

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**761112Orig1s000**

**ADMINISTRATIVE and CORRESPONDENCE  
DOCUMENTS**



IND 107609

**MEETING MINUTES**

Ablynx NV  
Attention: Sheela J. Mitta  
US Representative for Ablynx NV  
ERA Consulting (USA) LLC  
1410 Spring Hill Road  
McLean, VA 22102

Dear Ms. Mitta:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for ALX-0081.

We also refer to the meeting between representatives of your firm and the FDA on December 15, 2017. The purpose of the meeting was to discuss the adequacy of the proposed information package to support a Biologic License Application (BLA).

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 Beatrice Kallungal, Regulatory Project Manager at (301) 796-9304.

Sincerely,

*{See appended electronic signature page}*

Kathy Robie Suh, MD, PhD  
Clinical Team Leader  
Division of Hematology Products  
Office of Hematology and Oncology Products  
Center for Drug Evaluation and Research

Enclosure:  
Meeting Minutes



**FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH**

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**MEMORANDUM OF MEETING MINUTES**

**Meeting Type:** Type B  
**Meeting Category:** Pre-BLA

**Meeting Date and Time:** December 15, 2017; 3:00 PM – 4:00 PM EST  
**Meeting Location:** 10903 New Hampshire Avenue  
White Oak Building 22, Conference Room: 1421  
Silver Spring, Maryland 20903

**Application Number:** IND 107609

**Product Name:** ALX-0081  
**Indication:** (b) (4)

**Sponsor Name:** Ablynx NV

**Meeting Chair:** Kathy Robie Suh, MD, PhD  
**Meeting Recorder:** Beatrice Kallungal, MS

**FDA ATTENDEES**

**Office of Hematology and Oncology Products (OHOP)/Division of Hematology Products**

Albert Deisseroth, MD, PhD, Supervisory Associate Division Director  
Kathy Robie-Suh, MD, PhD, Clinical Team Leader  
R. Angelo de Claro, MD, Clinical Team Leader  
Andrew Dmytrijuk, MD, Clinical Reviewer  
Beatrice Kallungal, MS, Regulatory Project Manager

**OHOP/Division of Hematology, Oncology, Toxicology**

Natalie Simpson, PhD, Reviewer

**Office of Biostatistics/Division of Biometrics V**

Yuan-Li Shen, PhD, Team Leader  
Lola Luo, PhD, Reviewer

**Office of Clinical Pharmacology/Division of Clinical Pharmacology V**

Olanrewaju Okusanya, PharmD, MS, Acting Team Leader  
Liang Li, PhD, Reviewer

**Office of Biotechnology Products (OBP)**

**Division of Monoclonal Antibodies (DMab)**

Joslyn Brunelle, PhD, Team Leader

**Division of Microbiology Assessment (DMA)**

Monica Commerford, PhD, Microbiologist

**Office of Surveillance & Epidemiology/Division of Risk Management (DRISK)**

Mei-Yean Chen, PharmD, Risk Management Analyst

**SPONSOR ATTENDEES**

**Ablynx NV**

Robert Zeldin, MD, Chief Medical Officer  
Hilde De Winter, MD, Senior Medical Director  
Filip Callewaert, PhD, Senior Clinical Scientist  
Debjit Biswas, PhD, Senior Director Biostatistics  
Laura Sargentini, PharmD, PhD, Dir. MID3 & Clinical Pharmacology  
Cecile Pechaire, PharmD, Senior Regulatory Affairs Manager  
Bernard Delaey, PhD, Senior Director Regulatory Affairs

(b) (4)

**1.0 BACKGROUND**

Acquired thrombotic thrombocytopenic purpura (aTTP) is an extremely rare life-threatening autoimmune blood clotting disorder, manifested by systemic microvascular thrombosis. It is caused by inhibitory autoantibodies to the von Willebrand factor (vWF)-cleaving protease, ADAMTS13 (a disintegrin and metalloprotease with thrombospondin type 1 motif, member 13). Decreased ADAMTS13 activity leads to an accumulation of ultra-large vWF multimers (ULvWF) which bind to platelets and induce the formation of microthrombi. These microthrombi cause tissue ischemia and organ dysfunction commonly involving the brain, heart, and kidneys and may result in overt major thromboembolic complications or death.

Ablynx is developing ALX-0081 (caplacizumab), an anti-von Willebrand Factor (vWF) Nanobody intended to treat adults experiencing an episode of aTTP. The clinical development program of caplacizumab in aTTP patients encompasses a completed Phase 2 study (ALX-0681-2.1/10 TITAN) and an ongoing Phase 3 study to confirm the efficacy and safety of caplacizumab (ALX-0681-C301; HERCULES).

(b) (4)

Based on the outcome of the double-blind, placebo-controlled Phase 3 study ALX0681-C301 and the totality of the clinical evidence, the Sponsor intends to submit a Biologic License Application (BLA) in 2018 for caplacizumab for the treatment of patients experiencing an acute episode of aTTP.

The objectives of this pre-BLA meeting were to discuss the adequacy of the proposed information package to support a BLA. In particular,

- To discuss the Chemistry, Manufacturing, and Controls (CMC) package;
- To seek agreement on the proposed PK/PD modelling and Clinical package;
- To discuss Rolling Review of the BLA; and
- To discuss the suitability of the application for Priority Review.

FDA sent Preliminary Comments to Ablynx on December 8, 2017.

## 2. DISCUSSION

### REGULATORY

#### QUESTION 1

On 21 July 2017, FDA designated the investigation of caplacizumab for [REDACTED] (b) (4) [REDACTED] as a Fast Track development program. One of the provisions of Fast Track designation is eligibility for Rolling Review of the BLA. Ablynx plans to submit the complete Quality and Nonclinical sections of the application before the Clinical section, according to the schedule provided below.

Does the Agency agree with the proposed content and schedule for Rolling Review?

#### **FDA Response to Question 1:**

**We agree. The proposed content and schedule are acceptable for Rolling Review.**

#### **Meeting Discussion:**

*No discussion.*

#### QUESTION 2

A provision of Fast Track designation is eligibility for Priority Review. Acquired TTP is a serious life-threatening condition. Ablynx believes that the clinical evidence that will be submitted in the BLA demonstrates that treatment with caplacizumab represents a significant improvement in safety and effectiveness of the treatment of this condition. Ablynx believes that caplacizumab, therefore, meets the qualifying criteria for Priority Review and plans to include a request for Priority Review designation with the submission of the final component of the rolling BLA.

Does the Agency agree that the eligibility criteria for a Priority Review are met?

**FDA Response to Question 2:**

**FDA acknowledges that aTTP is a serious and life-threatening condition. However, the decision on Priority Review status is made after receipt of the application by the Agency.**

**Meeting Discussion:**

***No discussion.***

**QUESTION 3**

Per CFR 314.50 (d) (5), Ablynx must update periodically, with a safety update report, its pending submission with new safety information that may reasonably affect the statement of contraindications, warnings, precautions, and adverse reactions in the draft labeling. The proposed approach, extent of data and safety cut-off date is provided below.

Does the Agency concur with the proposed strategy with regard to the safety update report?

**FDA Response to Question 3:**

**The proposed strategy is acceptable. If submissions of additional safety information are needed they will be requested during the review.**

**Meeting Discussion:**

***No discussion.***

**QUALITY**

**QUESTION 4**

Ablynx intends to use a Limulus amoebocyte lysate (LAL) endotoxin test in place of the rabbit pyrogen test for the release of ALX-0081 drug product batches. The proposed approach is outlined below.

Does the Agency agree with the proposed approach?

**FDA Response to Question 4:**

**Your approach appears adequate provided there are no Low Endotoxin Recovery issues with your finished product. A determination of acceptable endotoxin recovery can be made by conducting endotoxin spike-hold recovery studies using undiluted finished product recovery (refer to the additional product quality microbiology comments provided at the end of this document). Drug product endotoxin specification in (b) (4) may not be adequate for a lyophilized product.**

**Meeting Discussion:**

***No discussion.***

**QUESTION 5**

Based on the draft Guidance for Industry on Established Conditions (May 2015), Ablynx intends to summarize the proposed established conditions in CTD Module 2.3 of the BLA.

Does the Agency agree with the proposed format for presenting the established conditions in the BLA?

**FDA Response to Question 5:**

**In general, your proposed format for presenting the established conditions in the BLA appears to be acceptable. However, we note that in table 4 you did not include section 3.2.S.7.2 as part of the established conditions. In accordance with the draft Guidance for Industry on Established Conditions, post-approval stability protocols and stability commitments are currently identified as established conditions.**

**The final determination on your proposed established conditions will be made upon review of the related information provided in your BLA.**

**Meeting Discussion:**

*No discussion.*

**CLINICAL PHARMACOLOGY**

**QUESTION 6**

At the End of Phase II meeting of January 30, 2015, the Agency requested to include the platelet data from study ALX-0681-2.1/10 to link the PK/PD model with the platelet count. Ablynx submitted a platelet-based PK/PD model and data to the IND in SN0129. While this categorical model described the data well and confirmed the advantage of using caplacizumab in addition to PE, it proved unsuitable for predicting the outcome(s) when using a different dosing scheme than that used in study ALX-0681-2.1/10. Therefore, in the same IND submission, Ablynx proposed to use an updated version of the vWF-based PK/PD model. In support of the BLA, this vWF-based model will be further updated with data from Phase III study ALX0681-C301.

Does the Agency agree that the proposed PK/PD modelling approach is suitable for inclusion in the BLA?

**FDA Response to Question 6:**

**Your proposed PK/PD modeling approach seems to be acceptable for the dose justification for the proposed indication by re-assessing the PK/PD model with all available data from Phase 1 trials in healthy subjects and Phase 2/3 trials in patients with aTTP. However, the appropriateness of your selected dosing regimen will be a review issue after BLA submitted.**

**Meeting Discussion:**

*No discussion.*

**EFFICACY AND SAFETY**

**QUESTION 7**

Results of the Phase III study ALX0681-C301 with caplacizumab in the treatment of adult patients who are experiencing an episode of aTTP are consistent with and extend those of Phase

II Study ALX-0681-2.1/10. The data from these studies will be submitted with the BLA in support of the proposed indication for this orphan product.

Does the Agency agree that the proposed safety and efficacy studies to be included in the BLA will be sufficient to support a benefit-risk evaluation by FDA of caplacizumab for the target indication?

**FDA Response to Question 7:**

**The safety and efficacy studies you propose to include in the BLA submission are acceptable for inclusion. However, refer to our previous advice regarding appropriate endpoints for establishing a clinically meaningful benefit and particularly noting that platelet count alone would not be sufficient to establish efficacy (see communications dated May 1, 2015 and April 4, 2017). Your current definition of platelet count response incorporates a requirement for stop of daily plasma exchange (PE), in addition to the rise in platelet count to  $\geq 150 \times 10^9/L$ . Based on your meeting Background Package, it is not clear whether this definition of response will provide adequate evidence of durability to support a labeling claim. Your BLA submission should include analyses and data presentations to show that patients who stopped PE remained PE-independent for a clinically meaningful period of time. You should also thoroughly address any inconsistencies in outcomes for your primary and secondary efficacy endpoints. You also should address any imbalances between treatment arms that may affect the overall efficacy result. The data to support the primary efficacy endpoint should be presented for each patient in such a way that it is very clear when the study drug was administered, when plasma exchange was started and stopped, the platelet count course during and after therapy with study drug/plasma exchange and the timing and duration of any concomitant TTP therapy. The adequacy of your studies to support benefit and risk assessments of caplacizumab for the proposed indication will be a review issue.**

**Meeting Discussion:**

*The Sponsor asked for clarification of the Agency's comment that, "Based on your meeting Background Package, it is not clear whether this definition of response will provide adequate evidence of durability to support a labeling claim." The Agency clarified its concern that, because assessments of response in the studies were based on fairly short-term follow-up, there is limited data on how long the treatment response will be maintained, i.e., durability of response. The Sponsor discussed that failure (recurrence) appears to be due to continuing disease activity, as reflected by ADAMTS13 levels, and patients need to be treated to resolution of disease activity.*

*The Sponsor will present patient profile figures for each patient to show time course of response, including all relevant data (platelet count, study drug administration, administration of other treatments, plasma exchange, ADAMTS13 levels, hospitalizations, etc.) The Sponsor will also provide tables with the corresponding data used to generate the figures.*

*The Sponsor stated that*

(b) (4)



*The Sponsor commented on baseline imbalances between treatment arms in the study stating that there were no differences favoring caplacizumab. The Agency acknowledged the Sponsor's comments. Acceptability will be a review issue. The Sponsor stated that there were no inconsistencies among the outcomes for the primary and secondary efficacy endpoints for the study. The Agency commented that this will be a review issue. Efficacy determination will depend on the totality of the evidence.*

#### **QUESTION 8**

The approach for the Integrated Summary of Efficacy (ISE) to be included in the BLA in support of the proposed indication is outlined below.

Does the Agency agree with the overall approach for the ISE?

#### **FDA Response to Question 8:**

**The approach for analyzing and presenting data for caplacizumab to support the proposed indication is acceptable. See also response to Question 7.**

#### **Meeting Discussion:**

*No discussion.*

#### **QUESTION 9**

The approach for the Integrated Summary of Safety (ISS) to be included in the BLA in support of the proposed indication is outlined below.

Does the Agency agree with the overall approach for the ISS?

#### **FDA Response to Question 9:**

**The approach to data analysis and presentation for the ISS is acceptable.**

#### **Meeting Discussion:**

*No discussion.*

#### **QUESTION 10**

Immunogenicity data from all completed clinical studies of caplacizumab will be included with the individual study data submitted in CTD Module 5 of the BLA. As explained below, an integrated assessment of the immunogenicity data interpretation across studies will be included in the Immunogenicity Risk Assessment report.

Does the Agency agree that this proposed approach can support the evaluation of the BLA for caplacizumab in the proposed indication?

**FDA Response to Question 10:**


The proposed integrated immunogenicity assessment is acceptable.

**Meeting Discussion:**

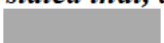
*No discussion.*

**ADDITIONAL COMMENTS:**

**Statistical**

- In regards to the timing of censoring of the primary analysis, the proposed censoring time may not be independent of the event time (e.g. censoring at the stop of study treatment drug may be informative). We request that that additional sensitivity analysis to be performed based on different censoring scheme, e.g. evaluated based on the last platelet count assessments, stop of daily PE or at 45 day cutoff during the double blind period, whichever occur the first.
- In your future submission, please plot the platelet count course and daily PE status for patients who are platelet responders, classify them according to the scenario 1, 2, 5 and 8 in the censoring and event plan table of the SAP and extend the days to day 45. Please also provide detailed justification for classification of each responder . Some scenarios are less clear. For example, it is not clear how you count 5 days of daily PE for patients who drop out early and for patients who had daily PE before or after a weekend.
- The proposed (b) (4)  


**Meeting Discussion:**

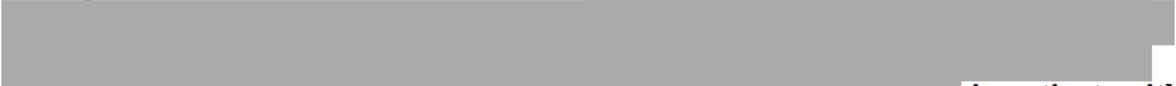

*The Sponsor stated potential difficulties in applying other imputation methods. The Agency stated that, due to the uncertainty about the adequacy of the (b) (4)  
 additional sensitivity analyses should be performed to demonstrate the robustness of the results. The Sponsor agrees with performing additional sensitivity analyses.*

- We have a few comments for the data submission:
  - FDA requests that an Analysis Data Reviewer's Guide (ADRG) and Study Data Reviewer's Guide (SDRG), an important part of a standards-compliant study and analysis data submission, be prepared and submitted in the sBLA. Please refer to the "Study Data Technical Conformance Guide: Technical Specifications Document," available at:  
<http://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/U>


**CM384744.pdf.**

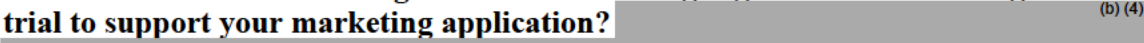

- Provide sufficient comments, adequate bookmarks, and hyperlinks in the define file(s) to ensure efficient review.
- Provide executable SAS program(s) with adequate document(s) to allow FDA to duplicate the analysis datasets derivation from raw datasets

**Clinical Pharmacology**


1. Your plan to address the use of ALX-0681 (b) (4)  
  
 in patients with renal impairment. You should also address the impact of plasma exchange on the PK and PD of ALX-0681.

***Meeting Discussion:***

 (b) (4)  
*The Sponsor proposes to address the lack of data in patients with hepatic insufficiency in labeling. The Sponsor also proposed to address the impact of renal impairment and plasma exchange using their population PK model. The Agency stated that the adequacy of this approach will be a review issue.*

2. Address the following questions in the Summary of Clinical Pharmacology:
- a) What is the basis for selecting the doses and dosing regimen used in the registration trial to support your marketing application? (b) (4)  
  
 in support of the proposed dose and administration.
  - b) What are the exposure-response relationships for efficacy, safety and biomarkers?
  - c) How do extrinsic (e.g., other drugs) and intrinsic factors (such as sex, race, body weight, organ dysfunctions, and disease) influence the exposure, efficacy, or safety of your drug? What dose modifications are recommended?
  - d) What is the impact of immunogenicity on exposure, efficacy and safety?
3. Apply the following advice in preparing the clinical pharmacology sections of the original submission:
- a) Submit bioanalytical methods and validation reports for all clinical pharmacology and biopharmaceutics trials.
  - b) Provide final study report for each clinical pharmacology trial. Present the pharmacokinetic parameter data as geometric mean with coefficient of variation (and mean  $\pm$  standard deviation) and median with range as appropriate.
  - c) Provide complete datasets for clinical pharmacology and biopharmaceutics trials. The subjects' unique ID number in the pharmacokinetic datasets should be consistent with the numbers used in the clinical datasets.
    - Provide all concentration-time and derived pharmacokinetic parameter datasets as SAS transport files (\*.xpt). A description of each data item should be provided in a define.pdf file. Any concentrations or subjects that have

been excluded from the analysis should be flagged and maintained in the datasets.

-  (b) (4)
4. Submit the following for the population pharmacokinetic analysis reports:
    - a) Standard model diagnostic plots
    - b) Individual plots for a representative number of subjects. Each individual plot should include observed concentrations, the individual prediction line and the population prediction line
    - c) Model parameter names and units in tables.
      - Summary of the report describing the clinical application of modeling results. Refer to the following pharmacometric data and models submission guidelines <http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm180482.htm>.
  5. Submit the following information and data to support the population pharmacokinetic analysis:
    - a) SAS transport files (\*.xpt) for all datasets used for model development and validation
    - b) A description of each data item provided in a Define.pdf file. Any concentrations or subjects that have been excluded from the analysis should be flagged and maintained in the datasets
    - c) Model codes or control streams and output listings for all major model building steps, e.g., base structural model, covariates models, final model, and validation model. Submitted these files as ASCII text files with \*.txt extension (e.g.: myfile\_ctl.txt, myfile\_out.txt)  
Refer to Guidance for Industry for population PK analysis at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072137.pdf>.
  6. Submit a study report describing exploratory exposure-response (measures of effectiveness, biomarkers and toxicity) relationships in the targeted patient population. Refer to Guidance for Industry for exposure-response analyses at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072109.pdf>.

### Product Quality Microbiology

We are providing additional product quality microbiology comments for you to consider during development of your commercial manufacturing process and preparation of your BLA submission.

All facilities should be registered with FDA at the time of the BLA submission and ready for inspection in accordance with 21 CFR 600.21 and 601.20(b)(2). The facility should be in operation and manufacturing the product during the inspection. A preliminary manufacturing schedule for both the drug substance and drug product should be provided in the Module 1 of the BLA submission to facilitate the planning of the pre-license inspections during the review cycle. Information and data for CMC

2 Page has been Withheld in Full as b4 (CCI/TS)  
immediately following this page

descriptions of the methods should be provided in addition to the compendial reference numbers.

- **Summary report and results of the Rabbit Pyrogen Test conducted on three batches of drug product in accordance with 21 CFR610.13(b).**
- **Certain formulations have been reported to interfere with endotoxin recoverability in the USP LAL test methods over time. The effect of hold time on endotoxin recovery should be assessed by spiking a known amount of standard endotoxin (RSE or CSE) into undiluted drug product and then testing for recoverable endotoxin over time.**
- **Microbiological studies in support of the post-reconstitution [REDACTED] (b) (4) storage conditions. Describe the test methods and results that employ a minimum countable inoculum [REDACTED] (b) (4) to simulate potential microbial contamination that may occur during reconstitution [REDACTED] (b) (4). The test should be run at the label's recommended storage conditions, be conducted for twice the recommended storage period, bracket the drug product concentrations which would be administered to patients, and use the label-recommended reconstitution solutions [REDACTED] (b) (4). Periodic intermediate sample times are recommended. Challenge organisms may include strains described in USP <51> plus typical skin flora or species associated with hospital-borne infections. In lieu of this data, the product labeling should recommend that the post-reconstitution [REDACTED] (b) (4) storage period is not more than 4 hours at 2-8°C.**

## 2.0 OTHER IMPORTANT INFORMATION

### DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

The content of a complete application was discussed. The Sponsor stated that the CMC and non-clinical portions will be submitted around the end of March 2018 and the clinical portion will be submitted around the end of May 2018. to complete the application.

- 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. The Sponsor agreed to provide this.
- A preliminary discussion was held on the need for a REMS or other risk management actions. The Sponsor has not identified serious risk and does not plan to propose a REMS. Agency commented that requirement for any post-marketing safety monitoring would be a review issue.
- Major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission. You stated you intend to submit a complete application and therefore, there are no agreements for late submission of application components.

## **PREA REQUIREMENTS**

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

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

## **PRESCRIBING INFORMATION**

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

The application should include a review and summary of the available published literature regarding drug use in pregnant and lactating women, a review and summary of reports from your pharmacovigilance database, and an interim or final report of an ongoing or closed pregnancy registry (if applicable), which 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.

**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 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).**

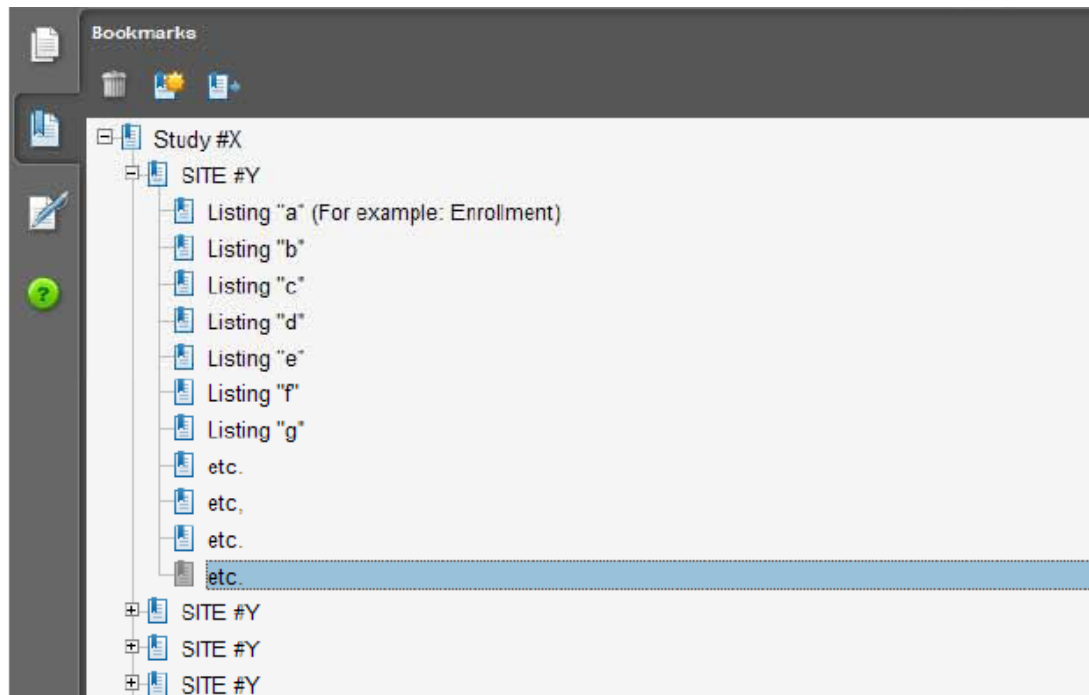
1. Please include the following information in a tabular format in the original NDA for each of the completed pivotal clinical trials:
  - a. Site number
  - b. Principal investigator
  - c. Site Location: Address (e.g., Street, City, State, Country) and contact information (i.e., phone, fax, email)
  - 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.”

<b>DSI Pre-NDA Request Item<sup>1</sup></b>	<b>STF File Tag</b>	<b>Used For</b>	<b>Allowable File Formats</b>
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.

<sup>1</sup> 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](mailto: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 for this meeting.

#### **6.0 ATTACHMENTS AND HANDOUTS**

The Sponsor's response to FDA Preliminary comments was used to aid in discussions during the meeting and has been appended to the meeting minutes.

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/s/  
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KATHY M ROBIE SUH  
12/21/2017



IND 107609

**MEETING MINUTES**

Ablynx NV  
c/o Cote Orphan, LLC  
Attention: Lisa Carlton, PhD  
Senior Director, Regulatory Affairs Activities  
8630 Fenton Street, Suite 222  
Silver Spring, MD 20910

Dear Dr. Carlton:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for caplacizumab/ALX-0081.

We also refer to the meeting between representatives of your firm and the FDA on January 30, 2015. The purpose of the meeting was to present the results of your Phase II study in detail and in the light of these data to discuss options for an approval based on a limited clinical program – given the medical need in this drug's orphan indication.

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 Beatrice Kallungal, Regulatory Project Manager at (301) 796-9304.

Sincerely,

*{See appended electronic signature page}*

Kathy Robie Suh, MD, PhD  
Clinical Team Leader  
Division of Hematology Products  
Office of Hematology and Oncology Products  
Center for Drug Evaluation and Research

Enclosure:  
Meeting Minutes



**FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH**

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**MEMORANDUM OF MEETING MINUTES**

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

**Meeting Date and Time:** January 30, 2015; 3:00 PM – 4:00 PM EST  
**Meeting Location:** 10903 New Hampshire Avenue  
White Oak Building 22, Room 1415  
Silver Spring, Maryland 20903

**Application Number:** IND 107609  
**Product Name:** Caplacizumab/ALX-0081, Anti-von Willebrand Factor Nanobody  
**Indication:** For the treatment (b) (4)  
**Sponsor/Applicant Name:** Ablynx NV

**Meeting Chair:** Kathy Robie Suh, MD, PhD  
**Meeting Recorder:** Beatrice Kallungal, BS

**FDA ATTENDEES**

**Office of Hematology and Oncology Products (OHOP)/Division of Hematology Products**

Ann Farrell, MD, Director  
Kathy Robie-Suh, MD, PhD, Clinical Team Leader  
Andrew Dmytrijuk, MD, Clinical Reviewer  
Beatrice Kallungal, BS, Regulatory Project Manager

**OHOP/Division of Hematology, Oncology, Toxicology**

Haw-Jyh Chiu, PhD, Team Leader (Acting)  
Christopher Sheth, PhD, Reviewer

**Office of Biostatistics/Division of Biometrics V**

Yuan-Li Shen, PhD, Team Leader  
Qing Xu, PhD, Reviewer

**Office of Biotechnology Products (OBP)/Division of Monoclonal Antibodies**

Audrey Jia, MD, PhD, Reviewer

**SPONSOR ATTENDEES**

Kristof De Beuf, PhD, Clinical Biostatistician, Ablynx NV  
Bernard Delaey PhD, Director Regulatory Affairs, Ablynx NV  
Laura Sargentini, PharmD, PhD, Associate Director PK Modelling & Simulations, Ablynx NV  
Dominique Tersago, MD, Chief Medical Officer Ablynx NV  
Hans Ulrichs, PhD, Associate Director Pharmacology, Ablynx NV

(b) (4)

**1.0 BACKGROUND**

ALX-0081/Caplacizumab is a humanized bivalent nanobody, produced in E. coli. The proposed indication is for the treatment of acquired thrombotic thrombocytopenic purpura (TTP), as adjunctive therapy to plasma exchange (PE). On April 14, 2009, caplacizumab received US Orphan Drug Designation for the treatment of TTP.

Caplacizumab was tested for its clinical pharmacodynamics and toxicological properties, as well as its clinical properties in four Phase I clinical trials. A Phase 1 bioequivalence study and tolerability study of a reconstituted lyophilized and a liquid formulation of caplacizumab on healthy volunteers has recently been completed.

(b) (4)

The TITAN study, a Phase II, multicenter, single-blinded, parallel design, randomized, placebo-controlled study (TITAN) has recently been terminated. The Sponsor considers the

(b) (4)

(b) (4)

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*Meeting Discussion:*  
*No discussion occurred.*

### **3.0 OTHER IMPORTANT INFORMATION**

#### **PREA REQUIREMENTS**

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, 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. 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**

CDER strongly encourages IND sponsors to consider the implementation and use of data standards for the submission of applications for investigational new drugs and product registration. Such implementation 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. CDER has produced a 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. The web page may be found at: <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.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 [CDER/CBER Position on Use of SI Units for Lab Tests](http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm) (<http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm>).

### **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).**

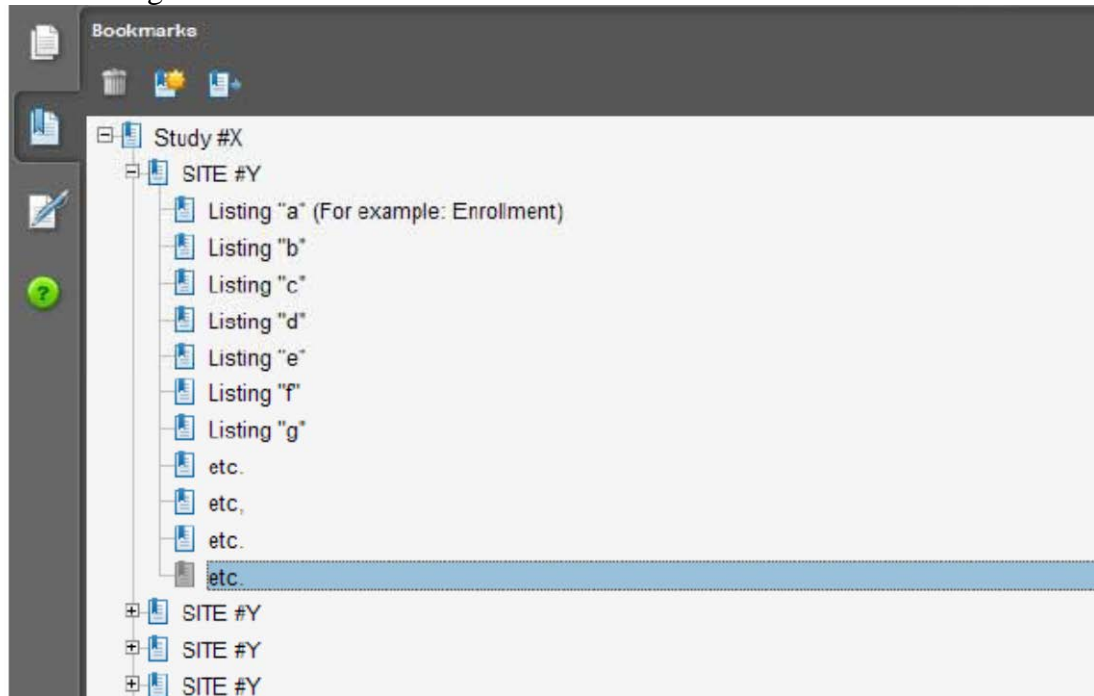
1. Please include the following information in a tabular format in the original NDA for each of the completed pivotal clinical trials:

- 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
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  - 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 <sup>1</sup>	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.

<sup>1</sup> 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](mailto:ESUB@fda.hhs.gov)

#### 4.0 ISSUES REQUIRING FURTHER DISCUSSION

There were no issues requiring further discussion

#### 5.0 ACTION ITEMS

Action Item/Description	Owner	Due Date
<i>Sponsor to provide additional information regarding their development plans and other potential clinical efficacy endpoints for Caplacizumab/ALX-0081</i>	<i>Ablynx nv</i>	<i>When available</i>

#### 6.0 ATTACHMENTS AND HANDOUTS

The Sponsor's response to the Agency's preliminary meeting comments has been appended to these meeting minutes.

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KATHY M ROBIE SUH  
02/12/2015