

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

214801Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

IND 121062

MEETING MINUTES

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

Dear Dr. Hu:¹

Please refer to your investigational new drug application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for futibatinib (TAS-120). We also refer to the meeting between representatives of your firm and the FDA on June 14, 2021. The purpose of the Multidisciplinary Breakthrough Therapy Designation meeting was to discuss and reach agreement on the content and format of the anticipated NDA for futibatinib (TAS-120).

A copy of the official minutes of the meeting/telecon is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at 301-796-0137.

Sincerely,

{See appended electronic signature page}

Kristin Jarrell, Pharm.D.
Regulatory Health Project Manager
Division of Regulatory Operations
Oncologic Diseases for DO3
Office of Regulatory Operations
Office of New Drugs
Center for Drug Evaluation and Research

Enclosure:

- Meeting Minutes

¹ 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>.



MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: Initial Multidisciplinary Breakthrough Therapy Designation
Meeting Date and Time: June 14, 2021; 12:00pm – 1:30pm ET
Application Number: IND 121062
Product Name: futibatinib (TAS-120)
Indication: treatment of patients with previously treated locally advanced or metastatic cholangiocarcinoma harboring FGFR2 gene rearrangements, including gene fusions
Sponsor Name: Taiho Oncology, Inc.
Regulatory Pathway: 505(b)(1) of the Federal Food, Drug, and Cosmetics Act

FDA ATTENDEES

'Lola Fashoyin-Aje, MD, MPH, Deputy Director, Division of Oncology 3 (DO3)
Sandra J. Casak, MD, Clinical Team Leader, DO3
Naomi Horiba, MD, MPH, Clinical Reviewer, DO3
Matthew Thompson, PhD, MPH, Nonclinical Team Leader, DHOT
Dubravka Kufrin, PhD, MS, Nonclinical Reviewer, DHOT
Xing Wang, Product Quality Team Leader, OPQ
Banu Zolnik, Biopharmaceutics Team Lead, OPQ
Mei Ou, Biopharmaceutics Reviewer, OPQ
Ramesh Raghavachari, Branch Chief, DPMA I/OLDP OPQ
Haripada Sarker, Drug Substance Team Leader, ONDP, OPQ
Paresma Patel, Branch Chief, Division of New Drug API, ONDP, OPQ
Hong Zhao, Clinical Pharmacology Team Leader, DCPII
Wentao Fu, Clinical Pharmacology Reviewer, DCPI
Jiang Liu, Associate Director, Division of Pharmacometrics, OCP
Joyce Cheng, Statistical Team Leader, DBV
Mengdie Yuan, Statistical Reviewer, DBV
Anand Pathak, Reviewer, Center for Devices and Radiological Health
Kristin Jarrell, PharmD, Regulatory Health Project Manager

SPONSOR ATTENDEES

Marty Birkhofer, MD SVP and Chief Medical Officer, Taiho Oncology
Karim Benhadji, MD SVP, Head of Clinical Development, Taiho Oncology
Kimberly Stranick, PhD SVP, Head of Regulatory Affairs, Taiho Oncology
Kathy Calarco, VP, Quality Assurance
Volker Wacheck, MD VP, Clinical Development, Taiho Oncology
Angela Hu, Ph.D., Sr. Director, Regulatory Affairs
Helen He, MD, PhD Sr. Director, Head of Biostatistics, Taiho Oncology
Partha Banerjee, Ph.D., Sr. Director, CMC Regulatory Affairs

Daniel Petrillo, Ph.D., Associate Director, CMC Regulatory Affairs
Cathleen Wilbur, Director, Project Management
Yasunori Abe, Chemical Technology Laboratory
Yuji Kanamoto, Formulation Research Laboratory
Tetsuya Nishiyama, Ph.D., CMC Strategy

(b) (4)

BACKGROUND

FDA sent Preliminary Comments to Taiho on Friday, June 11, 2021.

Taiho Oncology, Inc. (Taiho) is planning to submit a New Drug Application (NDA) for futibatinib for the treatment of patients with previously treated locally advanced or metastatic cholangiocarcinoma harboring FGFR2 gene rearrangements, including gene fusions, under the accelerated approval pathway (21 CFR Subpart H).

On April 19, 2021, Taiho submitted a meeting request providing high-level efficacy results from Study TPU-TAS-120-101 and to discuss the proposed content and format of the planned NDA. The meeting was granted on May 3, 2021. The meeting package was received on May 14, 2021.

Key Regulatory History

- On January 28, 2014, a new IND containing Study TPU-TAS-120-101 (Study 101), titled “Dose-Finding Phase 1 Study of TAS-120 in Patients with Advanced Solid Tumors With or Without Fibroblast Growth Factor/Receptor (FGF/FGFR)-Related Abnormalities Followed by a Phase 2 Study in Patients with Advanced Solid Tumors or Multiple Myeloma with FGF/FGFR-Related Abnormalities” (submitted on December 31, 2013) was placed on a partial clinical hold due to insufficient information to assess risk to human subjects relating to the proposed 20 mg strength capsule. FDA stated that Taiho may only proceed with the “Phase 1” dose escalation and expansion portion of the study. The partial clinical hold was subsequently removed on November 3, 2017.
- On September 23, 2019, Taiho submitted a new protocol, TPU-TAS-120-301, entitled “Phase 3, Open-Label, Randomized Study of Futibatinib Versus Gemcitabine-Cisplatin Chemotherapy as First-Line Treatment of Patients with Advanced Cholangiocarcinoma Harboring FGFR2 Gene Rearrangements”, a study intended to confirm the clinical benefit of TAS-120.
- On February 26, 2020, a written response only document was issued for a Type C guidance meeting to discuss Taiho’s proposals relating to the presentation of efficacy and safety data, presentation of clinical pharmacology, and data standardization requirements in the planned NDA.

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- On July 8, 2020, a teleconference was held with Taiho to discuss the content and format of the CMC section of the planned NDA,
- On October 1, 2020, FDA and the (b) (4) held a teleconference to discuss a proposed randomized master trial with a common control arm that might serve as the confirmatory trial for one of the experimental arms. Attendees including (b) (4) and Taiho.
- On April 21, 2020, Taiho requested a meeting to discuss the proposed content and format of the planned NDA. After review of the preliminary meeting minutes, Taiho elected to cancel the meeting.

Futibatinib has orphan designation for the indication of cholangiocarcinoma, fast track status, and breakthrough designation.

Clinical

Study TPU-TAS-120-101

Taiho plans to file an NDA based on the results of Part 3 of Study TPU-TAS-120-101, entitled “Phase 1/2 Study of TAS-120 in Patients with Advanced Solid Tumors Harboring FGF/FGFR Aberrations.” Study TPU-TAS-120-101 is an open-label, dose escalation and dose expansion study evaluating the safety, tolerability, pharmacokinetic (PK), pharmacodynamic (PD), and antitumor activity of TAS-120 in patients with unresectable solid tumors with various FGF/FGFR abnormalities in the second-line setting. The study consists of three parts: dose escalation, expansion cohorts in several disease harboring different FGFR gene fusions, and a single-arm cohort in patients with intrahepatic cholangiocarcinoma (iCCA) harboring FGFR2 fusions or other rearrangements as determined by a local or central (Foundation Medicine - FMI) diagnostic test and who have been treated with at least one prior chemotherapy regimen containing gemcitabine and a platinum (Part 3).

The primary endpoint of Part 3 is overall response rate (ORR) by independent central review (IRC) per RECIST 1.1. Secondary endpoints include duration of response (DOR), disease control rate, progression-free survival (PFS), health-related quality of life, and overall survival (OS). With a planned sample size of 100 patients in Part 3, assuming the true ORR is 20%, the study has approximately 81% power to reject the null hypothesis that the true ORR is $\leq 10\%$, considering a 2-sided alpha of 5%.

At the time of the data cutoff on October 1, 2020, the study had enrolled 103 patients, and all patients had at least 10 months (range 10.1, 29.6) of follow-up. The majority of responders had at least 6 months of follow-up from the onset of response.

The confirmed ORR was 41.7% (95% CI: 32.1, 51.9) based on IRC review. The median duration of response (DoR) by Kaplan-Meier analysis was 9.7 months and 72% of responders had responses lasting > 6 months.

Proposed content of the application:

Taiho plans to submit a rolling review package for the proposed indication to be reviewed under the accelerated approval pathway. The sequence of submissions is as follows:

- Module 4 nonclinical (overview, written and tabulated summaries) and partial Module 1 in July 2021.
- Module 5 clinical (introduction, overview, clinical summary) and partial Module 1 to include the USPI in August 2021
- Module 3 quality (overall summary) and the remainder of Module 1 in December 2021

Taiho proposes to submit a 90 or 120-day safety update report containing a summary of clinical safety based on a cutoff date of May 29, 2021. At the time of the safety update, Taiho plans to submit safety updates for each ongoing futibatinib monotherapy study in the form of line listings. Narratives and CRFs will also be provided.

The ISS will contain the following groupings:

- Safety Data Group 1 (n=145): patients with iCCA harboring FGFR2 rearrangement and treated with futibatinib at a dose of 20 mg orally daily in either Parts 2 or 3 of Study 101
- Safety Data Group 2 (n=469): patients with all solid tumors, treated at any dose level in any portion of Study 101, as well as patients treated in Study 10059010; data for all solid tumors at the dose of 20 mg daily (n=318) will be provided in summary tables separately
- Safety Data Group 3 (n=179): patients or healthy volunteers in all other studies, specifically healthy volunteer studies TAS-120-102, TAS-120-103, AS-120-104, TAS-120-105, TAS-120-106, TAS-120-107, and 10059020

At the time of the safety update, Taiho plans to submit safety updates for studies with combination treatments and recently initiated monotherapy studies (TAS-120-108 hepatic impairment study, TAS-120-201 metastatic breast cancer, TAS-120-202 tumor agnostic with FGFR alterations, and TAS-120-301 CCA).

SPONSOR QUESTIONS AND FDA RESPONSES

1. Does the Agency agree that the results of all 103 patients from the Phase 2 portion of the pivotal Phase 1/2 study where the majority of responders have been followed for >6 months from onset of response, the objective response rate (ORR) and duration of response for futibatinib are sufficient to support the filing

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of an NDA for the proposed indication under the accelerated approval pathway (21CFR subpart H)?

FDA Response: Yes, FDA agrees that the results of TAS-120-101 trial may support filing of a New Drug Application for futibatinib for the proposed indication; however, a final determination will be made during the filing review. Refer also to FDA's response to Question #5.

Sponsor response: The Sponsor acknowledges FDA's comment and no further discussion is needed

Discussion during meeting: No further discussion occurred.

2. Does the Agency agree that the proposed futibatinib NDA meets the requirements for a Priority Review designation?

FDA Response: Final determination of the review designation is made at the time the application is submitted.

Sponsor response: The Sponsor acknowledges FDA's comment and no further discussion is needed

Discussion during meeting: No further discussion occurred.

3. Does the Agency agree with the proposed rolling submission schedule?

FDA Response:

Although FDA does not object to the proposed rolling submission schedule, FDA recommends that, if possible, Taiho submits all CMC information in July 2021 except for the drug substance stability (S7) and drug product stability (P8) sections. These two sections may be submitted in December 2021 as proposed.

FDA notes that the proposed NDA qualifies for a Real-Time Oncology Review (RTOR) and encourages Taiho to submit the application using this program as well as the Assessment Aid. For additional information, refer to

<https://www.fda.gov/about-fda/oncology-center-excellence/real-time-oncology-review>

<https://www.fda.gov/about-fda/oncology-center-excellence/assessment-aid>

Sponsor response: The Sponsor acknowledges FDA's recommendation for submission of CMC section by July 2021. The Sponsor believes that the following submission timeline for CMC sections is achievable:

- Sections 3.2.S, 3.2.P.1, 3.2.P.3, 3.2.P.4, 3.2.P.6, and 3.2.P.7: August 31, 2021
- Sections 3.2.P.2 and 3.2.P.5: final timeline will be impacted by agreement on dissolution method; see Sponsor response to Question 19
- Section 3.2.P.8 and Module 2.3: December 31, 2021

Does the Agency agree with this timeline for the CMC sections in the rolling submission?

Discussion during meeting: FDA acknowledged the proposed submission timeline for the quality sections in three batches and stated this this would be acceptable. FDA specifically inquired about when the 2nd component would come in. Taiho stated that a timeline will be provided by June 30th. Refer also to meeting Discussion under Question #19.

4. Does the Agency agree to consider futibatinib for Type C (Written Report Only) Project Orbis to support collaborative review of the futibatinib marketing applications in the US and other Project Orbis Partners?

FDA Response: Yes, futibatinib can be considered a Type C Project Orbis. As early as possible but no later than at the time of NDA submission, provide a global submission plan (attachment 2) and individual Sponsor Authorization Letters (attachments 3 and 4) for each regulatory authority with whom FDA may share unredacted regulatory documents. You may fill out and submit the attached Product Quality Assessment Aid (PQAA) for CMC sections in m1 as a word file at the time of NDA submission (attachment 1).

Sponsor response: The Sponsor acknowledges FDA's recommendation and will provide the requested information to the Agency prior to the NDA submission. No further discussion is needed.

Discussion during meeting: During the meeting, Taiho stated that the Attachments referenced in FDA's Response in the preliminary comments were not included with correspondence they received. FDA stated that the attachments will be provided soon after the meeting.

5. Does the Agency agree that the efficacy and safety results from the pivotal study based on the pre-defined primary analysis using the October 1, 2020 cut-off date are acceptable to support the filing of the proposed NDA including the integrated summaries of clinical safety with the end of study results of the May 29, 2021 cut-off date to be included as a CSR addendum only?

FDA Response: FDA agrees that the data cutoff date (October 1, 2020) for efficacy will support the filing of an application. In the application submission, specify the number of patients with response that were not followed up for at

least 6 months following an initial response and provide the reason. FDA also requests that Taiho provide an efficacy update containing an updated duration of response (DoR) for those patients identified as responders by the October 1, 2020 date (i.e., do not provide data for patients that were identified as responders after the October 1, 2020 cutoff date). The update should contain the relevant datasets for both safety and efficacy in addition to the proposed addendum to the clinical study report.

Sponsor response: The Sponsor acknowledges FDA's comment and will provide the following documents as requested:

- A CSR addendum for TAS-120-101 with updated efficacy and safety information based on the May 29, 2021 study completion cut-off date. This addendum will be submitted by October 29, 2021.
- In addition, an update of efficacy (including DoR) and safety using the May 29, 2021 cut-off date only for patients identified as responders by the October 1, 2020 primary analysis cut-off date will be submitted by August 31, 2021 (including datasets).
- The Sponsor will provide the number of patients with response as of the October 1, 2020 primary analysis that were not followed up for at least 6 months following an initial response and provide the reason. This information will be submitted as part of the CSR for TAS-120-101 by August 31, 2021.

The Sponsor plans to provide SDTM and ADaM datasets with the May 29, 2021 cut-off date under a different directory from the October 1, 2020 primary analysis cut-off in Module 5 of the proposed NDA. Does the Agency agree with this approach?

Discussion during meeting: FDA acknowledged Taiho's response and confirmed that Taiho's understanding is consistent with FDA's intent.

6. Does the Agency agree that an integrated safety analysis using the 3 safety data groups previously agreed upon based on an October 1, 2020 cut-off date is acceptable for the proposed NDA submission?

FDA Response: Yes, FDA agrees and requests that datasets be provided for all groupings.

Sponsor response: The Sponsor acknowledges FDA's comment and no further discussion is needed

Discussion during meeting: No further discussion occurred.

7. Does the Agency agree with the Sponsor's proposal of data presentation for the 90/120-day safety update?

FDA Response: No. The safety update report should contain only updated safety data from Study TAS-120-101 based on a more recent data cut-off date; the written summary and datasets should also be provided. Taiho may include additional summary data from the ongoing futibatinib monotherapy studies.

Sponsor response: The Sponsor acknowledges FDA's comment and will provide updated safety data based on a more recent data cut-off date for the TAS-120-101 study including a written summary and datasets of the following:

- All serious adverse events (SAEs)
- All deaths reported on treatment or within 30 days after last dose of study drug
- Adverse events (AEs) leading to discontinuation
- Any significant update on adverse events of special interest (AESIs)

The Sponsor will also provide full narratives and case report forms (CRFs) for patients with SAEs considered to be possibly related and/or related to study treatment, patients who died during study treatment or within 30 days after last dose, and treatment discontinuations where the primary cause was an AE.

Does the Agency agree with the Sponsor's revised proposal?

Discussion during meeting: FDA acknowledged Taiho's revised proposal and stated that it was acceptable. FDA stated that because the trial is a single-arm study, FDA considers all SAEs to be related to study drug unless there is a clear alternative explanation for the SAE. Taiho stated that this approach seemed reasonable.

8. Does the Agency agree with the Sponsor's proposal for AESIs and PTs to be used?

FDA Response: FDA agrees.

Sponsor response: The Sponsor acknowledges FDA's comment and no further discussion is needed

Discussion during meeting: No further discussion occurred.

9. Does the Agency agree with the revisions made in the updated SAPs?

FDA Response: The updated SAPs appear acceptable.

Sponsor response: The Sponsor acknowledges FDA's comment and no further discussion is needed

Discussion during meeting: No further discussion occurred.

10. Does the Agency agree with the proposed files and format of the submission data?

FDA Response: The proposed files and format of the submission data appear acceptable.

Sponsor response: The Sponsor acknowledges FDA's comment and no further discussion is needed

Discussion during meeting: No further discussion occurred.

11. Does the Agency agree with the Sponsor's proposed analyses for safety, efficacy, and PopPK?

FDA Response: FDA agrees.

Sponsor response: The Sponsor acknowledges FDA's comment and no further discussion is needed

Discussion during meeting: No further discussion occurred.

12. Does CDER concur and support CDRH input as provided to Taiho and agree the proposed futibatinib NDA may be filed and considered for approval without a co-submission of an sPMA application?

FDA Response: CDER concurs with the advice provided to Taiho by CDRH in the final meeting minutes dated April 23, 2021. FDA also acknowledges Taiho's plan to submit as a PMC the PMA application for FGFR2 rearrangements in CCA based on the (b) (4), utilizing the currently ongoing Phase 3 study in first line CCA.

Sponsor response: The Sponsor acknowledges FDA's comment and no further discussion is needed

Discussion during meeting: No further discussion occurred.

13. Does the Agency agree that impurity strategy per ICH Q3A as proposed and confirmed previously by Taiho is acceptable?

FDA Response: As previously conveyed to Taiho (see meeting minutes dated January 25, 2019), controlling genotoxic impurities to Q3A would be acceptable for a drug within the Scope of S9.

Sponsor response: The Sponsor acknowledges FDA's comment and no further discussion is needed

Discussion during meeting: No further discussion occurred.

14. Does the Agency agree that a test for elemental impurities is not required in the futibatinib drug substance specification for commercial batches based on the analysis performed on representative batches of drug substance?

FDA Response: The omission of a test for elemental impurities in the Drug Substance specification may be acceptable provided the appropriate control for elemental impurities is performed in the Drug Product or adequate risk assessment is provided according to ICH Q3D. We refer Taiho to the response to Question 16 regarding the elemental impurities testing strategy for the drug product.

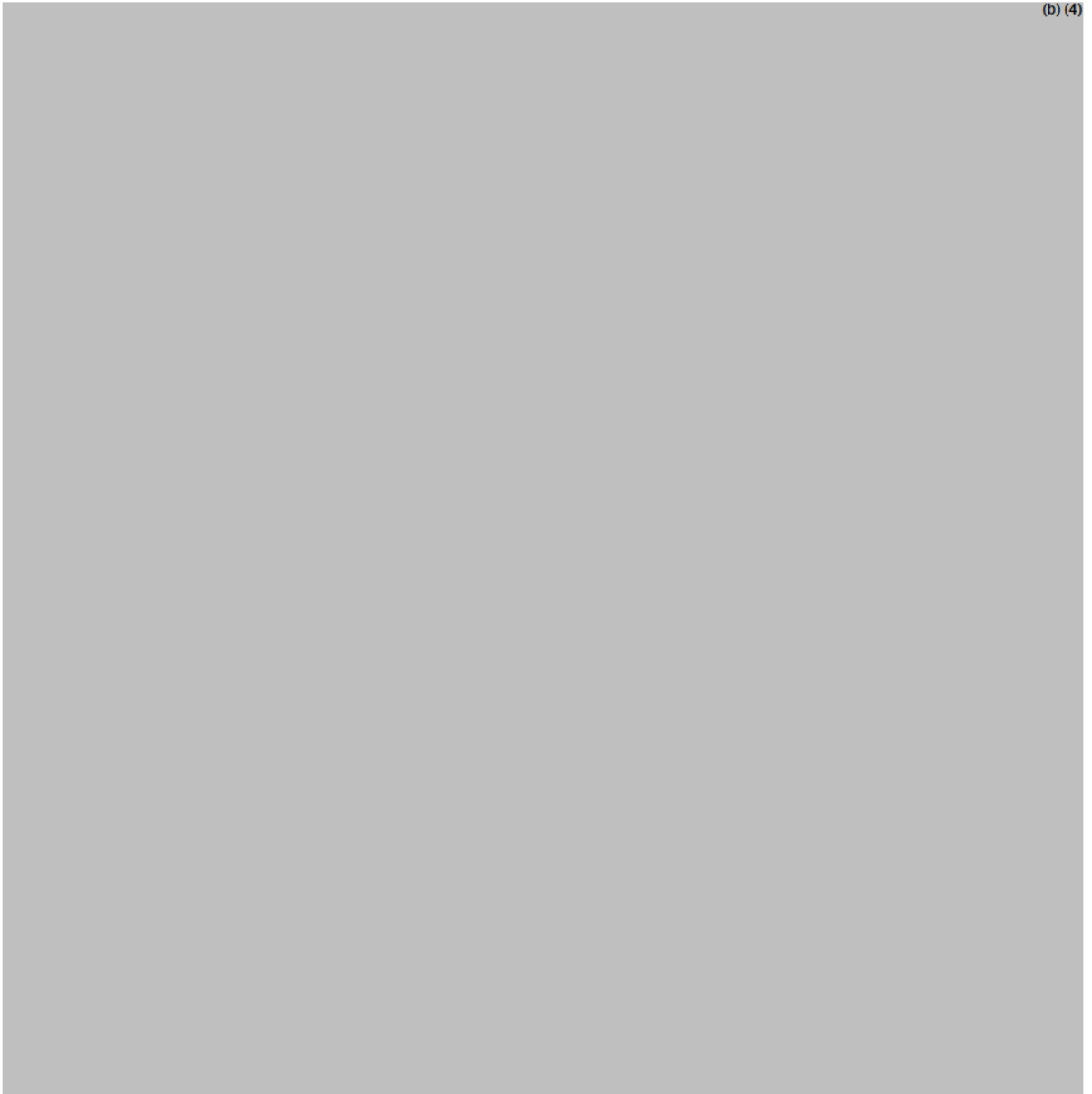
Sponsor response: The Sponsor acknowledges FDA's comment and no further discussion is needed

Discussion during meeting: No further discussion occurred.

- 15.



(b) (4)



Discussion during meeting: FDA acknowledged the clarification and stated that the proposal is acceptable. Taiho requested clarification as stated above; FDA clarified that no other studies will be needed.

16. Does the Agency agree that a test for elemental impurities is not required in the futibatinib drug product specification for commercial batches based on the comprehensive risk assessment performed?

FDA Response: The provided risk assessment for elemental impurities in the futibatinib drug product appears adequate. However, the final determination about the adequacy of the provided risk assessment for elemental impurities will

be made following review of the CMC information submitted in the original NDA submission.

Sponsor response: The Sponsor acknowledges FDA's comment and no further discussion is needed

Discussion during meeting: No further discussion occurred.

17. For detailed supporting information, please refer to Section 1.7.6.2

- a. Does the Agency agree that the proposed stability data is adequate for NDA filing and review?

FDA Response: Yes, FDA agrees that in the original NDA submission may include 24-month LTSS data and 6-month accelerated stability data from three commercial-scale batches (non-debossed tablets) manufactured at the Kitajima CTM facility along with 3-month LTSS and 3-month accelerated stability data from three commercial-scale batches (debossed tablets) made at (b) (4), the proposed commercial manufacturing facility.

- b. Does the Agency agree that the proposed stability data is adequate to consider a 36-month shelf-life designation assuming FDA review of the data is satisfactory, in accordance with ICH Q1E?

FDA Response: The adequacy of the provided stability data and the designation of the shelf-life will be determined following review of the CMC information submitted in the original NDA submission.

- c. Does the Agency agree that the inclusion of proposed data using debossed tablets is sufficient for NDA filing and review?

FDA Response: Yes, FDA agrees the inclusion of proposed data using debossed tablets deems sufficient to support NDA submission.

Sponsor response: The Sponsor acknowledges FDA's comment and no further discussion is needed

Discussion during meeting: No further discussion occurred.

18. Does the Agency agree that above approach is adequate to support filing and review of the proposed NDA to support commercial supplies for the US market?

FDA Response: Yes. Based on the information provided in the meeting package, it seems the approach is adequate to support filing and review of the

proposed NDA to support commercial supplies for the US market. Note that to validate proposed commercial packager using drug product manufactured at different manufacturing sites, a comparative report to demonstrate drug product (DP) equivalency on manufacturing (process and equipment), DP CQA and stability data should be provided. As a reminder, the FDA does not approve process validation approaches, protocols, or number of specific batches used in any process validation studies. The actual protocols, acceptance criteria, and study outcomes (as applicable) will be evaluated during an inspection of your manufacturing facilities. The product design and the suitability of manufacturing processes and control strategy will be evaluated during the NDA review cycle. It is your company's responsibility to conduct all studies necessary to assure your commercial manufacturing process including packaging is capable of consistently delivering quality product. For additional information on process validation, please refer to "Guidance for Industry, Process Validation: General Principles and Practices" posted at the following link.

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070336.pdf>.

For further information on Agency's drug compliance and pre-approval inspection programs please refer to the following links on FDA's website:

<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/ucm252671.htm>

Also as reminder, provide all necessary facility information in the 356h Form and relevant Manufacturer modules in the NDA submission as per FDA Guidance for Industry "Identification of Manufacturing Establishments in Applications Submitted to CBER and CDER Questions and Answers" (October 2019) to facilitate the Agency's review.

Sponsor response: The Sponsor acknowledges FDA's comment and no further discussion is needed

Discussion during meeting: No further discussion occurred.

19. Does the Agency agree that the proposed dissolution method development is satisfactory based on FDA preliminary comments in 2019 and adequate for filing and review of the NDA?

FDA Response:

The Division of Biopharmaceutics provided the comments and deficiencies regarding the proposed dissolution method in the Advice Letter dated 11/10/2020. Currently, the proposed dissolution method [*USP Apparatus II Paddle, 50 rpm, 900 mL of (b) (4) with 0.5% w/v polysorbate 80, 37°C*] appears not adequate. Please provide (a) response to the comments and deficiencies in the Advice Letter, (b) the complete dissolution data profiles of the pivotal clinical batches, primary registration batches, and (c) the dissolution data profiles of batches that are manufactured

from different manufacturing sites which are used in the proposed bridging stability study.

Sponsor response: The Sponsor was not able to locate the Advice Letter dated November 10, 2020 until after the FDA Preliminary Comments were received on June 11, 2021. Therefore, the Sponsor is unable to fully address item (a) during the meeting and respectfully proposes to address the comments and deficiencies in a follow-up response, to be submitted by June 30, 2021 and confirmed as a post-meeting note in the final minutes. In reference to items (b) and (c), the Sponsor commits to providing this information in the NDA submission.

Does the Agency concur with the Sponsor's proposal for item (a)?

Discussion during meeting: FDA stated that this proposal was acceptable. Refer also to discussion under Question 3. Taiho requested additional clarification on the FDA Advice Letter dated November 10, 2020. FDA stated that further justification/explanation are expected to address the deficiencies/comments in the letter. If Taiho will develop a new dissolution method, the new dissolution data on pivotal clinical batches and registration batches are expected. Taiho acknowledged.

20. Does the Agency agree that this executed batch record will be adequate to support filing and review of the proposed NDA?

FDA Response: Yes, the FDA agrees if the submitted executed batch record from the (b) (4) performance qualification (PQ) batch packaged in proposed commercial packaging is also one of the three stability batches for NDA submission

Sponsor response: The Sponsor would like to clarify that the performance qualification (PQ) batch is not one of the three stability batches for NDA submission. The PQ batch will be packaged for bulk storage but primary commercial packaging will not be completed.

Based on FDA's response, the Sponsor proposes to submit the executed batch record for one of the bridging stability batches, which has been manufactured at commercial scale at the proposed commercial tablet manufacturing site and has been packaged in the proposed commercial packaging. The Sponsor does not intend to submit the executed batch record from the PQ batch.

Does the Agency agree that the executed batch record from one of the bridging stability studies will be adequate to support filing and review of the proposed NDA?

Discussion during meeting: FDA acknowledged the proposal and stated that the proposal is acceptable.

ADDITIONAL COMMENTS

21. In the submission, include information about the demographic characteristics (e.g. race, ethnicity, age) of patients with cholangiocarcinoma and FGFR2-altered cholangiocarcinoma in the US and provide a justification of the applicability of the study results to the US population.

Sponsor response: The Sponsor acknowledges FDA's comment and will provide the requested information at the time of NDA submission. No further discussion is required.

Discussion during meeting: No further discussion occurred.

22. Provide a description of which narratives and case report forms will be submitted with the application (e.g., all deaths within 100 days, all SAE's, all AEs leading to discontinuation regardless of causality).

Sponsor response: The Sponsor acknowledges FDA's comment and will provide safety narratives and case report forms for all patients meeting one or more of the following criteria:

- Died on treatment or within 30 days after the last dose of futibatinib;
- Discontinued treatment due to an adverse event; or
- Experienced any treatment-emergent SAE that was considered to be related and/or possibly related to futibatinib.

Discussion during meeting: No further discussion occurred.

23. Sponsor Request for Clarification: The amended Initial Pediatric Study Plan (iPSP) was submitted to IND 121062 on March 29, 2021.

Can the Agency provide anticipated timing for the Sponsor to receive further comments or agreement on the amended iPSP?

Discussion during meeting: FDA stated that Taiho should expect to receive the amended iPSP in the next few weeks.

ADVANCING ONCOLOGY DECENTRALIZED TRIALS

FDA Oncology requests that applicants submitting data to support NDA/BLA applications to voluntarily add flags to datasets in order to discriminate between REMOTE assessments and TRIAL SITE assessments. The intent is to allow FDA to learn from trials conducted in the COVID-19 pandemic that permitted some aspects of trial conduct to be performed remote from trial sites to reduce potential COVID exposure. The FDA hopes to learn more about the opportunities and challenges of

these REMOTE modifications in order to foster use of “decentralize” aspects of clinical trials prospectively in the post-COVID era.

For details please refer to: <https://www.fda.gov/about-fda/oncology-center-excellence/advancing-oncology-decentralized-trials>.

INCLUSION OF MINORITIES IN CLINICAL TRIALS

The Agency encourages the inclusion of a diverse population in all phases of drug development. This inclusion helps to ensure that medical products are safe and effective for everyone. We strongly encourage the enrollment of populations most affected, specifically racial and ethnic minorities. Please incorporate strategies to ensure that a diverse population is included in your current and future clinical trials.

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (codified at section 505B of the Federal Food, Drug, and Cosmetic Act (FD&C Act), 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(s) in pediatric patients unless this requirement is waived or deferred (see section 505B(a)(1)(A) of the FD&C Act). Applications for drugs or biological products for which orphan designation has been granted that otherwise would be subject to the requirements of section 505B(a)(1)(A) are exempt pursuant to section 505B(k)(1) from the PREA requirement to conduct pediatric assessments.

Title V of the FDA Reauthorization Act of 2017 (FDARA) amended the statute to create section 505B(a)(1)(B), which requires that any original marketing application for certain adult oncology drugs (i.e., those intended for treatment of an adult cancer and with molecular targets that FDA has determined to be substantially relevant to the growth or progression of a pediatric cancer) that are submitted on or after August 18, 2020, contain reports of molecularly targeted pediatric cancer investigations. See link to list of relevant molecular targets below. These molecularly targeted pediatric cancer investigations must be “designed to yield clinically meaningful pediatric study data, gathered using appropriate formulations for each age group for which the study is required, regarding dosing, safety, and preliminary efficacy to inform potential pediatric labeling” (section 505B(a)(3)). Applications for drugs or biological products for which orphan designation has been granted and which are subject to the requirements of section 505B(a)(1)(B), however, will not be exempt from PREA (see section 505B(k)(2)) and will be required to include plans to conduct the molecularly targeted pediatric investigations as required, unless such investigations are waived or deferred.

Under section 505B(e)(2)(A)(i) of the FD&C Act, you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End of Phase 2 (EOP2) meeting, or such other

time as agreed upon with FDA. (In the absence of an EOP2 meeting, refer to the draft guidance below.) The iPSP must contain an outline of the pediatric assessment(s) or molecularly targeted pediatric cancer investigation(s) that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation; and any previously negotiated pediatric plans with other regulatory authorities. The iPSP should be submitted in PDF and Word format. Failure to include an Agreed iPSP with a marketing application could result in a refuse to file action.

For additional guidance on the timing, content, and submission of the iPSP, including an iPSP Template, please refer to the draft guidance for industry *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans*.

For the latest version of the molecular target list, please refer to FDA.gov.²

FDARA REQUIREMENTS

Sponsors planning to submit original applications on or after August 18, 2020 or sponsors who are uncertain of their submission date may request a meeting with the Oncology Center of Excellence Pediatric Oncology Program to discuss preparation of the sponsor's initial pediatric study plan (iPSP) for a drug/biologic that is intended to treat a serious or life-threatening disease/ condition which includes addressing the amendments to PREA (Sec. 505B of the FD & C Act) for early evaluation in the pediatric population of new drugs directed at a target that the FDA deems substantively relevant to the growth or progression of one or more types of cancer in children. The purpose of these meetings will be to discuss the Agency's current thinking about the relevance of a specific target and the specific expectations for early assessment in the pediatric population unless substantive justification for a waiver or deferral can be provided. Meetings requests should be sent to the appropriate review division with the cover letter clearly stating, "**MEETING REQUEST FOR PREPARATION OF iPSP MEETING UNDER FDARA.**" These meetings will be scheduled within 30 days of meeting request receipt. The Agency strongly advises the complete meeting package be submitted at the same time as the meeting request. Sponsors should consult the guidance for industry, *Formal Meetings Between the FDA and Sponsors or Applicants*, to ensure open lines of dialogue before and during their drug development process.

In addition, you may contact the OCE Subcommittee of PerC Regulatory Project Manager by email at OCEPERC@fda.hhs.gov. For further guidance on pediatric product development, please refer to FDA.gov.³

² <https://www.fda.gov/about-fda/oncology-center-excellence/pediatric-oncology>

³ <https://www.fda.gov/drugs/development-resources/pediatric-and-maternal-health-product-development>

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57 including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the PLR Requirements for Prescribing Information⁴ and Pregnancy and Lactation Labeling Final Rule⁵ websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products.
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential.
- Regulations and related guidance documents.
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of important format items from labeling regulations and guidances.
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

Pursuant to the PLLR, you should include the following information with your application to support the changes in the Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of labeling. The application should include a review and summary of the available published literature regarding the drug's use in pregnant and lactating women and the effects of the drug on male and female fertility (include search parameters and a copy of each reference publication), a cumulative review and summary of relevant cases reported in your pharmacovigilance database (from the time of product development to present), a summary of drug utilization rates amongst females of reproductive potential (e.g., aged 15 to 44 years) calculated cumulatively since initial approval, and an interim report of an ongoing pregnancy registry or a final report on a closed pregnancy registry. If you believe the information is not applicable,

⁴ <https://www.fda.gov/drugs/laws-acts-and-rules/plr-requirements-prescribing-information>

⁵ <https://www.fda.gov/drugs/labeling/pregnancy-and-lactation-labeling-drugs-final-rule>

provide justification. Otherwise, this information should be located in Module 1. Refer to the draft guidance for industry *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format*.

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

DATA STANDARDS FOR STUDIES

Under section 745A(a) of the FD&C Act, electronic submissions “shall be submitted in such electronic format as specified by [FDA].” FDA has determined that study data contained in electronic submissions (i.e., NDAs, BLAs, ANDAs and INDs) must be in a format that the Agency can process, review, and archive. Currently, the Agency can process, review, and archive electronic submissions of clinical and nonclinical study data that use the standards specified in the Data Standards Catalog.⁶

On December 17, 2014, FDA issued the guidance for industry *Providing Electronic Submissions in Electronic Format - Standardized Study Data*. This guidance describes the submission types, the standardized study data requirements, and when standardized study data are required. Further, it describes the availability of implementation support in the form of a technical specifications document, *Study Data Technical Conformance Guide*, as well as email access to the eData Team (cdeleredata@fda.hhs.gov) for specific questions related to study data standards. Standardized study data are required in marketing application submissions for clinical and nonclinical studies that started after December 17, 2016. Standardized study data are required in commercial IND application submissions for clinical and nonclinical studies that started after December 17, 2017. CDER has produced a Study Data Standards Resources web page⁷ that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers.

For commercial INDs and NDAs, Standard for Exchange of Nonclinical Data (SEND) datasets are required to be submitted along with nonclinical study reports for study types that are modeled in an FDA-supported SEND Implementation Guide version. The FDA Data Standards Catalog, which can be found on the Study Data Standards Resources web page noted above, lists the supported SEND Implementation Guide versions and associated implementation dates.

Although the submission of study data in conformance to the standards listed in the FDA Data Standards Catalog will not be required in studies that started on or before December 17, 2016, CDER strongly encourages IND sponsors to use the FDA

⁶ <http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm>

⁷ <http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm>

supported data standards for the submission of IND applications and marketing applications. The implementation of data standards should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. For clinical and nonclinical studies, IND sponsors should include a plan (e.g., in the IND) describing the submission of standardized study data to FDA. This study data standardization plan (see the FDA Study Data Technical Conformance Guide) will assist FDA in identifying potential data standardization issues early in the development program.

If you have not previously submitted an eCTD submission or standardized study data, we encourage you to send us samples for validation following the instructions at FDA.gov. For general toxicology, supporting nonclinical toxicokinetic, and carcinogenicity studies, submit data in the Standards for the Exchange of Nonclinical Data (SEND) format. The validation of sample submissions tests conformance to FDA supported electronic submission and data standards; there is no scientific review of content.

The Agency encourages submission of sample data for review before submission of the marketing application. These datasets will be reviewed only for conformance to standards, structure, and format. They will not be reviewed as a part of an application review. These datasets should represent datasets used for the phase 3 trials. The FDA Study Data Technical Conformance Guide (Section 7.2 eCTD Sample Submission pg. 30) includes the link to the instructions for submitting eCTD and sample data to the Agency. The Agency strongly encourages Sponsors to submit standardized sample data using the standards listed in the Data Standards Catalog referenced on the FDA Study Data Standards Resources web site. When submitting sample data sets, clearly identify them as such with **SAMPLE STANDARDIZED DATASETS** on the cover letter of your submission.

Additional information can be found at FDA.gov.⁸

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

The Office of Scientific Investigations (OSI) requests that the items described in the draft guidance for industry, *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions*, and the associated conformance guide, *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications*, be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA ORA investigators who conduct those inspections. This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials).

⁸ <https://www.fda.gov/industry/study-data-standards-resources/study-data-submission-cder-and-cber>

Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

Please refer to the draft guidance for industry *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions* (February 2018) and the associated *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications*.⁹

ONCOLOGY PILOT PROJECTS

The FDA Oncology Center of Excellence (OCE) is conducting two pilot projects, the Real-Time Oncology Review (RTOR) and the Assessment Aid. RTOR is a pilot review process allowing interactive engagement with the applicant so that review and analysis of data may commence prior to full supplemental NDA/BLA submission. Assessment Aid is a voluntary submission from the applicant to facilitate FDA's assessment of the NDA/BLA application (original or supplemental). An applicant can communicate interest in participating in these pilot programs to the FDA review division by sending a notification to the Regulatory Project Manager when the top-line results of a pivotal trial are available or at the pre-sNDA/sBLA meeting. Those applicants who do not wish to participate in the pilot programs will follow the usual submission process with no impact on review timelines or benefit-risk decisions. More information on these pilot programs, including eligibility criteria and timelines, can be found at the following FDA websites:

- RTOR¹⁰: In general, the data submission should be fully CDISC-compliant to facilitate efficient review.
- Assessment Aid¹¹

ATTACHMENTS AND HANDOUTS

1. Product Quality Assessment Aid (PQAA) for CMC sections
2. Project Orbis – Global Submission Plan
3. Sponsor Authorization – Foreign Government_Orbis TEMPLATE
4. Sponsor Authorization Letter Contacts and Process
5. Slide deck sent from Taiho in response to FDA Preliminary comments

⁹ <https://www.fda.gov/media/85061/download>

¹⁰ <https://www.fda.gov/about-fda/oncology-center-excellence/real-time-oncology-review-pilot-program>

¹¹ <https://www.fda.gov/about-fda/oncology-center-excellence/assessment-aid-pilot-project>

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/

KRISTIN D JARRELL
06/15/2021 02:27:56 PM

CDER Breakthrough Therapy Designation Determination Review Template (BTDDRT)

IND/NDA/BLA #	IND 121062 STN 244
Request Receipt Date	December 23, 2020
Product	Futibatinib (TAS-120)
Indication	Treatment of patients with advanced cholangiocarcinoma (CCA) harboring FGFR2 gene rearrangements (including gene fusions).
Drug Class/Mechanism of Action	small molecule inhibitor of the fibroblast growth factor receptor (FGFR).
Sponsor	Taiho Oncology, Inc.
ODE/Division	OOD/DO3
Breakthrough Therapy Request (BTDR) Goal Date (within 60 days of receipt)	February 12, 2021

*Note: This document must be uploaded into CDER's electronic document archival system as a **clinical review: REV-CLINICAL-24 (Breakthrough Therapy Designation Determination)** even if the review is attached to the MPC meeting minutes and will serve as the official primary Clinical Review for the Breakthrough Therapy Designation Request (BTDR). Link this review to the incoming BTDR. Note: Signatory Authority is the Division Director.*

Section I: Provide the following information to determine if the BTDR can be denied without Medical Policy Council (MPC) review.

1. Briefly describe the indication for which the product is intended (Describe clearly and concisely since the wording will be used in the designation decision letter):

Futibatinib (TAS-120) for previously treated patients with advanced cholangiocarcinoma (CCA) harboring FGFR2 gene rearrangements (including gene fusions).

2. Are the data supporting the BTDR from trials/IND(s) which are on Clinical Hold?

☐ YES ☒ NO

3. Was the BTDR submitted to a PIND?

☐ YES ☒ NO

If "Yes" do not review the BTDR. The sponsor must withdraw the BTDR. BTDR's cannot be submitted to a PIND.

If 2 above is checked "Yes," the BTDR can be denied without MPC review. Skip to number 5 for clearance and sign-off. If checked "No", proceed with below:

4. Consideration of Breakthrough Therapy Criteria:

- a. Is the condition serious/life-threatening¹?

☒ YES ☐ NO

If 4a is checked "No," the BTDR can be denied without MPC review. Skip to number 5 for clearance and sign-off. If checked "Yes", proceed with below:

¹ For a definition of serious and life threatening see Guidance for Industry: "Expedited Programs for Serious Conditions—Drugs and Biologics" <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf>

- b. Are the clinical data used to support preliminary clinical evidence that the drug may demonstrate substantial improvement over existing therapies on 1 or more clinically significant endpoints adequate and sufficiently complete to permit a substantive review?
- ☒ YES, the BTDR is adequate and sufficiently complete to permit a substantive review
- ☐ Undetermined
- ☐ NO, the BTDR is inadequate and not sufficiently complete to permit a substantive review; therefore, the request must be denied because (check one or more below):
- i. Only animal/nonclinical data submitted as evidence ☐
 - ii. Insufficient clinical data provided to evaluate the BTDR
(e.g. only high-level summary of data provided, insufficient information about the protocol[s]) ☐
 - iii. Uncontrolled clinical trial not interpretable because endpoints are not well-defined and the natural history of the disease is not relentlessly progressive (e.g. multiple sclerosis, depression) ☐
 - iv. Endpoint does not assess or is not plausibly related to a serious aspect of the disease (e.g., alopecia in cancer patients, erythema chronicum migrans in Lyme disease) ☐
 - v. No or minimal clinically meaningful improvement as compared to available therapy²/ historical experience (e.g., <5% improvement in FEV1 in cystic fibrosis, best available therapy changed by recent approval) ☐

5. Provide below a brief description of the deficiencies for each box checked above in Section 4b:

If 4b is checked “No”, BTDR can be denied without MPC review. Skip to number 6 for clearance and sign-off (Note: The Division always has the option of taking the request to the MPC for review if the MPC’s input is desired. If this is the case, proceed with BTDR review and complete Section II). If the division feels MPC review is not required, send the completed BTDDRT to Miranda Raggio for review. Once reviewed, Miranda will notify the MPC Coordinator to remove the BTDR from the MPC calendar. If the BTDR is denied at the Division level without MPC review, the BTDR Denial letter still must be cleared by Miranda Raggio, after division director and office director clearance.

If 4b is checked “Yes” or “Undetermined”, proceed with BTDR review and complete Section II, as MPC review is required.

6. Clearance and Sign-Off (no MPC review)

Deny Breakthrough Therapy Designation ☐

Reviewer Signature: {See appended electronic signature page}

Team Leader Signature: {See appended electronic signature page}

Division Director Signature: {See appended electronic signature page}

Section II: If the BTDR cannot be denied without MPC review in accordance with numbers 1-3 above, or if the Division is recommending that the BTDR be granted, provide the following additional information needed by the MPC to evaluate the BTDR.

7. A brief description of the drug, the drug’s mechanism of action (if known), the drug’s relation to existing therapy(ies), and any relevant regulatory history. Consider the following in your response.

- Information regarding the disease and intended population for the proposed indication.
- Disease mechanism (if known) and natural history (if the disease is uncommon).

² For a definition of available therapy refer to Guidance for Industry: “Expedited Programs for Serious Conditions—Drugs and Biologics” <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf>

Futibatinib is an oral FGFR1-4 inhibitor with antitumor activity in vitro cancer cell lines and in vivo animal tumor models driven by FGFR pathway aberrations.

The prognosis of patients with Stage III or IV CCA is extremely poor, with 5-year survival rates of 10% and 0% respectively and a median overall survival (OS) of 8 to 12 months. The combination gemcitabine+cisplatin is the current standard first-line chemotherapy regimen for patients with advanced, metastatic, unresectable CCA based on a randomized study comparing cisplatin plus gemcitabine with gemcitabine alone in 410 patients, with median progression-free survival (mPFS) 8.0 months in the cisplatin–gemcitabine group and 5.0 months in the gemcitabine-only group (hazard ratio, 0.64; 95% confidence interval, 0.52 to 0.80; $P < 0.001$) (Valle J., 2010). *FGFR2* gene rearrangements (including gene fusions) have been identified as an early driver of oncogenic events in 13-14% of CCA (Churi 2014; Arai 2014; Graham 2014). In a retrospective analysis of 377 patients with CCA, 95 had FGFR genetic alterations. There was no difference in OS between patients with CCA with FGFR2 fusions ($n = 63$) versus patients with CCA harboring other FGFR genetic alterations ($n = 29$). Median OS in 50 patients (all stages) with FGFR genetic alterations who did not receive FGFR-directed therapy was 24.3 months (95% CI 18.2; 49.8) compared with 44.8 months (95% CI 24.5 to NR) in 36 patients who received FGFR-directed therapy.

On December 2019, FDA approved pemigatinib – another FGFR inhibitor- for the treatment of adults with previously treated, unresectable locally advanced or metastatic cholangiocarcinoma with a fibroblast growth factor receptor 2 (FGFR2) fusion or other rearrangement. This accelerated approval is based on a single-arm study in 107 patients, with an observed objective response rate (ORR) of 36% (95% CI 27, 45) and a median duration of response (mDOR) of 9.1 months (95% CI 6.0, 14.5) (Pemizyre USPI).

8. Information related to endpoints used in the available clinical data:

- a. Describe the endpoints considered by the sponsor as supporting the BTDR and any other endpoints the sponsor plans to use in later trials. Specify if the endpoints are primary or secondary, and if they are surrogates.

The BTDR is supported by overall response rates (ORR) and duration of response (DOR) from a 103-patient cohort with long-term follow up enrolled in a “Phase 2” portion of Study TAS-120-101. The primary efficacy endpoint of this portion of Study TAS-120-101 was ORR by RECIST 1.1 as per an independent assessment. ORR is considered an outcome directly related to treatment and it has been used for approvals in oncology, both as a surrogate or as a direct demonstration of clinical benefit. In the relapsed FGFR2-rearranged CCA disease setting, ORR has been used for the accelerated approval of pemigatinib . In the first-line setting, ORR would be considered a surrogate endpoint.

- b. Describe the endpoint(s) that are accepted by the Division as clinically significant (outcome measures) for patients with the disease. Consider the following in your response:
 - *A clinical endpoint that directly measures the clinical benefit of a drug (supporting traditional approval).*
 - *A surrogate/established endpoint that is known to predict clinical benefit of a drug (i.e., a validated surrogate endpoint that can be used to support traditional approval).*
 - *An endpoint that is reasonably likely to predict clinical benefit of a drug (supporting accelerated approval), and the endpoint used in a confirmatory trial or trials to verify the predicted clinical benefit.*

Median survival in patients with refractory CCA is estimated in less than 12 months. ORR is an endpoint that has been used as a surrogate in this setting, particularly when the responses are durable. In the confirmatory study, progression-free survival and overall survival will be used.

- c. Describe any other biomarkers that the Division would consider likely to predict a clinical benefit for the proposed indication even if not yet a basis for accelerated approval.

There are no other biomarkers/endpoints that are likely to predict clinical benefit in this disease setting.

9. A brief description of available therapies, if any, including a table of the available Rx names, endpoint(s) used to establish efficacy, the magnitude of the treatment effects (including hazard ratio, if applicable), and the specific intended population. Consider the following in your response:

- *If the available therapies were approved under accelerated approval, provide the information for the endpoint used to support accelerated approval and the endpoint used to verify the predicted clinical benefit.*
- *In addition to drugs that have been approved by FDA for the indication, also identify those treatments that may be used off-label for that indication.*

There is no standard effective therapy for the second line treatment of CCA. Chemotherapy agents as single agents or in combination have not demonstrated significant improvement in overall survival, with response rates below 10%. A systematic literature review evaluated the evidence for use of second-line chemotherapy in a molecularly unselected population of patients with advanced biliary cancer who progressed on first-line therapy (Lamarca et al., 2014). The review included 761 subjects across 25 studies and showed a median PFS duration of 3.2 months (95% CI: 2.7 to 3.7), response rate of 7.7% (95% CI: 4.6 to 10.9), and a median OS duration of 7.2 months (95% CI: 6.2 to 8.2). The following table summarizes some of the studies included in the meta-analysis.

Treatment	Line	Study type	N pts	ORR (%)	mPFS (months)	mOS (months)
Gemcitabine	2 nd /3 rd	Retrospective	17	28.5	5.1	17
Fluoropyrimidine-based	2 nd	Retrospective	255	1.2	1.8	13.2
Gemcitabine-based	2 nd	Retrospective	29	0	6.1	6.5
Gemcitabine/cisplatin	2 nd	Retrospective	60	1.7	3.5	6.7
Everolimus	2 nd	Single arm, open label	39	5.1	3.2	7.7
Irinotecan	2 nd	RCT, open-label	30	6.7	2.4	7.3
Irinotecan	3 rd -4 th	Single-arm, open-label	13	7.7	1.8	6.7
5FU-cisplatin	2 nd	Retrospective	66	8.3	2.6	6.2
Sunitinib	2 nd	Single-arm, open-label	56	8.9	1.7	4.8
Capecitabine/irinotecan	2 nd	RCT, open-label	30	13.3	3.7	10.1
FOLFOX	2 nd	Single-arm, open-label	37	21.2	3.1	6.9
FOLFIRI/bevacizumab	2 nd	Retrospective	13	38.4	8	20

On December 2019, FDA approved pemigatinib – another FGFR inhibitor- for the treatment of adults with previously treated, unresectable locally advanced or metastatic cholangiocarcinoma with a fibroblast growth factor receptor 2 (FGFR2) fusion or other rearrangement. This accelerated approval is based on a single-arm study in 107 patients, with an observed objective response rate (ORR) of 36% (95% CI 27, 45) and a median duration of response (mDOR) of 9.1 months (95% CI 6.0, 14.5) (Pemizyre USPI).

10. A brief description of any drugs being studied for the same indication, or very similar indication, that requested breakthrough therapy designation³.

- Pemigatinib (IND 138179) requested breakthrough designation, which was granted based on a ORR of 36%.

- (b) (4)

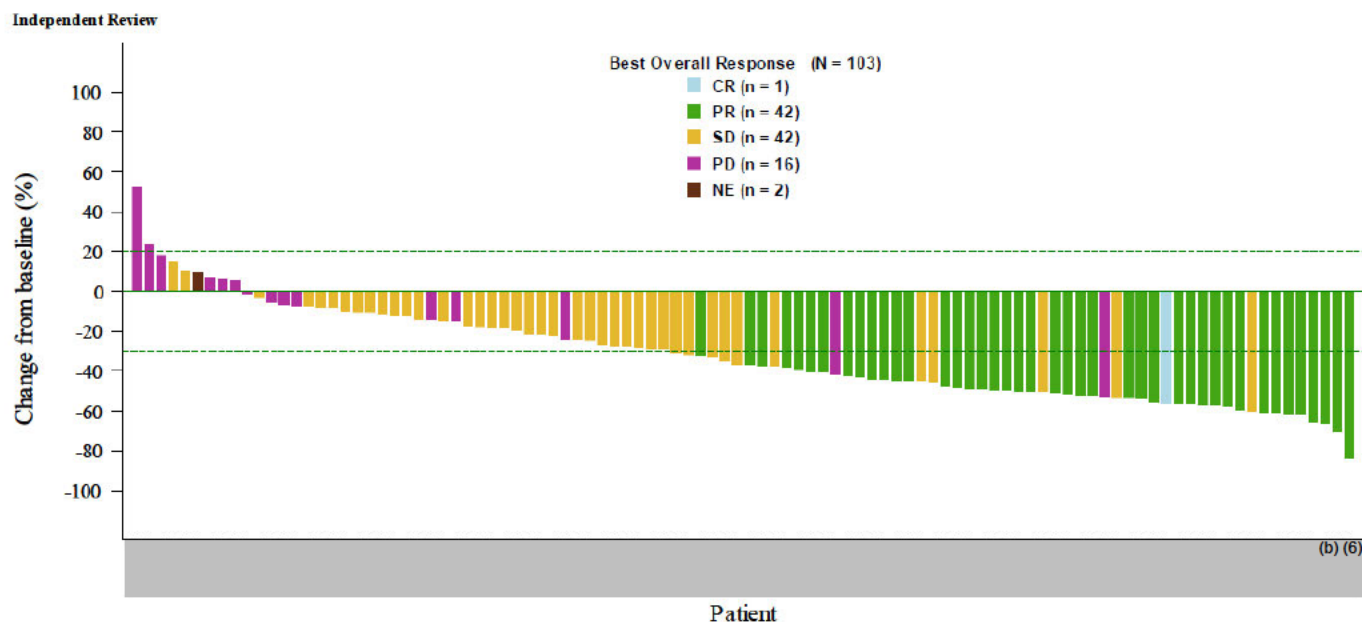
³ Biweekly reports of all BTDRs, including the sponsor, drug, and indication, are generated and sent to all CPMSs.

11. Information related to the preliminary clinical evidence:

- a. Table of clinical trials supporting the BTDR (only include trials which were relevant to the designation determination decision), including study ID, phase, trial design⁴, trial endpoints, treatment group(s), number of subjects enrolled in support of specific breakthrough indication, hazard ratio (if applicable), and trial results.
- b. Include any additional relevant information. Consider the following in your response:
 - *Explain whether the data provided should be considered preliminary clinical evidence of a substantial improvement over available therapies. In all cases, actual results, in addition to reported significance levels, should be shown. Describe any identified deficiencies in the trial that decrease its persuasiveness.*
 - *Identify any other factors regarding the clinical development program that were taken into consideration when evaluating the preliminary clinical evidence, such as trial conduct, troublesome and advantageous aspects of the design, missing data, any relevant nonclinical data, etc.*
 - *Safety data: Provide a brief explanation of the drug's safety profile, elaborating if it affects the Division's recommendation.*

The BTDR is supported by data from the "Phase 2" portion of Study TAS-120-101. Futibatinib 20 mg daily was administered to patients with intrahepatic CCA harboring *FGFR2* gene rearrangements (n=103) with disease progression after at least one prior line of systemic therapy. The independently assessed ORR was 41.7% (32.1, 51.9); the median duration of response was 9.7 months. DOR exceeded 6 months for 31 (72.1% of responders). A total of 6 patients to date had responses exceeding 12 months in duration, representing approximately 14% of responses.

⁴ Trial design information should include whether the trial is single arm or multi-arm, single dose or multi-dose, randomized or non-randomized, crossover, blinded or unblinded, active comparator or placebo, and single center or multicenter.



12. Division's recommendation and rationale (pre-MPC review):

☒ GRANT:

Provide brief summary of rationale for granting: The ORR of 41.7% (32.1, 51.9) observed with futibatinib in the subgroup of 103 patients with previously treated CCA with FGFR2 fusions represents an improvement over available second-line chemotherapy, which has a reported ORR of 7.7% (95% CI: 4.6 to 10.9) based on a meta-analysis of unselected patients with CCA in the second-line setting and beyond. Furthermore, the duration of response observed with futibatinib is clinically meaningful; the median duration of response is 9.7 months and 72% of responders had a DOR of 6 months or longer. The adverse event profile observed with futibatinib is acceptable in light of the serious nature and poor prognosis associated with CCA and consistent with the pharmacologic class.

For patients who received futibatinib of 20 mg (n: 103) across the drug development, the most frequently reported adverse event across all cohorts, regardless of grade or relationship to study therapy, was hyperphosphatemia (85%). Other frequently reported AEs across the population included diarrhea (35.9%), constipation (38.8%), dry mouth (35%), fatigue (34%), alopecia (34%), dry skin 29.1%), AST elevation (25.2), stomatitis (24.3%), nausea (24.3%), and decreased appetite (23.3%). The most frequently reported Grade ≥3 events regardless of relationship to study therapy were hyperphosphatemia (n=38 31) and elevations of AST (n=10).

Note, if the substantial improvement is not obvious, or is based on surrogate/pharmacodynamic endpoint data rather than clinical data, explain further.

☐ DENY:

Provide brief summary of rationale for denial:

Note that not looking as promising as other IND drugs is not a reason for denial; the relevant comparison is with available (generally FDA-approved) therapy. If the Division does not accept the biomarker/endpoint used as a basis for traditional approval or accelerated approval or as a basis for providing early clinical evidence of a substantial improvement over available therapy, explain why:

13. Division's next steps and sponsor's plan for future development:

- a. If recommendation is to grant the request, explain next steps and how the Division would advise the sponsor (for example, plans for phase 3, considerations for manufacturing and companion diagnostics, considerations for accelerated approval, recommending expanded access program):

Taiho plans to submit the results of the FGFR mutated CCA patients in Study TAS-120-101 to support an accelerated approval. To confirm the benefit of futibatinib in patients with FGFR-mutated CCA, Taiho is conducting Study FOENIX-CCA3, “A Phase 3, Open-Label, Randomized Study of Futibatinib Versus Gemcitabine-Cisplatin Chemotherapy as First-Line Treatment of Patients with Advanced Cholangiocarcinoma Harboring FGFR2 Gene Rearrangements”.

(b) (4)

- b. If recommendation is to deny the request and the treatment looks promising, explain how the Division would advise the sponsor regarding subsequent development, including what would be needed for the Division to reconsider a breakthrough therapy designation:

14. List references, if any:

15. Is the Division requesting a virtual MPC meeting via email in lieu of a face-to-face meeting? YES ☒ NO ☐

16. Clearance and Sign-Off (after MPC review):

Grant Breakthrough Therapy Designation ☐
Deny Breakthrough Therapy Designation ☐

Reviewer Signature: { See appended electronic signature page }
Team Leader Signature: { See appended electronic signature page }
Division Director Signature: { See appended electronic signature page }

Revised 3/18/19/M. Raggio

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/

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IND 121062

MEETING PRELIMINARY COMMENTS

Taiho Oncology, Inc.
Attention: Alpesh Patel
Director, Regulatory Affairs
101 Carnegie Center, Suite 101
Princeton, NJ 08540

Dear Mr. Patel:

Please refer to your investigational new drug application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for futibatinib.

We also refer to your April 21, 2020, correspondence, requesting a meeting to discuss the content and format of a New Drug Application for futibatinib for the treatment of patients with advanced intrahepatic cholangiocarcinoma harboring FGFR2 gene rearrangements, including gene fusions.

Our preliminary responses to your meeting questions are enclosed.

You should provide, to the Regulatory Project Manager, a hardcopy or electronic version of any materials (i.e., slides or handouts) to be presented and/or discussed at the meeting. In accordance with 21 CFR 10.65(e) and FDA policy, you may not electronically record the discussion at this meeting. The official record of this meeting will be the FDA-generated minutes.

If you have any questions, contact me at (240) 402-6611 or leah.her@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Leah S. Her, M.S., P.M.P.
Senior Regulatory Health Project Manager
Division of Regulatory Operations for Oncologic Diseases
Office of Regulatory Operations
Center for Drug Evaluation and Research

ENCLOSURE:

- Preliminary Meeting Comments



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PRELIMINARY MEETING COMMENTS

Meeting Type: B
Meeting Category: Pre-NDA

Meeting Date and Time: June 19, 2020 / 3:00 – 4:00 PM (EST)
Meeting Location: teleconference

Application Number: 121062
Product Name: futibatinib
Indication: treatment of patients with advanced intrahepatic cholangiocarcinoma (iCCA) harboring FGFR2 gene rearrangements (including gene fusion)

Sponsor/Applicant Name: Taiho Oncology, Inc.

Regulatory Pathway: 505(b)(1)

FDA ATTENDEES (tentative)

Center for Drug Evaluation and Research

Lola Fashoyin-Aje	Deputy Director (Acting), OOD/DO3
Sandra Casak	Clinical Team Leader, OOD/DO3
Naomi Horiba	Clinical Reviewer, OOD/DO3
Leah Her	Regulatory Health Project Manager, ORO/DRO-OD
Joyce Cheng	Statistical Team Leader (Acting), OB/DBV
Abhishek Bhattacharjee	Statistical Reviewer, OB/DBV
Jeanne Fourie-Zirkelbach	Clinical Pharmacology Team Leader, OCP/DCPV
Safaa Burns	Clinical Pharmacology Reviewer, OCP/DCPV
Matthew Thompson	Nonclinical Team Leader (Acting), OOD/DHOT
Dubravka Kufrin	Nonclinical Reviewer, OOD/DHOT
Xing Wang	Product Quality Reviewer, ONDP/DNDPI/NDPB1
Rosane Charlab Orbach	Genomics Team Leader, OCP/DTPM
Robert Schuck	Genomics Reviewer, OCP/DTPM
Abhi Nair	Associate Director for Safety, OOD
Karen Bleich	Reviewer, OSI
Sarah Thomas	Reviewer, OSE/DMEPA

Center for Devices and Radiological Health

Donna Roscoe	Supervisory Biologist, OIDRH/DMGP/MGB
Dun Liang	Reviewer, OIDRH/DMGP/MGB

SPONSOR ATTENDEES

Martin Birkhofer	Chief Medical Officer
Karim Benhadji	Clinical Development
Helen He	Biostatistics
Ikuo Yamamiya	Pharmacokinetics
Priya B. Patel	Pharmacovigilance
Abdel Halim	Biomarker and Companion Diagnostics
Alpesh Patel	Regulatory Affairs
Volker Wacheck	VP, Clinical Development
Noma Takahisa	Associate Manager, Regulatory Affairs, Japan
Maki Fukumoto	Manager, Regulatory Affairs, Japan

Introduction:

This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for June 19, 2020 / 3:00 – 4:00 PM (EST) between Taiho Oncology Inc., and the Division of Oncology 3. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda. Contact the Regulatory Project Manager (RPM) if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, as we may not be prepared to discuss or reach agreement on such changes at the meeting.

BACKGROUND

Taiho Oncology, Inc. (Taiho) is planning to submit a New Drug Application (NDA) for futibatinib for the treatment of patients with advanced intrahepatic cholangiocarcinoma (iCCA) harboring FGFR2 gene rearrangements (including gene fusions), under the accelerated approval pathway (21 CFR Subpart H).

On April 21, 2020, Taiho submitted a meeting request to discuss the proposed content and format of the planned NDA. The meeting was granted on April 27, 2020. The meeting package was received on May 20, 2020.

Key Regulatory History

- On January 28, 2014, a new IND containing Study TPU-TAS-120-101 (Study 101), titled “Dose-Finding Phase 1 Study of TAS-120 in Patients with Advanced Solid Tumors With or Without Fibroblast Growth Factor/Receptor (FGF/FGFR)-Related Abnormalities Followed by a Phase 2 Study in Patients with Advanced Solid Tumors or Multiple Myeloma with FGF/FGFR-Related Abnormalities” (submitted on December 31, 2013) was placed on a partial clinical hold due to insufficient

information to assess risk to human subjects relating to the proposed 20 mg strength capsule. FDA stated that Taiho may only proceed with the “Phase 1” dose escalation and expansion portion of the study. The partial clinical hold was subsequently removed on November 3, 2017.

- On May 23, 2018, FDA granted orphan drug designation to futibatinib for the treatment of cholangiocarcinoma.
- On August 20, 2018, Fast Track designation was granted for the investigation of TAS-120 for the first-line treatment of patients with unresectable or metastatic CCA harboring FGFR gene fusions to demonstrate a statistically significant improvement in overall survival for patients randomized to receive TAS-120 as compared to those randomized to receive cisplatin and gemcitabine.
- On February 26, 2020, a written response only document was issued for a Type C guidance meeting to discuss Taiho’s proposals relating to the presentation of efficacy and safety data, presentation of clinical pharmacology, and data standardization requirements in the planned NDA. FDA stated that in general, FDA does not consider efficacy results from an interim analysis in single arm trials and recommended that Taiho submit an NDA based on Study 101 only when the final analysis had been conducted. FDA requested that Taiho provide the anticipated date when efficacy results would be available for the approximately 33 patients not included in the interim analysis in Part 3, including sufficient follow up (e.g., a minimum of 6 months from onset of response in a majority of patients) to characterize duration of response.
- On April 1, 2020, the expanded access protocol TAS-120-401, titled “An Open-Label Expanded Access Program Of Futibatinib (TAS-120) In Patients With Advanced Cholangiocarcinoma Harboring FGFR2 Gene Rearrangements” (submitted on March 5, 2020) was allowed to proceed.

Taiho’s proposed proprietary name of (b) (4) submitted on May 1, 2020, is currently under review.

A separate product quality only pre-NDA meeting is scheduled for July 8, 2020.

Product Quality

Futibatinib is supplied as 4 mg tablets and is taken orally at a dose of 20 mg QD.

Nonclinical

Futibatinib is a small molecule inhibitor of FGFR 1-4. Taiho described nonclinical studies using human cancer cell lines bearing FGFR mutations, antitumor activity in mouse and rat models, safety pharmacology, pharmacokinetics, embryo-fetal toxicity, genotoxicity, and GLP 13-week repeat-dose toxicology studies in rats and dogs.

Clinical/Statistical

Taiho plans to file an NDA based on the results of Study TPU-TAS-120-101, entitled “Phase 1/2 Study of TAS-120 in Patients with Advanced Solid Tumors Harboring FGF/FGFR Aberrations.” Study TPU-TAS-120-101 is an open-label, dose escalation and dose expansion study evaluating the safety, tolerability, pharmacokinetic (PK), pharmacodynamic (PD), and antitumor activity of TAS-120 in patients with unresectable solid tumors with various FGF/FGFR abnormalities in the second-line setting. The study consists of three parts:

- Part 1: Dose-escalation to determine the maximum tolerated dose (MTD) and/or recommended Phase 2 dose (RP2D) of TAS-120;
- Part 2: Expansion cohorts to further evaluate the efficacy and safety of the MTD or RP2D of TAS-120 in patients with cholangiocarcinoma (CCA)
 - o Group 1 (Enrollment suspended as of Amendment 7): Patients with intrahepatic or extrahepatic CCA harboring FGFR2 gene fusions
 - o Group 2: Patients with intrahepatic or extrahepatic CCA harboring FGFR2 gene fusions that have not received or received less than 1 cycle of prior chemotherapy (due to intolerance or patient refusal)
 - o Group 3 (Enrollment suspended as of Amendment 7): Patients with intrahepatic or extrahepatic CCA harboring FGFR2 gene fusions that have been treated with prior FGFR inhibitors
 - o Group 4 (Enrollment suspended as of Amendment 7): Patients with intrahepatic or extrahepatic CCA harboring FGFR abnormalities other than FGFR2 gene fusions (for example, mutations, rearrangements, or amplifications)
 - o Group 5: Patients with primary CNS tumors harboring FGFR gene fusions or FGFR1 activating mutations
 - o Group 6 (Enrollment suspended as of Amendment 7): Patients with advanced urothelial carcinoma harboring FGFR3 gene fusions or FGFR3 activating mutations
 - o Group 7: Patients with any tumor type not included in one of the prior groups, harboring FGFR2 amplification (no minimum number of copies) (Figure 2).
 - o Group 8 (Enrollment suspended as of Amendment 7): Patients with any tumor type not included in one of the prior groups, harboring FGFR gene fusions or activating mutations
- Part 3: Single-arm cohort to estimate the overall response rate (ORR) of TAS-120 in patients with intrahepatic cholangiocarcinoma (iCCA) harboring FGFR2 fusions or other rearrangements as determined by a local or central (Foundation Medicine - FMI) diagnostic test and who have been treated with at least one prior chemotherapy regimen containing gemcitabine and a platinum; patients with prior exposure to FGFR inhibitors were excluded.

The primary endpoint of Part 3 is ORR by independent central review (IRC) per RECIST 1.1, and secondary endpoints include duration of response (DOR), disease control rate, progression-free survival (PFS), health-related quality of life, and overall

survival (OS). A total of 100 patients were planned for enrollment in Part 3. Assuming the true ORR is 20%, the study has approximately 81% power to reject the null hypothesis that the true ORR is $\leq 10\%$, considering a 2-sided alpha of 5%.

On August 13, 2019, Taiho submitted Protocol Amendment 9 (SDN 151) adding a formal interim analysis to be performed when approximately 70% of patients have 6 months of follow-up. Two-sided 95% CI and 99% CI will both be provided for the primary efficacy analysis. A safety analysis will also be performed at this time, and the results will be shared with the safety review committee.

A total of 103 patients have completed enrollment to Part 3. Table 1 summarizes the results in patients with iCCA treated with futibatinib at a dose of 20 mg orally daily (data cutoff date of January 31, 2020) and who have been followed for at least 6 months.

Table 1. Study TPU-TAS-120-101 Efficacy Results

	IRC (n=67)	Investigator (n=67)
Objective response rate, n (%) (95% CI)	25 (37.3%) (25.8, 50)	21 (31.3%) (20.6, 43.8)
Complete response, n (%)	1 (1.5)	0
Partial responses, n (%)	24 (35.8)	21 (31.3)
Not evaluable, n (%)	1 (1.5)	1 (1.5)

Reviewer table

Taiho states that central confirmation of *FGFR2* rearrangement/fusion per FMI was obtained for 60 of 67 treated patients (38 patients based on the FMI assay approved as a CDx with pemigatinib, and 22 patients enrolled based on FMI's FoundationOne test). However, at the time of the data cut (January 31, 2020), only 56 of 67 patients were reported as confirmed. IRC-assessed ORR in this subset was 37.5% (95% CI 24.9; 51.5) and investigator-assessed ORR was 33.9% (95% CI 21.8; 47.8).

The safety profile of Study 101 in patients with iCCA is consistent with the expected mechanism of action. Adverse events of special interest included: hyperphosphatemia (81%, 27% Grade ≥ 3), nail toxicities (42%, 1.5% Grade ≥ 3), palmar-plantar erythrodysesthesia syndrome (18%, 1.5% Grade ≥ 3), rash (10%) and other skin toxicities (49%), central serous retinopathy (9%) other eye disorders (51%) including dry eye (24%), blurred vision (9%), increased lacrimation (7.5%), trichomegaly (6%). Increase of liver enzymes was observed in approximately 20% of patients.

On September 23, 2019, Taiho submitted Study TPU-TAS-120-301 entitled "Phase 3, Open-Label, Randomized Study of Futibatinib Versus Gemcitabine-Cisplatin Chemotherapy as First-Line Treatment of Patients with Advanced Cholangiocarcinoma Harboring *FGFR2* Gene Rearrangements", planned to be the confirmation study if accelerated approval is granted. No patients have been enrolled to-date.

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The primary endpoint of the study is progression-free survival (PFS) by independent central review based on RECIST 1.1. Target enrollment is 216 patients. Assuming a median PFS of 10 months in the experimental arm and 6 months in the control arm, Taiho states that a total of 162 PFS events will be needed to detect a hazard ratio of 0.60 with 90% power at a 2-sided alpha level of 0.05.

Content of Proposed NDA

Taiho proposes to submit the planned NDA by September 30, 2020. The preassigned application number is NDA 214801.

The briefing document contains an updated proposed table of contents for the planned NDA.

Clinical/Statistical

The primary efficacy data supporting the proposed NDA will reflect data summarized above, supplemented by results from 42 patients enrolled in the dose range-finding portion of the study (of which 19 patients matched the eligibility criteria for the study portion supporting the proposed indication).

Taiho plans to submit a Summary of Clinical Efficacy with separate analyses of each portion of Study 101, and no integrated analyses to be presented in the Integrated Summary of Efficacy.

Additional safety information in the NDA will comprise data from Study 10059010 (a study conducted in Japan) and all other TAS-120 studies. For the purpose of safety analysis, three data groups will be defined:

- Safety Data Group 1: patients with iCCA harboring FGFR2 rearrangement and treated with futibatinib at a dose of 20 mg orally daily in either Parts 2 and 3 of Study 101
- Safety Data Group 2: patients with all solid tumors, treated at any dose level in any portion of Study 101, as well as patients treated in Study 10059010
- Safety Data Group 3: patients or healthy volunteers in all other studies, specifically healthy volunteer studies TAS-120-102, TAS-120-103, AS-120-104, TAS-120-105, TAS-120-106, TAS-120-107, and 10059020; and
- Safety Data Group 4: patients treated in combination studies; only one study, Study (b) (4) has enrolled patients.

For Safety Data Groups 1 and 2, Taiho proposes to provide integrated tabulations of safety data, including adverse events, laboratory results, and other findings, based on the clinical database. Taiho also proposes to include line listings of deaths, serious adverse events (SAEs), and withdrawals due to adverse event that occur between the cut-off date of a given study and the data of interim analysis cut-off of January 31, 2020

for Study 101. Safety narratives along with individual case report forms are planned for all individual patients who 1) died on treatment or within 30 days after the last dose of study medication, or 2) discontinued treatment due to an adverse event, or 3) experience any SAE, regardless of causality.

Clinical Pharmacology

The briefing document contains a listing of clinical pharmacology studies intended to be included in the NDA.

Taiho proposes to submit 8 studies conducted in healthy volunteers: food effect (TAS-120-102), mass balance (-106), BE of tablets vs. capsules (10059020), QT/QTc interval (-107), hepatic impairment (TBD), and DDI effect of futibatinib and itraconazole, rifampin, lansoprazole, and midazolam (-103, -104, -105) (See Appendix 1 of the briefing document).

Taiho stated that the QT/QTc study (-107) and the planned hepatic impairment study may be in progress by the time of the submission: all other studies to be included in the clinical pharmacology assessment are expected to be complete. Taiho proposes to complete the hepatic impairment study as a post-marketing commitment.

Taiho proposes to conduct exposure-response analysis using individual PK parameters estimated for patients in Study TAS-120-101.

TAIHO QUESTIONS AND FDA RESPONSES

GENERAL COMMENTS

FDA will not be able to reach agreement with Taiho regarding the contents of a complete NDA for futibatinib for the proposed indication of treatment of patients with advanced intrahepatic cholangiocarcinoma (iCCA) harboring FGFR2 gene rearrangements (including gene fusion) under the PDUFA VI program, because the pre-NDA meeting for discussion of quality components has not been held. FDA acknowledges that a separate pre-NDA meeting to discuss quality components is scheduled for July 8, 2020. During this meeting FDA and Taiho will need to reach agreement on the product quality information necessary to support a complete NDA and to reach agreement on submission of late components, if any are planned.

- 1. The Sponsor would like to propose a post-marketing pharmacokinetic study in patients with moderate-to-severe hepatic impairment in accordance with FDA Guidance for Industry entitled *Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling*. Does FDA agree?**

FDA Response: It is premature for FDA to provide concurrence on postmarketing requirements/commitments prior to submission and review of the

New Drug Application (NDA). The proposed plan to assess the effects of hepatic impairment on the pharmacokinetics (PK) of futibatinib using only data from patients with mild hepatic impairment is insufficient as it will not provide information on dosage adjustment for patients with moderate or severe hepatic impairment. FDA strongly recommends that the proposed dedicated hepatic impairment study be initiated as soon as possible. Provide an expected enrollment start date or consider the potential submission of topline results as an amendment to the initial NDA submission. The population PK approach to assess the effects of renal impairment on the PKs of futibatinib appears acceptable.

2. **Does the Agency agree that, based on the results of 67 patients followed for 6 months, the objective response rate and duration of response for futibatinib are of sufficient magnitude and duration to form the basis of an NDA, in support of the proposed indication, in an Accelerated Approval setting under subpart H?**

FDA Response: No. As stated in the February 26, 2020, Written Responses Only communication discussing Taiho's proposal for the presentation of efficacy and safety data in the planned NDA, FDA generally does not consider efficacy results from an interim analysis in single arm trials. For the planned NDA submission, submit a complete package including efficacy data for all patients enrolled in Part 3 of Study 101 and ensure that the majority of patients have sufficient follow up (i.e., a minimum of 6 months from onset of response) to enable FDA's assessment of the durability of the observed response rate.

Provide the anticipated date when efficacy results will be available for the approximately 33 patients in Part 3 who are not included in the interim analysis of ORR, including an estimate of when sufficient follow up (i.e., a minimum of 6 months from onset of response in a majority of patients) is expected.

3. **Does the agency agree with proposed Statistical Analysis Plan for efficacy?**

FDA Response: FDA does not agree with basing the primary analysis of efficacy on all treated patients with at least 6 months of follow-up as of the cut-off date (n=67). The primary ORR analysis population should include all treated patients (n=103). In general, FDA does not use inferential procedures to evaluate single-arm trials for the purposes of rendering a regulatory decision. Instead, the FDA assessment of efficacy will be based on 1) whether the lower limit of the 95% confidence interval of ORR exceeds a clinically relevant response rate, 2) adequate duration of response, and 3) the overall benefit/risk assessment. Time-to-event endpoints are uninterpretable in the absence of a control arm.

4. **The sponsor proposes to provide the full efficacy results based on 103 patients followed for 6 months at the time of the submission of the 120-day safety update. Does the agency agree?**

FDA Response: No. Refer to FDA's response to Question 2.

5. **Does the agency agree with the updated integrated safety analysis plan?**

FDA Response: No. As stated in the February 26, 2020, Written Responses Only communication, FDA requests that Taiho provide pooled data from all patients who received the proposed dose and schedule of futibatinib. As such, Safety Data Group 2 should only include those patients with solid tumors treated at the recommended dose of 20 mg daily. The safety data should include all patients enrolled in Study 101 Part 3 and the data cutoff for this analysis should be updated. If the data cutoff for the safety analysis is within 6 months of the NDA submission, FDA would accept an updated summary of adverse events of interest, unexpected adverse events, or any event that may have an impact on the safety assessment of the application or labeling, in lieu of a 120-day safety update. While FDA does not object to the submission of safety results from Study (b) (4)

at the time of the 120-day safety update, given the small number of patients and the fact that patients were treated with two agents, it is acceptable not to submit safety data from Safety Data Group 4.

6. **Does the agency agree that the safety database (including a total of 413 treated patients) is adequate to support review of the safety profile for futibatinib?**

FDA Response: FDA agrees.

7. **Does the agency agree with the Sponsor's proposal to provide safety narratives for all individual patients who meet the criteria above?**

FDA Response: FDA agrees with the submission of safety narratives and case report forms for all patients meeting who:

- died on treatment or within 30 days after the last dose of futibatinib;
- discontinued treatment due to an adverse event; or
- experienced any treatment-emergent SAE regardless of causality.

8. **Does the agency agree with proposed submission date of 28 January 2021 for the 120-day safety update?**

FDA Response: Refer to FDA's response to Question 5.

9. **If the Phase 3 protocol meets its primary endpoint, does the agency agree that it would allow futibatinib to be converted from accelerated approval to a standard approval?**

FDA Response: It is premature for FDA to provide agreement. The determination of whether a supplemental NDA seeking regular approval of futibatinib on the basis of the results of Study TPU-TAS-120-301 will depend on whether the trial demonstrates 1) a statistically significant and clinically meaningful difference in the primary endpoint and 2) a favorable risk-benefit assessment. This determination will be made at the time of the review of supplemental application. However, FDA agrees that based on its design, Study TPU-TAS-120-301 could confirm the benefit of futibatinib should accelerated approval be granted.

10. **Does the agency agree with the data cut-off dates for the efficacy and safety datasets?**

FDA Response: Refer to FDA's responses to Questions 2 through 5.

11. **Does the agency agree that the NDA Table of Contents is adequate to support review of the NDA?**

FDA Response: FDA agrees.

12. **Is the agency planning an application orientation meeting with Taiho Oncology, Inc.?**

FDA Response: At this time, FDA does not anticipate the need for an application orientation meeting.

13. **At what time during the review process is the agency anticipating a decision on whether an advisory committee (ODAC) meeting will be required in support of the futibatinib NDA?**

FDA Response: It is premature to discuss a potential ODAC at this time; a determination will be made during the NDA review.

14. **In light of the FDA final CDx labeling guidance released 13 April 2020 and since the FMI's test is widely accessible to patients, does the agency agree that futibatinib can be approved based on the availability of the FDA-approved test for the intended biomarkers in such unmet need niche indication?**

FDA Response: There is insufficient information to provide a definitive response at this time. Provide justification for the reason(s) a drug-companion diagnostic

(CDx) device co-approval is not feasible. For example, (b) (4)

(b) (4)

Patients were enrolled into Study TPU-TAS-120-101 based on testing using a variety of local tests including the Foundation MedicineOne (F1CDx) test. Provide information regarding the genetic variations and the detailed criteria on the basis of which patients were screened/enrolled in the trial and clarify whether these criteria align with the current FDA-approved F1CDx device. Indicate whether the protocol's definition for the variants was consistently applied across the different testing sites, specimen types (tumor vs ctDNA), and the local tests.

Taiho indicated that available specimens were tested with F1CDx device. Provide more details regarding this assessment and describe whether any discordance was observed. Taiho will also need to provide test negatives for the bridging study; therefore, FDA recommends that Taiho request a set of negative specimens from testing labs to facilitate this evaluation.

FDA notes that for Study TAS-120-301, local laboratories will screen patients for eligibility. Taiho should plan to bank specimens in the event that a bridge for a CDx device is needed. Collect the following information from each testing site that forwarded eligible patients to the trial:

- a. local test reports with all information captured (i.e., where the test was performed, the test methodology, the specimen type, minimal data on the analytical performance of the test, test name, etc.) in the Case Report Forms Test method (e.g., NGS, PCR), instrument, size of the panel;
- b. description of the test limit of detection for fusions specifically;
- c. description of the specific biomarkers evaluated (e.g., FGFR-BICC1 etc.) and the prevalence.

ADDITIONAL COMMENTS

15. In the NDA submission, provide a dataset (xpt file format) that includes the following patient-level data for Study TAS-120-101 Phase 2 Portion:
 - a. the specific FGFR2 alteration(s),
 - b. the alteration type as reported by the assay used (e.g., fusion, rearrangement, other),

- c. the corresponding assay used (e.g., FMI clinical trial assay, FMI FoundationOne Test, local NGS-based (tumor tissue), local NGS-based (cfDNA)). Include a flag (yes/no) for central confirmation with FMI clinical trial assay.

Also, provide the definitions for fusion vs rearrangement used by central tests and include assay reports. If available, also provide a dataset that includes the FGFR2 alterations identified in the CCA subgroup of patients in the Study TAS-120-101 Phase 1 Expansion Portion.

16. In the NDA submission, provide the financial disclosure information in .xlsx or .xpt format.
17. In the NDA submission, provide justification for not conducting any additional *in vivo* DDI studies with transporters and for providing only the *in vitro* information for futibatinib as an inhibitor of P-gp and BCRP.
18. Provide a clarification on which studies will be included in the exposure-response analyses for efficacy and safety that are included in the original NDA submission, and include data from trials to support efficacy and safety that included sparse PK sampling (including Study 10059010), as previously discussed in the February 26, 2020, Written Responses Only communication.
19. In the meeting package, Taiho states that futibatinib will be available as 4 mg tablets with a proposed recommended dose of 20 mg orally once daily over a (b) (4) Developing a product strength that is incongruent with the dosage and administration of the product complicates the calculation, preparation, and administration of a dose and may lead to medication errors. FDA is concerned that the requirement for 5 tablets to achieve one dose may increase the risk for medication dosing and administration errors. FDA encourages Taiho to consider how to mitigate the potential risk of medication error due to the multiple tablets of the proposed 4 mg strength necessary to achieve one full dose, in the development plan.

For more information, refer to the FDA Guidance for Industry Safety Considerations for Product Design to Minimize Medication Errors (2016), available at:

<https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm331810.pdf>.

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

As stated in our April 27, 2020, communication granting this meeting, if, at the time of submission, the application that is the subject of this meeting is for a new molecular entity or an original biologic, the application will be subject to “the Program” under

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PDUFA VI. Therefore, at this meeting be prepared to discuss and reach initial agreement with FDA on the content of a complete application, including preliminary discussions on the need for risk evaluation and mitigation strategies (REMS) or other risk management actions and, where applicable, the development of a Formal Communication Plan. Final agreement will be reached at the July 8, 2020, product quality only pre-NDA meeting. You and FDA may also reach agreement on submission of a limited number of minor application components to be submitted not later than 30 days after the submission of the original application. These submissions must be of a type that would not be expected to materially impact the ability of the review team to begin its review. All major components of the application are expected to be included in the original application and are not subject to agreement for late submission.

Discussions and agreements will be summarized at the conclusion of the meeting and reflected in FDA's meeting minutes. If you decide to cancel this meeting and do not have agreement with FDA on the content of a complete application or late submission of any minor application components, your application is expected to be complete at the time of original submission.

In addition, we remind you that the application is expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities.

Information on the Program is available at FDA.gov.¹

We note that a chemistry pre-submission meeting is scheduled for July 8, 2020. A summary of agreements reached at that meeting will be documented in the respective meeting minutes.

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (codified at section 505B of the Federal Food, Drug, and Cosmetic Act (FD&C Act), 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(s) in pediatric patients unless this requirement is waived or deferred (see section 505B(a)(1)(A) of the FD&C Act). Applications for drugs or biological products for which orphan designation has been granted that otherwise would be subject to the requirements of section 505B(a)(1)(A) are exempt pursuant to section 505B(k)(1) from the PREA requirement to conduct pediatric assessments.

Since futibatinib was granted orphan drug designation for treatment of cholangiocarcinoma on May 23, 2018, the planned NDA submission (if submitted prior to August 18, 2020) for futibatinib for the treatment of patients with advanced

¹ <https://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/default.htm>

intrahepatic cholangiocarcinoma (iCCA) harboring FGFR2 gene rearrangements (including gene fusions), would be exempt from the requirements of PREA. If an NDA for futibatinib is submitted prior to August 18, 2020, please include a statement that confirms this finding, along with a reference to this communication, as part of the pediatric section (eCTD module 1.9) of your application.

However, please be aware that Title V of the FDA Reauthorization Act of 2017 (FDARA) amended the statute to create section 505B(a)(1)(B), which requires that any original marketing application for certain adult oncology drugs (i.e., those intended for treatment of an adult cancer and with molecular targets that FDA has determined to be substantially relevant to the growth or progression of a pediatric cancer) that are submitted on or after August 18, 2020, contain reports of molecularly targeted pediatric cancer investigations. See link to list of relevant molecular targets below. These molecularly targeted pediatric cancer investigations must be “designed to yield clinically meaningful pediatric study data, gathered using appropriate formulations for each age group for which the study is required, regarding dosing, safety, and preliminary efficacy to inform potential pediatric labeling” (section 505B(a)(3)). Applications for drugs or biological products for which orphan designation has been granted and which are subject to the requirements of section 505B(a)(1)(B), however, will not be exempt from PREA (see section 505B(k)(2)) and will be required to include plans to conduct the molecularly targeted pediatric investigations as required, unless such investigations are waived or deferred.

Under section 505B(e)(2)(A)(i) of the FD&C Act, Taiho must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End of Phase 2 (EOP2) meeting, or such other time as agreed upon with FDA. (In the absence of an EOP2 meeting, refer to the draft guidance below.) The iPSP must contain an outline of the pediatric assessment(s) or molecularly targeted pediatric cancer investigation(s) that Taiho plans to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation; and any previously negotiated pediatric plans with other regulatory authorities. The iPSP should be submitted in PDF and Word format. Failure to include an Agreed iPSP with a marketing application could result in a refuse to file action.

FDA acknowledges receipt of Taiho's Agreed Initial Pediatric Study Plan (iPSP) submitted on June 11, 2018, and also refers to FDA's July 20, 2018, letter confirming agreement, for the proposed plan for a full waiver from PREA requirements for the proposed indication of “TAS-120 for the treatment of patients with advanced cholangiocarcinoma (CCA) harboring fibroblast growth factor receptor (FGFR)

(b) (4)

based on the reasoning that necessary studies are impossible or highly impractical.

As stated in the July 20, 2018 letter, if FDA determines that the molecular target of TAS-120 is relevant to one or more pediatric cancers and Taiho intends to submit a marketing application on or after August 18, 2020, Taiho will need to submit an amended Agreed iPSP as soon as possible and prior to the submission of a NDA for TAS-120 of this NDA. The amended iPSP must include molecularly targeted pediatric cancer investigation(s) that Taiho plan to conduct (including, to the extent practicable study objectives and design, age groups relevant endpoints, and statistical approach) and/or any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation.

For additional guidance on the timing, content, and submission of the iPSP, including an iPSP Template, please refer to the draft guidance for industry *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans*.

For the latest version of the molecular target list, please refer to FDA.gov.²

FDARA REQUIREMENTS

Sponsors planning to submit original applications on or after August 18, 2020 or sponsors who are uncertain of their submission date may request a meeting with the Oncology Center of Excellence Pediatric Oncology Program to discuss preparation of the sponsor's initial pediatric study plan (iPSP) for a drug/biologic that is intended to treat a serious or life-threatening disease/ condition which includes addressing the amendments to PREA (Sec. 505B of the FD & C Act) for early evaluation in the pediatric population of new drugs directed at a target that the FDA deems substantively relevant to the growth or progression of one or more types of cancer in children. The purpose of these meetings will be to discuss the Agency's current thinking about the relevance of a specific target and the specific expectations for early assessment in the pediatric population unless substantive justification for a waiver or deferral can be provided. Meetings requests should be sent to the appropriate review division with the cover letter clearly stating "**MEETING REQUEST FOR PREPARATION OF iPSP MEETING UNDER FDARA.**" These meetings will be scheduled within 30 days of meeting request receipt. The Agency strongly advises the complete meeting package be submitted at the same time as the meeting request. Sponsors should consult FDA's Guidance on Formal Meetings Between the FDA and Sponsors or Applicants³ to ensure open lines of dialogue before and during their drug development process.

In addition, sponsors may contact the OCE Subcommittee of PerC Regulatory Project Manager by email at OCEPERC@fda.hhs.gov. For further guidance on pediatric product development, please refer to FDA.gov.⁴

² <https://www.fda.gov/about-fda/oncology-center-excellence/pediatric-oncology>

³ See the guidance for industry "Formal Meetings Between the FDA and Sponsors or Applicants."

⁴ <https://www.fda.gov/drugs/development-resources/pediatric-and-maternal-health-product-development>

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57 including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the PLR Requirements for Prescribing Information⁵ and Pregnancy and Lactation Labeling Final Rule⁶ websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products.
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential.
- Regulations and related guidance documents.
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of important format items from labeling regulations and guidances.
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

Pursuant to the PLLR, you should include the following information with your application to support the changes in the Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of labeling. The application should include a review and summary of the available published literature regarding the drug's use in pregnant and lactating women and the effects of the drug on male and female fertility (include search parameters and a copy of each reference publication), a cumulative review and summary of relevant cases reported in your pharmacovigilance database (from the time of product development to present), a summary of drug utilization rates amongst females of reproductive potential (e.g., aged 15 to 44 years) calculated cumulatively since initial approval, and an interim report of an ongoing pregnancy registry or a final report on a closed pregnancy registry. If you believe the information is not applicable, provide justification. Otherwise, this information should be located in Module 1. Refer to the draft guidance for industry *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format*.

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

⁵ <https://www.fda.gov/drugs/laws-acts-and-rules/plr-requirements-prescribing-information>

⁶ <https://www.fda.gov/drugs/labeling/pregnancy-and-lactation-labeling-drugs-final-rule>

DISCUSSION OF SAFETY ANALYSIS STRATEGY FOR THE ISS

After initiation of all trials planned for the phase 3 program, you should consider requesting a Type C meeting to gain agreement on the safety analysis strategy for the Integrated Summary of Safety (ISS) and related data requirements. Topics of discussion at this meeting would include pooling strategy (i.e., specific studies to be pooled and analytic methodology intended to manage between-study design differences, if applicable), specific queries including use of specific standardized MedDRA queries (SMQs), and other important analyses intended to support safety. The meeting should be held after you have drafted an analytic plan for the ISS, and prior to programming work for pooled or other safety analyses planned for inclusion in the ISS. This meeting, if held, would precede the Pre-NDA meeting. Note that this meeting is optional; the issues can instead be addressed at the pre-NDA meeting.

To optimize the output of this meeting, submit the following documents for review as part of the briefing package:

- Description of all trials to be included in the ISS. Please provide a tabular listing of clinical trials including appropriate details.
- ISS statistical analysis plan, including proposed pooling strategy, rationale for inclusion or exclusion of trials from the pooled population(s), and planned analytic strategies to manage differences in trial designs (e.g., in length, randomization ratio imbalances, study populations, etc.).
- For a phase 3 program that includes trial(s) with multiple periods (e.g., double-blind randomized period, long-term extension period, etc.), submit planned criteria for analyses across the program for determination of start / end of trial period (i.e., method of assignment of study events to a specific study period).
- Prioritized list of previously observed and anticipated safety issues to be evaluated, and planned analytic strategy including any SMQs, modifications to specific SMQs, or sponsor-created groupings of Preferred Terms. A rationale supporting any proposed modifications to an SMQ or sponsor-created groupings should be provided.

When requesting this meeting, clearly mark your submission “**DISCUSS SAFETY ANALYSIS STRATEGY FOR THE ISS**” in large font, bolded type at the beginning of the cover letter for the Type C meeting request.

MANUFACTURING FACILITIES

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing

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Silver Spring, MD 20993
www.fda.gov

facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
(1)				
(2)				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
(1)				
(2)				

To facilitate our facility assessment and inspectional process for your marketing application, we refer you to the instructional supplement for filling out Form FDA 356h⁷ and the guidance for industry, *Identification of Manufacturing Establishments in Applications Submitted to CBER and CDER Questions and Answers*⁸. Submit all related manufacturing and testing facilities in eCTD Module 3, including those proposed for commercial production and those used for product and manufacturing process development.

⁷ <https://www.fda.gov/media/84223/download>

⁸ <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/identification-manufacturing-establishments-applications-submitted-cber-and-cder-questions-and>

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

The Office of Scientific Investigations (OSI) requests that the items described in the draft guidance for industry, *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions*, and the associated conformance guide, *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications*, be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA ORA investigators who conduct those inspections. This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

Please refer to the draft guidance for industry *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions* (February 2018) and the associated *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications*.⁹

SUBMISSION FORMAT REQUIREMENTS

The Electronic Common Technical Document (eCTD) is CDER and CBER's standard format for electronic regulatory submissions. The following submission types: **NDA, ANDA, BLA, Master File** (except Type III) and **Commercial INDs** must be submitted in eCTD format. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit FDA.gov.¹⁰

The FDA Electronic Submissions Gateway (ESG) is the central transmission point for sending information electronically to the FDA and enables the secure submission of regulatory information for review. Submissions less than 10 GB must be submitted via the ESG. For submissions that are greater than 10 GB, refer to the FDA technical specification document *Specification for Transmitting Electronic Submissions using eCTD Specifications*. For additional information, see FDA.gov.¹¹

SECURE EMAIL COMMUNICATIONS

Secure email is required for all email communications from FDA when confidential information (e.g., trade secrets, manufacturing, or patient information) is included in the

⁹ <https://www.fda.gov/media/85061/download>

¹⁰ <http://www.fda.gov/ectd>

¹¹ <http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway>

message. To receive email communications from FDA that include confidential information (e.g., information requests, labeling revisions, courtesy copies of letters), you must establish secure email. To establish secure email with FDA, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications (except for 7-day safety reports for INDs not in eCTD format).

ONCOLOGY PILOT PROJECTS

The FDA Oncology Center of Excellence (OCE) is conducting two pilot projects, the Real-Time Oncology Review (RTOR) and the Assessment Aid. RTOR is a pilot review process allowing interactive engagement with the applicant so that review and analysis of data may commence prior to full supplemental NDA/BLA submission. Assessment Aid is a voluntary submission from the applicant to facilitate FDA's assessment of the NDA/BLA application (original or supplemental). An applicant can communicate interest in participating in these pilot programs to the FDA review division by sending a notification to the Regulatory Project Manager when the top-line results of a pivotal trial are available or at the pre-sNDA/sBLA meeting. Those applicants who do not wish to participate in the pilot programs will follow the usual submission process with no impact on review timelines or benefit-risk decisions. More information on these pilot programs, including eligibility criteria and timelines, can be found at the following FDA websites:

- RTOR¹²: In general, the data submission should be fully CDISC-compliant to facilitate efficient review.
- Assessment Aid¹³

¹² <https://www.fda.gov/about-fda/oncology-center-excellence/real-time-oncology-review-pilot-program>

¹³ <https://www.fda.gov/about-fda/oncology-center-excellence/assessment-aid-pilot-project>

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/

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