CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214487Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

IND 120784

MEETING MINUTES

ChemoCentryx, Inc.
850 Maude Avenue
Mountain View, CA 94043

Attention: Suhasini Kanagala PhD
Associate Director, Regulatory Affairs

Dear Dr Kanagala:

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

We also refer to the telecon between representatives of your firm and the FDA on March 19, 2020. The purpose of the meeting was to discuss the content and format of an NDA submission.

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)796-4495.

Sincerely,

{See appended electronic signature page}

Brandi Wheeler, PharmD, RAC
Senior Regulatory Project Manager
Division of Regulatory Operations
Office of Immunology and Inflammation
Center for Drug Evaluation and Research

Enclosure:

- Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Type:	Type B
Meeting Category:	Pre-NDA
Meeting Date and Time:	March 19, 2020, 12:00 PM – 1:00 PM (ET)
Meeting Location:	Teleconference
Application Number:	120784
Product Name:	Avacopan
Indication:	For the treatment of adult patients with anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (granulomatosis with polyangiitis [GPA] and microscopic polyangiitis [MPA])
Sponsor Name:	ChemoCentryx, Inc.
Meeting Chair:	Nikolay Nikolov, MD
Meeting Recorder:	Brandi Wheeler, PharmD

FDA ATTENDEES

Julie Bietz, MD, Director, Office of Immunology and Inflammation (OII)
Nikolay Nikolov, MD, Acting Director, Division of Rheumatology and Transplant Medicine (DRTM), OII
Rachel Glaser, MD, Clinical Team Leader, DRTM
Suzette Peng, MD, Clinical Reviewer, DRTM
Timothy Robison, PhD, Pharmacology/Toxicology Team Leader, Division of Pharmacology and Toxicology for Immunology and Inflammation (DPT-II), OII
Ijeoma Uzoma, PhD, Pharmacology/Toxicology Reviewer, DPT-II, OII
Jianmeng Chen, PhD, Acting Team Lead, Division of Clinical Pharmacology II (DCPII), Office of Clinical Pharmacology (OCP)
Rebecca Rothwell, PhD, Biostatistics Team Leader, Division of Biometrics II, Office of Biostatistics (OB)
Ginto Pottackal, PhD, Biostatistics Reviewer, Division of Biometrics II, OB
Min Lu, MD, MPH, Medical Officer, Good Clinical Practice Assessment Branch (GCPAB) Division of Clinical Compliance Evaluation (DCCE), Office of Scientific Investigations (OSI)
Ashleigh Lowery, PharmD, Team Leader, Division of Medication Error Prevention and Analysis, Office of Surveillance and Epidemiology (OSE)
Saharat Patanavich, PharmD, Safety Regulatory Project Manager, OSE
Brandi Wheeler, PharmD, Senior Regulatory Project Manager, Division of Regulatory Operations, OII

SPONSOR ATTENDEES

(b) (4) Clinical Consultant
Catherine Kelleher, MD, Sr. Vice President, Clinical Development
Huibin Yue, PhD, Sr. Director, Biostatistics
(b) (4)
Sunita Sethi, PharmD, Head, Regulatory Affairs
Suhasini Kanagala, PhD, Associate Director, Regulatory Affairs

1.0 BACKGROUND

ChemoCentryx submitted a meeting request to discuss the upcoming NDA submission for avacopan in the treatment of adult patients with anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (granulomatosis with polyangiitis [GPA] and microscopic polyangiitis [MPA]). They would like to discuss the adequacy of the Phase 3 study, CL010_168 to support the proposed indication as well as content and format of the NDA.

A chemistry pre-submission meeting was held on September 12, 2019. ChemoCentryx received Written Responses, issued January 23, 2020, to address the nonclinical and clinical pharmacology content of the NDA.

The meeting request was submitted on January 29, 2020. The meeting was granted on February 11, 2020. ChemoCentryx's questions from the briefing document, dated February 18, 2020, are provided below in italics followed by the FDA responses. Discussion is in bold.

FDA sent Preliminary Comments to ChemoCentryx on March 16, 2020.

2.0 DISCUSSION

2.1. Clinical

Question 1: *Does the Agency agree that efficacy data from the randomized, double blind, double-dummy, active-controlled Phase 3 study CL010_168 meets substantial evidence standard to support NDA filing for the proposed indication noted herein?*

(b) (4)

FDA Response to Question 1:
The efficacy data from the phase 3 study CL010_168 as summarized in the briefing package appear adequate to support filing of the NDA. However, whether the data are

sufficient to support a favorable benefit risk assessment for the proposed indication of treatment of adult patients with ANCA-associated vasculitis (GPA or MPA) will be a review issue.

In Study CL010_168, you evaluated a prednisone taper over 26 weeks compared to avacopan for 52 weeks, in addition to standard of care treatment with cyclophosphamide (CYC) or rituximab (RTX) for induction and azathioprine for maintenance treatment. Based on the information in the meeting package, you have demonstrated an improvement in proportion of patients with AAV in sustained remission at Week 52; however, patients were continued on avacopan through Week 52, while steroids were discontinued at Week 20. As previously communicated (End of Phase 2 Meeting Minutes dated August 9, 2016), the benefit of steroids used with CYC or RTX is not well known. The complexity of the study design of CL0101_168 complicates the interpretation of a clinically meaningful benefit due to continued avacopan treatment. In your NDA submission, you will need to justify the clinical relevance of these results and address how you intend for avacopan to be used in clinical practice. This justification will be critical for the assessment of benefit-risk.

We also refer you to our additional statistical comments, which identify additional concerns and requests to facilitate our review.

Discussion

ChemoCentryx began the meeting by summarizing the phase 3 study design and results. The Sponsor confirmed that patients who received induction treatment with rituximab did not receive maintenance therapy which is consistent with other studies initiated at the time, while those who received cyclophosphamide for induction received azathioprine for maintenance therapy. The Sponsor stated that there was not a clear difference in relapse rates in the patients who received rituximab induction. FDA asked the Sponsor to include this analysis in the NDA submission.

FDA noted that the proposed indication (b) (4) **ChemoCentryx responded** (b) (4)

FDA asked ChemoCentryx how avacopan was intended to be used in practice. The Sponsor explained that avacopan was intended to be used instead of glucocorticoid tapering and as part of AAV treatment to achieve and sustain remission. FDA noted that the multiple interventions in the study (i.e., removing standard of care steroids in the first 6 months and addition of avacopan on top of standard of care in the second 6 months) complicate the assessment of the efficacy of avacopan treatment. Reduction of glucocorticoid use may be supportive of the efficacy of avacopan but would not be the primary basis to establish efficacy. FDA acknowledged that the study attempted to assess glucocorticoid toxicities systematically with the Glucocorticoid Toxicity Index

(GTI). However, FDA explained that the clinical meaningfulness of GTI, as a novel instrument that captures biomarkers and other assessments without including direct patient input, has not been characterized. Further, it is not clear whether replacing potential toxicities of treatment with glucocorticoids with potential toxicities with avacopan treatment represents a clinical benefit to patients. Additionally, there is limited long term safety data with avacopan treatment.

In light of the above considerations and the complexities of the clinical program, FDA indicated that external input may be required in the interpretation of the clinical benefits of the avacopan program.

FDA further noted that supportive information on the use of the SF-36 in this patient population should be provided. ChemoCentryx responded that they intend to submit a white paper to support its use.

Question 2: *Does the Agency agree with the proposal of presenting separate, non-integrated datasets for Phase 2 and 3 studies in ANCA-associated vasculitis in Module 5.3.5.3 Integrated Summary of Efficacy (ISE)?*

FDA Response to Question 2:
We acknowledge that there are differences between the study designs of the phase 2 and 3 studies of avacopan in ANCA-associated vasculitis (AAV), including differences in primary endpoints, concomitant therapy, and treatment duration. Thus, we agree with the proposal of presenting separate, non-integrated datasets for the phase 2 and 3 studies in AAV in Module 5.3.5.3 Integrated Summary of Efficacy.

Discussion
No discussion occurred.

Question 3: *Does the Agency agree with the proposal of presenting separate, non-integrated datasets for Phase 1, 2 and 3 studies in Module 5.3.5.3 Integrated Summary of Safety (ISS)?*

FDA Response to Question 3:
We agree that it will be important to analyze and present the safety of the phase 1, 2, and 3 studies separately. However, to better inform the assessment of rare adverse events, we recommend that you also present pooled analyses of the phase 2 and 3 studies for deaths, serious adverse events (SAEs), adverse events of special interest (AESIs), and adverse events leading to discontinuation. Given the differences in the study designs of your studies (i.e., randomization ratios), these integrated analyses should not be based on a simple pooling of data from across studies. Such an approach is subject to confounding by study (e.g., Simpson's Paradox)[1]. You should appropriately

[1] Chuang-Stein, C. and Beltangady, M. (2011), Reporting cumulative proportion of subjects with an adverse event based on data from multiple studies. Pharmaceutical Statistics, 10: 3–7.

account for study differences in integrated analyses, either by adjusting for or stratifying by study. Furthermore, you should provide exposure-adjusted incidence rates, in addition to raw cumulative incidence proportions, because of the differing follow-up times between treatment arms between and within studies. Refer to Question 4 for additional comments regarding safety analyses.

Discussion

ChemoCentryx proposed to adjust for study differences by calculating (1) study-size adjusted percentages for subject incidence, (2) exposure-adjusted first incidence rates, and (3) exposure-adjusted event rates for deaths, SAEs, events of special interest as defined in the ISS SAP, and AEs leading to discontinuation. FDA agreed that this approach was acceptable but noted that given the different follow-up times of the phase 2 and 3 studies, exposure-adjusted incidence rates would be the most useful. ChemoCentryx agreed with this advice and stated they would include all three analyses in the NDA. FDA commented that the ISS should be updated to reflect changes in their planned analyses.

Question 4: *Does the Agency agree that the proposed safety data analysis plan for the Phase 3 study is adequate to support the review of the NDA?*

FDA Response to Question 4:

Overall, your proposed safety data analysis plan for the phase 3 study is adequate to support the review of the NDA. We have the following additional recommendations:

1. Ensure that you include all unattributed adverse events (SAEs and non-SAEs) in your analyses.
2. We anticipate the presentation of overall deaths, SAEs, AESIs, and AEs leading to discontinuation for the study duration. Also, present these same categories of AEs, with a delineation of the period of the steroid taper (Week 0 to 20) and the period following the steroid taper (Week 21 through the end of study).

3. Your briefing package indicates that you will provide descriptive analyses of all safety data. For overall deaths, SAEs, AESIs, and AEs leading to discontinuation for the study duration, we recommend, in addition to raw cumulative incidence proportions, that you provide exposure-adjusted incidence rates. Include in your tables the exposure years for each adverse event and clearly identify how exposure is calculated. In analyses evaluating the incidence of a first event (e.g., the number of patients with at least one event per 100 patient-years), the exposure time for a subject who has an event should be terminated at the time of the event. We refer you to https://www.phuse.eu/documents/working-groups/cs-whitepaper-adverseevents-v10-4442.pdf.

This exposure time and the contributing events will also depend on the safety estimand you are targeting. Therefore, we recommend that both the protocol and statistical analysis plans include the estimands to be targeted by these descriptive analyses, for each adverse event specified above. Two common approaches for handling intercurrent events are (1) the treatment policy approach, where all observed data (including those collected while off treatment) are to be included in the analysis; and (2) the "while on treatment" approach, where the data to be included in the analysis are restricted to those collected up until a fixed amount of time after permanent treatment discontinuation. We recommend that for each adverse event specified above, you include analyses targeting both a treatment policy estimand and a "while on treatment" estimand. For the descriptive analyses targeting each estimand, we recommend that the statistical analysis plans specify methods to calculate (1) a point estimate for the comparison (e.g., risk difference, hazard ratio, etc.) of the two treatment arms; and (2) a measure quantifying the statistical uncertainty (e.g., a 95% confidence interval) for this point estimate.

Discussion

ChemoCentryx noted that they would prefer to use analyses on "all observed data" as opposed to "while on treatment" analyses. FDA stated that the preference is for "while on treatment" analyses for safety analyses. ChemoCentryx responded that both analyses would provide similar rates because they had a high retention rate and the "all observed data" should be sufficient. FDA acknowledged the importance of retention in the study but responded that the differences will depend on the number and timings of the treatment discontinuations. FDA, therefore, reiterated a preference for "while on treatment" analyses for safety analyses, but indicated that the sponsor could also supplement these analyses with a "treatment policy" approach if they so desired. ChemoCentryx asked FDA what timepoint after drug discontinuation would be appropriate to define the "on treatment" period. FDA explained that there was not a specific recommendation at this time, and ChemoCentryx should select a timepoint and provide justification based on the characteristics of the product.

Question 5: *Does the Agency agree that the summary text of all efficacy and safety data in the Summary of Clinical Efficacy (Module 2, Section 2.7.3) and Summary of Clinical Safety (Module 2, Section 2.7.4), respectively, can be identical to the summary text included in the ISE and ISS (Module 5, Section 5.3.5.3)?*

FDA Response to Question 5:

It would be important for you to perform and submit the integrated analyses required in an Integrated Summary of Efficacy (ISE) and Integrated Summary of Safety (ISS), as required by 21 CFR 314.50(d)(5)(v)-(vi). The Module 2 summaries were not intended to contain the level of detail expected for an ISS or ISE. Therefore, we recommend you submit the required integrated analyses in Section 5.3.5.3. However, if the narrative

portions of the ISE or ISS are suitable for use in Module 2.7.3 or Module 2.7.4, you may place these once in Module 2.7.3 and Module 2.7.4 and reference them in Section 5.3.5.3. For further detail regarding placement of the ISS and ISE in the electronic common technical document (eCTD) refer to the information at the following link: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm163558.htm

Discussion
No discussion occurred.

2.2. Content and Format of New Drug Application

Question 6: *Does the Agency agree with the proposed plan for submitting safety narratives for the Phase 3 study?*

FDA Response to Question 6:
We agree with the proposed plan to submit safety narratives for SAEs (including deaths) and all withdrawals from the study due to AEs. Also submit safety narratives for AESIs.

Discussion
ChemoCentryx proposed to submit narratives for patients with serious events and withdrawal from study and for serious adverse events of special interest (AESI). ChemoCentryx clarified that infections, liver-associated events, WBC decreases, and hypersensitivity reactions were considered AESIs. FDA commented that the review of avacopan would be better informed with submission of narratives for AESIs. ChemoCentryx noted that for certain AESIs (e.g., infections, WBC decreases, and hypersensitivity reactions), submission of narratives for non-serious AESIs would not be practical. FDA stated that further discussion was needed, and a post-meeting comment would be provided.

Post-Meeting Comment
For AESIs, submit the narratives for serious infections and all (serious and non-serious) events of opportunistic infections and TB. For the other AESIs, narratives for only serious events should be included.

Question 7: *Does the Agency agree with the proposed submission of Case Report Forms (CRFs) and Case Report Tabulations (CRTs)?*

FDA Response to Question 7:
We agree with the proposed submission of CRFs and CRTs.

Discussion

No discussion occurred.

Question 8: *Does the Agency agree with the proposed contents, structure, and format of the datasets?*

FDA Response to Question 8:
We agree.

Discussion
No discussion occurred.

Question 9: *Does the Agency agree with the proposed submission of statistical programs?*

FDA Response to Question 9:
Your proposed plan is acceptable. In addition, provide all programs and macros used to analyze baseline demographics, patient disposition, safety, and all efficacy endpoints proposed for inclusion in the product label. Provide the raw datasets with sufficient documentation which clearly details the creation of analysis dataset.

Discussion
ChemoCentryx agreed to submit all programs and macros used to analyze baseline demographics, patient disposition, safety, and all efficacy endpoints proposed for inclusion in the product label. ChemoCentryx stated that the creation of analysis datasets in the phase 3 study and ISS would be based on SDTM datasets. Therefore, ChemoCentryx will include SDTM datasets rather than raw data sets in the submission. FDA agreed to this approach.

Question 10. *Does the Agency agree that the proposed contents of the NDA, as shown in the table of contents for each Module, are sufficient to support the review of the NDA? Does the Agency have any additional comments on the contents of the NDA to support the NDA review?*

FDA Response to Question 10:
We have reviewed your proposed table of contents for each Module, including the revisions to Modules 3 and 4. We agree that the proposed contents of the NDA are sufficient to support the review of the application. We do not have any additional comments.

Discussion
No discussion occurred.

2.3. Regulatory

Question 11: *Does the Agency agree that the Phase 3 data as summarized herein could fulfill the criteria for Priority Review Designation?*

FDA Response to Question 11:
We acknowledge that AAV is a serious, life-threatening disease with significant unmet need. The determination of whether the submission meets criteria for priority review designation as outlined in the draft Guidance for Industry: *Expedited Programs for Serious Conditions – Drugs and Biologics* (June 2013) will be made at the time of the NDA submission, based on your justification.

Discussion
No discussion occurred.

Question 12: *As all studies conducted with avacopan for the treatment of ANCA-associated vasculitis will have been completed at the time of the NDA review, does the Agency agree with a waiver of the requirement to submit additional safety data at Day 120 (or Day 90) of the NDA review?*

FDA Response to Question 12:
We acknowledge that all studies conducted with avacopan for the treatment of AAV will be completed at the time of the NDA submission. If no new safety data from clinical studies, off-label use, or literature are available, provide a cover letter at Day 120 (or Day 90) stating that there is no new safety information.

Discussion
ChemoCentryx confirmed that only blinded data from non-AAV studies would be available at the time of the Day 120 (or Day 90) safety update, and, therefore, these would not be included. FDA agreed with the sponsor's proposal to include any SAEs reported in compassionate use studies in AAV in the safety update and to include a descriptive analysis of the completed phase 1 and phase 2 studies in other indications as supportive data in the ISS.

Question 13: *Does the Agency agree, due to the Phase 3 study CL010_168 providing the majority of the safety and efficacy data to support the proposed indication for avacopan, that this study can be considered the only covered study for the purposes of Financial Disclosure and Bioresearch Monitoring?*

FDA Response to Question 13:

We do not agree. As you intend that Studies CL002_168 and CL003_168 will provide supportive evidence of efficacy and safety, these would also be covered clinical studies, and financial disclosure documents should be submitted.

Discussion

ChemoCentryx agreed to provide financial disclosure documents for Studies CL002_168 and CL003_168. ChemoCentryx questioned if BIMO listings would be required for these studies. FDA confirmed that BIMO listings would not be required for these studies.

Additional Statistical Comments:

We note that you have submitted an SAP in this meeting package. This SAP was not previously submitted for review and it appears you have already unblinded your data, limiting the utility of major comments and revisions. However, to facilitate our review, we have the following additional recommendations and we reiterate important points made in previous communications. We may request additional analyses during the review.

1. We note that we provided several other statistical comments during our previous meetings (e.g., the Preliminary Comments dated October 28, 2016) on secondary endpoints such as glucocorticoid-induced toxicity (worsening and aggregate score), SF-36 (PCS, MCS, and individual domains) and EQ-5D-5L. It is not clear if you implemented these recommendations. Support for use of these endpoints within this population and the interpretability of the results given these tests were not multiplicity controlled (i.e., no control for type 1 error inflation over multiple tests) will be an additional review issue.

2. We refer you to our previous comments regarding the utility and interpretability of the non-inferiority comparisons and support for the selected margin. As such, we do not agree with your statements in your SAP (b) (4) The determination of substantial evidence will be a review issue.

3. We recommend that you define the estimand that you are targeting in your primary analyses based on the latest version of ICH E9 R1 Addendum[2]. Ideally this is defined at the design stage, however, clarifying the estimand at this time will also help facilitate our review and interpret results targeting the clinical question of interest. In particular, it appears that your estimand differs in your analyses based on the ITT and PP analysis. A targeted estimand for each key analysis should include: (1) the treatment condition of interest; (2) the population being targeted; (3) the variable or outcome assessed for each patient; (4) the specification of how intercurrent events (e.g., treatment discontinuation,

[2] E9(R1) Statistical Principles for Clinical Trials: Addendum: Estimands and Sensitivity Analysis in Clinical Trials https://database.ich.org/sites/default/files/E9-R1_Step4_Guideline_2019_1203.pdf

modification of background medications, use of rescue therapy) are handled; and (5) the population-level summary measure (e.g., difference in means or proportions) being used to compare treatment groups.

4. The details on your missing data handling procedures are extremely limited. In particular, it is not clear how you are handling missing data in the components of the primary endpoint (e.g., missing glucocorticoid use) or intermittent missing data (e.g., missing data at Week 26 but observed data at Week 52).

5. Your proposed main estimator for the secondary continuous efficacy endpoints is based on the MMRM approach. We note that this approach relies on strong parametric assumptions as well as an unverifiable assumption that data is missing at random. We prefer that you conduct a supplementary analysis based on ANCOVA model using all observed data regardless of adherence or use of rescue. This approach relies less heavily on parametric assumptions unlike the MMRM model. Alternatively, another approach with minimal assumptions, could be a linear regression with Huber-White sandwich errors, allowing for heteroskedasticity across arms, including covariates similar to the ANCOVA model. Any missing data imputation used in these analyses should be based on multiple imputation and include details such that results based on multiple imputation can be replicated based only on the SAP. If you continue with your MMRM approach, sensitivity analyses to adequately assess the robustness of the results to this assumption and supplemental analyses targeting alternative estimands will be important (see additional details below).

6. Perform sensitivity analyses to explore the effect of violations in assumptions about the missing data on the reliability of the results. In particular, for your analyses of primary endpoints, we recommend the inclusion of tipping point sensitivity analyses that vary assumptions about the missing outcomes on the two treatment arms. The tipping point analyses should be two-dimensional, i.e., should allow assumptions about the missing outcomes on the two arms to vary independently, and should include scenarios where dropouts on avacopan arm have dissimilar outcomes than dropouts on the placebo arm. The goal is to evaluate the plausibility of the assumed expected values for missing outcomes on each treatment arm under which the conclusions change, i.e., under which there is no longer evidence of similarity. In the tipping point analysis, ensure that all observed data is included as non-missing, regardless of adherence to treatment or use of prohibited medications.

7. You have provided several potential subgroup analyses to be performed. 21 CFR 314.50 requires the presentation of effectiveness data by gender, age and racial subgroups. Ensure that these subgroup analyses are included for your primary efficacy endpoints. This also requires safety data be presented by gender, age and racial subgroups; and that safety data from other subgroups of the populations of patients treated be presented, as appropriate.

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.

In addition, we note that a chemistry pre-submission meeting was held on September 12, 2019. We refer you to the minutes of that meeting for any additional agreements that may have been reached.

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[3] and Pregnancy and Lactation Labeling Final Rule[4] websites, which include:

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

Pursuant to the PLLR, you should include the following information with your application to support the changes in the Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of labeling. The application should include a review and summary of the available published literature regarding the drug's use in pregnant and lactating women and the effects of the drug on male and female fertility (include 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.

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

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

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

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

- Description of all trials to be included in the ISS. Please provide a tabular listing of clinical trials including appropriate details.

- ISS statistical analysis plan, including proposed pooling strategy, rationale for inclusion or exclusion of trials from the pooled population(s), and planned analytic strategies to manage differences in trial designs (e.g., in length, randomization ratio imbalances, study populations, etc.).

- For a phase 3 program that includes trial(s) with multiple periods (e.g., double-blind randomized period, long-term extension period, etc.), submit planned criteria for analyses across the program for determination of start / end of trial period (i.e., method of assignment of study events to a specific study period).

- Prioritized list of previously observed and anticipated safety issues to be evaluated, and planned analytic strategy including any SMQs, modifications to specific SMQs, or sponsor-created groupings of Preferred Terms. A rationale supporting any proposed modifications to an SMQ or sponsor-created groupings should be provided.

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

MANUFACTURING FACILITIES

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

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

The Office of Scientific Investigations (OSI) requests that the items described in the draft guidance for industry *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions* (February 2018) and the associated *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications* be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA ORA investigators who conduct those inspections. This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

Please refer to the draft guidance for industry *Standardized Format for Electronic*

Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions (February 2018) and the associated *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications*.[5]

4.0 ISSUES REQUIRING FURTHER DISCUSSION

There were no issues requiring further discussion.

5.0 ACTION ITEMS

There were no action items.

6.0 ATTACHMENTS AND HANDOUTS

See attached ChemoCentryx slides.

49 Page(s) have been Withheld in Full as B4 (CCI/TS) immediately following this page

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

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/s/

BRANDI E WHEELER
04/14/2020 02:06:36 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 120784

MEETING MINUTES

ChemoCentryx, Inc.
850 Maude Avenue
Mountain View, CA 94043

Attention: Pirow Bekker, M.D., Ph.D.
Chief Medical Officer

Dear Dr. Bekker:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for CCX168.

We also refer to the meeting between representatives of your firm and the FDA on July 14, 2016. The purpose of the meeting was to nonclinical and clinical data prior to beginning phase 3 studies.

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 (301) 796-4495.

Sincerely,

{See appended electronic signature page}

Brandi Wheeler, PharmD
Regulatory 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:	July 14, 2016, 2:00 – 3:00 PM EST
Meeting Location:	FDA White Oak, Building 22, Room 1313
Application Number:	120784
Product Name:	CCX168
Indication:	Anti-Neutrophil Cytoplasmic Antibody Associated Renal Vasculitis
Sponsor/Applicant Name:	ChemoCentryx, Inc.
Meeting Chair:	Badrul Chowdhury, MD, PhD
Meeting Recorder:	Brandi Wheeler, PharmD

FDA ATTENDEES

Badrul A. Chowdhury, MD, PhD, Director, Division of Pulmonary, Allergy, and Rheumatology Products (DPARP), Office of Drug Evaluation II (ODEII)
Lydia Gilbert-McClain, MD, Deputy Director, DPARP, ODEII
Sarah Yim, MD, Supervisory Associate Director, DPARP
Janet Maynard, MD, Clinical Team Leader, DPARP
Suzette Peng, MD, Clinical Reviewer, DPARP
Timothy Robison, PhD, Pharmacology/Toxicology Supervisor, DPARP
Matthew Whittaker, PhD, Pharmacology/Toxicology Reviewer, DPARP
Anshu Marathe, PhD, Team Lead, Division of Clinical Pharmacology II (DCPII), Office of Clinical Pharmacology (OCP)
Yunzhao Ren, PhD, Clinical Pharmacology Reviewer, DCPII, OCP
Gregory Levin, PhD, Biostatistics Team Leader, Division of Biometrics II, Office of Biostatistics (OB)
Yongman Kim, PhD, Biostatistics Reviewer, Division of Biometrics II, OB
Craig Bertha, PhD, CMC Lead, Division of New Drug Products Branch IV, Office of New Drug Products (ONDP), Office of Pharmaceutical Quality (OPQ)
Kathryn O'Connell, MD PhD, Senior Medical Officer, CDER Rare Diseases Program
Mishale Mistry, PharmD, Team Leader, Safety Evaluator, Division of Medication Error Prevention and Analysis, Office of Surveillance and Epidemiology (OSE)
Nichelle Rashid, Team Leader, Safety Regulatory Health Project Management, OSE
Jiang Liu, PhD, Lead Pharmacologist, Division of Pharmacometrics, OCP
John Milto, MD, Medical Officer, Office of Orphan Products Development

Brandi Wheeler, PharmD, Regulatory Project Manager, DPARP

SPONSOR ATTENDEES
Thomas Schall, Ph.D. President
Pirow Bekker, M.D., Ph.D.,Chief Medical Officer
Andrew Pennell, Ph.D., Executive Director, Preclinical Drug Development
Shichang Miao, Ph.D. , Executive Director Discovery & Clinical DMPK
Becky Schulz, R.N., Manager, Regulatory Affairs
Kelly Conoscenti, B.S., Regulatory Affairs Specialist
(b) (4) Medical (AAV)
(b) (4) Consultant, Medical (AAV)
(b) (4) Consultant, Medical and Regulatory
(b) (4) Consultant, Medical (Cardiology)
(b) (4) Consultant, Statistician
(b) (4) Consultant, Regulatory Affairs

1.0 BACKGROUND

ChemoCentryx has requested an End of Phase 2 (EOP2) Meeting to discuss the initiation of phase 3 studies for CCX168 for the treatment for anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis. Prior to this request, a Pre-IND meeting took place on April 21, 2014.

ChemoCentryx is seeking agreement on the adequacy of the nonclinical and clinical data provided to date, to begin phase 3 studies. They would like to discuss whether two phase 2 studies would be sufficient to support an NDA. In addition, they are requesting guidance on their proposed phase 3 clinical program.

A meeting request was submitted on April 8, 2016. The meeting was granted on April 27, 2016. FDA sent Preliminary Comments to ChemoCentryx, Inc. on July 12, 2016. ChemoCentryx's questions from the briefing document dated June 14, 2016, are provided below in italics followed by the FDA responses in normal font. Discussion is in bold.

2. DISCUSSION

2.1. Nonclinical

Question 1: *Does the Division agree that the completed safety pharmacology and toxicology studies with CCX168 are sufficient to support the initiation of the proposed Phase 3 clinical trial?*

FDA Response to Question 1:
Based on our initial review of the draft study reports of your chronic toxicology studies in rats and monkeys (Studies PC0655-168 & PC0654-168), there are sufficient exposure margins to support the proposed 30 mg b.i.d. clinical CCX168 dose in Study CL010_168.

We remind you that finalized quality assured reports should be submitted no later than 120 days after submission of draft reports. Each final study report must be accompanied by a description of any differences between the finalized study reports and the information presented in the initial draft reports or clearly state that there are no changes to the study report.

Discussion:
No discussion occurred.

Question 2: *Does the Division agree that it is acceptable to complete nonclinical carcinogenicity studies (rat and hamster) post-approval?*

FDA Response to Question 2:
Yes, we agree that it would be acceptable to conduct carcinogenicity studies in rats and hamsters post-approval.

Discussion:
No discussion occurred.

Question 3: *Are the currently completed preclinical safety studies, which include dose range-finding embryo-fetal (Seg II) hamster and rabbit toxicology studies (designed as indicated in ICH guidance M3(R2) Note 4 for the inclusion of women of childbearing potential), sufficient to support initiation of a Phase 3 clinical trial of approximately 230 patients with AAV including women of childbearing potential?*

FDA Response to Question 3:
We acknowledge the receipt of the draft study reports for the dose range-finding EFD studies in rabbits and hamsters on July 7, 2016, as well as the summary of the results of these studies included in sections 12.4.10 and 12.4.11 of the End of Phase 2 (EOP2) Meeting Briefing Document.

Based on the nature and severity of AAV and the established contraception requirements in the study protocol given that patients will be exposed to the known human teratogen cyclophosphamide, Study CL010_168 can include women of childbearing potential.

Discussion:
No discussion occurred.

Question 4: *Does the Division agree that it is reasonable to complete the perinatal and postnatal development (PPND) Seg III study using hamsters prior to submission of the NDA?*

FDA Response to Question 4:
Yes, we agree.

Discussion:
No discussion occurred.

Question 5: *Although AAV is extremely rare in children, ChemoCentryx is considering enrollment of children as young as 6 to 12 years in clinical trials in AAV and potentially other orphan indications. Does the Division agree that, based on lack of relevant findings in our toxicology studies to date, that it is reasonable to enroll children as young as 6 to 12 years in serious orphan disease indications?*

FDA Response to Question 5:
From a nonclinical perspective, no additional nonclinical studies are required to include children aged ≥ 6 years and older in clinical trials in AAV patients. However, as per 21 CFR 50 Subpart D—Additional Safeguards for Children in Clinical Investigations, clinical investigations involving greater than minimal risk, such as your proposed study, should present the prospect of direct benefit to individual subjects. This should include justification that the risk is justified by the anticipated benefit to the subjects, and the relation of the anticipated benefit to the risk is at least as favorable to the subjects as available alternative approaches. Based on the currently available data, it is not clear whether you will be able to meet the requirements of these regulations. Consider incorporating a staged approach, where preliminary data in adults can be used to support inclusion of adolescents, and then preliminary data in older children can be used to support inclusion of younger children.

Discussion:
No discussion occurred.

FDA Post Meeting Comment
We acknowledge your post-meeting comment with your justification for enrollment of children in your phase 3 study. It is difficult to comment on your proposal to enroll children in a clinical study in AAV given the ongoing discussion on the design of your proposed trial. In general, we do not agree that you have provided adequate justification that the risk of CCX168 is justified by the anticipated benefit to children, and the relation of the anticipated benefit to the risk is at least as favorable to the children as available alternative approaches. Of note, if you decide to pursue development of CCX168 for children after establishing an adequate risk/benefit profile in adults, we do not anticipate controlled efficacy data in children will be necessary.

Introductory Comments to Clinical Questions
We agree that AAV is a serious disease with unmet medical need. However, we have several areas of concern in regards to your proposed development program in AAV. Based on interim data available at this time, it is unclear if CCX168 has the potential to be beneficial in AAV. A review of data provided for studies CL002_168 and CL003_168 is included below, followed by suggestions for your development program.

Review of data for studies CL002_168 and CL003_168
In study CL002_168, the primary endpoint was BVAS response, which you defined as at least 50% reduction in the BVAS score from baseline. The clinical meaningfulness of BVAS

response is unknown. Further, the results of BVAS response are not supported by additional endpoints, such as BVAS remission at Week 12. This is further complicated by the fact that two of the treatment arms (the standard-of-care control group and the low dose steroid group) are still taking prednisone at Week 12, making it difficult to interpret the results as presented. In the 12-week follow-up, you note that the "response appeared to be lost in a few subjects in the two CCX168 treatment groups." Therefore, we maintain that week 12 assessment of efficacy may not translate to long-term clinical benefit. Further, while there were few patients who experienced worsening of vasculitis during the 12-month treatment period, there were numerically more events in the CCX168 + no steroid group compared to the other groups. More importantly, in your safety data, there were more serious adverse events in the CCX168 + no steroids group. Many of the SAEs that were numerically higher in the CCX168 treatment arms might be attributed to active disease, such as the preferred terms of renal vasculitis, hematuria, renal impairment, vasculitis, microscopic polyangiitis, CRP increased, and rash. We acknowledge your proposal to replace steroids to minimize steroid associated adverse events. However, it is unclear based on the submitted data if use of CCX168 is associated with fewer of these adverse events. As presented in Table 37 of the EOP2 briefing package, you note that 15 subjects (65%) of the SOC group (high dose steroids) developed AEs as compared to 4 (18%) and 11 (50%) in the CCX168 + low dose steroids and CCX168 + no steroids groups, respectively. If the events you selected are to be attributed to steroids, it is unclear why there are more events in the no steroid group compared to the low dose steroid group.

For study CL003_168, the efficacy assessments included in this briefing package are limited. It is notable that the results are similar to CL002_168 in that the results for BVAS response at Week 12 are not supported by BVAS remission at week 12. Although the proportion of subjects who achieved BVAS remission at Week 4 (while taking prednisone 25mg) was higher in the CCX168 30mg group, this same group had the lowest proportion of BVAS remission at Week 12 (while taking prednisone 10mg). Thus, we do not agree that the data presented support that CCX168 as add-on therapy show improved clinical response as compared to the SOC control. We recognize the concerns for serious infections in the safety data. However, it is difficult to disentangle what can be attributed to steroids and background therapy and what can be attributed to the addition of CCX168.

Suggested development program

We acknowledge your proposal for CCX168 to be a replacement for glucocorticoids. However, steroids are standard of care for the treatment of AAV, and certain steroids are approved for the treatment of vasculitis. Thus, removing steroids from the AAV treatment regimen and replacing it with CCX168 makes your clinical development plan more complicated. Further, it is unclear whether you intend for CCX168 to be part of the regimen for induction or for both induction and maintenance. Elucidating how you intend for CCX168 to be part of the AAV treatment regimen will assist in designing the ideal study design and efficacy assessment (outcome measure, timing, etc.). Based on the design of Study CL010_168, it appears that you plan to compare a prednisone taper over (b) (4) weeks to use of CCX168 for 52 weeks. We acknowledge there are toxicities associated with chronic steroid use. However, if you intend for patients to substitute steroids with CCX168, you will need to compare the adverse events associated with each therapy during the time period they are given.

We suggest some study designs for your consideration. We ask that you consider these as possible options dependent on your overall goals for the development program.

(1) You currently propose a non-inferiority study, comparing 2 treatment arms (b) (4) (b) (4) A non-inferiority study would not be sufficient to show that CCX168 can replace glucocorticoids. There are no historical placebo-controlled trials evaluating the efficacy of glucocorticoids as an add-on therapy to CYC or RTX, and your determination of the extent of the contribution of glucocorticoids to the historical estimated remission rate on glucocorticoids + CYC or RTX is based on key, implausible, and unverifiable assumptions. There are many issues with your assumptions, including but not limited to the following: (1) it is unlikely that the efficacy of glucocorticoids alone is similar to that of glucocorticoids when added on to CYC or RTX; and (2) the relevance of many of the historical studies you cited for the setting of the proposed NI study is questionable because of potential differences in important factors such as the patient population, standard of medical care, and treatment regimen (e.g., rate and amount of glucocorticoid tapering). Therefore, with the proposed NI margin of -20%, it would be very difficult to determine if a finding of similar remission rates on the proposed comparator arms was due to the efficacy of CCX168 or to the fact that the remission rates on both arms were primarily driven by the underlying CYC or RTX (with little to no benefit provided from CCX168). Given these concerns, we recommend performing a superiority trial to show the benefit of CCX168 vs. glucocorticoids. We acknowledge your concerns regarding the sample size necessary to directly assess superiority in the proposed study design. Other possibilities would be changing the time point of assessment (2) or changing the study arms (3).

(2) You could also consider changing the timing of efficacy assessment. In your currently proposed study, you will assess your primary endpoint at Week 26, just 6 weeks after steroid taper in your SOC treatment arm. You could instead assess your primary endpoint at Week 52. In this way, your study might be powered to assess superiority of (b) (4)

(3) If you believe and can justify that glucocorticoids cause more toxicity than benefit in AAV, you could consider doing a superiority study with the following 3 treatment arms:
    a. CCX168 + CYC or RTX
    b. PBO + CYC or RTX
    c. Steroids + CYC or RTX (standard of care)

With just one changing variable (CCX168) in the comparison between treatment arms a. and b., it would be easier to attribute benefit to CCX168. In addition, the benefit of glucocorticoids used with CYC or RTX is not well known. This study design would address both of these issues. In such a design, you would need to provide support for the position that it is safe and ethical to treat patients with AAV with only CYC or RTX and not steroids. In addition, we recommend that such a treatment design include an escape option for patients with ongoing disease or disease flares, so that patients could receive steroids if needed.

(4) You have argued that, as a replacement for glucocorticoids, CCX168 will provide an improved benefit-risk profile through similar efficacy and less toxicity than glucocorticoids. Therefore, another possible study design is to maintain the same treatment arms as you have proposed and evaluate whether CCX168 is superior to glucocorticoids with respect to a direct measure that combines benefit and risk, such as time to ESRD or death (with the possibility of justifying the inclusion of other serious direct measures of patient benefit or risk in the composite outcome). This would likely require a longer term study than is currently proposed.

Discussion

ChemoCentryx reviewed their proposed phase 3 clinical trial design and discussed the similarity of their phase 3 trial to the (b) (4) study. They expressed their concerns over the suggested options for their development program. Specific concerns related to the required sample size for a superiority, rather than a noninferiority, study design. The FDA acknowledged the sponsor's concerns, but noted that the proposed noninferiority study would not be sufficient to show that CCX168 can replace steroids. FDA's specific concern was that the proposed study would not be able to reliably evaluate the treatment effect of CCX168, given that the benefit of steroids on top of CYC or RTX is not well-understood.

Further, the FDA noted that the sponsor's planned use of CCX168 in the treatment of AAV is unclear. Specifically, it is unclear whether CCX168 would be continued for 52 weeks or longer. ChemoCentryx noted that they are considering CCX168 as a replacement for steroids during induction with potential long-term use of CCX168. The FDA encouraged the sponsor to define the intended use of CCX168 in practice and use that definition to inform their phase 3 study design.

ChemoCentryx and FDA discussed several possible design options. One of the sponsor's proposals was (b) (4) The FDA expressed reservations about this potential study design given that the study would also need to show long-term benefits other than just reaching remission faster. Subsequently, ChemoCentryx proposed (b) (4)

ChemoCentryx questioned whether, in addition (b) (4) could be considered a basis for approval. The FDA noted that there were residual concerns that the proposed noninferiority study would not be sufficient to show that CCX168 can replace steroids.

ChemoCentryx asked, if they were to pursue a 52 week endpoint, would (b) (4) be acceptable. The FDA responded that assessment of BVAS remission at week 26 and/or 52 would be acceptable. There was some discussion about a (b) (4) study in which (b) (4) ChemoCentryx questioned if the proposed (b) (4) study design (b) (4) would be

ethical, and the FDA encouraged the sponsor to discuss this potential study design further with experts in the field. It was noted that such a study design would incorporate (b) (4) **The sponsor expressed concern** (b) (4) **The FDA acknowledged that AAV is a rare disease and expressed willingness to consider feasible study designs. The sponsor noted** (b) (4)

At the end of the meeting, the FDA reiterated that the Agency did not agree with the sponsor's proposed phase 3 study design but would like to work with the sponsor. The FDA encouraged the sponsor to request another meeting before beginning the phase 3 study.

FDA Post Meeting Comment

We continue to have concerns regarding the proposed non-inferiority study design. Based on internal discussions following our meeting, we are providing three possible study designs for your consideration for your development program:

1) **Time to remission analysis**

Study arms:

1. CCX168 + CYC or RTX
2. Steroids + CYC or RTX (Standard of Care, SOC)

Primary endpoint:

The suggested endpoint is time to event for BVAS remission (up to 26 weeks)

Primary analysis:

The primary analysis assesses superiority of CCX168 + CYC or RTX vs. steroids + CYC or RTX

Supportive endpoint and analysis:

The study would include a supportive analysis in all randomized patients to compare the treatment groups with respect to the probability of either remission at Week 52 or sustained remission (remission at Weeks 26 and 52). Superiority would not need to be demonstrated in this supportive analysis, but it would be considered important to understand the overall benefit-risk of CCX168.

2) **Rapid steroid taper design**

Study arms:

1. CCX168 + CYC or RTX
2. CYC or RTX + rapid steroid taper

3. CYC or RTX + SOC steroid taper

Primary Endpoint:
The suggested endpoint is BVAS remission at week 26 and/or 52.

Primary analysis:
The primary analysis assesses superiority of CCX168 + CYC or RTX vs. CYC or RTX + rapid steroid taper. The SOC arm is included for descriptive purposes only. The study would not be anticipated to be powered for comparisons with the SOC arm.

3) Steroids included in all comparator arms design

Study arms:
1. CCX168 + CYC or RTX + rapid steroid taper
2. CYC or RTX + rapid steroid taper
3. CYC or RTX + steroid taper (SOC)

Primary Endpoint:
The suggested endpoint is BVAS remission at week 26 and/or 52.

Primary analysis:
The primary analysis assesses superiority of CCX168 + CYC or RTX + rapid steroid taper vs. CYC or RTX + rapid steroid taper. The SOC arm is included for descriptive purposes only. The study would not be anticipated to be powered for comparisons with the SOC arm.

With the potential design options described above, we think you would have adequate power to detect moderate effect sizes with reasonable sample sizes. For example, in a design to evaluate superiority with respect to BVAS remission at a specific time point, sample sizes per arm of roughly 100–125 would provide high power to detect a 20% absolute increase in the proportion of patients who achieve remission, assuming a remission probability on the control arm of around 0.5–0.6. Alternatively, in a design to evaluate superiority with respect to time to BVAS remission, 87 events (or sample sizes per arm of roughly 75 patients, assuming a remission probability on the control arm of around 0.5) would provide high power to detect a hazard ratio of 2.0, an alternative hypothesis that roughly corresponds to halving the median time to remission.

2.2. Clinical

Question 6: *Does the Division agree that the absorption, distribution, metabolism, and excretion (ADME) of CCX168 have been adequately characterized to support a New Drug Application in the treatment of patients with AAV?*

FDA Response to Question 6:

No, we do not agree. It appears that CCX168 is mostly eliminated by hepatic pathway. Therefore, the effect of hepatic impairment on CCX168 PK should be evaluated.

Discussion:
No discussion occurred.

ChemoCentryx Post Meeting Comment
We agree with the Agency's assessment. Based on results from Mass Balance study CL004_168, CCX168 is mostly cleared through hepatic metabolism followed by biliary excretion of metabolites.

We agree that the effect of hepatic impairment on the PK profile of CCX168 needs to be assessed. We propose to conduct a hepatic impairment PK study during the course of Phase 3 study CL010_168. Phase 3 study CL010_168 will exclude patients with significant hepatic disease (hepatic enzymes or bilirubin >3x upper limit of normal).

Recommendations on dose adjustment in patients with hepatic impairment will be made after the hepatic impairment PK study.

FDA Post Meeting Comment
Yes, we agree. Your proposal appears reasonable.

Question 7: *Does the Division agree that ChemoCentryx has adequately characterized the potential cardiovascular safety risk of CCX168 such that another QT/QTc study is not required?*

FDA Response to Question 7:
The following comments are conveyed from FDA QT Interdisciplinary Review Team:

No, we do not agree for the following reasons:

a. A placebo control was not included in the study CL007_168. An adequate placebo cohort is generally required for thorough QTc assessment to control for potential bias introduced by study procedures. A placebo control is especially important for this study, which is a fixed (not randomized) 2-sequence (ABCD and BACD) study with a baseline ECG assessment for all subjects performed in period 1. Study procedures, however, are quite different in each period making the baseline from Period 1 inadequate when pooling QTc response across study periods without a placebo control.

b. Without a separate positive control for ECG assay sensitivity, the QTc response should be characterized at a sufficiently high multiple (ideally at least 2-fold) of highest expected drug exposure in patients when considering increases in exposure due to intrinsic and extrinsic factors (Refer to ICH E14 Q&A (R3)). The exposure to CCX168 is expected to increase 2-fold with metabolic inhibition and the exposure margin from the 100 mg bid dose does not provide sufficient exposure margin to waive the requirements for assay sensitivity.

c. Food is known to affect QTc assessment and the concentration-QTc assessment should control for or exclude the effects of food.

Discussion:
No discussion occurred.

FDA Post Meeting Comments
Without a placebo control, the study is not designed to exclude small effects (10 ms) on the QTc interval. In addition, the following are our comments to your response:

a. We do consider that the study procedures in this fixed 2-sequence (ABCD and BACD) study are different in each period because the baseline ECG assessment for all subjects was only performed in period 1, therefore the time of ECG monitoring in each period relative to the baseline is quite different (especially ECG monitoring for Period 3 and Period 4 is approximately 1 month after baseline measurement which is very different from those for Period 1 and 2).

b. As presented in your Table 1, the mean C_{max} of CCX168 is (b) (4) ng/mL for the 100 mg b.i.d. MD which is (b) (4)-fold the C_{max} of (b) (4) for the 30 mg b.i.d. MD with itraconazole. We do not consider less than 2-fold as a sufficiently high multiple to waiver the requirements of assay sensitivity (Refer to ICH E14 Q&A (R3)).

c. Acceptable.

Question 8: *In this orphan disease of AAV, would the Division consider CCX168 to be eligible for accelerated approval according to 21 CFR part 314, subpart H, based on the two CCX168 Phase 2 clinical trials (CL002_168 and CL003_168) in 109 patients, with a post marketing commitment to complete the proposed Phase 3 clinical trial?*

FDA Response to Question 8:
Acknowledging that AAV is a rare and serious disease, we do not agree with your proposal for accelerated approval according to 21 CFR Subpart H. Under Subpart H (21 CFR 314), new drugs for serious or life-threatening illnesses are approved based on a surrogate endpoint or an effect on a clinical endpoint other than survival or irreversible morbidity. A post-marketing confirmatory trial is required to verify the anticipated effect on irreversible morbidity or mortality or other clinical benefit. You propose to utilize efficacy data based on the Birmingham Vasculitis Activity Score (BVAS) at 12 weeks from two phase 2 clinical trials (CL002_168 and CL003_168). Your proposed post-marketing trial CL010_168 will assess BVAS remission at Week 26.

We disagree with your proposal regarding accelerated approval based on two primary issues:

a. First, as noted in the breakthrough designation request denials dated October 24, 2014, and May 24, 2016, we continue to have concerns regarding the results and their

interpretability from your phase 2 clinical trials. See the Introductory Comment. The clinical meaningfulness of BVAS response (as you have defined as at least 50% reduction in the BVAS score from baseline) is unknown and is not supported by other important endpoints, such as BVAS remission, in either phase 2 study. Further, in study CL002_168, many of the SAEs that were numerically higher in the CCX168 treatment arms might be attributed to active disease, such as the preferred terms of renal vasculitis, hematuria, renal impairment, vasculitis, microscopic polyangiitis, CRP increased, and rash. Based on the interim data available at this time, it is unclear if CCX168 has the potential to be beneficial in AAV. Thus, we do not agree that the data from CL002_168 and CL003_168 are sufficiently compelling to justify accelerated approval according to 21 CFR 314, subpart H.

b. Second, the Agency has precedent for accepting BVAS remission at Month 6 as a basis for a full approval in AAV[1]. Since a phase 3 trial of 6 months' duration using this endpoint has been demonstrated to be feasible, it would be preferable to obtain data to support a traditional full approval. As stated in the Guidance for Industry: *Expedited Programs for Serious Conditions—Drugs and Biologics*, "FDA will not grant accelerated approval to products that meet standards for traditional approval."

Discussion:
No discussion occurred.

Question 9: *Does the Division agree with the proposed Phase 3 clinical trial CL010_168 in patients with AAV, specifically the:*
a. Efficacy and safety objectives
b. Study design
c. Inclusion and exclusion criteria
d. Dose regimen of CCX168
e. Primary efficacy endpoint
f. Secondary efficacy endpoints and the safety endpoints, and
g. Statistical analysis approach and sample size.

FDA Response to Question 9:
We do not agree with the proposed phase 3 clinical trial CL010_168 in patients with AAV. See the Introductory Comment for our general recommendations. We anticipate that the design of your phase 3 study may change significantly based on these recommendations. However, we are providing the following general comments in response to your specific questions:

a. While it is reasonable to assess the efficacy of CCX168 plus rituximab or cyclophosphamide compared to prednisone plus rituximab or cyclophosphamide, we do not agree with the overall study design. See the Introductory Comment.

b. See the Introductory Comment.

[1] Approval of sBLA 103705/5344, April 19, 2011, http://www.accessdata.fda.gov/drugsatfda_docs/bla/2011/103705Orig1s5344.pdf

c. The inclusion and exclusion criteria are generally reasonable for a trial in AAV. Of note, if you plan to enroll children in your phase 3 study, provide a justification as outlined in Subpart D and this will be reviewed and considered by the Agency.

d. Limited dose ranging data are available to inform dose selection in your phase 3 study. Data from Study CL002_168 show similar results for the lower dose of 10 mg b.i.d and the 30mg b.i.d. doses. In the context of your development program, it is your own discretion to evaluate the proposed dose in your phase 3 study.

e. The proposed primary efficacy endpoint, BVAS remission at Week 26, is reasonable, to evaluate efficacy in AAV. However, the primary endpoint for your study may be impacted by the overall study design selected as discussed in the Introductory Comment.

f. We do not agree with the proposed secondary efficacy endpoints or the time point of assessment. The key secondary endpoints are BVAS 0 at Week 4 (b) (4) (b) (4) urinary albumin:creatinine ration (UACR), and EQ-5D-5L at Week 4. The clinical importance of changes in clinical endpoints at Week 4 is unclear, since it is unclear if changes in the proposed endpoints at Week 4 represent long-term clinical benefit. Further, assessment of endpoints at earlier time points is complicated by the fact that steroids will be tapered during the first 20 weeks of treatment. Thus, assessments of clinical improvement should be assessed at Week 26 or 52 to assess for longer term clinical benefits. Further, the endpoints should reflect significant clinical improvement, such as BVAS remission or normalization in renal parameters, rather than change in parameters, such as change in albuminuria.

We have the following additional statistical comments:

a. In order to minimize missing data in the evaluation of intention-to-treat or de facto estimands (e.g., the difference between treatment groups in remission rate at Week 26 in all randomized patients regardless of treatment adherence or use of ancillary therapies), patients who discontinue study treatment early or initiate medication changes (including those prohibited by the protocol) should continue to be followed for all regularly scheduled visits for safety and efficacy assessments. To help prevent missing data, we also recommend that: (1) the protocols and informed consent forms clearly differentiate treatment discontinuation from study withdrawal; (2) the only reasons for study withdrawal are patient withdrawal of consent to contribute additional outcome information and loss to follow-up; (3) site investigators are trained about the importance of retention and steps to prevent missing data; (4) the consent forms include a statement educating patients about the continued scientific importance of their data even if they discontinue study treatment early; and (5) 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.).

b. The use of (b) (4) to handle missing data is not appropriate. (b) (4)

(b) (4)

Your protocol and SAP should clearly outline and justify procedures to prevent and address missing data.

Discussion:
No discussion occurred.

Question 10: *If regulatory filing under 21 CFR part 314, subpart H, is not considered appropriate, does the Division agree that the two Phase 2 clinical trials (CL002_168 and CL003_168) plus the proposed Phase 3 clinical trial (CL010_168) are sufficient to support a file for registration for the indication of treatment of patients with ANCA-associated vasculitis?*

FDA Response to Question 10:
As presented in the EOP2 meeting briefing document, we do not agree that the two phase 2 clinical trials plus the proposed phase 3 clinical trial (CL010_168) are sufficient to support a submission for the indication of treatment of patients with AAV. See the Introductory Comment and FDA's response to Question 9 for detailed recommendations regarding study CL010_168.

We do note that, in principle, it is possible that a single phase 3 study may be sufficient to support this indication if it is a multicenter trial, with a clinically and statistically persuasive treatment effect, and consistency of effect among efficacy endpoints (primary, secondary, exploratory). This would also depend on a lack of new safety signals in the treatment population that would require further characterization.

Discussion:
No discussion occurred.

Question 11: *Does the Division agree that a Pediatric Study Plan is not required for CCX168 in AAV because orphan designation has been granted?*

FDA Response to Question 11:
Because orphan designation has been granted for AAV, we agree that a Pediatric Study Plan is not required for CCX168. See FDA's response to Questions 5 and 9c regarding your proposal to enroll patients less than 18 years of age. We recommend you submit a meeting request to discuss revised plans for including pediatric patients in your phase 3 study(ies).

Discussion:
No discussion occurred.

2.3. Electronic Data Standards

Question 12: *Does the Division agree with the current status of our Study Data Standardization Plan that is in preparation to support NDA submission?*

FDA Response to Question 12:
We acknowledge your plan to request all study data to be in CDISC compliant formats (i.e., SDTM and ADaM for clinical studies and SEND format for nonclinical data). In general, we agree with your Study Data Standardization Plan to support NDA submission.

Although the Agency currently does not have a standard policy on the use of SI units for laboratory values, we recommend that you convert clinical laboratory values into US conventional units in the safety datasets and clinical study reports of the phase 2 and phase 3 studies. Specifically, we request these conversions for any laboratory values of interest and any abnormal laboratory values.

Discussion:
No discussion occurred.

3.0 Additional Information

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 (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.

SECURE EMAIL COMMUNICATIONS

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

Office of Scientific Investigations (OSI) Requests

The Office of Scientific Investigations (OSI) requests that the following items 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 field investigators who conduct those inspections (Item I and II). 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.

The dataset that is requested in Item III below is for use in a clinical site selection model that is being piloted in CDER. Electronic submission of the site level dataset is voluntary and is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process.

This request also provides instructions for where OSI requested items should be placed within an eCTD submission (Attachment 1, Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format).

I. Request for general study related information and comprehensive clinical investigator information (if items are provided elsewhere in submission, describe location or provide link to requested information).

1. Please include the following information in a tabular format in the original NDA for each of the completed pivotal clinical trials:
   a. Site number
   b. Principal investigator

c. Site Location: Address (e.g., Street, City, State, Country) and contact information (i.e., phone, fax, email)
d. Location of Principal Investigator: Address (e.g., Street, City, State, and Country) and contact information (i.e., phone, fax, email). If the Applicant is aware of changes to a clinical investigator's site address or contact information since the time of the clinical investigator's participation in the study, we request that this updated information also be provided.

2. Please include the following information in a tabular format, *by site*, in the original NDA for each of the completed pivotal clinical trials:
   a. Number of subjects screened at each site
   b. Number of subjects randomized at each site
   c. Number of subjects treated who prematurely discontinued for each site by site

3. Please include the following information in a tabular format in the NDA for each of the completed pivotal clinical trials:
   a. Location at which sponsor trial documentation is maintained (e.g., , monitoring plans and reports, training records, data management plans, drug accountability records, IND safety reports, or other sponsor records as described ICH E6, Section 8). This is the actual physical site(s) where documents are maintained and would be available for inspection
   b. Name, address and contact information of all Contract Research Organization (CROs) used in the conduct of the clinical trials and brief statement of trial related functions transferred to them. If this information has been submitted in eCTD format previously (e.g., as an addendum to a Form FDA 1571, you may identify the location(s) and/or provide link(s) to information previously provided.
   c. The location at which trial documentation and records generated by the CROs with respect to their roles and responsibilities in conduct of respective studies is maintained. As above, this is the actual physical site where documents would be available for inspection.

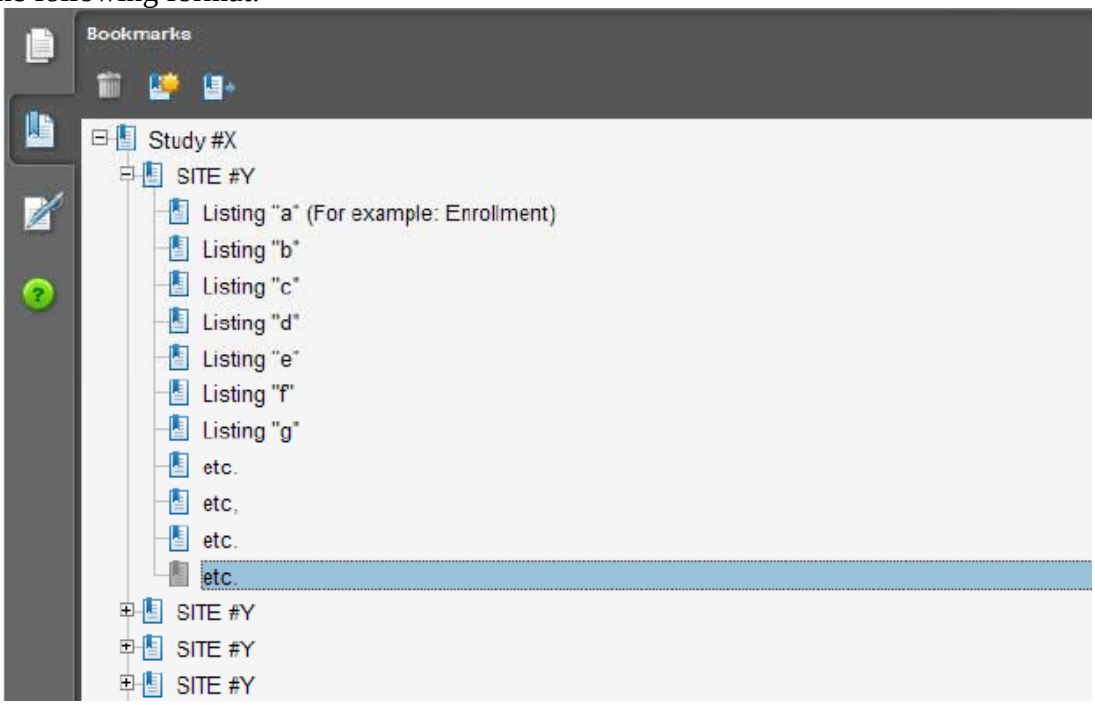
4. For each pivotal trial, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).
5. For each pivotal trial provide original protocol and all amendments ((or identify the location and/or provide a link if provided elsewhere in the submission).

II. Request for Subject Level Data Listings by Site

1. For each pivotal trial: Site-specific individual subject data listings (hereafter referred to as "line listings"). For each site, provide line listings for:
   a. Listing for each subject consented/enrolled; for subjects who were not randomized to treatment and/or treated with study therapy, include reason not randomized and/or treated
   b. Subject listing for treatment assignment (randomization)

c. Listing of subjects that discontinued from study treatment and subjects that discontinued from the study completely (i.e., withdrew consent) with date and reason discontinued
d. Listing of per protocol subjects/ non-per protocol subjects and reason not per protocol
e. By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)
f. By subject listing, of AEs, SAEs, deaths and dates
g. By subject listing of protocol violations and/or deviations reported in the NDA, including a description of the deviation/violation
h. By subject listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint.
i. By subject listing of concomitant medications (as appropriate to the pivotal clinical trials)
j. By subject listing, of testing (e.g., laboratory, ECG) performed for safety monitoring

2. We request that one PDF file be created for each pivotal Phase 2 and Phase 3 study using the following format:



III. Request for Site Level Dataset:

OSI is piloting a risk based model for site selection. Voluntary electronic submission of site level datasets is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. If you wish to voluntarily provide a dataset, please refer to the draft Guidance for Industry Providing Submissions in Electronic Format – Summary Level Clinical Site Data for CDER's Inspection

Planning" (available at the following link http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf) for the structure and format of this data set.

Attachment 1

Technical Instructions:
Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format

A. Data submitted for OSI review belongs in Module 5 of the eCTD. For items I and II in the chart below, the files should be linked into the Study Tagging File (STF) for each study. Leaf titles for this data should be named "BIMO [list study ID, followed by brief description of file being submitted]." In addition, a BIMO STF should be constructed and placed in Module 5.3.5.4, Other Study reports and related information. The study ID for this STF should be "bimo." Files for items I, II and III below should be linked into this BIMO STF, using file tags indicated below. The item III site-level dataset filename should be "clinsite.xpt."

DSI Pre-NDA Request Item[2]	STF File Tag	Used For	Allowable File Formats
I	data-listing-dataset	Data listings, by study	.pdf
I	annotated-crf	Sample annotated case report form, by study	.pdf
II	data-listing-dataset	Data listings, by study (Line listings, by site)	.pdf
III	data-listing-dataset	Site-level datasets, across studies	.xpt
III	data-listing-data-definition	Define file	.pdf

B. In addition, within the directory structure, the item III site-level dataset should be placed in the M5 folder as follows:

C. It is recommended, but not required, that a Reviewer's Guide in PDF format be included. If this Guide is included, it should be included in the BIMO STF. The leaf title should be "BIMO Reviewer Guide." The guide should contain a description of the BIMO elements being submitted with hyperlinks to those elements in Module 5.

[2] Please see the OSI Pre-NDA/BLA Request document for a full description of requested data files

References:

eCTD Backbone Specification for Study Tagging Files v. 2.6.1
(http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf)

FDA eCTD web page
(http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm)

For general help with eCTD submissions: ESUB@fda.hhs.gov

4.0 ISSUES REQUIRING FURTHER DISCUSSION
There were no issues requiring further discussion.

5.0 ACTION ITEMS
There were no action items.

6.0 ATTACHMENTS AND HANDOUTS
See attached slides and post meeting comments.

33 Page(s) have been Withheld in Full as B4 (CCI/TS) immediately following this page

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

/s/

BRANDI E WHEELER
08/09/2016