretinal fluid (3 patients, 2.9%), chorioretinopathy (2 patients, 1.9%), detachment of retinal pigment epithelium, maculopathy, and serious retinal detachment (1 patient, 1.0% each). No Grade ≥ 3 events were reported (Table 18). The median time to onset of AEs of any grade for patients with retinal disorders was 42.0 days (range: 25.0 to 362.0 days; Table 14b.3.2.7.3). Seven (6.8%) patients who experienced AESI in this category experienced 1 event, and 1 patient (1.0%) had 2 or 3 events (Table 14b.3.2.9.2). Three patients (2.9%) had Grade 2 retinal disorders, all of which resolved to Grade < 2 . Three (2.9%) patients experienced retinal disorders leading to dose interruption and/or reduction, which includes 1 event of each of chorioretinopathy, detachment of retinal pigment epithelium, and subretinal fluid (Table 14b.3.2.5.5.1.1; Table 14b.3.2.5.5.2.1). No AESIs in this category were Grade 3, 4, or 5, were serious, or led to futibatinib withdrawal (Table 16; Listing 16b.2.7.3).

Reviewer's Comments: *The retinal pigment detachments have described under multiple different terms. Subretinal fluid, chorioretinopathy, detachment of the retinal pigment epithelium, maculopathy and serious retinal detachment are all likely to be the same adverse event in different patients. The use of the CTCAE grading system for ophthalmic events is misleading and should be actively discouraged.*

Table 18: Adverse Events of Special Interest in the Category Retinal Disorders

All Treated Subjects (N=103)					
AESI Category Preferred Term	Grade 1 (N %)	Grade 2 (N %)	Grade 3 (N %)	Grade 4/5 (N %)	Total (N %)
Retinal disorder	5 (5%)	3 (3%)	0	0	8 (8%)
Chorioretinopathy	1 (1%)	1 (1%)	0	0	2 (2%)
Detachment of retinal pigment epithelium	0	1 (1%)	0	0	1 (1%)
Maculopathy	1 (1%)	0	0	0	1 (1%)
Serious retinal detachment	1 (1%)	0	0	0	1 (1%)
Subretinal fluid	2 (2%)	1 (1%)	0	0	3 (3%)

Abbreviation: AESI = adverse event of special interest

Notes: Summary includes all events reported between first dose and 30 days after last dose of study drug. If a patient had 2 or more adverse events in the same system organ class (or with the same preferred term) with different Common Terminology Criteria for Adverse Event (CTCAE) grades, the event with the highest grade was used for that patient. Adverse events terms were coded using Medical Dictionary for Regulatory Activities (MedDRA) version 22.0. Adverse events were graded using CTCAE Version 4.03 except for hyperphosphatemia and blood phosphorus increased.

Reviewer's Comments: *The retinal pigment detachments have described under multiple different terms. Subretinal fluid, chorioretinopathy, detachment of the retinal pigment epithelium, maculopathy and serious retinal detachment are all likely to be the same adverse event in different patients.*

Table 22: Adverse Events Leading to Dose Reductions by System Organ Class, and Preferred Term

All Treated Patients (N=103)

Patients with any adverse events leading to dose reduction	60 (58.3)
Eye disorders	4 (3.9)
Chorioretinopathy	1 (1.0)
Detachment of retinal pigment epithelium	1 (1.0)
Subretinal fluid	1 (1.0)
Ulcerative keratitis	1 (1.0)

Table 11: Reported Adverse Events by Preferred Term (N=103)

Patients with any adverse event	103 (100.0)
Dry mouth	36 (35.0)
Dry skin	30 (29.1)
Dry eye	22 (21.4)

Reviewer's Comments: *There is greater than a 20% incidence of dry eye. This is a significant concern because this condition can lead to ulcerative keratitis.*

Reported Ophthalmic Examinations

	Screen Abnormal Finding		
	Normal	Abnormal, not clinically significant	Abnormal clinically significant
Anterior Ocular Structures Cycle 2			
Right Eye (n=73)			
Normal	43 (59%)	3 (4%)	0
Abnormal, not clinically significant	6 (8%)	18 (25%)	0
Abnormal, clinically significant	0	1 (1%)	2 (3%)
Left Eye (n=73)			
Normal	43 (59%)	2 (3%)	1 (1%)
Abnormal, not clinically significant	6 (8%)	18 (25%)	0
Abnormal, clinically significant	0	1 (1%)	2 (3%)
Anterior Ocular Structures End of Treatment			
Right Eye (n=16)			
Normal	11 (69%)	1 (6%)	0
Abnormal, not clinically significant	2 (12.5%)	0	0
Abnormal, clinically significant	2 (12.5%)	0	0
Left Eye (n=15)			
Normal	11 (73%)	1 (7%)	0
Abnormal, not clinically significant	1 (7%)	0	0
Abnormal, clinically significant	2 (13%)	0	0
Anterior Ocular Structures 30-Day Safety Follow-up			
Right Eye (n=14)			
Normal	9 (64%)	1 (7%)	1 (7%)
Abnormal, not clinically significant	2 (14%)	0	0
Abnormal, clinically significant	1 (7%)	0	0
Left Eye (n=14)			
Normal	9 (64%)		
Abnormal, not clinically significant	2 (14%)		
Abnormal, clinically significant	1 (7%)		
Anterior Retinal Exam Cycle 2			
Right Eye (n=47)			
Normal	41 (87%)	0	0
Abnormal, not clinically significant	1 (2%)	3 (6%)	1 (2%)
Abnormal, clinically significant	0	0	1 (2%)
Left Eye (n=49)			
Normal	42 (86%)	0	0
Abnormal, not clinically significant	1 (2%)	3 (6%)	1 (2%)
Abnormal, clinically significant	0	0	2 (4%)
Anterior Retinal Exam End of Treatment			
Right Eye (n=14)			
Normal	11 (79%)	0	0
Abnormal, not clinically significant	1 (7%)	0	1 (7%)
Abnormal, clinically significant	0	1 (7%)	0
Left Eye (n=14)			
Normal	11 (79%)	0	0
Abnormal, not clinically significant	1 (7%)	0	1 (7%)
Abnormal, clinically significant	0	0	1 (7%)
Anterior Retinal Exam 30-Day Safety Follow-up			
Right Eye (n=11)			
Normal	8 (73%)	0	0

Abnormal, not clinically significant	2 (18%)	0	0
Abnormal, clinically significant	0	1 (9%)	0
Left Eye (n=11)			
Normal	8 (73%)	0	0
Abnormal, not clinically significant	1 (9%)	1 (9%)	0
Abnormal, clinically significant	0	0	1 (9%)
External Ocular Exam Cycle 2			
Right Eye (n=58)			
Normal	43 (74%)	3 (5%)	0
Abnormal, not clinically significant	4 (7%)	5 (9%)	0
Abnormal, clinically significant	1 (2%)	1 (2%)	1 (2%)
Left Eye (n=58)			
Normal	43 (74%)	3 (5%)	0
Abnormal, not clinically significant	5 (9%)	5 (9%)	0
Abnormal, clinically significant	0	1 (2%)	1 (2%)
External Ocular Exam End of Treatment			
Right Eye (n=14)			
Normal	11 (79%)	1 (7%)	0
Abnormal, not clinically significant	0	1 (7%)	0
Abnormal, clinically significant	1 (7%)	0	0
Left Eye (n=14)			
Normal	11 (79%)	1 (7%)	0
Abnormal, not clinically significant	0	1 (7%)	0
Abnormal, clinically significant	1 (7%)	0	0
External Ocular Exam 30-Day Safety Follow-up			
Right Eye (n=13)			
Normal	9 (69%)	1 (7%)	0
Abnormal, not clinically significant	0	0	0
Abnormal, clinically significant	3 (23%)	0	0
Left Eye (n=11)			
Normal	9 (82%)	0	0
Abnormal, not clinically significant	0	0	0
Abnormal, clinically significant	2 (18%)	0	0
Posterior Retinal Exam Cycle 2			
Right Eye (n=49)			
Normal	42 (86%)	0	1 (2%)
Abnormal, not clinically significant	1 (2%)	0	0
Abnormal, clinically significant	2 (4%)	1	2 (4%)
Left Eye (n=49)			
Normal	42 (86%)	0	1 (2%)
Abnormal, not clinically significant	1 (2%)	0	0
Abnormal, clinically significant	2 (4%)	1 (2%)	2 (4%)
Posterior Retinal Exam End of Treatment			
Right Eye (n=14)			
Normal	11 (79%)	0	0
Abnormal, not clinically significant	1 (7%)	0	0
Abnormal, clinically significant	1 (7%)	0	1 (7%)
Left Eye (n=14)			
Normal	11 (79%)	0	0
Abnormal, not clinically significant	1 (7%)	0	0
Abnormal, clinically significant	1 (7%)	0	1 (7%)
Posterior Retinal Exam 30-Day Safety Follow-up			
Right Eye (n=10)			
Normal	8 (80%)	0	0

Abnormal, not clinically significant	1(10%)	0	0
Abnormal, clinically significant	0	0	1 (10%)
Left Eye (n=10)			
Normal	8 (80%)	0	0
Abnormal, not clinically significant	1(10%)	0	0
Abnormal, clinically significant	0	0	1 (10%)

Reviewer's Comments:

1. *Considering that there are over 100 patients enrolled in the clinical trial, there are a large number of missing examinations. The anterior ocular structures exam is missing in 29% of patients at Cycle 2 (the visit with the most examinations). The anterior and posterior retinal exams are missing over half of the patients, although it is unknown what constituted an the anterior or posterior retinal exam.*
2. *The use of the terms abnormal, not clinically significant, and abnormal clinically significant are not interpretable to this study. These terms should not be used in describing ophthalmic findings.*

Proposed Labeling:

2 DOSAGE AND ADMINISTRATION

2.3 Dose Modification for Adverse Reactions

The recommended dose reductions for adverse reactions are provided in Table 1.

Table 1: Recommended Dose Reductions for TRADENAME for Adverse Reactions

Dose Reduction	Recommended Dosage (once daily)
First dose reduction	16 mg (four 4 mg tablets)
Second dose reduction*	12 mg (three 4 mg tablets)

*Permanently discontinue TRADENAME if unable to tolerate 12 mg once daily.

Recommended dose adjustments and management guidelines for adverse reactions are provided in [Table 2](#).

Table 2: Recommended Dosage Modifications for TRADENAME Adverse Reactions

Adverse Reaction	Severity	TRADENAME Dose Modifications
Retinal Pigment Epithelial Detachment (RPED) [<i>see Warnings and Precautions (5.1)</i>]		(b) (4)
		(b) (4)

Reviewer's Comments: *Disagree with the applicant's monitoring and dose adjustments for ocular adverse events. Dosage Modifications for TRADENAME are recommended as listed above.*

5 WARNINGS AND PRECAUTIONS

5.1 Ocular Toxicity

Retinal Pigment Epithelial Detachment (RPED)

TRADENAME (b) (4) cause RPED, which (b) (4) cause (b) (4)

Perform a comprehensive ophthalmological examination prior to initiation of therapy and every (b) (4) for the first 6 months. (b) (4) (b) (4) [see Dosage and Administration (2.3)].

(b) (4)

Dry Eye/Corneal Keratitis

(b) (4)

6 ADVERSE REACTIONS

The following adverse reactions are discussed elsewhere in the labeling:

- Ocular Toxicity [see Warnings and Precautions (5.1)]
- Hyperphosphatemia [see Warnings and Precautions (5.2)]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The pooled safety population described in the WARNINGS AND PRECAUTIONS reflect exposure to TRADENAME as a single agent at 20 mg orally once daily in 318 patients including 145 patients with cholangiocarcinoma and 173 patients with other advanced solid tumors. Among 318 patients who

received TRADENAME, 36.5% were exposed for 6 months or longer and 12.9% were exposed for greater than 12 months.

Previously Treated, Unresectable Locally Advanced or Metastatic Cholangiocarcinoma

The safety of TRADENAME was evaluated in (b) (4) of Study TAS-120-101, which included 103 patients with previously treated, locally advanced or metastatic cholangiocarcinoma harboring FGFR2 gene rearrangements, including gene fusions [see *Clinical Studies (14.1)*]. Patients were treated with TRADENAME 20 mg orally once daily until disease progression or unacceptable toxicity. The median duration of treatment was 276 days (range: 14 to 747 days).

(b) (4)

Serious adverse reactions occurred in 39% of patients receiving TRADENAME. Serious adverse reactions in $\geq 2\%$ of patients who received TRADENAME included pyrexia, ascites, (b) (4) gastrointestinal hemorrhage, and bile duct obstruction. (b) (4)

(u) (4)

Permanent discontinuation due to an adverse reaction occurred in (b) (4) (4.9%) patients who received TRADENAME. Adverse reactions requiring permanent discontinuation included esophagitis, oral dysesthesia, bile duct obstruction, and anemia.

Dosage interruptions due to an adverse reaction occurred in 66% of patients who received TRADENAME. Adverse reactions requiring dosage interruption in $\geq 5\%$ of patients included hyperphosphatemia, palmar-plantar erythrodysesthesia syndrome, increased alanine aminotransferase, increased aspartate aminotransferase, fatigue.

Dose reductions due to an adverse reaction occurred in 58% of patients who received TRADENAME. Adverse reactions requiring dosage reductions in $\geq 2\%$ of patients who received TRADENAME included hyperphosphatemia, palmar-plantar erythrodysesthesia syndrome, fatigue, increased alanine aminotransferase, increased aspartate aminotransferase, nail (b) (4), and stomatitis.

The most common ($\geq 20\%$) adverse reactions were nail toxicity, constipation, diarrhea, dry mouth, alopecia, fatigue, dry skin, nausea, stomatitis, decreased appetite, arthralgia, abdominal pain, dry eye, palmar-plantar erythrodysesthesia syndrome, and dysgeusia.

The most common laboratory abnormalities ($\geq 20\%$) were increased phosphate, increased creatinine, decreased hemoglobin, decreased lymphocyte, decreased platelets, decreased leukocytes, decreased neutrophils, increased glucose, increased calcium, decreased sodium, decreased phosphate, increased alanine aminotransferase, increased alkaline phosphatase, increased aspartate aminotransferase, increased creatine kinase, decreased albumin, increased activated partial thromboplastin time, increased prothrombin Intl. Normalized Ratio, increased bilirubin, decreased glucose, and decreased potassium.

Table 3 summarizes the adverse reactions in TAS-120-101. Table 4 summarizes laboratory abnormalities in TAS-120-101.

Table 3: Adverse Reactions (≥15%) in Patients Receiving TRADENAME in (b) (4) Study TAS-120-101

	TRADENAME N= 103	
Adverse Reaction	All Grades ^a (%)	Grades 3 ^b (%)
Skin and subcutaneous tissue disorders		
Nail toxicity ^c	(b) (4) 46.6)	(b) (4) 1.9)
Alopecia	34.0)	0
Dry skin	29.1)	0
Palmar-plantar erythrodysesthesia syndrome	21.4)	(b) (4) 4.9)
Gastrointestinal disorders		
Constipation	38.8)	0
Diarrhea	(b) (4)	(b) (4) 1.0)
Dry mouth	35.0)	0
Nausea	24.3)	(b) (4) 1.9)
Stomatitis	(b) (4)	5.8)
Abdominal pain	(b) (4)	2.9)
Vomiting	19.4)	1.0)
General disorders		
Fatigue	(b) (4)	(b) (4) 7.8)
Metabolism and nutrition disorders		
Decreased appetite	23.3)	(2.9)
Musculoskeletal and connective tissue disorder		
Arthralgia	(b) (4)	0
(b) (4)	(b) (4)	(b) (4) (b) (4)
Eye disorders		
Dry eye	(b) (4)	1.0)
Nervous system disorders		
Dysgeusia	(b) (4)	0
Infections (b) (4)		
Urinary tract infection	(b) (4)	(b) (4) 2.9)
Investigations		
Weight decreased	18.4)	3.9)

^a Graded per NCI CTCAE 4.03.

^b (b) (4)

^c Includes nail toxicity, nail disorder, nail discoloration, nail dystrophy, nail hypertrophy, nail infection, nail pigmentation, onychalgia, onychoclasia, onycholysis, onychomadesis, onychomycosis, and paronychia.
[2.5 Clinical Overview, Section 5.2.11, Table 10]

Table 4: Select Laboratory Abnormalities ($\geq 10\%$) Worsening from Baseline in Patients Receiving TRADENAME in TAS-120-101

Laboratory Abnormality ^a	TRADENAME N= 103	
	All Grades ^b (%)	Grades ≥ 3 (%)
Hematology		
Decreased hemoglobin	52.4	5.8
Decreased lymphocytes	46.3	10.0
Decreased platelets	42.0	1.0
Decreased leukocytes	33.0	1.1
Decreased neutrophils	31.3	1.6
Chemistry		
Increased phosphate ^c	96.7	38.5
Increased creatinine ^d	58.1	0
Increased glucose	52.0	4.9
Increased calcium	51.2	1.2
Decreased sodium	50.5	14.6
Decreased phosphate	49.5	19.6
Increased alanine aminotransferase	49.5	7.4
Increased alkaline phosphatase	46.6	4.9
Increased aspartate aminotransferase	45.6	12.6
Increased creatine kinase	30.7	5.3
Decreased albumin	30.6	2.4
Increased bilirubin	28.4	0
Decreased glucose	25.4	0
Decreased potassium	21.9	2.1
Increased potassium	16.2	2.0
Coagulation		
Increased activated partial thromboplastin time	36.4	8.0
Increased prothrombin international normalized ratio	25.3	0

^a Graded per NCI CTCAE 4.03.

^b Percentages are based on the number of subjects with (b) (4) data at both baseline and at least one relevant post-baseline data value

^c NCI CTCAE 4.03 does not define grades for increased phosphate. Laboratory value shift table categories were used to assess increased phosphorus levels (Grades ≥ 3 defined as >7 mg/dL).

^d Graded based on comparison to upper limit of normal.

[\[2.5 Clinical Overview, Section 5.2.11, Table 11\]](#)

Response to Consult Questions:

1. Is the characterization of the ophthalmologic events adequate?

Reviewer's Comments: *No. The applicant did not monitor either the cornea or the retina sufficiently. Visual function should have been monitored. A large percentage of patients did not have an ophthalmic examination. The information collected was not interpretable. Ophthalmic examinations including optical coherence tomography should have been collected more frequently.*

2. Do you agree with the Applicant's analysis of ophthalmologic events?

Reviewer's Comments: *No. The information collected was not interpretable.*

3. Regarding the Sponsor's proposed revision of labeling –information and recommendations for dose modifications (Sections 2, 5, and 6) adequate?

Reviewer's Comments: *No. It is recommended that the labeling be revised as described in this review.*

Summary Recommendations:

1. The ophthalmic case report forms contain confusing questions for the investigator, raising questions about the interpretation of the reported results. The case report form included Retinal Exam of the Anterior Chamber and Retinal Exam of the Posterior Chamber; however, there is no retina in either the Anterior or Posterior chamber. The case report form suggests that it is possible to have stromal staining without epithelial staining; however, this is not possible since the epithelium is exterior to the stroma. The case report form requests specification for negative staining; however, negative staining is no staining.
2. Considering that there are over 100 patients enrolled in the clinical trial, there is a large number of missing examinations. The anterior ocular structures exam is missing 29% of patients at Cycle 2 (the visit with the most examinations). The anterior and posterior retinal exams are missing over half of the patients, although it is unknown what constituted an the anterior or posterior retinal exam.
3. The schedule of examinations was too infrequent to evaluate ophthalmic adverse events.
4. Optical coherence tomography should have been included to evaluate the retina.
5. Visual acuity and potentially other measures of visual function should have been included in the ophthalmic examinations.
6. The ophthalmic monitoring of the cornea was not sufficient, potentially leading to the development of an ulcerative keratitis in a patient noted to have developed dry eyes.
7. Fluorescein and Rose Bengal stain different structures. They cannot be used interchangeably as described in the protocol.
8. The retinal pigment detachments have described under multiple different terms. Subretinal fluid, chorioretinopathy, detachment of the retinal pigment epithelium, maculopathy and serious retinal detachment are all likely to be the same adverse event in different patients.
9. The use of the CTCAE grading system for ophthalmic events is misleading and should be actively discouraged.
10. The use of the terms abnormal, not clinically significant and abnormal clinically significant are not interpretable to this study. These terms should not be used in describing ophthalmic findings.
11. It is recommended that the labeling be revised as described in this review.

Wiley A. Chambers, M.D.
Supervisory Physician, Ophthalmology

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/s/

WILEY A CHAMBERS
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FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

******Pre-decisional Agency Information******

Memorandum

Date: July 21, 2022

To: Kristin Jarrell, PharmD, Regulatory Project Manager,
Division of Oncology 3 (DO3)

Doris Auth, PharmD, Associate Director for Labeling, (DO3)

From: Rebecca Falter, PharmD, BCACP, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Emily Dvorsky, PharmD, RAC, Team Leader, OPDP

LCDR Maryam Khazraee, PharmD, MBA, MS, BCPS, Regulatory Health
Project Manager, (DO3)

Subject: OPDP Labeling Comments for LYTGOBI™ (futibatinib) tablets, for oral use

NDA: 214801

In response to DO3's consult request dated February 11, 2022, OPDP has reviewed the proposed product labeling (PI), patient package insert (PPI), and carton and container labeling for the original NDA submission for LYTGOBI™ (futibatinib) tablets, for oral use (Lytgobi).

Labeling: OPDP's comments on the proposed labeling are based on the draft labeling received by electronic mail from DO3 (Kristin Jarrell) on July 13, 2022, and are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review will be completed, and comments on the proposed PPI will be sent under separate cover.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room on July 8, 2022, and we do not have any comments.

Thank you for your consult. If you have any questions, please contact Rebecca Falter at (301) 837-7107 or Rebecca.Falter@fda.hhs.gov.

21 Pages of Draft Labeling have been Withheld in Full
as B4(CCI/TS) Immediately Following this Page

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/s/

REBECCA A FALTER
07/21/2022 02:17:47 PM

LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	April 21, 2022
Requesting Office or Division:	Division of Oncology 3 (DO3)
Application Type and Number:	NDA 214801
Product Name, Dosage Form, and Strength:	Lytgobi (futibatinib) tablets, 4 mg
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Taiho Oncology, Inc.
FDA Received Date:	September 3, 2021 and December 20, 2021
OSE RCM #:	2021-1536
DMEPA 2 Safety Evaluator:	Sarah Thomas, PharmD
DMEPA 2 Team Leader:	Janine Stewart, PharmD

1 REASON FOR REVIEW

As part of the approval process for Lytgobi (futibatinib) tablets, the Division of Oncology 3 (DO3) requested that we review the proposed Lytgobi prescribing information (PI), patient information, container labels and carton labeling for areas of vulnerability that may lead to medication errors.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B – N/A
Human Factors Study	C – N/A
ISMP Newsletters*	D – N/A
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Other	F – N/A
Labels and Labeling	G

N/A=not applicable for this review

*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Upon review of the proposed packaging for Lytgobi, we find that the proposed 21-tablet, 28-tablet, and 35-tablet count unit-dose blister card packaging will support the proposed Lytgobi dosing, such that the full range of recommended dosage can be facilitated by the proposed blister card packaging. In addition, the proposed unit-dose blister card packaging may help to mitigate the risk of medication dosing and administration errors associated with the requirement of up to 5 tablets for a dose.

Our review of the proposed container labels and carton labeling, as well as the proposed PI and patient information for Lytgobi identified areas where the labels and labeling may be improved to promote the safe use of the product.

4 CONCLUSION & RECOMMENDATIONS

We conclude that the proposed Lytgobi PI, patient information, container labels and carton labeling may be improved to promote the safe use of the products as described in Sections 4.1 and 4.2.

4.1 RECOMMENDATIONS FOR THE DIVISION OF ONCOLOGY 3 (DO3)

A. General Recommendation

1. We recommend replacing the TRADENAME placeholder with the conditionally acceptable proprietary name, Lytgobi, on the carton labeling and in the PI and patient information.

B. Prescribing Information

1. Dosage and Administration Section, Highlights of PI

- a. We recommend adding the following statement at the end of the Highlights, Dosage and Administration section to alert the end-user that there are additional dosage modifications for adverse reactions provided in the Dosage and Administration section of the full PI: “See full Prescribing Information for dosage modifications for adverse reactions.”

2. How Supplied/Storage and Handling Section

- a. We recommend adding the tablet description from Section 3 (e.g., round, white, film-coated 4 mg tablets debossed with “4MG” on one side, and “FBN” on the other side) to Section 16.
- b. Consider reorganizing the description of the different blister packaging configurations in a table as follows:

Daily Dose	Each carton contains	Each blister pack contains	NDC
20 mg (five 4 mg tablets) daily dose	1 blister card (35 tablets total)	A 7-day supply of 35 tablets (4 mg futibatinib per tablet)	NDC 64842-120-35
16 mg (four 4 mg tablets) daily dose	1 blister card (28 tablets total)	A 7-day supply of 28 tablets (4 mg futibatinib per tablet)	NDC 64842-120-28
12 mg (three 4 mg tablets) daily dose	1 blister card (21 tablets total)	A 7-day supply of 21 tablets (4 mg futibatinib per tablet)	NDC 64842-120-21

4.2 RECOMMENDATIONS FOR TAIHO ONCOLOGY, INC.

We recommend the following be implemented prior to approval of this NDA:

A. General Comments (Container labels & Carton Labeling)

1. Consider decreasing the size of the graphics present on the container labels and carton labeling, as they can potentially compete in size with the presentation of the proprietary name and distract the reader from other important information on the labeling.^a

B. Container Labels

1. In order to ensure consistency of instruction provided across the labels and labeling, consider revising the instructions “(b) (4)” to the similar instructions provided on the carton labeling: “Swallow tablets whole. Do not crush, chew, split, or dissolve tablets.”
2. In order to clearly specify the daily dose and ensure consistency with similar information provided on the carton labeling, we recommend revising the following statement on the 35-count blister container label: “(b) (4)” to the following “20 mg daily dose. Take five 4 mg tablets once daily.” Also apply this edit to the 28-count blister and 21-count blister container labels.
3. We are concerned the numbering on the blister cells (for example, “(b) (4)”) may cause confusion to the end-user. We recommend removing the numbers from the blister cells and replacing the numbers on the blister cells with the strength per tablet of “4 mg”. Alternatively, you may provide justification for the use of the current numbering system on the blister cells for our consideration.

C. Carton Labeling

1. We note the three different blister pack configurations are not adequately differentiated to prevent selection errors in the pharmacy during dispensing, and so we recommend differentiating by providing a daily dose statement in place of the “4 mg per tablet” strength statement that appears beneath the established name on the carton labeling. Also consider highlighting the daily dose statements in different colors to provide differentiation amongst the 3 blister

^a Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. Food and Drug Administration. 2013. Available from <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf>

packaging configurations. An example is provided below for the 21-count blister carton labeling:

LYTGOBI
(futibatinib) tablets
12 mg daily dose
Take three 4 mg tablets orally once daily.

In addition, we recommend replacing the net quantity statement in the bottom right corner of the top two panels of the carton labeling with the strength statement “4 mg per tablet”, followed by a revised net quantity statement, as follows:

“4 mg per tablet

One blister card containing XX tablets

7-day supply”

2. We recommend deleting the “_ _ _ _” between “Futibatinib” and “4 mg” after the following phrase “Each tablet contains:” on the back panel.
3. We recommend deleting the redundant instructions, “Do not crush, cut or chew tablets. Tablets must be swallowed whole.” on the panel containing the white space for Rx label, as the instructions are already presented on the panel containing the Push and Pull instructions.
4. Clarify if the word “cards” should be revised to “card” in the “Pull” instructions (e.g., “While holding the button down, pull out cards.”), as each blister card carton contains one blister card.
5. We recommend specifying the number of tablets needed for a daily dose in the statement “(b) (4)” presented on the side panel with the “Push” and “Pull” instructions on each carton labeling (e.g., for the carton labeling for the blister card containing 35 tablets: “Lytgobi 20 mg daily dose: Take five 4 mg tablets orally once daily.”).
6. We recommend revising the usual dose statements on the carton labeling (e.g., “(b) (4)” to specify the dosage for each blister card packaging configuration (e.g., for the 21-tablet count blister card packaging configuration: “Recommended Dosage: 12 mg (three 4 mg tablets) orally once daily.”).

7. We recommend separating the year, month, and day in the proposed expiration date format with hyphens or forward slashes (e.g., 2023-SEP-30 or 2023/SEP/30).^b

^b Guidance for Industry: Product Identifiers Under the Drug Supply Chain Security Act Questions and Answers. 2021. Available from <https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM621044.pdf>

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Lytgobi received on September 3, 2021 from Taiho Oncology, Inc.

Table 2. Relevant Product Information for Lytgobi							
Initial Approval Date	N/A						
Active Ingredient	futibatinib						
Indication	Indicated for the treatment of patients with previously treated locally advanced or metastatic cholangiocarcinoma harboring FGFR2 gene rearrangements, including gene fusions (b) (4)						
Route of Administration	oral						
Dosage Form	tablets						
Strength	4 mg						
Dose and Frequency	The recommended dosage of Lytgobi is 20 mg (five 4 mg tablets) taken orally once daily until disease progression or unacceptable toxicity occurs. Take Lytgobi with or without food at approximately the same time each day. Swallow tablets whole. Do not crush, chew, split, or dissolve tablets. If the patient misses a dose of Lytgobi for more than 12 hours or if vomiting occurs, resume dosing with the next scheduled dose. Recommended Dose Reductions for Lytgobi for Adverse Reactions <table border="1"> <tr> <th>Dose Reduction</th><th>Recommended Dosage (once daily)</th></tr> <tr> <td>First dose reduction</td><td>16 mg (four 4 mg tablets)</td></tr> <tr> <td>Second dose reduction*</td><td>12 mg (three 4 mg tablets)</td></tr> </table> *Permanently discontinue Lytgobi if unable to tolerate 12 mg once daily. See Table 2 for Recommended Dosage Modifications for Lytgobi Adverse Reactions.	Dose Reduction	Recommended Dosage (once daily)	First dose reduction	16 mg (four 4 mg tablets)	Second dose reduction*	12 mg (three 4 mg tablets)
Dose Reduction	Recommended Dosage (once daily)						
First dose reduction	16 mg (four 4 mg tablets)						
Second dose reduction*	12 mg (three 4 mg tablets)						
How Supplied	Lytgobi tablets are packaged in blister cards and supplied in child resistant DosePak® as follows: 20 mg daily dose: Each carton contains 1 blister card containing						

	a 7-day supply (35 tablets; 4 mg futibatinib per tablet). [NDC-64842-120-35] • 16 mg daily dose: Each carton contains 1 blister card containing a 7-day supply (28 tablets; 4 mg futibatinib per tablet). [NDC-64842-120-28] • 12 mg daily dose: Each carton contains 1 blister card containing a 7-day supply (21 tablets; 4 mg futibatinib per tablet). [NDC-64842-120-21]
Storage	Store Lytgobi tablets at room temperature 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C and 30°C (59°F to 86°F).
Container Closure	Blister pack consisting of (b) (4) and (b) (4) with aluminum foil lidding with one tablet per cavity. Each blister card will be packaged into a child-resistant Dosepak®.

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,^c along with postmarket medication error data, we reviewed the following Lytgobi labels and labeling submitted by Taiho Oncology, Inc.

- Unit-Dose Blister Card Container labels received on December 20, 2021
- Unit-Dose Blister Card Carton Labeling received on December 20, 2021
- Prescribing Information (PI) and Patient Information (Image not shown) received on September 3, 2021, available from <\\CDSESUB1\evsprod\nda214801\0003\m1\us\114-labeling\draft\labeling\draft-labeling-text-word.docx>

G.2 Label and Labeling Images



4 Pages of Draft Labeling have been Withheld in Full as B4(CCI/TS) Immediately Following this Page

^c Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/

SARAH E THOMAS
04/21/2022 08:59:10 PM

JANINE A STEWART
04/21/2022 10:22:00 PM

Interdisciplinary Review Team for Cardiac Safety Studies

QT Study Review

Submission	NDA-214801
Submission Number	001 (New NDA)
Submission Date	8/2/2021
Date Consult Received	10/1/2021
Drug Name	Futibatinib
Indication	Advanced or metastatic cholangio-carcinoma (harboring FGFR2 gene rearrangements, including gene fusions)
Therapeutic Dose	20 mg once daily.
Clinical Division	DO3
Protocol Review	Protocol ; Revised Protocol

Note: Any text in the review with a light background should be considered to be copied from the sponsor's document.

This review responds to your consult dated 10/1/2021 regarding the sponsor's QT evaluation. We reviewed the following materials:

- Previous IRT review for IND-121062 dated 11/15/2019 in DARRTS ([link](#));
- Previous IRT review for IND-121062 dated 01/13/2020 in DARRTS ([link](#));
- Sponsor's clinical study protocol # TAS-120-107 (SN0001; [link](#));
- Sponsor's statistical analysis plan # TAS-120-107 (SN0001; [link](#));
- Sponsor's clinical study report # TAS-120-107 (SN0001; [link](#));
- Investigator's brochure V 8.0 under IND-121062 (SN0301; [link](#)); and
- Highlights of clinical pharmacology and cardiac safety (App #1; SN0001; [link](#)).

1 SUMMARY

Futibatinib does not cause significant QTcF prolongation in this thorough QT study assessment.

The effect of futibatinib was evaluated in a TQT study (Study # TAS-120-107). This was a randomized, double-blind, single-dose, placebo- and positive-controlled, crossover (4-period) study evaluating the effect of futibatinib on the QT/QTc interval in healthy subjects. The highest dose studied is 80 mg, which is the supratherapeutic dose and provides a C_{max} approximately 4-fold the RP2D. Data were analyzed using the by-time analysis as the primary analysis which did not suggest that futibatinib is associated with significant QTc prolonging effect – see Table 1 for overall results. The findings of this analysis are further supported by the exposure-response analysis (Section 4.5) and categorical analyses (Section 4.4).

Table 1: Point Estimates and the 90% CIs (FDA Analysis)

ECG Parameter	Treatment	Time (h)	$\Delta\Delta\text{QTcF}$ (msec)	90% CI (msec)
QTcF	Futibatinib 20 mg	6.0	2.1	(-0.7 to 4.9)
QTcF	Futibatinib 80 mg	10.0	1.8	(-1.0 to 4.6)

For further details of the FDA analysis, please Section 4.

1.1 RESPONSES TO QUESTIONS POSED BY SPONSOR

Not applicable.

1.2 COMMENTS TO THE REVIEW DIVISION

Not applicable.

2 RECOMMENDATIONS

2.1 ADDITIONAL STUDIES

Not applicable.

2.2 PROPOSED LABEL

Below are proposed edits to the proposed label submitted to SN0003 ([link](#)). Our changes are highlighted (*addition*, *deletion*). Each Section is followed by a rationale for the changes made. Please note that this is a suggestion only and that we defer final labeling decisions to the Division.

12.2 Pharmacodynamics

Cardiac Electrophysiology

 (b) (4)
At a dose 4 times the maximum approved recommended dose, <TRADENAME> does not prolong the QT interval to any clinically relevant extent.

We propose to use labeling language for this product consistent with the “Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products – Content and Format” guidance.

3 SPONSOR’S SUBMISSION

3.1 OVERVIEW

3.1.1 Clinical

Taiho Oncology, Inc. is developing futibatinib for the treatment of advanced or metastatic cholangiocarcinoma (who are previously treated locally and harboring FGFR2 gene rearrangements, including gene fusions). Futibatinib (TAS-120; MW: 418 g/mol) is a tyrosine kinase inhibitor that irreversibly inhibits fibroblast growth factor receptor.

The product is formulated as immediate-release film-coated tablet formulation containing 4 mg futibatinib for oral administration. The maximum proposed therapeutic dose for the present indication is 20 mg once daily (five 4 mg tablets; until disease progression or unacceptable toxicity occurs). The peak concentrations of ~144 ng/mL (T_{max}: ~2 h; half-life: ~3 h) are expected at steady state with the anticipated therapeutic dose (Model Predicted). No significant accumulation is expected at steady state with the proposed maximum therapeutic dose (C_{max} Racc: ~1). The sponsor states that the maximum tolerated dose is 20 mg once daily and the maximum studied dose is 24 mg once daily (C_{max}: ~1292 ng/mL).

The studies indicate that futibatinib is extensively metabolized forming glucuronide, cysteine, and cysteinylglycine conjugates. Concomitant administration of futibatinib with a strong inhibitor of CYP3A4 is expected to result in increased exposures of futibatinib (C_{max}: ~1.5-fold & AUC: ~1.6-fold). The human mass balance study indicates that ~64% of the drug (as TR) is excreted in feces, and ~6% of the drug (as TR) in urine with negligible unchanged fraction excreted. The pharmacokinetics of futibatinib in subjects with severe renal impairment and subjects with moderate to severe hepatic impairment have not been studied. However, the sponsor states that futibatinib will not be administered in these populations.

Previously, the sponsor proposed to characterize QT effects of their product in a thorough QT study (Protocol # Study # TAS-120-107) which was revived by the IRT. This was a randomized, double-blind, single-dose, placebo- and positive-controlled, crossover (4-period) study in healthy subjects. Refer to previous IRT reviews under IND-121062 dated 11/15/2019 and 01/13/2020 in DARRTS.

3.1.2 Nonclinical Safety Pharmacology Assessments

Refer to the sponsor's highlights of clinical pharmacology and clinical safety.

3.2 SPONSOR'S RESULTS

3.2.1 By-Time Analysis

In the sponsor's by-time analysis using averaged baseline, Futibatinib excluded the 10 msec threshold at both the therapeutic and the suprathreshold dose level for $\Delta\Delta Q_{TcF}$.

Reviewer's comment: *The result from reviewers' default model also shows maximum upper confidence limit below 10 msec.*

3.2.1.1 Assay Sensitivity

Assay sensitivity was established by the moxifloxacin arm based on the model prespecified in protocol. The lower bound of 2-sided 97.5% CIs above 5 msec at all four time points (1.5, 2, 3, and 4 hour).

Reviewer's comment: *The results from reviewers' default model shows the largest lower confidence limit with multiplicity adjustment at 4 time points is 11.3 msec. Please Section 4.3.1.1 for more details.*

3.2.1.1.1 QT Bias Assessment

Not applicable.

3.2.2 Categorical Analysis

There were no significant outliers per the sponsor's analysis for QTc (i.e., >500 msec or >60 msec over baseline), PR (>200 msec and 25% over baseline), and QRS (>120 msec and 25% over baseline). There was one subject with HR >100 beats/min and 25% over baseline from Futibatinib 20 mg group.

Reviewer's comment: FDA reviewer's analysis results are the same as sponsor's analysis results. Please Section 4.4 for details.

3.2.3 Exposure-Response Analysis

In addition to the primary analysis, the sponsor performed PK/PD analysis to explore the relationship between concentration of futibatinib and $\Delta\Delta\text{QTcF}$ (placebo corrected change from baseline in QTcF) using a linear mixed-effects approach on all subjects in the analysis data set for cardiac assessment.

The model predicted $\Delta\Delta\text{QTcF}$ (upper confidence interval) values of 1.08 (1.94) msec at the mean peak concentrations for the highest dose studied (i.e., 80 mg: geomean C_{max} ~542 ng/mL) following single dose. Similarly, the model predicted $\Delta\Delta\text{QTcF}$ (upper confidence interval) values of 1.06 (1.48) msec at the mean peak concentrations for 20 mg (geomean C_{max} ~165 ng/mL) following single dose. Thus, the results of the sponsor's analysis suggest an absence of significant QTc prolongation at the highest studied dose (i.e., 80 mg single dose).

Reviewer's comment: Although there are numerical differences, the results of the reviewer's analysis agreed with the sponsor's conclusion. Please Section 4.5 for additional details.

3.2.4 Safety Analysis

A total of 48 subjects were enrolled in the study and 44 subjects completed the study. All 48 enrolled subjects were included in the cardiodynamic, PK, and safety analyses.

There were no deaths, serious adverse events (SAEs), or subjects discontinued due to an AE in this study. One (1) subject experienced the laboratory-related AE of afebrile neutropenia following placebo.

Overall, a total of 64 TEAEs were reported by 19 (40%) subjects, including 7 subjects each following 20 mg Futibatinib and 80 mg Futibatinib, 9 subjects following Placebo, and 6 subjects following Moxifloxacin. A total of 57 AEs were Grade 1 (mild) in severity, 6 were Grade 2 (moderate), and 1 (afebrile neutropenia following Placebo) was Grade 3 (severe). The PI considered 15 AEs to be related to futibatinib and 49 AEs unrelated, and considered 10 AEs related to moxifloxacin and 54 AEs unrelated. There were no treatment-related trends noted in the vital sign measurements, clinical laboratory tests, physical examination, or 12-lead safety ECG data in this study.

Reviewer's comment: *None of the events identified to be of clinical importance per the ICH E14 guidelines (i.e., unexplained syncope, seizure, significant ventricular arrhythmias, or sudden cardiac death) occurred in this study.*

4 REVIEWERS' ASSESSMENT

4.1 EVALUATION OF THE QT/RR CORRECTION METHOD

The sponsor used QTcF for the primary analysis. This is acceptable, as no large increases or decreases in heart rate (i.e., $|\text{mean}| < 10$ beats/min) were observed (Section 4.3.2).

4.2 ECG ASSESSMENTS

4.2.1 Overall

Overall, ECG acquisition and interpretation in this study appear acceptable.

4.2.2 QT Bias Assessment

Not applicable.

4.3 BY-TIME ANALYSIS

The analysis population used for by-time analysis included all subjects with a baseline and at least one post-dose ECG.

The statistical reviewer used a linear mixed model to analyze the drug effect by-time for each biomarker (e.g., ΔQTcF , ΔHR) independently. The default model includes treatment, sequence, period, time (as a categorical variable), and treatment-by-time interaction as fixed effects, and baseline as a covariate. The default model also includes subject as a random effect and an unstructured covariance matrix to explain the associations among repeated measures within the period.

4.3.1 QTc

Figure 1 displays the time profile of $\Delta\Delta\text{QTcF}$ for different treatment groups. The maximum $\Delta\Delta\text{QTcF}$ values by treatment are shown in Table 2.

The maximum estimated 90% CI upper limits are below 10 msec for all time points.

Figure 1: Mean and 90% CI of $\Delta\Delta\text{QTcF}$ Time-course (unadjusted CIs).

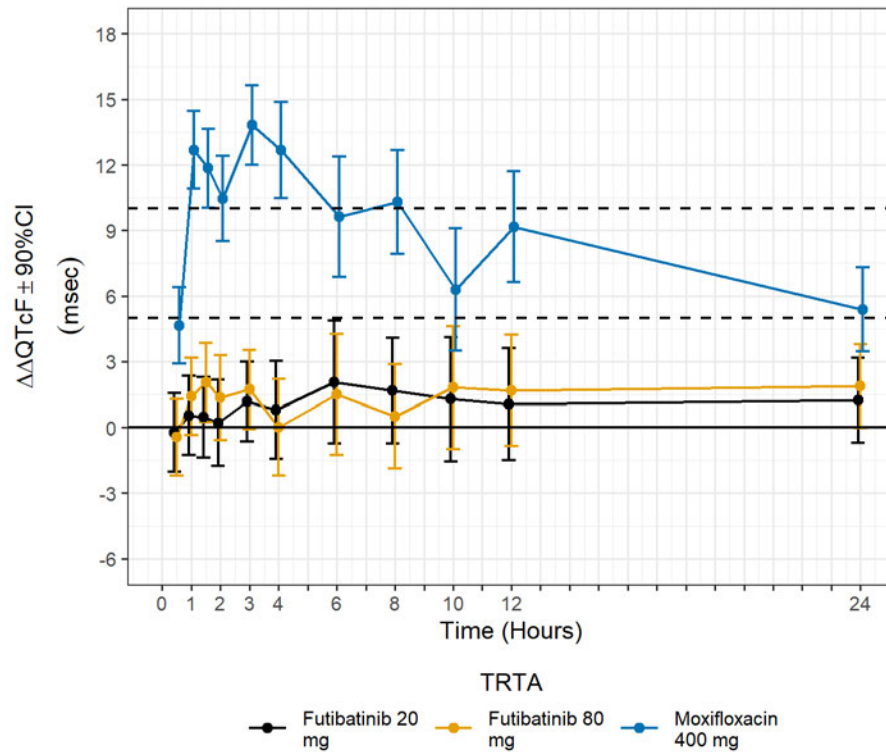


Table 2: Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for $\Delta\Delta\text{QTcF}$

Actual Treatment	Nact / Npbo	Time (Hours)	$\Delta\Delta\text{QTcF}$ (msec)	90.0% CI (msec)
Futibatinib 20 mg	45 / 46	6.0	2.1	(-0.7 to 4.9)
Futibatinib 80 mg	47 / 47	10.0	1.8	(-1.0 to 4.6)

4.3.1.1 Assay Sensitivity

Assay sensitivity was assessed using by-time analysis. The statistical reviewer used the same linear mixed model as treatment arms to analyze the moxifloxacin effect by time for the biomarker $\Delta\Delta\text{QTcF}$ independently. The time-course of changes in $\Delta\Delta\text{QTcF}$ is shown in Figure 1 and includes the expected time-profile with a mean effect of >5 msec after Bonferroni adjustment for 4 time points (Table 3).

The time-course of changes in $\Delta\Delta\text{QTcF}$ includes the expected time-profile with a mean effect of >5 msec after Bonferroni adjustment for 4 time points (Table 4).

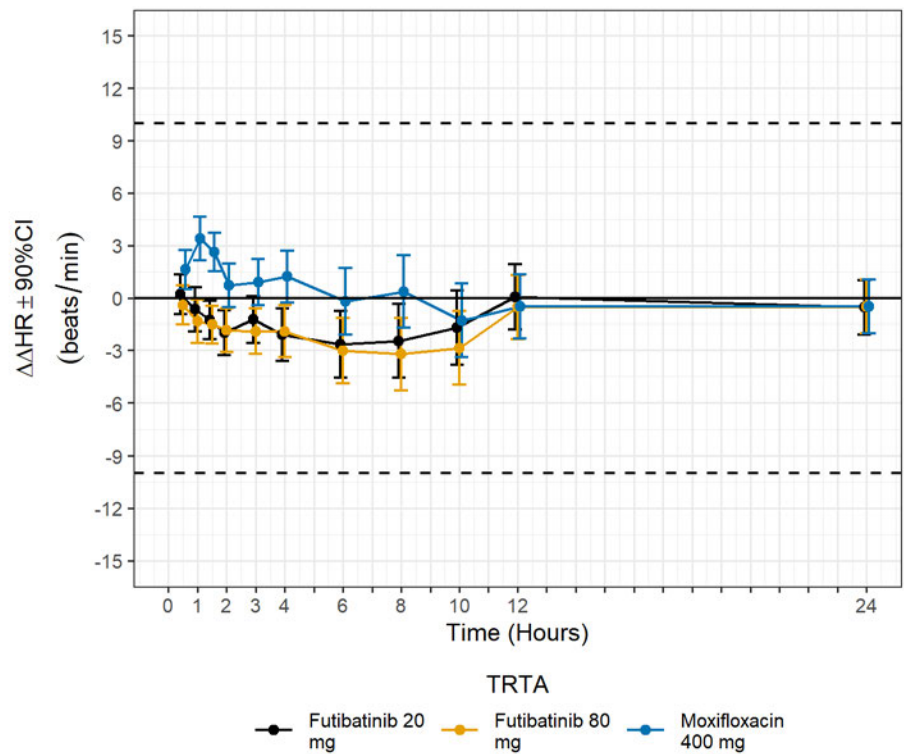
Table 3: The Point Estimates and the 90% CIs Corresponding to the Largest Lower Bounds for $\Delta\Delta\text{QTcF}$

Treatment	N _{act} /N _{pbo}	Time (hours)	$\Delta\Delta\text{QTcF}$ (msec)	90.0% CI (msec)	97.5% CI (msec)
Moxifloxacin 400 mg	47/47	3.0	13.8	(12.0 to 15.6)	(11.3 to 16.3)

4.3.2 HR

Figure 2 displays the time profile of $\Delta\Delta\text{HR}$ for different treatment groups.

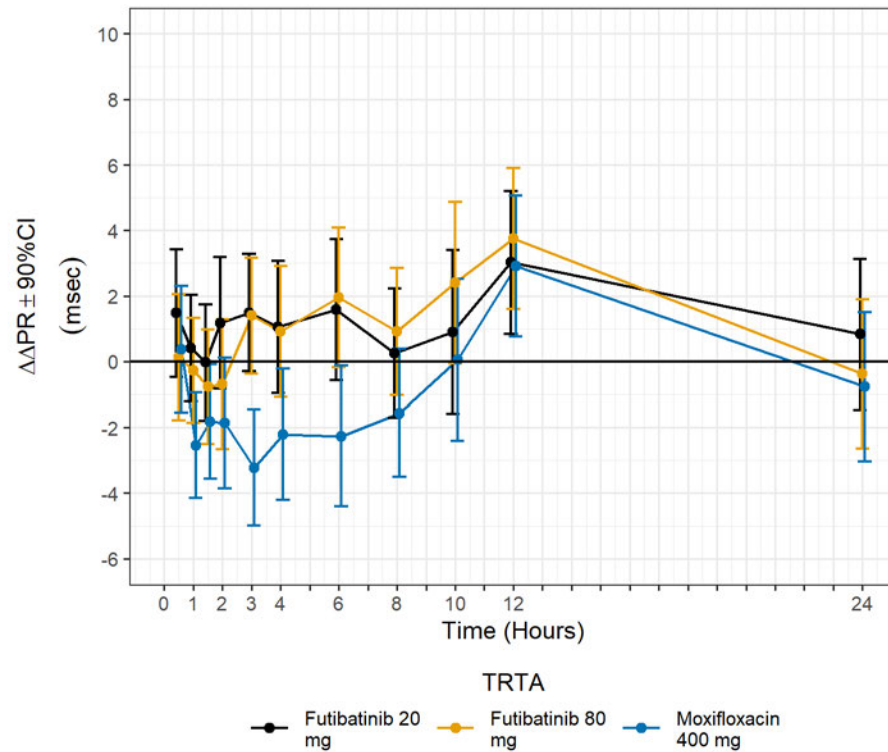
Figure 2: Mean and 90% CI of $\Delta\Delta\text{HR}$ Time-course



4.3.3 PR

Figure 3 displays the time profile of $\Delta\Delta\text{PR}$ for different treatment groups. $\Delta\Delta$

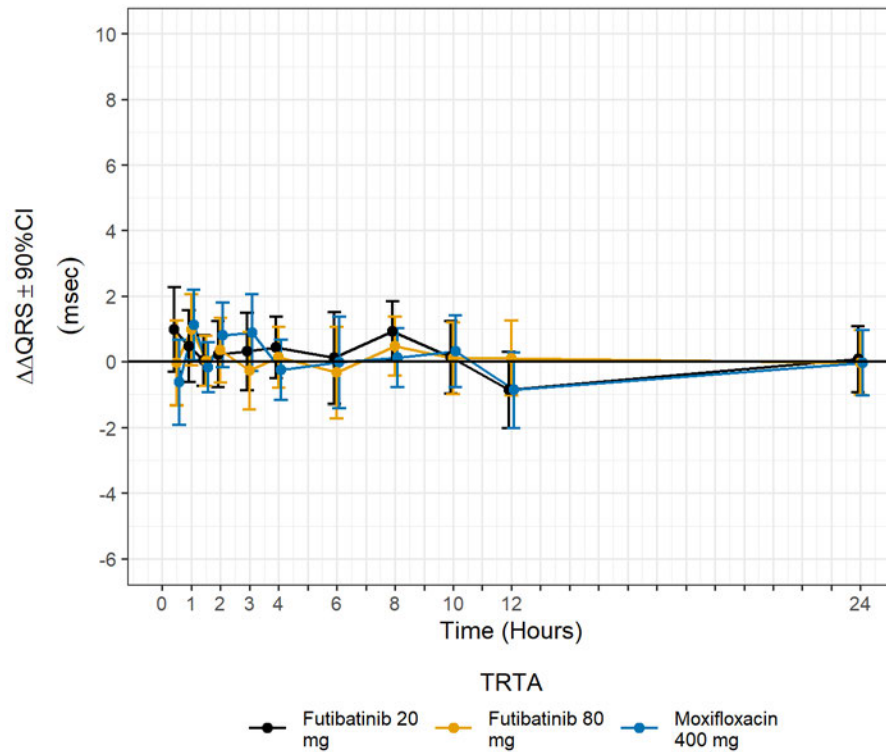
Figure 3: Mean and 90% CI of $\Delta\Delta PR$ Time-course



4.3.4 QRS

Figure 4 displays the time profile of $\Delta\Delta QRS$ for different treatment groups. $\Delta\Delta$

Figure 4: Mean and 90% CI of $\Delta\Delta$ QRS Time-course



4.4 CATEGORICAL ANALYSIS

Categorical analysis was performed for different ECG measurements, either using absolute values, change from baseline, or a combination of both. The analysis was conducted using the safety population, which includes both scheduled and unscheduled ECGs. In the following categorical tables, an omitted category means that no subjects had values in that category.

4.4.1 QTc

There were no subjects having observed QTcF above 450 msec or change from baseline above 60 msec after receiving Futibatinib.

4.4.2 HR

Table 4 lists the categorical analysis results for maximum HR (≤ 100 beats/min and >100 beats/min). One subject had observed HR above 100 bpm and 25% increase over baseline at two time points in Futibatinib 20 mg group.

Table 4: Categorical Analysis for HR (maximum)

Actual Treatment	Total (N)		Value ≤ 100 beats/min		Value >100 beats/min	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
Fut batin b 20 mg	45	495	44 (97.8%)	493 (99.6%)	1 (2.2%)	2 (0.4%)
Fut batin b 80 mg	47	517	47 (100.0%)	517 (100.0%)	0 (0%)	0 (0%)

Actual Treatment	Total (N)		Value ≤100 beats/min		Value >100 beats/min	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
Placebo	47	516	46 (97.9%)	514 (99.6%)	1 (2.1%)	2 (0.4%)

4.4.3 PR

None of the subjects experienced PR >220 msec and 25% increase over baseline in any of the treatment groups.

4.4.4 QRS

None of the subjects experienced QRS >120 msec in any of the treatment groups.

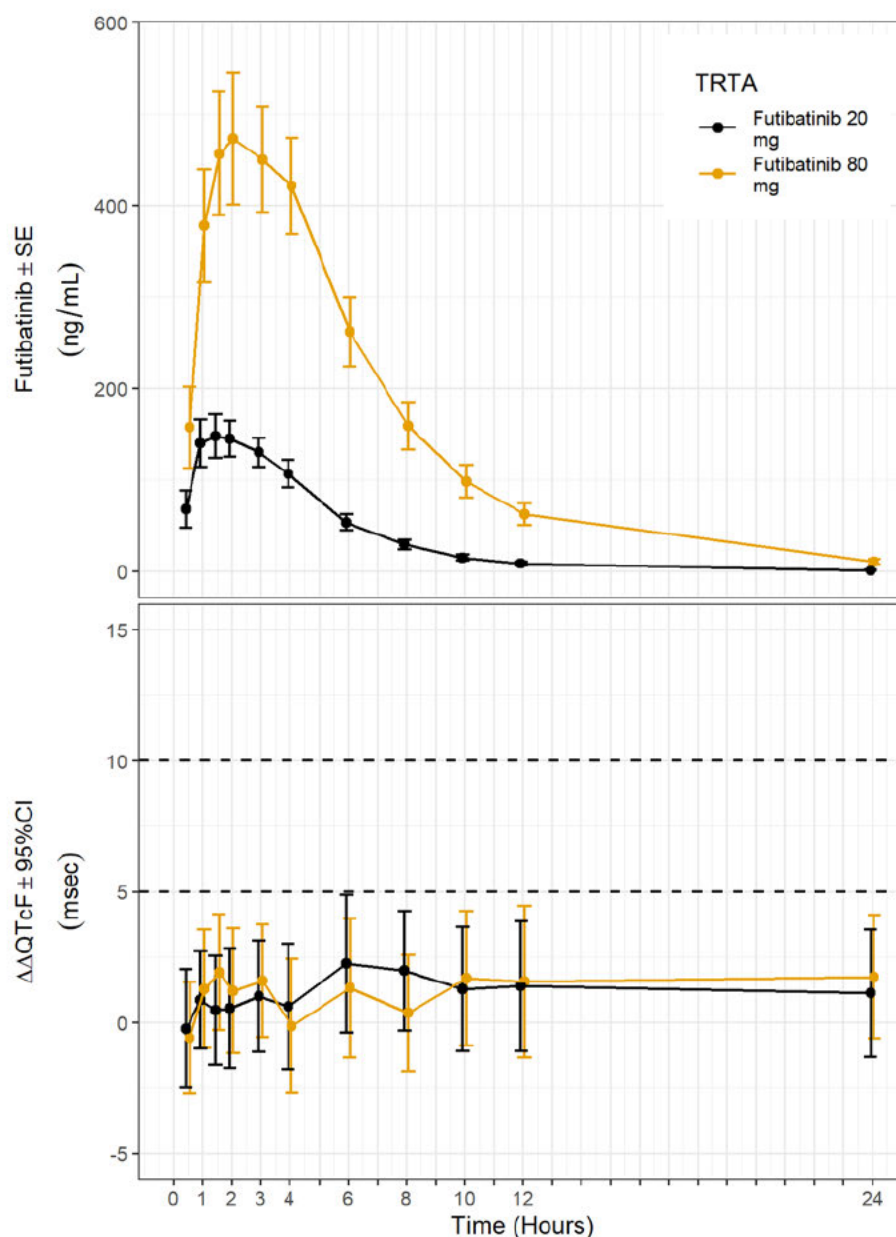
4.5 EXPOSURE-RESPONSE ANALYSIS

The objective of the clinical pharmacology analysis was to assess the relationship between plasma concentration of futibatinib and $\Delta\Delta\text{QTcF}$. Exposure-response analysis was conducted using all subjects with baseline and at a least one post-baseline ECG with time-matched PK.

Prior to evaluating the relationship between futibatinib concentration and QTc using a linear model, the three key assumptions of the model were evaluated using exploratory analysis: absence of - 1) significant changes in heart rate (more than a 10-bpm increase or decrease in mean HR); 2) delay between futibatinib concentration and ΔQTc and 3) a non-linear relationship.

An evaluation of the time-course of futibatinib concentration and changes in $\Delta\Delta\text{QTcF}$ is shown in Figure 5. There was no apparent correlation between the time at maximum effect on $\Delta\Delta\text{QTcF}$ and peak concentrations of futibatinib indicating no significant hysteresis. Figure 2 shows the time-course of $\Delta\Delta\text{HR}$, which shows an absence of significant $\Delta\Delta\text{HR}$ changes and the maximum change in heart rate is below 6 bpm (Sections 4.3.2 and 4.4.2).

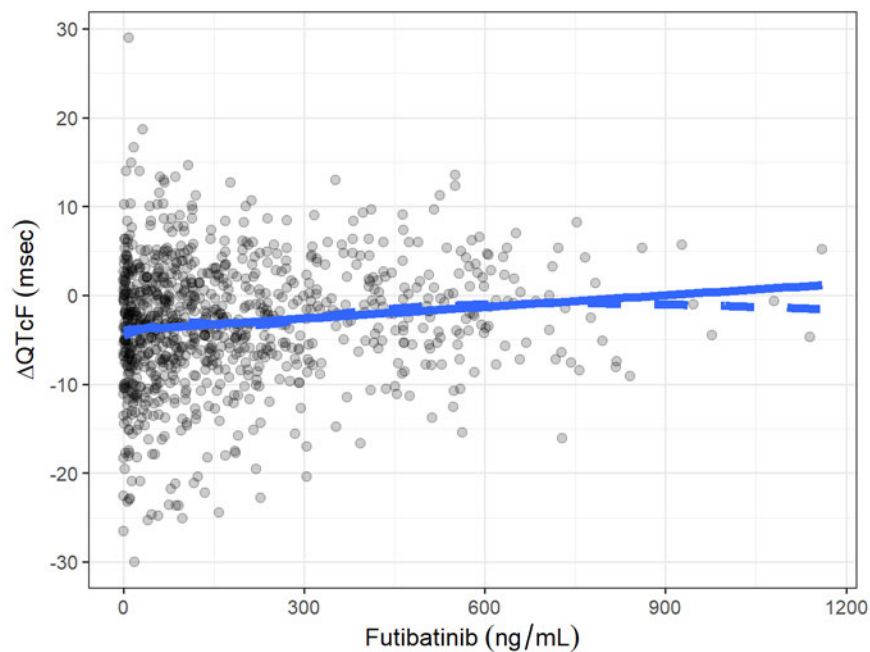
Figure 5: Time-course of futibatinib Concentration (top) and QTcF (bottom)¹



After confirming the absence of significant heart rate changes or delayed QTc changes, the relationship between futibatinib concentration and $\Delta\Delta\text{QTcF}$ was evaluated to determine if a linear model would be appropriate. Figure 6 shows the relationship between futibatinib concentration and $\Delta\Delta\text{QTcF}$ and supports the use of a linear model.

¹ $\Delta\Delta\text{QTcF}$ shown were obtained via descriptive statistics and might differ from Figure 1

Figure 6: Assessment of Linearity of the Concentration-QTcF Relationship



Finally, the linear model was applied to the data, and the goodness-of-fit plot is shown in Figure 7. Predictions from the concentration-QTcF model are provided in Table 5.

Figure 7: Goodness-of-fit Plot for QTcF

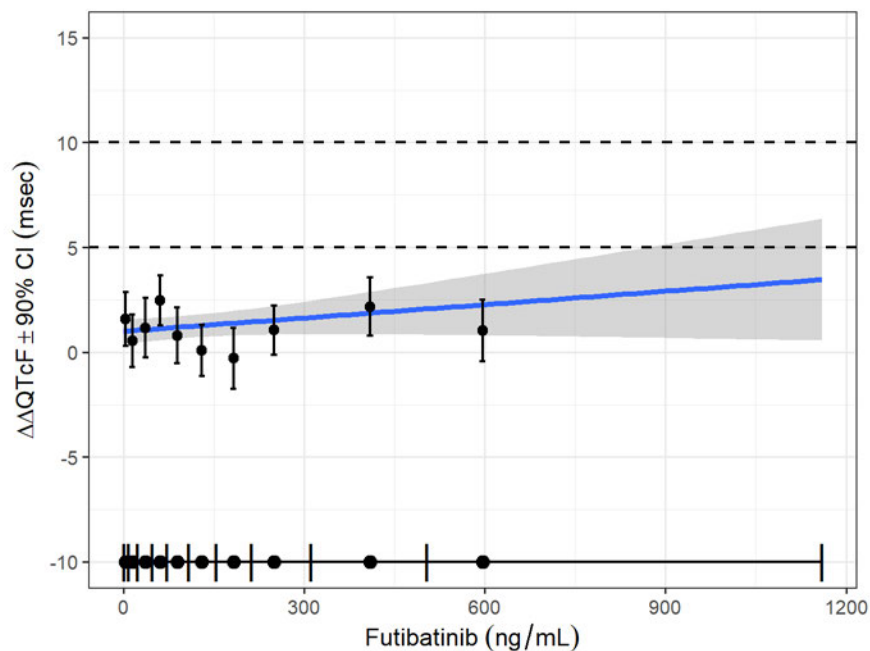


Table 5: Predictions from Concentration-QTcF Model

Actual Treatment	Analysis Nominal Period Day (C)	Futibatinib (ng/mL)	$\Delta\Delta\text{QTcF}$ (msec)	90.0% CI (msec)
Futibatinib 20 mg	1	165.2	1.4	(0.8 to 1.9)

Actual Treatment	Analysis Nominal Period Day (C)	Futibatinib (ng/mL)	$\Delta\Delta\text{QTcF}$ (msec)	90.0% CI (msec)
Futibatinib 80 mg	1	541.5	2.1	(0.8 to 3.5)

4.6 SAFETY ASSESSMENTS

See Section 3.2.4. No additional safety analyses were conducted.

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