CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

219685Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

IND 132668

MEETING MINUTES

Principia Biopharma, Inc.
Attention: Antonia Martinez
Global Regulatory Strategist
55 Corporate Drive
Bridgewater, NJ, 08807

Dear Antonia Martinez:

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

We also refer to the video conference between representatives of your firm and the FDA on July 15, 2024. The purpose of the meeting was to seek the Agency's concurrence regarding your plan to submit a new drug application (NDA) for rilzabrutinib for the treatment of immune thrombocytopenia (ITP).

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

If you have any questions, call Rolanda Bailey, Regulatory Project Manager at 240-402-5631.

Sincerely,

{See appended electronic signature page}

Carrie Diamond, MD
Clinical Team Lead
Division of Nonmalignant Hematology
Office of Cardiology, Hematology,
Endocrinology, and Nephrology
Center for Drug Evaluation and Research

Enclosure:

- Meeting Minutes

U.S. FOOD & DRUG ADMINISTRATION

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: Pre-NDA

Meeting Date and Time: July 15, 2024, 2:00 p.m. – 3:00 p.m. (EDT)
Meeting Location: Video conference

Application Number: IND 132668
Product Name: rilzabrutinib

Indication: Treatment of adult patients with persistent or chronic immune thrombocytopenia (ITP) who have had an insufficient response (b) (4) to a previous treatment

Sponsor Name: Principia Biopharma, Inc.
Regulatory Pathway: 505(b)(1) of the Federal Food, Drug, and Cosmetic Act

Meeting Chair: Carrie Diamond, MD
Meeting Recorder: Carleveva Thompson, MS

FDA ATTENDEES

Office of Cardiology, Hematology, Endocrinology, and Nephrology (OCHEN)
Hylton Joffe, MD, MMSc, Director
Lisa Yanoff, MD, Deputy Director

Office of Cardiology, Hematology, Endocrinology, and Nephrology (OCHEN), Division of Nonmalignant Hematology (DNH)
Tanya Wroblewski, MD, Deputy Director
Rosanna Setse, MD, MPH, PhD, Deputy Director for Safety
Qin Ryan, MD, PhD Medical Officer, Safety
Caden Brennen, MS, Safety Regulatory Project Manager
Carrie Diamond, MD, Clinical Team Lead
Kristen Snyder, MD, Clinical Reviewer
Gary Crouch, MD, Clinical Reviewer

Office of Biostatistics (OB), Division of Biometrics IX
Lola Luo, PhD, Statistical Team Lead
Fei Wu, PhD, Statistical Reviewer

Office of Clinical Pharmacology (OCP)
Jaya Vaidyanathan, PhD, Associate Director for Therapeutic Review
Deepa A. Rao, PhD, Clinical Pharmacology Reviewer

Division of Pharmacology & Toxicology (DPT-OCHEN)
Pedro Del Valle, MS, PhD, ATS, Supervisor
Shaji Theodore, MVSc, PhD, DABT, Team Lead (Acting)
C M Sabbir Ahmed, PhD, Nonclinical Reviewer
Bo Lee, PhD, Nonclinical Reviewer

Office of Surveillance and Epidemiology (OSE), Division of Medication Error Prevention and Analysis II (DMEPA II)
Cmdr Carol Corbie, RN, BSN, MS, Safety Regulatory Project Manager (Acting)

Office of Regulatory Operations (ORO), Division of Regulatory Operations for Cardiology, Hematology, Endocrinology, and Nephrology (DRO-CHEN)
Sejal Kiani, MHS, Chief, Project Management Staff
Carleveva Thompson, MS, Senior Regulatory Project Manager
Youngeun Kim, PharmD, Regulatory Project Manager

SPONSOR ATTENDEES
Karin Knobe, MD, PhD, Global Head Rare Diseases and RBD, Clinical Development
Michelle Lee, MD, PhD, Global Project Head, Rare Diseases and Rare Blood Disorders
Ahmed Daak, MD, MSc, PhD, DPM/MFPM, Senior Clinical Research Director, Rare Diseases and Rare Blood Disorders
Hailing Guo, MSc, MBA, Senior Statistical Project Leader, Rare Diseases and Rare Blood Disorders
Heidi Krenz, MD, Global Safety Officer Lead
Mark Blazka, PhD, DABT, Distinguished Scientist, Preclinical Safety
Dario De Angelis, MSc, Global Regulatory Affairs, Therapeutic Area Head, Rare Diseases and Rare Blood Disorders
Santosh Ramamurthy, PhD, Global Regulatory Lead
Antonia Martinez, MSc, Global Regulatory Affairs Strategist
Faiza Rharbaoui, PharmD, PhD, Clinical Pharmacology
Manda Pasarkar, Director, GRA CMC and Devices Small Molecule
Brigitte Barreau, Head CMC Dossiers Synthetics portfolio

1.0 BACKGROUND

Rilzabrutinib is being investigated for the treatment of persistent or chronic immune thrombocytopenia (ITP) in adults and in pediatric patients (age ≥12 to <18 years) who have had an insufficient response to a previous treatment. IND 132668 was submitted on April 12, 2017, and was placed on full clinical hold on May 10, 2017, due to insufficient nonclinical data. The full clinical hold was removed on August 1, 2017.

Rilzabrutinib was granted Orphan Drug Designation on October 15, 2018, and granted Fast Track Designation on October 15, 2020, for the treatment of ITP.

There are currently 2 ongoing clinical studies in the development program:

1. A phase 1/2, open-label, 2-part study in participants with ITP (PRN1008-010): The 24-week main treatment period has been completed for both Parts A and B. Parts A and B long-term extension (LTE) portion is still ongoing.

2. A phase 3, blinded, randomized, placebo-controlled study in adult and adolescent participants with ITP (PRN1008-018) is ongoing. The double-blind period is complete for adults and enrollment ongoing for adolescents. The Open-Label and LTE periods are ongoing for all participants.

A Type C meeting with written responses only was granted on November 2, 2023, and responses regarding the assessment of clinical efficacy and safety, the statistical analysis plan (SAP) of the Integrated Summary of Safety (ISS), the Study Data Standardization Plan (SDSP), and the studies for the Bioresearch Monitoring (BIMO) package were provided on January 10, 2024.

The Sponsor submitted a meeting request for a Type B Pre-NDA meeting granted on June 7, 2024, to seek FDA concurrence regarding plans to submit rilzabrutinib NDA for the treatment of ITP and to discuss the following:

- Adequacy of the efficacy and safety data package to support the filing and review of an NDA for the proposed indication
- Drug Abuse Liability Assessment (DALA) strategy
- Proposed plan for the 120-day safety update
- Proposed NDA table of contents (TOC)
- Proposed study data standardization plan (SDSP)
- Regulatory milestones including application orientation meeting (AOM) and advisory committee meeting

FDA sent Preliminary Comments to Principia Biopharma on July 11, 2024.

2.0 DISCUSSION

Question 1: Does the Agency agree that the clinical efficacy and safety data package including a single adequate and well-controlled Phase 3 trial, Study PRN1008-018 and confirmatory evidence including the Open-Label and LTE periods of Study PRN1008-018 and the Phase 1/2 trial, Study PRN1008-010 is adequate to support the filing and review of an NDA for the proposed indication?

FDA Response to Question 1: Study PRN1008-018 is a double-blind,

placebo-controlled, randomized (2:1) phase 3 study in adults (n=194) and adolescents (n=30) with chronic or persistent ITP who had a response to intravenous immunoglobulin (IVIG)/anti-D or corticosteroids (CS) that was not sustained and who have documented intolerance or insufficient response to standard of care therapy for ITP. Randomization was conducted separately for the two age groups and participants were stratified by splenectomy status (yes/no), and by severity of thrombocytopenia (platelet counts <15,000/mcL or ≥15,000/mcL). The study consists of a 24-week blinded treatment period followed by an open-label period of 28 weeks and LTE period. At the end of 12 weeks of treatment, participants were assessed for achieving platelet response. Non-responders could enter the open-label period after week 12. The primary efficacy endpoint is durable platelet response (defined as platelet counts ≥50,000/mcL for ≥ two-thirds of at least 8 non-missing weekly scheduled platelet measurements during the last 12 weeks of the 24-week blinded treatment period in the absence of rescue therapy, provided that at least 2 non-missing weekly scheduled platelet measurements are ≥50,000/mcL during the last 6 weeks of the 24-week blinded treatment period).

A total of 202 participants were randomized (rilzabrutinib: 133 participants, placebo: 69 participants) from 92 sites in 25 countries. The mean platelet count at baseline was 15,000/mcL and the median number of prior unique therapies was 4 (including splenectomy, CS, IVIG or thrombopoietin receptor agonists (TPO-RA)). In total, 46.6% of participants in the rilzabrutinib arm completed the 24-week double-blind treatment period, compared to 14.5% in the placebo arm. In the rilzabrutinib arm, 31/133 (23%) participants achieved a durable platelet response versus 0/69 participants in the placebo group (95% CI: 15.95, 30.31; p-value <0.0001). Key secondary endpoints including number of weeks with platelet response, time to first platelet response, percentage of participants requiring rescue therapy, and change from baseline fatigue score were reported to have a statistically significant effect in favor of the rilzabrutinib arm.

The most common treatment-emergent adverse events (TEAEs) (≥10%) reported for participants treated with the rilzabrutinib was diarrhea (32.3% in the rilzabrutinib arm versus 10.1% in the placebo arm), nausea (20.3% versus 5.8%, respectively), headache (18.0% versus 7.2%), and COVID-19 (13.5% versus 4.3%). A lower percentage of participants experienced a serious adverse event (SAE) in the rilzabrutinib arm (n=12 [9.0%]) than in the placebo arm (n=8 [11.6%]). There was one fatal TEAE of pneumonia in the rilzabrutinib arm.

You intend to establish substantial evidence of effectiveness (SEE) with a single adequate and well-controlled study (Study PRN1008-018) and confirmatory evidence. You propose the following for confirmatory evidence of effectiveness:

1. PRN1008-018 Open-Label period and LTE period
   You report 180 participants continued on rilzabrutinib treatment during the

Open-Label period and 155 participants completed the Open-Label period. Participants who experienced a durable platelet response included 11/60 (18.3%) of those treated with placebo during the double-blind period. As of the data cutoff, 50 participants achieved eligibility for the LTE and at a median duration of 209.5 days (2 to 695 days), 45 (90%) participants continued to receive rilzabrutinib. The median platelet count during the LTE period was >80,000/mcl.

2. PRN1008-010 (Parts A and B)
   This was a phase 1/2, multicenter, dose-finding study in participants with relapsed or refractory ITP. In participants who initiated and maintained rilzabrutinib at a dose of 400 mg twice daily (BID) throughout the study (n=45), 40% of participants achieved the primary platelet response (95% CI, 25.7% to 55.7%) and 10 participants achieved durable platelet response (22.2% 95% CI, 11.2%-37.1%).

3. Nonclinical confirmatory evidence of effectiveness based on the pharmacological effect of rilzabrutinib studied in a mouse model of immune thrombocytopenia.

Overall, your proposed clinical efficacy and safety data package appears reasonable to support filing and review. Refer to draft guidance for industry, *Demonstrating Substantial Evidence of Effectiveness With one Adequate and Well-Controlled Clinical Investigation and Confirmatory Evidence*,[1] which states, the quantity of confirmatory evidence needed in a development program will be impacted by the features of, and results from, the single adequate and well-controlled clinical investigation that the confirmatory evidence is intended to substantiate. Confirmatory evidence should be evidence generated from quality data derived from appropriate sources. We strongly recommend you submit multiple sources of confirmatory evidence. You should consider mechanistic evidence and pharmacodynamic evidence, along with the pathophysiology and natural history of the disease, and the likelihood of spontaneous remission. In addition, we have the following comments below.

- The majority of participants in the rilzabrutinib arm and the placebo arm did not complete the 24-week double-blind treatment period. While we acknowledge this was prespecified in your clinical trial design, we are concerned how this may impact interpretability of the safety and efficacy results. This will be a significant review issue.

- Clarify if there was a difference in treatment effect in participants with previous exposure to TPO-RA vs no exposure to TPO-RA.

- We reiterate the information request sent on September 30, 2022, in which we stated, “We continue to have concern regarding the use of a single item to measure a multidimensional concept like fatigue, particularly over a lengthy time frame (i.e., 4 weeks), but will review the completed qualitative and quantitative

[1] We update guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

data to evaluate content validity and other measurement properties for item 10 of the Immune Thrombocytopenia Patient Assessment Questionnaire (ITP-PAQ) at the time of NDA submission."

- To further enhance your safety database, in your NDA submission, include a summary of SAEs, TEAEs leading to drug discontinuation, adverse events of special interests based on experience with other Bruton's Tyrosine Kinase (BTK) inhibitors (including gastrointestinal toxicity, serious infections, hepatotoxicity and cardiac arrhythmias) and deaths across the various clinical development programs for other indications.

(b) (4)

Meeting Discussion: **The Sponsor outlined the confirmatory evidence that will be included with the NDA submission to support substantial evidence of effectiveness (See Sponsor's slides and response document attached). The Agency noted the Sponsor's approach appeared reasonable and recommended the Sponsor to provide a summary on how substantial evidence of effectiveness was demonstrated, including a summary of confirmatory evidence in the Clinical Overview, Module 2 of the NDA submission.**

The Sponsor provided further justification for the trial design for Study PRN1008-018, in which patients who were non-responders could discontinue the double-blind portion of the study and receive open-label rilzabrutinib. The Sponsor highlighted that this approach was used in prior approvals for ITP and there were ethical considerations with continuing a therapy that does not work for patients at risk for bleeding related morbidity. The Sponsor also stated the impact of removing non-responders by Week 13 is more likely to penalize the active rilzabrutinib arm compared to the placebo arm. In addition, the crossover of patients who received placebo during the double-blind period and their subsequent response in the open-label period provides evidence of rilzabrutinib efficacy. With respect to the interpretability of the safety results, the Sponsor states they will provide exposure adjusted data in the Integrated Summary of Safety. The Agency stated the study design and potential impact on interpretation of efficacy and safety data will be a review issue.

The Sponsor proposed to submit additional safety data 60 days after the NDA submission for completed clinical trials in indications other than ITP. This timeframe would allow for a comprehensive review and organization of data. The Agency noted the Sponsor's proposal is reasonable, however, the Agency may request additional information to help facilitate review which may include studies that are not completed. The Agency noted if a safety signal is identified this could cause delays in review and approval.

Question 2: Does the Agency agree with Sponsor's DALA assessment and that no additional data are required?

FDA Response to Question 2: Yes, clinical and nonclinical safety assessments including primary pharmacology, mechanism of action, lack of neurological signs, lack of behavioral effects, and lack of detectable exposure in brain to rilzabrutinib provide evidence that no further DALA assessments are warranted.

Meeting Discussion: The Sponsor acknowledged the Agency's response; no discussion occurred.

Question 3: Does the Agency agree with the Sponsor's proposed plan for the 120-day safety update?

FDA Response to Question 3: No, we do not agree. You propose to submit the Day 120-Safety Update Report, approximately at the end of February 2025 when all participants will have completed the Open-Label period of study PRN1008-018, instead of the actual Day 120 at the end of January 2025 to allow for the inclusion of safety data from the completed Open-Label period with the cutoff date in October 2024. In order for the Agency to have sufficient time to review the Safety Update Report, it must be submitted at Day 120. Please clarify how much additional data will be collected after the Day 120-Safety Update Report (i.e., from end of January 2025 to end of February 2025). We request the corresponding safety datasets be included with the Day 120 submission.

Meeting Discussion: The Sponsor plans to submit the NDA on August 30, 2024. The Sponsor explained to provide a Day 120 safety report by December 2024, they will need to consider an earlier cut-off on September 1st. With the September cutoff date, approximately 95 patient visits (from ~54 patients) would not be part of this update. The Agency recommended to submit the safety data that is available by December 2024 in order for the Agency to have sufficient time to review the safety data. The Sponsor agreed.

Question 4: Does the Agency have comments on the proposed TOC for the planned NDA?

FDA Response to Question 4 In the TOC, please include the following studies listed in the SDSP and submitted to the IND that need to be submitted to the NDA and are not included in the TOC:

a. Study # DVR0107: In Vivo PK/PD BTK Occupancy in Rat Type II Collagen Arthritis Model.

b. Study # DVR0294: A Pharmacokinetic-Pharmacodynamic Study of BTK Occupancy from Sprague Dawley Rats Orally Dosed with PRN1008 for Three Days in Passive Arthus Model.

5. The study number DVR0375 for the primary pharmacology study, "Biochemical and cellular activity of major metabolites of PRN1008" is incorrectly identified as DVR0528 in the TOC. The report for this study has been submitted to the IND file but your proposed TOC lists this study as ongoing. At the NDA submission, please change the status of the study to "complete" and revise the study number to reflect the correct study number in the IND file.

6. Your TOC lists a safety pharmacology study # PAT0302, "*Effect of SAR444671 on cloned hERG potassium channels expressed in human embryonic kidney cells*" which is different from study # DVR0111, "Effects of PRN1008 on Cloned hERG Potassium Channels Expressed in Human Embryonic Kidney Cells (HEK293)" listed in your SDSP and submitted to the IND. Revise the listing in your TOC to be consistent with the study identified in the SDSP and submitted to IND.

Meeting Discussion: The Sponsor acknowledged the Agency's response; no discussion occurred.

Question 5: Does the Agency agree with the proposed SDSP?

FDA Response to Question 5: The proposed SDSP appears reasonable. Please submit the SAS programs used to create the safety tables in the body of the Clinical Study Report for PRN1008-018 and in the body of the ISS report.

Meeting Discussion: The Sponsor acknowledged the Agency's response; no discussion occurred.

Question 6: Does the Agency plan on requesting an AOM?

FDA Response to Question 6: Yes. We recommend you provide an overview of your clinical development program. In addition, we recommend you discuss baseline differences among participants in Study PRN1008-018, particularly prior treatments and splenectomy. In addition, you should also comment on the impact of the majority of participants not completing the 24-week double-blind period, see comments to FDA Question 1.

Meeting Discussion: The Sponsor acknowledged the Agency's response; no discussion occurred.

Question 7: Does the Agency agree that an Advisory Committee is not required based upon the data shared to date?

FDA Response to Question 7: The Agency will determine the need for an Advisory Committee meeting during the NDA review.

Meeting Discussion: The Sponsor acknowledged the Agency's response; no discussion occurred.

ADDITIONAL COMMENTS

Clinical Pharmacology

We have the following comments and questions related to clinical pharmacology assessments of rilzabrutinib:

1. From in vitro studies, you have identified that rilzabrutinib inhibits CYP3A4. Additionally, based on the data from the in vivo drug-drug interaction (DDI) study of rilzabrutinib with midazolam (Study PRN1008-011), rilzabrutinib is a moderate inhibitor of CYP3A4 as it increased midazolam exposure by more than 2-fold. Refer to the guidance for industry, *Clinical Drug Interaction Studies With Combined Oral Contraceptives (COC) Guidance for Industry*. The sponsor should conduct a clinical COC DDI study (see Figure 2 in the Appendix) to quantify the magnitude of the DDI if: (1) prior clinical DDI studies suggest that the investigational drug is a moderate or strong CYP3A inhibitor (i.e., it increases the AUC of a sensitive CYP3A substrate by 2-fold or more); and (2) in vitro or in vivo data suggest that the investigational drug also inhibits one or more other enzymes involved in the metabolism of EE (e.g., CYP2C9, UGT1A1, and SULT1E1)". From in vitro studies, you have identified that rilzabrutinib is not an inhibitor of CYP2C9. However, clarify whether rilzabrutinib is an inhibitor of either UGT1A1 or SULT1E1. Conduct in vitro studies if these assessments are not done. If rilzabrutinib inhibits UGT1A1 or SULT1E1, a clinical DDI study with combined oral contraceptives will be required.

2. You state that the renal elimination of rilzabrutinib is minimal. However, an impact of severe renal impairment on the pharmacokinetic (PK) of drugs predominantly eliminated via the hepatic route cannot always be excluded. Therefore, you should consider conducting a reduced pharmacokinetic study design in participants with severe renal impairment or kidney failure not on dialysis. Refer to guidance for industry, *Pharmacokinetics in Patients with Impaired Renal Function – Study Design, Data Analysis, and Impact on Dosing* for additional information. Such a study will assist in labeling rilzabrutinib for patients with renal impairment.

3. Clarify whether rilzabrutinib is a substrate for BCRP. If rilzabrutinib is a substrate of BCRP, what clinical DDI assessments have been conducted to characterize the DDI potential with a BCRP inhibitor?

Chemistry, Manufacturing, and Controls (CMC)

We have the following comments regarding the dissolution specification for your proposed drug product that should be provided in your NDA.

1. Dissolution Test: Include the dissolution method development report supporting the selection of the proposed dissolution test. The dissolution report should include the following information:

    a. Solubility data for the drug substance covering the pH range.

    b. Detailed description of the dissolution test being proposed for the evaluation of your product and the developmental parameters (*i.e., selection of the equipment/apparatus, in vitro dissolution/release media, agitation/rotation speed, pH, assay, sink conditions, etc.*) used to select the proposed dissolution method as the optimal test for your product. If a surfactant was used, include the data supporting the selection of the type and amount of surfactant. The testing conditions used for each test should be clearly specified. The dissolution profile should be complete and cover at least 85% of drug release of the label amount or whenever a plateau (i.e., no increase over 3 consecutive time-points) is reached. We recommend use of at least twelve samples per testing variable.

    c. Provide the complete dissolution profile data (*individual, mean, SD, profiles*) for your product. The dissolution data should be reported as the cumulative percentage of drug dissolved with time (*the percentage is based on the product's label claim*).

    d. Data to support the discriminating ability of the selected dissolution method. In general, the testing conducted to demonstrate the discriminating ability of the selected dissolution method should compare the dissolution profiles of the reference (target) product and the test products that are intentionally manufactured with meaningful variations for the most relevant critical manufacturing variables (i.e., ± 10-20% change to the specification-ranges of these variables).

    e. Supportive validation data for the dissolution method (i.e., method robustness, etc.) and analytical method (precision, accuracy, linearity, stability, etc.).

2. Dissolution Acceptance Criterion: For the selection of the dissolution acceptance criterion of your product, the following points should be considered:

    a. The dissolution profile data from the pivotal clinical batches and primary (registration) stability batches should be used for the setting of the dissolution

acceptance criterion of your product (i.e., specification-sampling time point and specification value).

b. The in vitro dissolution profile should encompass the timeframe over which at least (b) (4)% of the drug is dissolved or where the plateau of drug dissolved is reached, if incomplete dissolution is occurring.

c. For immediate release product the selection of the specification time point should be where Q=(b) (4)% dissolution occurs.

Note that the final determination on the acceptability of the dissolution method is a review issue that can be determined during the IND or NDA. However, the acceptability of the proposed dissolution criterion for your product will be made during the NDA review process based on the totality of the provided dissolution data. If you wish to have the dissolution method assessed prior to NDA filing, submit the detailed information separately as an IND amendment, stating in the cover letter that FDA review for acceptability of the dissolution method is being requested. Alternatively, acceptability of the dissolution method can be determined during NDA review.

We note that several actual and potential impurities that may form in the drug substance and drug product are (b) (4) with significant potential to form (b) (4) impurities, including (b) (4) which is a related substance that is controlled in the current drug substance specification for the IND. We recommend that you complete a comprehensive risk assessment for (b) (4) impurities and conduct additional testing as appropriate. If (b) (4) impurities are found to exceed acceptable limits, implement changes as needed to eliminate, mitigate, or reduce these impurities. This risk assessment also needs to support the proposed limits for (b) (4) impurities such as (b) (4) in the drug substance and/or drug product specifications. Refer to guidance for industry, (b) (4)

Meeting Discussion: The Sponsor acknowledged the Agency's response; no discussion occurred.

3.0 ADDITIONAL INFORMATION

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

- The content of a complete application was discussed.

- 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.

Because this drug product for this indication has an orphan drug designation, you are exempt from these requirements. Please include a statement that confirms this finding, along with a reference to this communication, as part of the pediatric section (1.9 for eCTD submissions) of your application. If there are any changes to your development plans that would cause your application to trigger PREA, your exempt status would change.

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[2] and Pregnancy and Lactation Labeling Final Rule[3] 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

[2] https://www.fda.gov/drugs/laws-acts-and-rules/plr-requirements-prescribing-information
[3] https://www.fda.gov/drugs/labeling/pregnancy-and-lactation-labeling-drugs-final-rule

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.

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

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

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*.[6]

REAL-WORLD EVIDENCE

CDER strongly encourages sponsors to include information in their submission cover letters that identifies uses or proposed uses of real-world evidence (RWE) to support a regulatory decision regarding product safety and/or effectiveness. For recommendations on specific information to include in submission cover letters, see the guidance for industry *Submitting Documents Using Real-World Data and Real-World Evidence to FDA for Drug and Biological Products.*[7] For questions or clarification, contact cdermedicalpolicy-realworldevidence@fda.hhs.gov.

4.0 ISSUES REQUIRING FURTHER DISCUSSION

No issues were identified during the meeting.

5.0 ACTION ITEMS

No action items were identified during the meeting.

6.0 ATTACHMENTS AND HANDOUTS

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

[6] https://www.fda.gov/media/85061/download
[7] https://www.fda.gov/media/124795/download

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/s/

CARRIE E DIAMOND
08/14/2024 08:56:57 AM

IND 132668

MEETING MINUTES

Principia Biopharma Inc.
Attention: Ana Sousa, MSJ
Head of Global Regulatory Affairs
220 East Grand Avenue
South San Francisco, CA 94080

Dear Ms. Sousa:

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

We also refer to the telecon between representatives of your firm and the FDA on May 27, 2020. The purpose of the meeting was to discuss the development plan that consists of PRN1008-010 phase 2 (Part B) study with historical cross study comparison and a proposed phase 3 randomized placebo-controlled trial in support of a marketing application.

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 Latrice Wilson, PharmD, RAC, Senior Regulatory Project Manager at (240) 402-5317.

Sincerely,

{See appended electronic signature page}

Kathy Robie Suh, MD, PhD
Clinical Team Leader
Division of Non-Malignant Hematology
Office of Cardiology, Hematology,
Endocrinology, & Nephrology
Center for Drug Evaluation and Research

Enclosure:

- Meeting Minutes

U.S. FOOD & DRUG ADMINISTRATION

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: End of Phase 2

Meeting Date and Time: May 27, 2020; 3:00 p.m. to 4:00 p.m. EST
Meeting Location: Conference Call

Application Number: IND 132668
Product Name: Rilzabrutinib (PRN1008)
Indication: Treatment of immune thrombocytopenic purpura
Sponsor Name: Principia Biopharma Inc.
Regulatory Pathway: 505(b)(1) of the Food, Drug, and Cosmetics Act

Meeting Chair: Kathy Robie Suh, MD, PhD
Meeting Recorder: Latrice Wilson, PharmD, RAC

FDA ATTENDEES

Office of Cardiology, Hematology, Endocrinology, and Nephrology (OCHEN)
Ellis Unger, MD, Director
Ilan Irony, MD, Deputy Director (acting)

OCHEN, Division of Non-Malignant Hematology (DNH)
Albert Deisseroth, MD, PhD, Supervisory Associate Director
Kathy Robie-Suh, MD, PhD, Clinical Team Lead
Hyon-Zu Lee, PharmD, Clinical Reviewer

OCHEN, Division of Pharm/Tox (DPT)
Todd Bourcier, PhD, Nonclinical Team Lead (Acting)
David Carlson, 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
Anusha Ande, PhD, Clinical Pharmacology Reviewer

Office of Drug Evaluation Science (ODES), Division of Clinical Outcome Assessment (DCOA)
Onyeka Illoh, OD, MPH, Clinical Outcome Assessment Team Leader (Acting)

Mira Patel, PhD, Clinical Outcome Assessment Reviewer

SPONSOR ATTENDEES
Principia Biopharma Inc.
Dolca Thomas, MD, Chief Medical Officer
Ana Sousa, MSJ Sr., Vice President, Regulatory Affairs & Quality
Philip Nunn, PhD, Vice President, Early Development and Pharmacology
Olga Bandman, MD, Sr. Director, Clinical Development
Adel Al-Shaikh, MSc, RAC, Director, Regulatory Affairs
Stefani Wolff, Chief Development Officer
Olivia Ware, SVP, BTK Franchise, Team Leadership and Portfolio Analytics

Principia Consultants
(b) (4)

1.0 BACKGROUND

The purpose of this meeting is to discuss the Sponsor's clinical development plan that consists of PRN1008-010 phase 2 (Part B) study with historical cross study comparison and a proposed phase 3 randomized placebo-controlled trial in support of a marketing application.

FDA sent Preliminary Comments to Principia Biopharma on May 21, 2020.

2.0 DISCUSSION

2.1. Nonclinical

Question 1: Principia provided the list for completed and ongoing nonclinical safety and toxicity studies of rilzabrutinib, in Table 13-2. Does the Agency agree that the completed and ongoing nonclinical studies are sufficient for a marketing application?

FDA Response to Question 1: We agree the completed and ongoing nonclinical studies constitute a comprehensive nonclinical development program and supports proposed phase 3 clinical trials. The nonclinical studies as described appear sufficient for filing a marketing application.

Meeting Discussion: No further discussion.

2.2. Clinical

Question 2: Principia is planning to initiate Part B of the Phase 2 PRN1008-010 single arm trial with a historical placebo control for the ITP rare disease population.

Question 2a: Does the Agency agree that the Phase 2 Open-Label (Part B) single-arm trial in patients who had an insufficient response to prior treatments with a historical placebo cross study comparison/control trial design, dose selection, eligibility criteria, and endpoints, can be considered an adequate one of two clinical trials supporting registration for the proposed ITP indication?

FDA Response to Question 2a: No. Study PRN1008-010 is a phase 1/2 single-arm trial comprised of an initial dose finding part of PRN1008 (part A) followed by an expansion part (part B) that evaluates the safety and efficacy of PRN1008 at the recommended dose in patients with ITP who had a response to IVIg/anti-D or corticosteroid that was not sustained and failed at least one other ITP therapy.

We do not agree that the expansion part (part B) of study PRN1008-010 with a historical placebo cross control comparison is adequate to substitute a well-controlled pivotal trial for the proposed ITP indication. The expansion part B of study PRN1008-010 can be included in the NDA application as a supportive study.

We strongly recommend that you conduct two adequate and well-controlled trials to support the proposed indication. For a single randomized trial to support licensure, the trial should be well designed, well conducted, internally consistent, provide statistically persuasive and clinically meaningful efficacy findings. For further information, please refer to the FDA guidance "Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products" at https://www.fda.gov/media/71655/download.

Meeting Discussion: The Agency emphasized that results from a single adequate and well-controlled study must be particularly clear and persuasive to be acceptable to support efficacy of a drug for the indication. In your proposed PRN1008-010 study, we are concerned that early cross-over of patients who have not shown evidence of a response (i.e., a single platelet count of ≥50,000/µL OR >30,000/µL and <50,000/µL and doubled from baseline) at 12 weeks will complicate the analysis and interpretation of the study results. For example, patients who cross over will be "missing" from the analysis of the primary efficacy endpoint because they will not have completed the 24-week treatment period, even though they will be counted early as failures. Should a large proportion of patients cross over early, it is likely that only the less severely affected patients will be evaluable for efficacy by actual assessment at 24 weeks. Moreover, these patients will reflect a selected sub-population of the enrolled patients and there likely will be imbalances in the numbers of these patients in the two treatment arms. Finally, if large numbers of patients in the placebo arm cross over to rilzabrutinib at 12 weeks, analysis and interpretation of the safety data for the two treatment arms during the study may be compromised, because the crossover placebo arm patients will also have received rilzabrutinib. The results will be examined for completeness of data and internal consistency (such

as across sub-groups and endpoints). The sponsor commented that they propose to increase the study sample size from 111 (74 rilzabrutinib; 37 placebo) proposed in the background package to 153 (102 rilzabrutinib; 51 placebo) to increase the statistical power and provide better balance for the strata (See sponsor slide #4). The Sponsor expressed understanding of the Agency's concerns. The sponsor commented that analyses of study results by stratum also will be conducted. The sponsor provided arguments and rationale for the crossover (see attached sponsor slide #6). The Agency commented that the utility of the study for establishing efficacy will be a review issue.

The Agency also expressed concern that a robust safety database (such as at least 300 patients for the targeted population) will be needed to support an NDA submission. The Sponsor is considering 60 sites for the ITP trial. (b) (4)

Question 2b: Does the Agency agree that showing a rilzabrutinib response rate above 16% (two-fold increase over the conservative assessment of historical placebo control response rate) would demonstrate substantial evidence of effectiveness?

FDA Response to Question 2b: No, we do not agree. See response to Question #2a.

Meeting Discussion: No further discussion.

Question 2c: Does the Agency agree that enrollment can be stopped after 40 patients if there are 16 or more durable responders (i.e. platelet counts at or above 50,000/μL for 8 out of the last 12 weeks of the 24-week treatment period)?

FDA Response to Question 2c: No. We do not agree that expansion part B of the phase 1/2 single-arm trial (PRN1008-010) with a historical placebo cross control comparison is adequate to substitute for a well-controlled pivotal trial for the proposed ITP indication. See response to Question #2a.

Meeting Discussion: No further discussion.

Question 3: Principia is planning to initiate a Phase 3 randomized, double-blind, placebo-controlled, parallel-group clinical trial in adult and pediatric patients (12 – < 18 years) with ITP who had insufficient response to at least one prior treatment.

Question 3a: Does the Agency agree with the proposed Phase 3 study design, dose selection, eligibility criteria & endpoints in the adult population to provide data in support of the proposed ITP indication?

FDA Response to Question 3a: No. The proposed phase 3 study (PRN1008-018) is a randomized (PRN1008: placebo, 2:1), double-blind, parallel group multicenter clinical trial in patients with primary ITP who had a response to either IVIg or corticosteroid that was not sustained. The primary efficacy endpoint is the proportion of patients able to achieve platelet counts ≥ 50,000/mcL for 8 out of the last 12 weeks of the 24-week blinded treatment period.

Based on the submitted synopsis, we do not agree that the proposed phase 3 study is adequate to support the proposed indication. We have the following comments regarding the study design:

- **Stratification should also include prior splenectomy (yes or no) and severity of thrombocytopenia (platelets < or ≥ 15,000/mcL) in addition to by age.**

- **Provide justification for allowing patients who were on active study treatment with no response to start the open-label maintenance period at Week 12. Patients who do not respond by Week 12 with active study treatment should be discontinued from the study treatment.**

- **Any increase in doses of concomitant ITP medications during study treatment should be considered as rescue medication.**

- **Patients who were on other ITP treatment (that are not allowed during the study treatment) should undergo adequate washout period before treatment with the study drug.**

- **The study should stop if there are more than one rilzabrutinib-related deaths or more than two Grade 4 rilzabrutinib-related TEAEs.**

We have the following comment regarding the eligibility criteria:

- **The proposed indication is for the treatment of thrombocytopenia with persistent or chronic immune thrombocytopenia who have had an insufficient response to a previous treatment. However, the eligibility criteria allow enrollment of patients who had prior treatment with only IVIg/anti-D or corticosteroids. Considering the number of currently available treatments for ITP, the study should enroll patients who had documented intolerance or insufficient response to appropriate courses of standard of care ITP therapies.**

We have the following comments regarding the analysis plan:

- **For the primary efficacy analysis, patients who discontinue treatment prior to Week 24 due to lack of efficacy or an AE, or who receive rescue**

treatment (including increase in concomitant ITP medication dose) should be considered non-responders.

- **For the primary and key secondary efficacy assessments, any week(s) with missing platelet counts should be considered no platelet response.**

- **For the following secondary efficacy analyses:**
  - **Number of weeks with platelet count ≥50,000/mcl or ≥30,000/mcl and <50,000/mcl and doubled from baseline over the 24-week blinded treatment period in the absence of rescue therapy; and**

  - **Number of weeks with platelet counts ≥ 30,000/mcl and <50,000/mcl and doubled from baseline over the 24-week blinded treatment period**

Patients who discontinue treatment prior to Week 24 due an AE or who receive rescue treatment, only the platelet count data up to the start date of rescue therapy or the AE should be used for the statistical analysis. Patients who take rescue therapy or who are withdrawn due to an AE should be censored as having a loss of platelet response at the time of the event occurring.

The proposed endpoints and dose selection are acceptable.

The above comments were based on the provided synopsis. The full study protocol should be submitted for review.

Meeting Discussion: The sponsor indicated the changes described the first 5 bullets of the response to this question have been made in the protocol (see attached sponsor slide #3). The sponsor also made proposals and arguments for handling of rilzabrutinib-treated patients who did not respond to treatment, with regard to cross-over and efficacy analysis for patients who discontinue study drug due to reasons unrelated to AE.

The Agency requested that the sponsor provide detailed reasons for discontinuation for each patient and conduct a sensitivity analysis using non-responder imputation. The Agency stated that the Sponsor should submit the full protocol for review. See also discussion under response to Question 2a.

Post-meeting note: With respect to reasons for study discontinuation, "Patient withdrew consent" is not an adequate justification for study discontinuation. The actual reason should be sought by the sponsor.

Question 3b: Does the Agency agree [redacted] (b) (4)

(b) (4)

Meeting Discussion: **No further discussion.**

Question 4: Does the Agency agree that current and planned collection of a safety database of approximately 250 ITP patients and 162 PV patients at 400 mg BID will adequately characterize the safety profile of rilzabrutinib and form the basis for drug approval given the orphan prevalence of the ITP indication?

FDA Response to Question 4: The adequacy of the safety database will be determined during the review of the NDA application. Also see responses to Question #2a and 3b.

Meeting Discussion: **No further discussion.**

2.3. Biostatistics

Question 5: Does the Agency agree with the proposed statistical design and analyses presented in Phase 2 Open-Label (Part B) protocol [IND 132668; Serial 0038] are adequate to support a marketing application?

FDA Response to Question 5: See response to Question 2a.

Meeting Discussion: **No further discussion.**

Question 6: Does the Agency agree with the proposed statistical design and analyses presented in Phase 3 Protocol Synopsis in Appendix 15.1 are adequate to support a marketing application?

FDA Response to Question 6: See response to Question 3a. The full study protocol with detail statistical analysis plan (SAP) should be submitted for review. Your SAP should include key features including prespecifying primary and key secondary endpoints, multiple testing procedure to control overall type I error and missing data handling methods, etc.

Meeting Discussion: **No further discussion.**

2.4. Clinical Pharmacology

Question 7: Principia provided a comprehensive clinical pharmacology plan for rilzabrutinib in [redacted] (b) (4) An updated version of the plan is summarized in the Company Position, and the highlights of the clinical pharmacology and cardiac safety data are provided in Appendix 15.2. Does the Agency agree that the overall clinical pharmacology plan as presented below is adequate to support a marketing application?

FDA Response to Question 7: The sponsor's clinical pharmacology plan includes characterizing the single and multiple dose PK in healthy volunteers and patients with ITP, assessing DDI liability by evaluating rilzabrutinib as a victim and perpetrator of CYP enzymes and transporters, conducting a TQT study, characterizing PK in a special population study such as hepatic impairment study, conducting a human mass balance study, a food effect study with the to-be-marketed formulation, and conducting pop PK and exposure-response analyses. Yes, we agree that the overall clinical pharmacology plan is adequate to support a marketing application.

Meeting Discussion: No further discussion.

2.5. Health Economics and Outcome Research

Question 8: Does the Agency agree that the ITP-PAQ [redacted] (b) (4) are fit for purpose as measures of patient disease experience?

FDA Response to Question 8: At this time, it is premature to fully comment on whether the ITP-PAQ [redacted] (b) (4) are fit for purpose for the context of this drug development program as you have not provided sufficient information to support their use. While the concepts of bruising, petechiae, bleeding episodes, and fatigue, as measured by the ITP-PAQ, [redacted] (b) (4) are clinically relevant concepts to measure, it is unclear whether these concepts are the most important and relevant to your target population from the patient's perspective.

A critical piece in determining trial endpoints is the use of patient input. The submitted literature for the ITP-PAQ [redacted] (b) (4) (Mathias, 2007; Mathias, 2009; Klaassen, 2007; Klaassen, 2013), has insufficient documentation of the qualitative development of the instruments (e.g., results of concept elicitation and cognitive debriefing with patients, including item tracking matrix). It is important to note that it is not possible to interpret the quantitative findings without first having confidence that the instrument is content valid (i.e., the instrument is measuring the concept(s) of interest) and well-understood (i.e., instrument instructions, item stems, recall period, and response options). Testing other measurement

properties (reliability, validity, sensitivity to change), while important, will not replace or rectify problems with content validity. We recommend reaching out to the authors for additional qualitative evidence, and/or obtain qualitative data through patient input.

See Additional Comments for obtaining patient input and other ITP-PAQ (b) (4) considerations.

Meeting Discussion: No further discussion.

Question 9: Does the Agency agree (b) (4)

FDA Response to Question 9: At this time, it is premature to comment (b) (4) The following are general comments for your consideration (b) (4)

1. (b) (4)

2. (b) (4)

3. (b) (4)

Meeting Discussion: **No further discussion.**

Additional Comments

General Comments:

1. **We understand the challenges of measurement in diseases that are rare and heterogeneous across patients and symptoms. Because ITP is a rare condition, it requires more sensitive outcome measures to quantify disease. As such, you should consider the following factors when selecting instruments for your clinical trial(s):**
    - **A fit-for-purpose instrument (i.e., an instrument that is appropriate for its intended use; validly and reliably measures concepts that are both clinically relevant and important to patients; and data can be communicated in labeling in a way that is accurate, interpretable and not misleading)**
    - **Instrument sensitivity**
2. **We recommend that you obtain ITP patients' input to provide you a complete understanding of the disease or condition, including presentation of symptoms and associated impacts in this population, as well as inform the endpoint selection and hierarchy. COAs should assess the most important and relevant symptoms and impacts from the patient's perspective. It is**

important to understand the condition of interest and what aspect of the condition the drug is expected to improve when selecting and/or developing a COA. The choice of an outcome assessment depends upon the concept (e.g., sign, symptom, or impact) that one seeks to measure as well as the intended context of use. The concepts you select to measure should be based on aspects of the condition that are expected to have a meaningful impact on how patients feel or function in daily life, as well as guided by patient input. If you have already obtained patient input from your target population, please submit this information if available (e.g., qualitative reports, transcripts, literature, etc.). Without this information, we cannot agree that the proposed PRO instruments are fit-for-purpose for the context of your drug development program.

3. **Provide details of the planned COA endpoints and general plans for analysis for us to provide a more concrete recommendation. We recommend that you request a separate Type C guidance meeting focused on COAs prior to conducting your phase 3 clinical trial to further discuss your COA measurement strategy.**

Comments regarding proposed COA instruments:

4. **It may be helpful to confirm the content relevance of the ITP-PAQ** (b) (4) **for the target population either via leveraging patient input from the Externally-led Patient Focused Drug Development meeting (https://pdsa.org/2019-conference-pfdd-mtg.html) and/or qualitative interviews with ITP patients.**

5. **The ITP-PAQ appears to include disease and treatment-related symptoms and impacts that may overlap (e.g., "In the past 4 weeks, how much have your ITP symptoms or the effects of its treatment interfered with your ability to exercise?"), which may be difficult for patients to separate some of these concepts.**

6. **You propose the ITP-PAQ Symptoms, Bother and Activity domains as secondary endpoint(s). The Symptoms domain may be a more sensitive measure than the other domains, however, it is not without limitations (refer to Comment 7). The relevancy of the symptoms measured in this domain should be further explored in your target population. You should plan to provide item-level analyses to allow evaluation of whether or not individual items in this domain are overly influencing changes observed in this domain score.**

7. **There is concern that the ITP-PAQ is susceptible to recall error due to the 4-week recall period. Consider using a shorter recall period to minimize any recall error. The choice of recall period that is most suitable depends on the instrument's purpose and intended use; the variability, duration, frequency, and intensity of the concept measured; the disease or condition's**

characteristics; and the tested treatment (e.g., frequency of treatment administration).

8. (b) (4)

9.

10.

11. The ITP-PAQ (b) (4) **measure health-related quality of life (HRQL). HRQL is a complex, multi-domain concept that can be challenging to measure as it consists of concepts that might be influenced by factors beyond the treatment and consequently not sensitive to treatment effect. Therefore, we recommend that you consider collecting and separately analyzing the most important disease-related symptoms (e.g., bruising, bleeding, fatigue) and functional impacts (e.g., physical function, mobility) that are responsive to treatment to the extent possible using well-defined and reliable instruments. One important clinical trial objective is the collection of PRO data that can inform tolerability. We remain open to assessment of symptomatic adverse events (i.e., treatment side effects).**

12. Propose and justify a threshold or range of threshold(s) for a meaningful within-patient score change in the ITP-PAQ (b) (4) **to help with interpretation of your study results. The Mathias et al. (2009) publication focused on evaluation of a minimal important difference in the ITP-PAQ. From a regulatory standpoint, we are more interested in what constitutes a clinically meaningful within-patient change in scores (i.e., improvement threshold), from the patient perspective, rather than a minimal clinically important difference across all patients. The threshold for within-patient meaningful change (i.e., responder definition) should be derived from anchor-based methods supplemented with anchor-based empirical cumulative distribution function and probability density function curves. Distribution-based methods (e.g., effect sizes, certain proportions of the standard deviation and/or standard error of measurement) are only considered supportive to anchor-based methods.**

13. **Plan to include at least the following patient global rating scales as anchors to help interpret a meaningful within-patient score change in the target instrument:**
    a. **Static, current state patient global impression of severity (PGIS) scale**

    b. **Patient global impression of change (PGIC) scale**

    Note that a target instrument (e.g., ITP-PAQ, (b) (4)) should have a corresponding anchor scale (e.g., an anchor scale specific to concept(s) being measured) with a matching recall period. Anchor scales should be assessed at the same time points as, but completed after, the target instrument.

14. **Exit interviews or surveys may be an option to collect additional qualitative data. Exit interviews or surveys can be helpful in affording sponsors the opportunity to cognitively interview patients with regard to:**
    - **Whether any important symptoms should be added or removed from an instrument, as well as assess patient comprehension of an instrument**
    - **Their thoughts on what they believe constitutes a meaningful improvement from baseline in their symptoms in terms of each item**
    - **What they consider to be a meaningful improvement in terms of PGIS category changes (e.g., 1-category change, 2-category change, etc.), as well as in PGIC categories (e.g., reporting "a little better," "a lot better")**
    - **Whether they believe they experienced a meaningful improvement from baseline.**
    - **Whether they believe they were on the treatment arm or placebo arm to aid in determining whether the treatment assignment blind was maintained.**

    If you choose to conduct exit interviews/surveys, we recommend you submit an exit interview/survey protocol and interviewer guide (if applicable) for review and comment. The interviews/surveys should be conducted after the patients complete the main portion of the study to avoid any potential compromise to trial integrity.

    You may refer to the following literature references and relevant FDA review document where an exit interview, or one-on-one qualitative interview, strategy was successfully implemented in helping determine meaningful change.

- **Lowell A, Horsch D, Ervin C, et al. Assessing Treatment Benefit of Telotristat Etiprate in Patients with Carcinoid Syndrome: Patient Exit Interviews. Poster presented at the 2015 North American Neuroendocrine Tumor Society (NANETS) Annual Meeting; October 16-17, 2015, Austin, TX.**

- **Gelhorn H, Kulke M, O'Dorisio T, et al. Patient-reported Symptom Experiences in Patients With Carcinoid Syndrome After Participation in a Study of Telotristat Etiprate: A Qualitative Interview Approach. Clin Ther. 2016; 38 (4): 759-68.**

- **FDA COA Consult Review for telotristate ethyl (Xermelo) approval 34TUhttps://www.accessdata.fda.gov/drugsatfda_docs/nda/2017/208794Orig1s000OtherR.pdf.**

15. **The EQ-5D-5L is a generic preference-based measure intended to provide a single health utility index value for use in economic analyses and lacks evidence of content validity for use in estimating clinical benefit for labeling claims. However, we acknowledge that the EQ-5D-5L may be necessary for other regulatory authorities and/or payers.**

Comments regarding trial design for COA measurement:

16. **Provide the assessment schedule for the proposed instruments. Note that the open-label maintenance period of Study PRN1008-018 poses a limitation to COA data interpretation as patients' knowledge of treatment assignment may lead to systematic over- or underestimation of the treatment effect, the magnitude of which is currently unknown.**

17. **COA measurement should be obtained before or shortly after patient withdrawal from treatment should early withdrawal be unpreventable.**

18. **COAs will need to be culturally adapted and adequately translated for all intended study populations for use in multinational trials. We refer you to the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) principles for the translation and cultural adaptation process.[1]**

19. **We recommend electronic data capture using a device with a reminder or alarm function, when appropriate and feasible, as this tends to facilitate operation, minimize the extent of missing data, and allows for the collection of**

[1] Wild D, Grove A, Martin M, Eremenco S, McElroy S, Verjee-Lorenz A, Erikson P; ISPOR Task Force for Translation and Cultural Adaptation. Principles of Good Practice for the Translation and Cultural Adaptation Process for Patient-Reported Outcomes (PRO) Measures: report of the ISPOR Task Force for Translation and Cultural Adaptation. Value Health. 2005 Mar-Apr;8(2):94-104.

other important information (e.g., timestamps for data input). You may refer to the FDA guidance for industry on electronic source data.[2]

If you proceed with electronic data capture, we recommend you perform usability testing of the selected devices with patient cognitive interviews to assess device functionality, questionnaire comprehension, and ease of use in the patient population. This would minimize the likelihood of having poor quality data due to patients' misunderstanding or incomplete understanding of how to use the device. We also recommend you implement a back-up plan prior to using the devices in your clinical trials, in case of any electronic device malfunctions.

3.0 OTHER

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.

Because this drug product for this indication has an orphan drug designation, you are exempt from these requirements. Please include a statement that confirms this finding, along with a reference to this communication, as part of the pediatric section (1.9 for eCTD submissions) of your application. If there are any changes to your development plans that would cause your application to trigger PREA, your exempt status would change.

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.[3]

On December 17, 2014, FDA issued the guidance for industry *Providing Electronic*

[2] Guidance for Industry: Electronic Source Data in Clinical Investigations (http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm328691.pdf)
[3] http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm

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 (cder-edata@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 page[4] 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 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

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

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.[5]

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

[5] https://www.fda.gov/industry/study-data-standards-resources/study-data-submission-cder-and-cber

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.

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 Study Data Standards Resources[6] and the CDER/CBER Position on Use of SI Units for Lab Tests website.[7]

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*.[8]

[6] http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm
[7] https://www.fda.gov/media/109533/download
[8] https://www.fda.gov/media/85061/download

NEW PROTOCOLS AND CHANGES TO PROTOCOLS

To ensure that the Division is aware of your continued drug development plans and to facilitate successful interactions with the Division, including provision of advice and timely responses to your questions, we request that the cover letter for all new phase 2 or phase 3 protocol submissions to your IND or changes to these protocols include the following information:

(1) Study phase

(2) Statement of whether the study is intended to support marketing and/or labeling changes

(3) Study objectives (e.g., dose finding)

(4) Population

(5) A brief description of the study design (e.g., placebo or active controlled)

(6) Specific concerns for which you anticipate the Division will have comments

(7) For changes to protocols only, also include the following information:

- A brief summary of the substantive change(s) to the protocol (e.g., changes to endpoint measures, dose, and/or population)
- Other significant changes
- Proposed implementation date

We recommend you consider requesting a meeting to facilitate discussion of multiple and/or complex issues.

UNITED STATES PATIENT POPULATION

FDA expects sponsors to enroll participants who are relevant to the planned use of the drug in the US population. Describe the steps you are taking to ensure that the clinical trial population will be relevant to the US patient population that will receive the drug. Include a discussion of participation of US vs. non-US sites and discuss whether the subjects likely to be enrolled will adequately represent the US patient population in terms of disease characteristics, sex, race/ethnicity, age, and standards of care. See 21 CFR 312.33(a)(2) and 21 CFR 314.50(d)(5)(v) and the guidance for industry *Collection*

of Race and Ethnicity Data in Clinical Trials for more information.

We recommend you consider requesting a meeting to facilitate discussion of multiple and/or complex issues.

4.0 ISSUES REQUIRING FURTHER DISCUSSION

There are no issues requiring further discussion.

5.0 ACTION ITEMS

There are no action items.

6.0 ATTACHMENTS AND HANDOUTS

(b) (4)

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/

KATHY M ROBIE SUH
06/17/2020 03:50:13 PM