CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214094Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

IND 135058

MEETING MINUTES

BioCryst Pharmaceuticals, Inc.
4505 Emperor Boulevard
Nottingham Hall, Suite 200
Durham, NC 27703

Attention: Elliott Berger, Ph.D.
Senior Vice President, Regulatory Affairs

Dear Dr. Berger:
Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for BCX7353.

We also refer to the teleconference between representatives of your firm and the FDA on May 29, 2019. The purpose of the meeting was to discuss the planned NDA submission for BCX7353.

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

If you have any questions, call me at (301) 796-1230.

Sincerely,

{See appended electronic signature page}

Colette Jackson
Senior Regulatory Health Project Manager
Division of Pulmonary, Allergy, and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure:
- Meeting Minutes

U.S. FOOD & DRUG ADMINISTRATION

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: Pre-NDA

Meeting Date and Time: May 29, 2019 4:00 – 5:00 PM EST
Meeting Location: White Oak Building 22 Conference Room 1421

Application Number: 135058
Product Name: BCX7353
Indication: Hereditary Angioedema
Sponsor/Applicant Name: BioCryst Pharmaceuticals, Inc.

Meeting Chair: Sally Seymour, M.D.
Meeting Recorder: Colette Jackson

FDA ATTENDEES

Division of Pulmonary, Allergy, and Rheumatology Products
Sally Seymour, M.D., Acting Division Director
Stacy Chin, M.D., Clinical Team Leader
Katherine Clarridge, M.D., Clinical Reviewer
Carol Galvis, Ph.D., Pharmacology/Toxicology Team Leader
Colette Jackson, Senior Regulatory Health Project Manager

Office of Clinical Pharmacology
Renu Singh, Ph.D., Clinical Pharmacology Reviewer
Bhawana Saluja, Ph.D., Clinical Pharmacology Team Leader

Office of Biostatistics
Yongman Kim, Ph.D., Statistical Team Leader

SPONSOR ATTENDEES

BioCryst
Elliott Berger, Ph.D., Senior VP Regulatory Affairs
Philip Collis, Ph.D., Vice-President Development & HAE Team Leader
Melanie Cornpropst, Ph.D., Vice-President Clinical Development
Sylvia Dobo, M.D., Vice-President Product Safety & Medical
Amanda Mathis, Ph.D., Director, Clinical Pharmacology .
Sharon Murray, Ph.D., Director, Biostatistics
Nicole McMillan, BSN, Senior Manager, Regulatory Affairs
William Sheridan, M.D., Senior Vice-President and Chief Medical Officer

David Essayan, M.D., Executive Vice-President

1.0 BACKGROUND

BioCryst, Incorporated (BioCryst) sent in a meeting request dated March 15, 2019, requesting a Pre-NDA meeting to discuss the planned NDA submission for BCX7353. The Division granted the meeting on April 16, 2019. BioCryst provided the briefing packages on April 22, 2019. The FDA sent Preliminary Comments to BioCryst on May 22, 2019.

2. DISCUSSION

Question 1:

a. Does the Division agree with the proposal to summarize clinical efficacy and safety in Module 2 summary documents only?

FDA Response:

Yes, we agree with your proposal to submit the clinical efficacy and safety summaries in Module 2 only, provided that all relevant information can be included within the space confines. A separate Integrated Summary of Efficacy (ISE) and Integrated Summary of Safety (ISS) is not necessary for small development programs such as the one for BCX7353 for HAE.

Discussion:

There was no discussion held for this response.

b. Does the Division agree that the proposed content of Sections 2.7.3 and 2.7.4 provide adequate information to support the NDA review?

FDA Response:

Yes, we agree that the proposed content of the Module 2 summaries for clinical efficacy and clinical safety appears adequate for review; however, you should also include sections on Benefit/Risk Assessment and Patient Experience Data relevant to your application. In addition, we expect your eCTD submission to include all information for the individual studies (e.g., study protocols, complete study reports, CRFs, datasets) in Module 5.

Discussion:

There was no discussion held for this response.

Question 2: Does the Division agree with the proposal for CRFs to be included in the NDA?

FDA Response:
Yes, we agree with your proposal to submit CRFs for subjects experiencing death, discontinuation due to a treatment emergent adverse event (TEAE), or non-fatal serious treatment emergent adverse event (SAE). We also ask that you include CRFs for any subject who experienced one or more HAE attacks during the placebo-controlled portion of Study BCX7353-302.

Discussion:
The sponsor stated that patient level data is derived from two sources: an e-CRF completed at the investigative site and an electronic diary kept by the subject. The e-CRF includes the demographics, quality of life data, vitals, PK, and ECG. The eCRF for each patient (aka "the log") also includes the medical history, concomitant medications, adverse events, and HAE attack confirmation by the investigator. However, the eCRF does not contain patient-reported details about each HAE attack. A single eCRF will be approximately 400 pages.

The information maintained within the electronic diary includes study drug dosing information (date, time, number of capsules taken, and closest meal) as well as detailed information about HAE attacks. In the event of an attack, the time, trigger, location, associated symptoms, severity, and need for further intervention was recorded by the subject. In the event of no attack, subjects checked "no attack" and left the remaining fields blank. As such, "no attack" days generate a large amount of empty pages that may not be informative. As an alternative to sending blank pages, the sponsor proposed an option to provide only attack-related information for each patient in lieu of the entire daily diary. The FDA inquired whether any e-diary information is captured in "the log", to which the sponsor responded it is not; only whether or not an attack occurred (Y/N) is documented in the log. The sponsor proposed to submit examples of both the eCRF and "the log" for review prior to NDA submission for feedback, and the FDA agreed with this plan. The sponsor stated they will send this information to the IND file for FDA review and comment.

The sponsor further requested feedback on the Post Marketing Safety Monitoring and Reporting. The sponsor believes that the safety profile of BCX7353 for the proposed dose and indication is benign based on available safety data which includes dosing up to 1 year. Therefore, the sponsor thinks that routine post-marketing surveillance will be sufficient and that a REMS is not needed. The FDA stated that this strategy seemed reasonable, but is ultimately a review issue. Regardless, the NDA submission should include adequate justification for any risk mitigation strategy or safety surveillance program that is proposed.

Question 3: Does the Division agree with the proposal for subject narratives to be included in the NDA?

FDA Response:
Yes, we agree with your proposal to include written narrative summaries for any subject who experienced death, discontinuation due to TEAE, SAE, pregnancy, adverse event of special interest (AESI), or Grade 3 liver function test abnormality.

Discussion:
There was no discussion held for this response.

Question 4: Does the Division agree that the safety data to be included in the NDA will support the NDA review?

FDA Response:
It appears that your safety database will include 24 weeks of placebo-controlled safety data in approximately 80 patients with HAE (~40 per dose arm) along with long-term safety following exposure for a minimum of 48 weeks in 100 patients to support the 150 mg dose and in 70 patients to support the 110 mg dose. You note that open-label safety data from ongoing studies have not identified a dose-dependent safety signal. While acceptability will ultimately be a review issue, the size and scope of your proposed safety database appear adequate to support an NDA for a rare disease such as HAE.

Discussion:
There was no discussion held for this response.

Question 5: Does the Division agree with the proposal for summarization of safety and efficacy data for Study BXC7353-302 and Study BCX7353-204?

FDA Response:
Overall, your plan to combine and summarize safety data from Study BCX7353-302 and Study BCX7353-204 to support integrated analyses of long-term safety appears reasonable. We agree the efficacy data collected from these studies should be analyzed individually. Provided the interim Clinical Study Reports (CSRs) for BCX7353-302 and BCX7353-204 are sufficiently complete for review, it is acceptable to submit the interim CSRs to the NDA. Again, while summaries may be submitted in Module 2, complete ADaM and SDTM datasets should be submitted under Module 5 along with the programming codes used to derive efficacy variables in ADaM datasets.

Discussion:
There was no discussion held for this response.

Question 6: Does the Division agree with the proposal for providing SDTM datasets in the NDA?

FDA Response:
We appreciate the opportunity to review your test SDTM datasets included in the meeting package and agree with your overall proposal. Additionally, you may want to consider submitting a sample ADaM dataset for which the following comments would apply:

1. *In the DM or DS dataset, include a variable to provide the reason for screen failure.*
2. *In your AE dataset, include flags for Treatment Emergent Adverse Events and Treatment Discontinuation due to Adverse Event.*
3. *In your CE / SuppCE datasets for HAE attacks, ensure that each row represents a distinct HAE attack and include additional variables for each HAE attack, such as attack number (for the individual subject), rescue medications administered (Y/N and medication name), specific symptoms reported (e.g., GI, peripheral, facial, laryngeal), symptom onset, duration, severity, and investigator confirmed HAE attack (Y/N).*

Refer to the FDA's Study Data Technical Conformance Guide regarding the specific requirements for data submission. For additional study data questions, refer to https://www.fda.gov/industry/study-data-standards-resources/study-data-submission-cder-and-cber.

Discussion:
There was no discussion held for this response.

Question 7: Does the Division agree that no further evaluation of the effect of food on the bioavailability of BCX7353 is required?

FDA Response:
The food effect study (Study BCX7353-103) was conducted with a (b) (4) capsule formulation that is different from the proposed to-be-marketed formulation. Further, the relative bioavailability study (Study BCX7353-113) was conducted between the (b) (4) capsule formulation used in Study BCX7353-103 and the proposed to-be-marketed formulation under fasted state. We also note that your phase 3 studies were conducted in fed state. Pending review of the data, the studies conducted appear adequate to address the effect of food for BCX7353. The labeling of BCX7353 with respect to food will be a review issue.

Discussion:
There was no discussion held for this response.

Question 8: Does the Division agree with the approach for including safety information from Japanese Study BCX7353-301 in the US NDA?

FDA Response:
Yes, we agree this approach is acceptable.

Discussion:
There was no discussion held for this response.

Non-Clinical Questions

Question 9: Does the Division agree with the proposal for providing SEND datasets in the NDA?

FDA Response:
Yes, we agree with your proposal that only SEND datasets for the two carcinogenicity studies will be provided in the NDA.

Discussion:
There was no discussion held for this response.

Chemistry Manufacturing and Controls Questions

Question 10: Does the Division agree that the proposed specifications are appropriate for release of the drug substance?

FDA Response:
While the quality tests in your drug substance specification are reasonable, the adequacy of the acceptance criteria will be evaluated in your proposed NDA. Include in the specification table a reference for each analytical method used in the drug substance specification.

Discussion:
There was no discussion held for this response.

Question 11: Does the Division agree that the proposed specifications are adequate for the release of commercial drug product?

FDA Response:
We agree that the tests you propose for the drug product specification include all of those that are recommended for hard capsule dosage forms for oral administration by ICH Q6A. The acceptance criteria will be evaluated later in conjunction with the related batch analyses and stability data, during review of your NDA.

Discussion:
There was no discussion held for this response.

Question 12: Does the Division agree that the validation strategy at both suppliers is adequate?

FDA Response:
We do not approve process validation protocols or reports during an application review. The actual protocols, acceptance criteria, study outcomes, as well as supportive development and qualification studies will be evaluated during an inspection of your manufacturing facilities. It is your responsibility to conduct all studies necessary to assure your commercial manufacturing process is capable of consistently delivering quality product.

Discussion:
There was no discussion held for this response.

Question 13: Does the Division agree that the validation strategy at both sites is adequate?

FDA Response:
We do not approve process validation protocols or reports during an application review. The actual protocols, acceptance criteria, study outcomes, as well as supportive development and qualification studies will be evaluated during an inspection of your manufacturing facilities. It is your responsibility to conduct all studies necessary to assure your commercial manufacturing process is capable of consistently delivering quality product. We remind you that your process validation should be performed on an adequate number of batches for each strength at each manufacturing site to provide statistically representative data during the assessment.

Discussion:
There was no discussion held for this response.

Additional Clinical Pharmacology Comments:
1. *Submit a tabulated summary of the bioanalytical assay method and validation parameters and the performance of the bioanalytical assay method for all the clinical pharmacology studies in Module 2.7.1. Refer to FDA guidance on bioanalytical method validation (https://www.fda.gov/media/70858/download) for the format of the tabulated summary.*
2. *Submit the PK/PD data and analysis per the general expectations for Pharmacometrics data (https://www.fda.gov/about-fda/center-drug-evaluation-and-research/modeldata-format).*

Discussion:
There was no discussion held for these additional comments.

3.0 OTHER IMPORTANT MEETING INFORMATION

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

As stated in our April 16, 2019, communication granting this meeting, if, at the time of submission, the application that is the subject of this meeting is for a new molecular entity or an original biologic, the application will be subject to "the Program" under PDUFA VI. Therefore, at this meeting be prepared to discuss and reach agreement with FDA on the content of a complete application, including preliminary discussions on the need for risk evaluation and mitigation strategies (REMS) or other risk management actions and, where applicable, the development of a Formal Communication Plan. You and FDA may also reach agreement on submission of a limited number of minor application components to be submitted not later than 30 days after the submission of the original application. These submissions must be of a type that would not be expected to materially impact the ability of the review team to begin its review. All major components of the application are expected to be included in the original application and are not subject to agreement for late submission.

Discussions and agreements will be summarized at the conclusion of the meeting and reflected in FDA's meeting minutes. If you decide to cancel this meeting and do not have agreement with FDA on the content of a complete application or late submission of any minor application components, your application is expected to be complete at the time of original submission.
In addition, we remind you that the application is expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities.

Information on the Program is available at
https://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/default.htm.

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* at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf. 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: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm.

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* and *Pregnancy and Lactation Labeling Final Rule* websites, which include:

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

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

provide justification. Otherwise, this information should be located in Module 1. Refer to the draft guidance for industry – *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format* (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425398.pdf).

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

DISCUSSION OF SAFETY ANALYSIS STRATEGY FOR THE ISS

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

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

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

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

Office of Scientific Investigations (OSI) Requests

U.S. Food and Drug Administration
Silver Spring, MD 20993
www.fda.gov

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:

https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332466.pdf

https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf.

4.0 ISSUES REQUIRING FURTHER DISCUSSION

There were no issues requiring further discussion.

5.0 ACTION ITEMS

There were no action items identified at the meeting.

6.0 ATTACHMENTS AND HANDOUTS

There were no attachments or handouts for the meeting.

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/

COLETTE C JACKSON
07/16/2019 04:13:10 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND135058

MEETING MINUTES

BioCryst Pharmaceuticals, Inc.
4505 Emperor Boulevard Nottingham Hall
Suite 200
Durham, NC 27703

Attention: Elliott Berger, Ph.D.
Senior Vice President, Regulatory Affairs

Dear Dr. Berger:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for BCX7353.

We also refer to the meeting representatives of your firm and the FDA on November 2, 2017. The purpose of the meeting was to discuss and obtain concordance with the agency regarding the overall development plan for your product, BCX7353.

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 me, at (240) 402-3720.

Sincerely,

{See appended electronic signature page}

Laura Musse, R.N., M.S., C.R.N.P.
Regulatory Health Project Manager
Division of Pulmonary, Allergy, and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: End of Phase 2

Meeting Date and Time: November 2, 2017, 9:00 AM-10:00 AM
Meeting Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1419
Silver Spring, Maryland 20903

Application Number: 135058
Product Name: BCX7353

Indication: Prevention of hereditary angioedema attacks
Sponsor: BioCryst Pharmaceuticals, Inc.

Meeting Chair: Badrul A. Chowdhury, M.D., Ph.D.
Meeting Recorder: Laura Musse, R.N., M.S. C.R.N.P.

FDA ATTENDEES
Badrul A. Chowdhury, M.D., Ph.D., Director, Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)
Anthony G. Durmowicz, M.D., Clinical Team Leader, DPARP
Stacy Chin, M.D., Clinical Reviewer, DPARP
Anshu Marathe Ph.D., Clinical Pharmacology Team Leader, Division of Clinical Pharmacology II (DCPII)
Yunzhao Ren, Ph.D., Clinical Pharmacology Reviewer, DCPII
Yongman Kim, Ph.D., Acting Statistical Team Leader, Division of Biometrics II (DBII)
Yu (Jade) Wang, Ph.D., Statistical Reviewer, DBII
Carol Galvis, Ph.D., Acting Nonclinical Team Leader, DPARP
Luqi Pei, Ph.D., Nonclinical Reviewer, DPARP
Laura Musse, R.N., M.S. C.R.N.P., Regulatory Health Project Manager, DPARP

SPONSOR ATTENDEES
Elliott Berger, Ph.D., Sr. Vice President, Regulatory Affairs
Phil Collis, Ph.D., Vice President, Clinical Development & BCX7353 Project Leader
Melanie Cornpropst, Ph.D., Executive Director, Clinical Development
Sylvia Dobo, M.D., Executive Director, Product Safety and Clinical Development
David Essayan, M.D., Clinical and Regulatory Consultant
Lei Fang, M.S., Statistical Consultant

Stephen MacLennan, Ph.D., Executive Director, Non-clinical Development
Sharon Murray Ph.D., Director, Biostatistics
Nicole McMillan, B.S.N., Sr. Manager, Regulatory Affairs
William Sheridan, M.B., B.S., Chief Medical Officer

1.0 BACKGROUND

On September 5, 2017, BioCryst Pharmaceuticals, Inc. submitted an End of Phase 2 meeting request. The purpose of the meeting was to request guidance from the Division and reach concurrence on their proposed nonclinical and clinical development plan for their product, BCX7353. BioCryst Pharmaceuticals, Inc, is intending that their clinical program support an NDA application for the prevention of angioedema attacks in adult and adolescent patients with hereditary angioedema. The electronic version of the background information package was received on October 6, 2017 and the desk copies were received on October 10, 2017.

FDA sent Preliminary Comments to BioCryst Pharmaceuticals, Inc on October 30, 2017.

2.1. Nonclinical

Question 1: Deferral of Final Report of Two-Year Rat Carcinogenicity Study.
Does the Agency agree with this approach?

FDA Response to Question 1:
No, we do not agree. Submit the final report of the 2-year carcinogenicity study of BCX7353 in rats in your NDA submission. Submission of a draft report of the two-year carcinogenicity study would have been acceptable for your application if the Agency had reviewed and concurred with the protocol and dose selection of the study prior to its initiation and any major deviations from the protocol during the conduct of the study. However, it appears that the Agency has had no input on the design and conduct of your 2-year carcinogenicity study.

Discussion
The Sponsor acknowledged the Division's response. No discussion occurred.

2.2. Clinical

Question 2: Clinical Approach to Assess Potential Occurrence of Phospholipidosis (PLD)

Does the Agency agree with the proposal not to measure the experimental biomarker for drug- induced phospholipidosis, (BMP), in the Phase 3 program and to monitor end organ toxicity with standard laboratory measures?

FDA Response to Question 2:
We agree that BMP does not appear to be a clinically useful measurement to monitor for phospholipidosis in the phase 3 program. However, given the potential for phospholipidosis to occur, with no means of detection other than end organ toxicity, we believe that your proposed safety database is inadequate, (see response to question 17).

Discussion
The Sponsor acknowledged the Division's response. No discussion occurred.

Question 3: QTc Study Waiver and ECG Monitoring Proposal

a. Does the Agency agree with the proposal for ECG Monitoring in the Phase 3 Program?

***b. Does the Agency agree that in light of the demonstrated lack of effect on J-T peak interval in the Phase 1 & 2 studies, a Thorough QTc Study is not required*?**

FDA Response to Question 3a:
No, we cannot agree with the proposed ECG monitoring plan for Phase 3 before we have reviewed the data described in our response to Question 3b.

FDA Response to Question 3b:
The proposed study design for study BCX7353-101 appears adequate to characterize the potential for BCX7353 to prolong the QTc and can potentially serve as an alternative to the TQT study. Whether these data exclude a 10-ms mean QTc effect at the highest clinical relevant exposure will be a review issue when the data are submitted.

1. When you submit your 'QT study' report(s), please include the following items:
    a. Copies of the study report(s) for any other clinical studies of the effect of product administration on the QT interval that have been performed.
    b. Electronic copy of the study report.
    c. Electronic or hard copy of the clinical protocol.
    d. Electronic or hard copy of the Investigator's Brochure.
    e. Annotated CRF.
    f. A data definition file which describes the contents of the electronic data sets.
    g. Electronic data sets as SAS.xpt transport files (in CDISC SDTM format – if possible) and all the SAS codes used for the primary statistical and exposure-response analyses
    h. Please make sure that the ECG raw data set includes at least the following: Subject ID, treatment, period, ECG date, ECG time (down to second), nominal day, nominal time, replicate number, heart rate, intervals QT, RR, PR, QRS and QTc (including any corrected QT, e.g, QTcB, QTcF, QTcN, QTcI, along with the correction factors for QTcN and QTcI), Lead, and ECG ID (link to waveform files, if applicable).
        i. Data set whose QT/QTc values are the average of the above replicates at each nominal time point
        j. Narrative summaries and case report forms for any

i. Deaths

ii. Serious adverse events

iii. Episodes of ventricular tachycardia or fibrillation

iv. Episodes of syncope

v. Episodes of seizure

vi. Adverse events resulting in the subject discontinuing from the study

k. A completed Highlights of Clinical Pharmacology Table

l. Electronic copies of study reports for patch clamp experiments used to support the assessment of cardiac safety of your product together with the following information for each experiment:

i. Raw and unaltered electrophysiology records (e.g. no baseline subtraction or zero'ing of baseline). The file format for the raw electrophysiology records can be abf or CSV, and contain at a minimum information about time, voltage and current signals (note specific units for these signals).

ii. An overview file, e.g. in CSV or txt, describing the experimental conditions for each of the raw electrophysiology records. The description should include at a minimum the name of the file, temperature of the recording, when drugs and at what concentrations were added, and other information relevant to interpret the results.

2. Submit all related ECG waveforms to the ECG warehouse (www.ecgwarehouse.com)

3. Advancing in this field – and possibly reducing the burden of conducting QT studies –depends critically upon obtaining the most comprehensive understanding of existing data. Please consider making your data, at least placebo and positive control data, available for further research purposes; see, for examples, the Data Request Letter at http://www.cardiacsafety.org/ecg-database/.

Discussion question 3a

The Sponsor acknowledged the information requested by the Division and plan to submit the information requested.

Discussion question 3b

The Sponsor requested clarification regarding the request for study report data (item a) and whether the request is for data from all four electrophysiology studies or only the two patch clamp studies.

The Division responded that since a representative from the QT team was not present the QT team would provide the answer in post-meeting comments.

The Sponsor stated that ECG monitoring in phase 3 would be the same as in study 203, clarifying that ECGs (performed in triplicate at baseline and once at all other study visits) would be read and evaluated in real time at each visit with confirmation and follow-up of any abnormalities identified. The Sponsor also noted that in the APeX -1 study which included dose exposures twice of that planned for the phase 3 study, no abnormal QTc values were reported. The Sponsor stated that their proposed program is adequate and inquired if they could proceed with their phase 3 study with the monitoring as described above.

The Division stated that their proposal might be acceptable, but cannot rule out the possible need to conduct a subsequent TQT study, elaborating that typically, a TQT study is conducted early in the development program to inform the exact timing of ECG monitoring in clinical studies. Therefore, the Sponsor should submit additional rationales as to why they think their clinical program is sufficient. The Division added that the requested information would not impede the start of their phase 3 clinical protocol.

Question 4: Evaluation and Monitoring of Liver Function Tests in the Clinical Program
Does the Agency agree with the approach to evaluation and monitoring of liver function tests for the planned Phase 3 Controlled and Long-term Safety studies?

FDA Response to Question 4:
We agree with following the Agency's published *Guidance for Industry on Drug-induced Liver Injury: Premarketing Clinical Evaluation* and with the proposed schedule for evaluating and monitoring liver function tests in your clinical program. In your final protocol, you should clearly outline a plan to address elevated LFTs (i.e., re-testing, discontinuing study drug, re-challenge).
https://www.fda.gov/downloads/Drugs/.../Guidances/UCM174090.pdf

Discussion
The Sponsor acknowledged the Division's response. No discussion occurred.

Question 5: Evaluation and Monitoring of Rash in the Clinical Program
Does the Agency agree with the approach to evaluation and monitoring of rash?

FDA Response to Question 5:
Your approach is reasonable. We strongly encourage obtaining skin biopsies in the patients who develop severe skin rashes.

Discussion
The Sponsor acknowledged the Division's response. No discussion occurred.

Question 6: Evaluation of Drug-Drug Interactions and Plan for Managing Concomitant Therapies in the Clinical Program

Does the Agency agree with the approach to concomitant medication use in BCX7353 Phase 3 and Long-term Safety trials?

FDA Response to Question 6:
Your approach appears reasonable.

Discussion
The Sponsor acknowledged the Division's response. No discussion occurred.

Question 7: Proposed Drug-Drug Interaction Studies

Does the Agency agree with the approach to drug interaction studies for BCX7353?

FDA Response to Question 7:
Your approach appears reasonable.

Discussion
The Sponsor acknowledged the Division's response. No discussion occurred.

Question 8: Proposal for Radiolabeled ADME Study

Does the Agency agree that the planned human study with the proposed radiolabeled compound is sufficient to characterize the metabolism and disposition of BCX7353?

FDA Response to Question 8:
We are unable to comment on this question as you have not submitted the protocol of this mass balance study in this meeting package. The appropriateness of the radio-labeling position of BCX7353 for characterizing metabolism will depend on the study results.

Discussion
The Sponsor acknowledged the Division's response. No discussion occurred.

Question 9: Relative Bioavailability of Phase 2 and Proposed Commercial Formulations
BCX7353-103 is a Phase 1, single-dose, open-label, randomized, 3- period cross-

Does the Agency agree that the results from Study BCX7353-103 indicate that no further clinical study between the early formulation used in Phase 1 and 2 studies and the proposed commercial formulation is required for the NDA?

FDA Response to Question 9:
Pending the review of your bioanalytical assay, we agree.

Discussion
The Sponsor acknowledged the Division's response. No discussion occurred.

Question 10: Main Inclusion and Exclusion Criteria for Phase 3 Study BCX7353-302

Does the Agency agree with the proposed inclusion and exclusion criteria for Study BCX7353- 302 (APeX-2)?

FDA Response to Question 10:

No, we do not agree. Currently, your exclusion criteria are too extensive to fully characterize the safety profile of BCX7353. For instance, (b) (4) has the potential to minimize safety signals in the study and to create uncertainty about the ability to generalize the observed safety findings to a broader HAE patient population. Therefore, we recommend relaxing the exclusion criteria where possible.

Furthermore, (b) (4) This point is especially pertinent for adolescent subjects who cannot provide informed consent. While we understand (b) (4) for the purposes of the study. We recommend you discuss this issue internally, with the appropriate consultants, and the HAE community to devise an approach (whether through modified eligibility criteria, alternate study designs, etc.) that is both ethically acceptable and able to provide sufficient evidence of efficacy and safety for your product.

Discussion

The Sponsor acknowledged the Division's concerns and stated that they would review and modify their phase 3 inclusion/exclusion criteria in a medically sound manner. The Sponsor commented that they had (b) (4)

The Division reiterated the point raised in the preliminary responses (b) (4) The Sponsor replied (b) (4) Finally, the Division recommended that the informed consent should clearly outline the risks and benefits of study participation.

Because adolescent patients cannot provide informed consent, the protocol should [redacted] (b) (4)

Question 11: Eligibility of Adolescent Patients in Study BCX7353-302 (APeX-2)

Does the Agency agree that adolescent patients ages 12-17 years who meet the inclusion criteria and none of the exclusion criteria are eligible for enrollment in APeX-2?

FDA Response to Question 11:

The inclusion of adolescent patients in the APeX-2 study is acceptable; however, the rationale/need for an adolescent sub-study is not clear. Instead, we recommend that adolescent patients be enrolled in the main study with age included as a stratification factor. Also, refer to response to question 10.

Discussion

[redacted] (b) (4) The Sponsor intends to randomize adolescents separately. The Division responded that the justification provided was reasonable; however, for our review purposes, the data from adolescents and adults will be pooled. While acknowledging the challenges of recruiting adolescent patients, the Division stated that the number of adolescents enrolled will impact whether an indication is approved for that population.

Question 12: Inclusion of HAE Patients in APeX-2 who Participated in a Study of BCX7353 [redacted] (b) (4) in a Study of the Pharmacokinetics of BCX7353

Does the Agency agree that patients who participated in a previous study of BCX7353 [redacted] (b) (4) single dose clinical pharmacology study are eligible for enrollment in APeX-2?

FDA Response to Question 12:

We acknowledge the enrollment challenges that exist when studying a rare disease such as HAE. While we do not typically agree with enrolling patients in the pivotal trials who have previously received study drug due to concerns about the potential risks of unblinding patients who might be more aware of the side effects and selecting for patients who have previously tolerated study drug and/or demonstrated a potential treatment response, in this case, the inclusion of patients who have participated in single dose studies is acceptable.

Discussion

The Sponsor acknowledged the Division's response. No discussion occurred.

Question 13: Definition and Assessment of Primary Efficacy Measurement
Does the Division agree with the plan for Investigator confirmation of HAE attacks and translation of screens for use in the e-Diary?

FDA Response to Question 13:

Although the rate of investigator-confirmed HAE attacks is an acceptable primary endpoint for your study to evaluate the effectiveness of BCX7353 for the prophylactic treatment of HAE attacks, we have concerns about the proposed (b) (4) As currently written in the protocol, (b) (4) we recommend that you change (b) (4) We agree with the use of the e-Diary to collect other important clinical features (b) (4) In addition, we recommend adding questions to capture the number of doses of rescue medication administered and if the attack symptoms improved or resolved following rescue treatment. While HAE attacks are the efficacy outcome of interest, the attacks, including investigator-defined attacks which may not meet the protocol specified definition, should also be captured in the safety database for completeness with explanations provided for any discrepancies. Note that complete information for any subject-reported attack, even those not confirmed by an investigator, must be submitted for review by the Agency.

Regarding the analysis and presentation of data for the proposed primary endpoint, we recommend that you analyze the number of attacks per treatment group over the entire treatment period rather than the effective treatment period and that you present the data as HAE attack rate per month rather than per week.

Discussion

The Sponsor agreed with the Division that (b) (4) and will ensure that this is clear in the protocol, the patient diary, and to investigators who would be adjudicating the reported attacks. The Sponsor affirmed that their intent is to (b) (4) The Sponsor will also require investigators to contact subjects within 48 hours of a reported attack to review and will review the patient diaries and the case report forms to ensure that a consistent definition is being applied for HAE attack adjudication.

The Division agreed with the Sponsor's plan, (b) (4) and should be revised for the final version. The Division also emphasized the need to capture complete details of

each HAE attack in the patient diary since the Division would be reviewing this data to verify the number of adjudicated attacks. Finally, the Sponsor asked for clarification regarding the Division's request to present the HAE attack rate per month, given that data will be captured weekly and that one month could be greater or less than 4 weeks. The Division responded that a "regulatory" month is 28 days, therefore from a statistical standpoint, the analyses can be described as 4-weeks and the attack rate results may be presented by month (i.e, 28 days or 4 weeks).

2.3: Biometrics

Question 14: ***Does the Agency agree that the statistical analysis for the Phase 3 study BCX7353-302 (APeX-2) as described is an appropriate approach to the analysis of the primary efficacy endpoint?***

Does the Agency agree that the statistical analysis for the Phase 3 study BCX7353-302 (APeX-2) as described is an appropriate approach to the analysis of the primary efficacy endpoint?

FDA Response to Question 14:

We agree with your statistical approach in general, however, we have the following comments:

1. Since the number of attacks is a count variable, instead of a normality-based ANCOVA model, we recommend you conduct a Poisson regression model with adjustment for over-dispersion or a negative binomial regression model with appropriate covariate(s). You should include the logarithm of duration at risk as an offset variable in either model.
2. No, we do not agree with your proposal to use the full analysis set as defined in your draft protocol as the primary population for efficacy analysis. We recommend the evaluation of the intention-to-treat or de facto estimand, e.g., the ratio in mean HAE attack rates in all randomized patients regardless of adherence or use of ancillary therapies. If you propose an alternative estimand, you should justify that it is clinically meaningful and can be estimated with minimal and plausible assumptions. Regardless of the estimand chosen, the evaluation of de facto estimands will be critical to support claims of effectiveness. In addition, the use of baseline observation carried forward to impute missing HAE attack data is not appropriate. As discussed in the 2010 National Research Council report *The Prevention and Treatment of Missing Data in Clinical Trials*, BOCF is generally not based on reasonable scientific assumptions and is also statistically inappropriate because it does not take into account the uncertainty in the imputation process.
3. In addition, we have several recommendations to minimize missing data in your phase 3 study:
    a. The protocols and informed consent forms clearly differentiate treatment discontinuation from study withdrawal.

    b. Site investigators are trained about the importance of retention and steps

to prevent missing data.

c. The consent forms include a statement educating patients about the continued scientific importance of their data even if they discontinue study treatment early.

4. Several approaches are implemented to retain patients who fail to actively maintain contact with the investigator (e.g., telephone calls to friends or family members, emails, offers for transportation to the clinic, etc.).

5. We recommend you submit the statistical analysis plan for further advice.

Discussion
The Sponsor acknowledged the Division's response. No discussion occurred.

Question 15: Blinded Interim Analysis for Purpose of Resizing the Phase 3 Clinical Study (APeX-2)
Does the Agency agree with the proposal for an interim analysis to potentially resize the study?

FDA Response to Question 15:
Your blinded (non-comparative) interim analysis is acceptable.

Discussion
The Sponsor acknowledged the Division's response. No discussion occurred.

Question 16: Doses Selected for Inclusion in the Phase 3 Clinical Study (APeX-2)
Does the Agency agree with 110 mg and 150 mg once daily as the selected doses for the Phase 3 clinical study?

FDA Response to Question 16:
Due to the short 28-day treatment period of Study 203, we are unable to comment on your selection of doses to carry forward into Phase 3. In Study 203, all the doses above 62.5 mg appeared to have a positive effect, and there was no clear dose-response relationship for reduction of HAE attacks. Although you provided further justification of the dose selection with results from an *ex vivo* kallikrein inhibition assay, the clinical meaning of these results is unclear.

Discussion
The Sponsor agreed with the Division's preliminary comment that 62.5 mg was not effective based on results from Study 203. The Sponsor explained that they will not investigate the two higher doses (250 mg and 350 mg) in the proposed Phase 3 Study 302 due to the gastrointestinal AEs observed in Study 203. The proposed low dose group (110 mg free base) for Study 302 was the lowest effective dose (125 mg salt) identified by Study 203. The rationale for choosing the proposed high dose (150 mg free base) was to find a dose more effective than 110 mg but with fewer side effects than 250 or 350 mg. The sponsor referred to plasma kallikrein

biomarker data as additional justification for the doses selected. Finally, the Sponsor shared that they would like to allow for dose titration between the two doses for tolerability issues, and that this would give them additional data on the product's safety profile. The Sponsor stated that, if they could separate the doses based on efficacy, they envision including both doses in the label.

The Division responded that the Sponsor's approach to dose selection was reasonable. However, because the proposed high dose group (150 mg free base) for Study 302 has not been previously evaluated in a clinical study, the following two main concerns arise:

1. Since the150 mg dose is only about one-third higher than 110 mg dose, the extra benefit of this marginal dose increase may not be detected by Study 302 (i.e., it is unlikely to show a dose separation).
2. The proposed dose titration scheme complicates the safety evaluation and may result in insufficient long-term safety data to support the proposed dose for labeling.

In response to the first concern, the Sponsor stated that BCX7353 pharmacokinetics is nonlinear; therefore, an increase from 110 mg to 150 mg is expected to result in a 2-fold increase of C_{trough}, a dose exposure range that may be reasonable to evaluate in a Phase 3 study.

Elaborating upon the second concern involving potential dose titration, the Division noted that substantial down-titration from 150 mg to 110 mg in the long-term safety study (LTSS) would indicate an unfavorable benefit/risk profile for the high dose, even if controlled study 302 results are positive for both doses. In the event that Study 302 shows that the 110 mg dose is the only approvable dose (for example if the 150 mg dose has a safety concern), then the LTSS would not provide adequate long term safety data for the 110 mg dose. In this scenario, the safety data generated for the 150 mg dose would be applied to the 110 mg dose. Therefore, when considering the benefit to risk profile, any significant safety findings would become a review issue. The Division inquired how the Sponsor would proceed if the 110 mg dose did not work – would all subjects go up to the 150 mg dose? The Sponsor stated they would start at 110 mg and then increase to 150 mg. While the Division needs more information before commenting further, they cautioned against trying to separate the population with such a small number of patients in the study. The Sponsor acknowledged the Divisions' concerns and stated that they will consider the best way to obtain the long-term safety data on both the 110 and 150 mg doses, whether it be the with an addition of adding another study arm to the existing LTSS, or as a new study.

The Division added that in other programs for genetic diseases such as cystic fibrosis in which the gene expression and transcript processing have been well laid out, extensive *in vitro* and PK data have not necessarily been predictive of a clinical response.

The Sponsor stated that the biomarker data was to provide the rationale as to why some patients may require more drug than others. The Sponsor finalized by

indicating that they would consider the Division's input and would provide adequate safety data for both doses.

Question 17: Size of the NDA Safety Database

Does the Agency agree with the proposed size of the NDA safety database?

FDA Response to Question 17:

Given the potential safety signals identified in the BCX7353 clinical program to date, the intent for BCX7353 to be used chronically over a patient's entire life, and your desire to provide data from a single phase 3 study to support approval both the size and scope of your proposed safety database are inadequate to support an NDA. In general, open label safety data is not very informative due to lack of a control arm; therefore, your placebo-controlled treatment period should be at least 6 months in duration. If there are no safety issues with either dose evaluated in the phase 3 study, then BCX7353 exposure in approximately 65-70 patients in the controlled portion of the study may be sufficient. However, if significant safety signals are observed in the remainder of your program, you assume greater risk in having a limited safety database. In addition, safety data should encompass one year of patient exposure (~100 patients exposed for one year). Note that extension studies must have a pre-defined treatment period as well (i.e., cannot be continued indefinitely).

Discussion

The Sponsor acknowledged that the Division wanted patient exposure data on at least 100 patients for one year, and provided details regarding the sources for these patients, noting that some would roll-over directly from the phase 3 study, while others would come from the phase 2 study.

The Division inquired about the duration and the presence of a control arm. The Sponsor intends to conduct a 24-week, placebo-controlled study with an uncontrolled open-label extension study to collect long term safety data.

The Division reiterated that the open-label extension study should have a clearly defined and finite treatment period (i.e., cannot be open-ended). The Sponsor plans to have an OLE period of 48 weeks with the intent to periodically extend treatment until regulatory review. That being the case, the Division noted that some patients would have been exposed to the study drug longer than one year, and therefore the data from these patients may provide additional data on the safety of the drug product.

Finally, the Division recommended ongoing monitoring of the study. Specifically, as the landscape of available therapy changes and clinical practice/standard of care follows suit, the Sponsor should re-evaluate the study and reconsent subjects as necessary. The Division cautioned the Sponsor that if there is a change in practice, their study may not be doable. Given the global nature of their study, the Sponsor would need to consider how changes to the standard of care and available therapies affect the entire study rather than any particular region. For instance, if a new HAE drug is approved in the US, the Sponsor would need to provide the drug to other ex-US sites. The Sponsor

confirmed their intent to conduct their study in an environment where patients have access to standard of care treatment and that they will take into consideration new approvals for HAE prophylaxis.

Question 18: Studies BCX7353-203 (APeX-1) and BCX7353-302 (APeX-2) Provide Adequate Support of Efficacy for a NDA
Does the Agency agree studies BCX7353-203 and BCX7353-302 (as designed) provide adequate support of efficacy for a NDA?

FDA Response to Question 18:
As currently designed, studies BCX7353-203 and BCX7353-302 will not be sufficient to provide substantial evidence of the safety and efficacy of BCX7353 as a prophylactic treatment in patients with HAE for the purposes of an NDA. As mentioned in the responses above, we have the following concerns about your clinical program as currently proposed:

a. Trial duration of BCX7353-302 with a controlled treatment period of only 16 weeks (response to Question 17)
b. Dose selection (response to Question 16)
c. Eligibility criteria (response to Question 10)
d. (b) (4) (response to Question 13)
e. Statistical analyses plan (response to Question 14)
f. Size and scope of the safety database (response to Question 17)

Discussion
The Sponsor summarized the Divisions feedback and asked if a successfully conducted study with a small p-value for efficacy, along with the supportive studies would support approval of an NDA.

The Division stated it is premature to address this question and recommended keeping the study design straightforward without confounding factors.

2.0 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* at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf. 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: 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 (Catalog) (See http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm).

On December 17, 2014, FDA issued final guidance, *Providing Electronic Submissions in Electronic Format--- Standardized Study Data* (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292334.pdf). 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 (Conformance Guide) (See http://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM384744.pdf), 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 start on or after December 17, 2016. Standardized study data will be required in commercial IND application submissions for clinical and nonclinical studies that start on or after December 17, 2017. CDER has produced a *Study Data Standards Resources* web page 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 start 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.

Additional information can be found at http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm.

For general toxicology, supporting nonclinical toxicokinetic, and carcinogenicity studies, CDER encourages sponsors to use Standards for the Exchange of Nonclinical Data (SEND) and submit sample or test data sets before implementation becomes required. CDER will provide feedback to sponsors on the suitability of these test data sets. Information about submitting a test submission can be found here: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm174459.htm

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 and the CDER/CBER Position on Use of SI Units for Lab Tests website found at http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/ucm372553.htm.

3.0 ISSUES REQUIRING FURTHER DISCUSSION

5.0 ACTION ITEMS

Action Item/Description	Owner	Due Date
Send the Agency an email requesting clarification of the nonclinical studies (patch clamp) requested in the Divisions response to Question 3b to support the review by the QT team.	Sponsor	November 5, 2017
Provide the detailed the ECG monitoring for the planned placebo-controlled phase 3 study.	Sponsor	No set date

Submit the requested items outlined in the Divisions response to Question 3b as soon as possible for the QT team to assess the need for a TQT study.	Sponsor	No set date

6.0 ATTACHMENTS AND HANDOUTS

There were no handouts for the meeting minutes.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

LAURA MUSSE
12/23/2017