CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208712Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

IND 078406

MEETING MINUTES

CTI BioPharma Corporation
Attention: John Volpone
VP Strategic Operations
3101 Western Avenue, Suite 800
Seattle, WA 98121

Dear Mr. Volpone:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for pacritinib.

We also refer to the telecon between representatives of your firm and the FDA on September 16, 2020. The purpose of the meeting was to discuss a proposal to file a NDA under 21 CFR Subpart H for the accelerated approval of pacritinib for patients with myelofibrosis and severe thrombocytopenia (baseline platelet counts <50 × 10^9/L).

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

If you have any questions, contact me at 240-402-9981 or at Maureen.DeMar@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Andrew Dmytrijuk, MD
Clinical Reviewer
Division of Nonmalignant Hematology
Office of Cardiology, Hematology, Endocrinology, and Nephrology
Center for Drug Evaluation and Research

Enclosure:

- Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: Pre-NDA

Meeting Date and Time: September 16, 2020, 3-4 PM (ET)
Meeting Location: WebEx

Application Number: IND 078406
Product Name: pacritinib

Indication: for the treatment of adult patients with intermediate- or high-risk MF, including primary myelofibrosis (PMF), post-polycythemia vera myelofibrosis (PPV-MF) and post-essential thrombocythemia myelofibrosis (PET-MF), who have severe thrombocytopenia

Sponsor Name: CTI BioPharma Corporation
Regulatory Pathway: 505(b)(1) of the Food, Drug, and Cosmetics Act

Meeting Chair: Andrew Dmytrijuk, MD
Meeting Recorder: Maureen DeMar

FDA ATTENDEES

Office of Cardiology, Hematology, Endocrinology, and Nephrology (OCHEN)
Ellis Unger, MD, Director

OCHEN, Division of Nonmalignant Hematology (DNH)
Ann Farrell, MD, Director
Albert Deisseroth, MD, PhD, Supervisory Associate Director
Andrew Dmytrijuk, MD, Clinical Reviewer
Donna Whyte-Stewart, MD, ScM, Clinical Reviewer

OCHEN, Division of Pharm/Tox (DPT)
Todd Bourcier, PhD, Nonclinical Team Lead (Acting)
Anthony Parola, PhD, Nonclinical Reviewer

Office of Biostatistics (OB), Division of Biometrics IX
Yeh-Fong Chen, PhD, Statistical Team Lead
Kate Li Dwyer, PhD, Statistical Reviewer

Office of Clinical Pharmacology (OCP)

Sudharshan Hariharan, PhD, Clinical Pharmacology Team Leader
Xiaolei Pan, PhD, Clinical Pharmacology Reviewer

Office of Regulatory Operations (ORO)
Charlene Wheeler, MSHS, Chief, Project Management Staff (Acting)
Maureen DeMar, BSN, RN, Regulatory Project Manager

SPONSOR ATTENDEES

Sarah Buckley, MD, Director, Clinical Development
Adam Craig, MD, President, CEO, and Interim Chief Medical Officer
Jennifer Smith, PhD, Senior VP, Biostatistics
Shanthakumar Tyavanagimatt, PhD, Senior VP, Global Pharmaceutical Operations and Early Development
John Volpone, Senior VP, Strategic Operations

1.0 BACKGROUND

Pacritinib is a kinase inhibitor proposed for the treatment of adult patients with intermediate- or high-risk MF, including primary myelofibrosis (PMF), post-polycythemia vera myelofibrosis (PPV-MF) and post-essential thrombocythemia myelofibrosis (PET-MF), who have severe thrombocytopenia (platelet count less than 50×10^9/L).

In May of 2008, pacritinib was granted orphan drug designation for the treatment of myeloproliferative neoplasms (MPNs), including MF. Patients with MF and severe thrombocytopenia (platelet counts less than 50×10^9/L) constitute a subset of patients within this orphan disease. On August 5, 2014, pacritinib was granted fast track designation for treatment of intermediate- and high-risk MF (PMF, PPV-MF, and PET-MF) including, but not limited to, patients with severe thrombocytopenia.

The purpose of this Type B meeting is to obtain Agency concurrence on the proposed registration strategy for the accelerated approval of pacritinib for the treatment of adult patients with intermediate or high-risk MF, including PMF, PPV-MF, and PET-MF who have severe thrombocytopenia (platelet count less than 50×10^9/L).

FDA sent Preliminary Comments to CTI BioPharma on September 10, 2020.

2.0 Questions and Responses

Question 1*:* Does the Agency agree that the risk mitigation strategies for life-threatening and fatal cardiac and hemorrhagic events implemented in the PAC203 phase 2 and PACIFICA studies address the Agency's concerns about the safety profile of pacritinib?

FDA Response: Possibly. It is not clear from the background package whether the risk mitigation strategies used in PAC203, which were carried out in patients

previously exposed to ruxolitinib, will be effective in the patient population proposed in the indication, i.e., treatment-naïve adult patients with intermediate- or high-risk MF, including primary myelofibrosis (PMF), post-polycythemia vera myelofibrosis (PPV-MF) and post-essential thrombocythemia myelofibrosis (PET-MF), who have severe thrombocytopenia (platelet count less than 50 × 10^9/L). You should provide analyses that evaluate the safety profile (with an additional focus on bleeding adverse events and cardiac adverse events) of pacritinib 200 mg administered orally twice daily in patients with platelet counts less than 50 × 10^9/L in studies PAC203, PERSIST-1 and PERSIST-2. These analyses should be conducted on patients from PERSIST-1 and PERSIST-2 (both treatment-naïve), excluding patients from PAC2303 (who were previously exposed to ruxolitinib). Data from PACIFICA would be needed to support definitively the position that that the risk mitigation strategies for life-threatening and fatal cardiac and hemorrhagic events implemented in the PAC203 achieved their goals.

Meeting Discussion: FDA corrected the response above regarding treatment-naïve and notes that in only the PERSIST-1 study were patients enrolled with no prior JAK2 inhibitor therapy. The Sponsor acknowledged FDA's concerns regarding the potential effectiveness of the proposed bleeding and cardiac risk mitigation strategy that were incorporated into the PACFICA study. The Sponsor asked for clarification regarding analyses of safety data from treatment naïve patients with myelofibrosis who were enrolled in PERSIST-1. The Agency stated that this analysis would exclude those patients who received or are receiving myelofibrosis therapy and did not bleed in order to decrease any potential confounding effect of prior myelofibrosis therapy on analysis of the safety of pacritinib and effectiveness of the risk mitigation strategy.

Question 2: Does the Agency agree that the available efficacy and safety data from PAC203 phase 2 and the PERSIST phase 3 studies, including the analyses of the data from patients with intermediate and high-risk primary and secondary MF patients with severe thrombocytopenia (platelet counts less than 50 × 10^9/L), are clinically meaningful and adequate for the filing and review of an NDA for the accelerated approval of pacritinib based on the endpoint of spleen volume reduction?

FDA Response: In order to assess the benefits and risks of pacritinib, a substantial number of patients treated at the proposed dose (200 mg administered orally twice daily) with thrombocytopenia (platelet count less than or equal to 50,00/µL) would need to be evaluated from the three studies (PAC203, PERSIST-1 and PERSIST-2). From the background information, the number of

patients who would inform the benefit-risk analysis supporting the proposed indication is uncertain, i.e., patients in PAC203, PERSIST-1, and PERSIST-2 who received oral pacritinib 200 mg BID with a baseline platelet count ≤ 50,000/μL and were included in the safety and efficacy databases. Please provide the numbers of patients for each of these studies.

We remind you that during the previous IND meetings, we have informed you that in addition to the evidence from spleen volume reduction (SVR), the total symptom score (TSS) should be assessed and a specific effect size (based on the TSS from the PAC203 phase 3 PACIFICA study) will be needed for considering accelerated approval.

We understand that because of the pandemic, you are not able to conduct the PACIFICA phase 3 study as originally planned. Of the projected 168 patients in the primary cohort that were planned to be enrolled by December 2020, you have enrolled a total of only 7 patients since January 2020.

Regarding PERSIST phase 3 studies, you showed us that PERSIST1 has statistically significant results in 35% reduction of SVR (19.1% vs. 4.7% p=0.0003) and PERSIST2 also has statistically significant results in 35% reduction of SVR (18.1% vs. 2.8%, p=0.0011). For TSS, you did not include any results for PERSIST 1, but PERSIST2 had non-significant 50% reduction of TSS results (24.8 vs. 13.9, p=0.079).

Although you indicated that the pivotal studies leading to approval of both ruxolitinib and fedratinib used a modified version of TSS (excluding "tiredness") and the pooled pacritinib arms demonstrated a statistically significantly greater proportion of patients achieving ≥ 50% reduction in TSS compared to best available therapy (BAT) (31% vs. 15%, p=0.014), these results were based on the pooled study arm and not the target patients you sought. Therefore, you should conduct the exploratory analyses for the TSS endpoint for the target patient population (i.e., baseline platelet count ≤ 50,000/μL) in addition to the SVR endpoint. Post hoc changes in the TSS analyses will be a concern that will merit consideration during the review.

The overall data package supporting the proposed indication (i.e., patients with platelet counts < 50,000/μL) is small (i.e., n=90 from PERSIST-1, PERSIST-2 and PAC203). In addition, when considering the benefit risk-analysis for pacritinib at the 200-mg dose, adverse events appeared to show a dose-response with respect to overall bleeding and cardiac events. The benefit-risk analysis for the PERSIST-2 and PERSIST-2 studies also disfavors pacritinib compared to BAT.

<u>Meeting Discussion:</u> The Sponsor conducted a post-hoc analysis of TSS that excludes tiredness, the so-called 6-Item TSS score, for the target population of MF patients with severe thrombocytopenia treated with pacritinib at 200 mg BID

from the PERSIST-2 study. They showed that patients with severe thrombocytopenia who were treated with pacritinib had a >50% improvement in TSS of 25.8% vs 12.5% for the BAT arm.

Based on this analysis, the Sponsor revised the PACIFICA study by conservatively powering it to detect a difference of 13% (27% pacritinib vs 14% physician's choice) with 80% power in a sample of 348 patients. They indicated that the revised PACIFICA study could have 84% power to detect the difference observed with the 200 mg BID dose in PERSIST-2 in patients with platelet counts less than 50 x 10^9/L. The FDA stated that the Sponsor's proposal appears reasonable.

Question 3: Over 1100 patients have been exposed to pacritinib across the development program, including patients who crossed-over from BAT to pacritinib in the phase 3 studies. Of these 1100 patients, 720 were patients with MF (not including patients who crossed-over). Of the 720 patients with MF, approximately 280 patients were severely thrombocytopenic at baseline. Approximately 260 patients with severe thrombocytopenia were exposed to pacritinib for approximately six months. Does the Agency concur that the safety database is adequate for an NDA filing?

FDA Response: No. As above, it is not clear from the background information how many patients in PAC203, PERSIST-1 and PERSIST-2 with a baseline platelet count ≤ 50,000/μL received oral pacritinib 200 mg BID. Also, see response to Question 2.

<u>Meeting Discussion:</u> The Sponsor provided an analysis of the number of patients from the PERSIST-2 study (including those who crossed over from best available therapy (BAT) to treatment with pacritinib) and the PAC203 study. (See Sponsor's responses submitted September 14, 2020 appended to these meeting minutes). The Sponsor acknowledged that the available patient safety and efficacy databases from patients with thrombocytopenia who were treated with pacritinib (defined as a platelet count <50 x 10^9/L) is small. FDA stated that the adequacy of the data from these databases to support the marketing application for pacritinib for the treatment of adult patients with intermediate or high-risk MF, including PMF, PPV-MF, and PET-MF who have severe thrombocytopenia (platelet count <50 × 10^9/L) will be a review issue. FDA stated that any additional data from patients with intermediate or high-risk MF, including PMF, PPV-MF, and PET-MF with higher platelet counts would be evaluated but considered supportive.

Question 4: Does the Agency agree that the nonclinical safety pharmacology and toxicology program as described is acceptable for the filing of the NDA?
FDA Response: Yes, safety pharmacology and toxicology programs described appear acceptable, but the adequacy of the nonclinical program to support an

NDA filing or approval will be a review issue. Consider the following recommendations:

- **Ensure that your submitted NDA includes complete data and discussion of major or reactive metabolites, impurities, and the safety pharmacology endpoints incorporated into the chronic toxicology studies.**

- **Submit carcinogenicity tumor data from mouse and rat carcinogenicity studies in electronic format for statistical analysis as per The Study Data Specification Ver.2.0 (SDS 2.0) (2012) (https://www.fda.gov/media/83880/download).**

- **SEND datasets for single dose toxicity, repeat dose toxicity, and carcinogenicity studies initiated after 17 December 2016, and cardiovascular and respiratory test results collected in safety pharmacology or toxicity studies initiated after March 15, 2019, are required**.

Meeting Discussion: No discussion took place during the meeting.

Question 5: Is the biopharmaceutical and clinical pharmacology program as described adequate to support the NDA?

FDA Response: The biopharmaceutical and clinical pharmacology program proposed to be submitted by the time of NDA appears to be appropriate.

Meeting Discussion: No discussion took place during the meeting.

Question 6: The original NDA (NDA 208712) was submitted as an eCTD submission and subsequently withdrawn by CTI. For the new NDA:

6a) Is a new NDA number required?

6b) If the electronic filing of the original NDA is still in the Agency's electronic database, does CTI need to submit all module components again, regardless if the sections did not change OR should CTI submit only the submission components that have changed?

FDA Response:
a. No, a new NDA number is not required.

b. Yes, all modules should be submitted again even if the sections did not change.
Meeting Discussion: No discussion took place during the meeting.

Question 7: CTI plans to submit a Summary of Clinical Efficacy (SCE) in Module 2 as part of the NDA but does not plan to prepare an Integrated Summary of Efficacy (ISE). Does the Agency agree with this proposal?

FDA Response: No. You should submit an Integrated Summary of Efficacy (ISE) and Integrated Summary of Safety (ISS) for this application that incorporates study data from PERSIST-1, PERSIST-2 and PAC203. Data from patients treated at the proposed dose of pacritinib and platelet count supporting the indication, i.e., a 200 mg twice daily dose with platelet counts <50,000/μL at baseline, should be presented separately. Any additional available data from the PACIFICA study should also be presented in the application in the ISE and ISS.

Meeting Discussion: The Sponsor stated that an Integrated Summary of Efficacy (ISE) will be included in the marketing application for pacritinib. The Sponsor states that for the PACIFICA study it is anticipated that fewer than 20 patients will have enrolled by the time of NDA filing. The Sponsor proposed to submit serious adverse event (SAE) reports and death listings from the ongoing PACIFICA study and submit safety reports from the Independent Data Monitoring Committee (IDMC). The Agency agreed with the Sponsor's proposal regarding submission of SAE reports and death listings from the ongoing PACIFICA study and submission of safety reports from the IDMC. The Agency stated that additional Information Requests (IRs) would be sent to the Sponsor as the review of the pacritinib application progresses.

Question 8: The Sponsor proposes to submit the NDA as a rolling application according to the schedule below. Does the Agency concur?

FDA Response: The proposed rolling application schedule, i.e., part 1 (Module 4 and non-clinical information) no later than September 20, 2020; part 2 (Module 3 and Quality information) no later than October 21, 2020, and part 3 (Module 1, Module 5 and clinical information) no later than February 28, 2021, is acceptable.

Meeting Discussion: The Sponsor stated that part 1 (Module 4 and non-clinical information) and part 2 (Module 3 and Quality information) of the rolling NDA application for pacritinib would be delayed by approximately 2 weeks. The Agency stated that this would be acceptable.

Question 9: Does the Agency concur with the proposed plan for pooling and analysis of data for the ISS and ISE including the plans for the PAC325 and PAC326 crossover patients?

FDA Response: Your proposed plan for pooling and analysis of data for the ISS and ISE including the plans for the PAC325 and PAC326 crossover patients seems to be reasonable. Please provide statistical analysis plans for the ISS and ISE for our assessment. See also response to Question 7 above.

Meeting Discussion: **No discussion took place during the meeting.**

Post Meeting Note: **The Agency is willing to file the application if it is complete. The Agency reminds the Sponsor that the data should be convincing and the risk mitigation plan should address the safety issues observed with PERSIST-1.**

3.0 DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

- The content of a complete application was discussed. The Agency agreed to the Sponsor's plan for a rolling submission.

- All applications are expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities included or referenced in the application.

- Major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission. You stated you intend to submit a complete application and therefore, there are no agreements for late submission of application components.

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End-of-Phase-2 (EOP2) meeting. In the absence of an EOP2 meeting, refer to the draft guidance below. The iPSP must contain an outline of the pediatric study or studies 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.[1] In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email Pedsdrugs@fda.hhs.gov. For further guidance on pediatric product development, please refer to FDA.gov.[2]

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 Information[3] and Pregnancy and Lactation Labeling Final Rule[4] 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

[1] When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.
[2] https://www.fda.gov/drugs/development-resources/pediatric-and-maternal-health-product-development
[3] https://www.fda.gov/drugs/laws-acts-and-rules/plr-requirements-prescribing-information
[4] https://www.fda.gov/drugs/labeling/pregnancy-and-lactation-labeling-drugs-final-rule

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.

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 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).

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 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 356h[5] and the guidance for industry, *Identification of Manufacturing Establishments in Applications Submitted to CBER and CDER Questions and Answers*[6]. 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.

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

[5] https://www.fda.gov/media/84223/download
[6] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/identification-manufacturing-establishments-applications-submitted-cber-and-cder-questions-and

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*.[7]

4.0 ISSUES REQUIRING FURTHER DISCUSSION

There were no issues requiring further discussion.

5.0 ACTION ITEMS

There were no action items.

6.0 ATTACHMENTS AND HANDOUTS

See attached.

13 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page

[7] https://www.fda.gov/media/85061/download

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/

ANDREW DMYTRIJUK
09/23/2020 05:02:35 PM

IND 078406

MEETING MINUTES

CTI BioPharma Corporation
Attention: Sarah Telzrow
Director, Regulatory Affairs
3101 Western Avenue, Suite 800
Seattle, WA 98121

Dear Ms. Telzrow:[1]

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for pacritinib.

We also refer to the meeting between representatives of your firm and the FDA on June 27, 2019. The purpose of the meeting was to discuss the dose for the Phase 3 portion of the PAC203 study.

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

If you have any questions, call Laura Wall, Senior Regulatory Project Manager, at 301-796-2237.

Sincerely,

{See appended electronic signature page}

Kathy Robie Suh, MD, PhD
Clinical Team Leader
Division of Hematology Products
Office of Hematology and Oncology Products
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:	Type B
Meeting Category:	End-of-Phase 2 (EOP2)
Meeting Date and Time:	June 27, 2019 from 10:00 AM to 11:00 AM (EDT)
Meeting Location:	White Oak Building 22, Conference Room 1419
Application Number:	IND 078406
Product Name:	pacritinib
Indication:	For the proposed treatment of adult patients with intermediate or high-risk myelofibrosis (MF), including patients with primary myelofibrosis (PMF), post-polycythemia vera myelofibrosis (PPV-MF), and post-essential thrombocythemia myelofibrosis (PET-MF), who have severe thrombocytopenia (platelet counts <50,000/μL)
Sponsor:	CTI BioPharma Corporation
Meeting Chair:	Kathy Robie Suh, MD, PhD, Clinical Team Leader
Meeting Recorder:	Laura Wall, MS, APHN, Senior Regulatory Project Manager

FDA ATTENDEES

Office of Hematology and Oncology Products (OHOP), Division of Hematology Products
Ann Farrell, MD, Director
Albert Deisseroth, MD, PhD, Supervisory Associate Division Director
Kathy Robie Suh, MD, PhD, Clinical Team Leader
Andrew Dmytrijuk, MD, Clinical Reviewer
Laura Wall, MS, APHN, Senior Regulatory Project Manager

Office of Clinical Pharmacology, Division of Clinical Pharmacology V
Olanrewaju Okusanya, PharmD, MS, Clinical Pharmacology Team Leader
Lauren Price, PharmD, Clinical Pharmacology Reviewer
Lian Ma, PhD, Pharmacometrics Team Leader

Office of Biostatistics, Division of Biometrics V
Yute Wu, Biometrics Team Leader

Office of Surveillance and Epidemiology
Elizabeth Everhart, MSN, ACNP, Team Leader, DRISK
Stephanie DeGraw, PharmD, Safety Evaluator, DMEPA
Nichelle Rashid, Acting CPMS, OSE Chief, Project Management Staff

Eastern Research Group
Sraavya Polisetti, Eastern Research Group, Inc.

SPONSOR ATTENDEES
Adam Craig, MD, MBA, President, CEO and Interim CMO
Jennifer Smith, PhD, SVP Biometrics
Shanthakumar Tyavanagimatt, PhD, SVP Pharmaceutical Operations and Clinical Pharmacology
Beth Ziemba, BS, VP Pharmacovigilance, Quality and Clinical Operations
John Volpone, BS, VP Strategic Operations
Sarah Buckley, MD, Director, Clinical Development
(b) (4) Regulatory Affairs Consultant
(b) (4) Pharmacometrics Consultant
(b) (4) Consultant Hematologist

1.0 BACKGROUND

The purpose of the meeting was to discuss the dose for the Phase 3 portion of the PAC203 study in patients with MF who have baseline platelet counts <50,000/µL. The proposed indications are for treatment of adult patients with intermediate or high-risk myelofibrosis (MF), including patients with primary myelofibrosis (PMF), post polycythemia vera myelofibrosis (PPV-MF), and post- essential thrombocythemia myelofibrosis (PET-MF), who have severe thrombocytopenia (platelet counts <50,000/µL).

2. DISCUSSION

2.1. Clinical Pharmacology

Question 1: *Does the FDA concur that the methodologies by which the optimal dose of pacritinib will be identified to treat the proposed Phase 3 patient population is appropriate?*

FDA Response to Question 1: In general, we agree with the approach to utilize population PK, PK/PD, and dose- and exposure-response for safety and efficacy modeling as well as an assessment of the safety and efficacy data to identify the optimal dose of pacritinib for Phase 3. However, the current models are premature to make such an assessment and your models must include all of the data from PAC203 as previously stated in our previous comment at the Type C meeting held December 12, 2018.

Discussion: The Sponsor provided additional information detailing the number of patients remaining on study in PAC203 whose data at Week 24 was not included in the most recent models. See discussion under Question 5 regarding dose selection for the Phase 3 component of PAC203.

Question 2: *Does the FDA concur that the modeling and risk-benefit assessment based on the currently available data may be used for the identification of the optimal dose?*

FDA Response to Question 2: No. See response to Question 1.

Discussion: See discussion under Question 1.

Question 3: *The PAC203 study identified 200 mg BID as the optimal dose, and the results of the integrated PK/PD and ER analyses do not demonstrate a discernable difference in clinical efficacy and safety between 400 mg QD or 200 mg BID. Therefore the Sponsor proposes that evaluation of pacritinib efficacy and safety should be based on the totality of evidence from both posologies. Does the FDA concur?*

FDA Response to Question 3: The evaluation of pacritinib risk-benefit must be based on all available safety, efficacy, PK, and PD data. We note the previously identified safety and efficacy concerns for the 400 mg QD dose utilized in the PERSIST-1 and PERSIST-2 studies and for the 200 mg BID dose in PAC203.

Discussion: The Sponsor asked if the Agency would like to see pooled analyses of the 400 mg QD and 200 mg BID doses. The Agency responded that presentation of the 200 mg BID data and 400 mg QD data separately is most appropriate and customary. The Sponsor may submit any additional analyses the Sponsor feels are useful.

Question 4: *CTI will continue to update the population PK and the exposure-response models as pacritinib moves towards registration. Does the FDA have any recommendations regarding additional modeling that should be conducted?*

FDA Response to Question 4: We agree that you should continue to update your population PK and exposure-response models as you obtain more data. We recommend that in addition to your analysis, you should:

- Conduct E-R efficacy and safety analysis separately for each trial (instead of pooling), due to difference in baseline disease characteristics across trials
- Evaluate an Emax function for the drug effect instead of linear slope in the PKPD model

Discussion: **None**

2.2. Clinical

Question 5: *Does the FDA concur that the risks for patients treated with pacritinib were adequately managed in the PAC203 study, which included the implemented risk mitigation measures? Does the FDA have additional recommendations for risk minimization measures?*

FDA Response to Question 5: No. Based on the safety data presented it is not possible at this time to concur that the risk mitigation measures implemented in study PAC203 were able to adequately manage the key risks identified with pacritinib therapy in the proposed patient population, i.e., patients with myelofibrosis (MF) including intermediate-1, intermediate-2 and higher DIPSS scores. For example, although the exclusion criteria for study PAC203 called for exclusion of patients with prolonged QTc interval, the data appear to show that among the 161 patients treated with pacritinib there were approximately 7% of patients treated with pacritinib 200mg twice daily, 4% of patients treated with pacritinib 100mg twice daily and 2% of patients treated with pacritinib 100mg once daily who had prolonged QTc at study entry. The data appear to demonstrate a possible pacritinib dose adverse effect relationship for prolonged QT interval which can be a serious and potentially fatal adverse reaction. Ejection fraction was decreased in four (2%) patients despite the study PAC203 exclusion criterion which excluded patients with NYHA Class II or higher heart failure. Also, Grade 3 or higher hemorrhagic events were reported among 8/161 (5%) patients despite exclusion of patients with an increased risk for bleeding.

Please discuss your data on 300 mg daily.

Discussion: The Sponsor discussed the measures that have been implemented in studies to decrease the risk of prolonged QT, impairment of cardiac ejection fraction and hemorrhagic events. The Agency cannot agree that the measures the sponsor has instituted are/will be adequate to manage the risks. We will need to see what the data show. The Agency commented that it has no additional recommendations at this time. More comments may be provided when the protocol is submitted for review.

Regarding the 300 mg daily dose, the sponsor commented that considering the range of doses studied thus far, the Sponsor feels that further investigation of 300mg daily will not yield additional useful data. The Sponsor would like to go forward with the 200 mg BID dose. The Agency indicated that there does not appear to be a clinical hold issue for 200 mg BID. However, the Agency still is concerned that because the risk appears to be dose-related, benefit/risk for 200 mg BID may not turn out to be as favorable as it might be for 300 mg daily.

2.3. Regulatory

Question 6: *Does the FDA agree that the indication described in Section 1 of the Target Product Profile (TPP) is supported by the populations studied throughout the clinical development program for pacritinib?*

FDA Response to Question 6: No. You are seeking a broad indication for pacritinib for the treatment of patients with MF. See responses to Questions 1, 3, and 5.

Discussion: The Sponsor asked for clarification of what FDA means by "broad indication". The Agency commented that the indication stated in the meeting background package (section 4) is "for the treatment of adult patients with intermediate or high-risk myelofibrosis (MF), including patients with primary myelofibrosis (PMF), post-polycythemia vera myelofibrosis (PPV-MF), and post-exxential thrombocythemia myelofibrosis (PET-MF), who have severe thrombocytopenia (platelet counts <50,000/uL)" that includes patients classified as Dynamic International Prognostic Scoring System (DIPSS) INT-1, INT-2 and high risk patients which can be considered a broad patient population. It is not clear whether lower risk patients (e.g., INT-1) are being excluded from study. Because the risk in patients with MF differs with type and underlying disease, strong evidence for favorable benefit/risk must be provided to support all populations proposed for labeling. It may be more difficult to establish favorable benefit/risk for lower-risk MF patients.

Question 7: *Does the FDA agree that the intended population with an acknowledged unmet therapeutic need is appropriately identified in the Indications and Usage section of the TPP and that the presented data are supportive for use in the severely thrombocytopenic MF patient population (patients with platelet counts <50,000/μL)?*

FDA Response to Question 7: See Response to Question 5.

Discussion: **None**

Question 8: *Does the FDA agree that the data for patients with baseline platelet counts <50,000/μL from PERSIST-1 and PERSIST-2 along with the data from PAC203 are supportive of the indication described in Section 1 of the TPP?*

FDA Response to Question 8: Clinical data from the previous studies PERSIST-1 and PERSIST-2 would be considered in the safety and efficacy analyses for pacritinib for the proposed indication.

Discussion: **None**

Question 9: *Does the FDA agree that the inclusion/exclusion criteria for the Phase 3 component of the PAC203 protocol are reflective and appropriate for the indication described in Section 1 of the TPP?*

FDA Response to Question 9: No. See response to Question 5.

Discussion: **None**

Question 10: *The Sponsor has:*

- *Submitted full integrated safety datasets and final CSRs for two Phase 3 studies (PERSIST-1 and PERSIST-2)*
- *Submitted data from the fully-enrolled Phase 2 component of the PAC203 study to allow determination of the optimal dose*
- *A design for a confirmatory Phase 3 trial agreed upon by the FDA (see Type C Meeting, December 12, 2018).*

Based on the unmet need in patients with MF who have platelet counts <50,000/μL and a review of the data presented here, does the FDA agree there is sufficient data to discuss the filing of an application under the Subpart H accelerated approval pathway?

FDA Response to Question 10: No, it is not clear from the clinical data that a safe and effective dose of pacritinib has been established to support the proposed broad indication for the treatment of MF.

Discussion: **None**

3.0 OTHER IMPORTANT MEETING INFORMATION

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

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*.

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]

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[2] https://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/OCE/ucm5 44641.htm

[3] http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm

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.[4]

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 will be required. Further, it describes the availability of implementation support in the form of a technical specifications document, Study Data Technical Conformance Guide,[5] as well as email access to the eData Team (cder-edata@fda.hhs.gov) for specific questions related to study data standards. Standardized study data will be required in marketing application submissions for clinical and nonclinical studies that started after December 17, 2016. Standardized study data will be 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 page[6] 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.

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 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 Conformance Guide) will assist FDA in identifying potential data standardization issues early in the development program.

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[4] http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm

[5] http://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM384744.pdf

[6] http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm

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.[7] 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[8] (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.[9] 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.[10]

LABORATORY TEST UNITS FOR CLINICAL TRIALS

CDER strongly encourages IND sponsors to identify the laboratory test units that will be reported in clinical trials that support applications for investigational new drugs and product registration. Although Système International (SI) units may be the standard reporting mechanism globally, dual reporting of a reasonable subset of laboratory tests in U.S. conventional units and SI units might be necessary to minimize conversion needs during review. Identification of units to be used for laboratory tests in clinical trials and solicitation of input from the review divisions should occur as early as possible in the development process. For more information, please see the FDA website entitled

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[7] https://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/Electro nicSubmissions/ucm174459.htm

[8] https://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM384744.pdf

[9] https://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm

[10] http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm

Study Data Standards Resources[11] and the CDER/CBER Position on Use of SI Units for Lab Tests website.[12]

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* (February 2018) and the associated *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*.[13]

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:

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[11] http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm

[12] https://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM587505.pdf

[13] https://www.fda.gov/media/85061/download

- RTOR[14]: In general, the data submission should be fully CDISC-compliant to facilitate efficient review.
- Assessment Aid[15]

4.0 ISSUES REQUIRING FURTHER DISCUSSION

The Agency recommended that the Sponsor stay in close communication with the Agency as development progresses. The Sponsor should request a teleconference to discuss their protocol, as needed, with specific questions to be addressed.

5.0 ACTION ITEMS

There are no action items.

6.0 ATTACHMENTS AND HANDOUTS

The Sponsor submitted their response document to the Agency's Meeting Preliminary Comments via e-mail on June 26, 2019.

17 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page

[14] https://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/OCE/ucm61292 7.htm

[15] https://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/OCE/ucm61292 3.htm

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