

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

219019Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**



IND 125632

MEETING MINUTES

Genzyme Corporation
Attention: Amanda Meisel, PharmD, RPh
Regulatory Strategist, GRA
55 Corporate Drive
Bridgewater, NJ 08807

Dear Dr. Meisel:

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

We also refer to the video conference between representatives of your firm and the FDA on March 19, 2024. The purpose of the meeting was to seek the Agency's concurrence regarding your plan to submit an NDA in March/April 2024, and to discuss the clinical data package to support the filing and review of the planned NDA, the proposed indication in the label, and planned NDA regulatory milestones.

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

If you have any questions, call Bijal Patel, Regulatory Project Manager, at 240-402-4829 or at bijal.patel1@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Ann T. Farrell, MD
Division Director
Division of Nonmalignant Hematology
Office of Cardiology, Hematology, Endocrinology,
and Nephrology
Office of New Drugs
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, 2024, 2:00PM – 3:00PM EDT
Meeting Location: Video conference

Application Number: IND 125632
Product Name: fitusiran
Indication: Routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adult and adolescent patients (>12 years old) with hemophilia A with and without inhibitors.

Sponsor Name: Genzyme Corporation
Regulatory Pathway: 505(b)(1) of the Federal Food, Drug, and Cosmetic Act

Meeting Chair: Ann Farrell, MD
Meeting Recorder: Bijal Patel, MS

FDA ATTENDEES

Office of Cardiology, Hematology, Endocrinology, and Nephrology (OCHEN)
Hylton Joffe, MD, Director

Office of Cardiology, Hematology, Endocrinology, and Nephrology (OCHEN), Division of Nonmalignant Hematology (DNH)
Ann Farrell, MD, Director
Tanya Wroblewski, MD, Deputy Director
Patricia Oneal, MD, Clinical Reviewer

Division of Pharmacology & Toxicology (DPT-OCHEN)
Pedro Del Valle, MS, PhD, Fellow ATS, Supervisor
Bo Lee, PhD, Nonclinical Reviewer

Office of Immunology and Inflammation, Division of Hepatology and Nutrition, Drug-induced Liver Injury Team (DILI)
Eileen NavarroAlmario, Clinical Reviewer

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

Office of Clinical Pharmacology (OCP)
Sudharshan Hariharan, PhD, Master Pharmacokineticist

Tian Zhou, Clinical Pharmacology Reviewer

Center for Devices and Radiological Health (CDRH), Office of Health Technology 7 (OHTVII)

Brittany Schuck, Deputy Office Director

Takeesha Taylor-Bell, Deputy Director, Division of Hematology and Immunology Devices

Office of Regulatory Operations (ORO), Division of Regulatory Operations for Cardiology, Hematology, Endocrinology, and Nephrology (DRO-CHEN)

Sejal Kiani, MHS, Chief, Project Management Staff

Bijal Patel, MS, Regulatory Project Manager

SPONSOR ATTENDEES

Karin Knobe, MD, PhD, Global Head Rare Diseases and RBD, Clinical Development

Craig Benson, MD, Sr. Global Project Head, Rare Diseases and Rare Blood Disorders

Marek Demissie, MD, PhD, Global Project Head, Rare Diseases and Rare Blood Disorders

Marja Puurunen, MD, PhD, Global Submission Lead, fitusiran, Senior Clinical Research Director, Rare Diseases and Rare Blood Disorders

Ekta Seth Chhabra, Global Research Lead, Rare and Rare Blood Disorders

Yingwen Dong, PhD, Global Biostatistics Head, Rare Diseases and Rare Blood Disorders

Zhiying Qiu, PhD, Senior Statistical Project Leader, Rare Diseases and Rare Blood Disorders

Meijing Wu, Statistical Project Leader, Rare Diseases and Rare Blood Disorders

Barbara Kittner, MD, Therapeutic Area Head, Rare Diseases and Rare Blood Disorders

Laurel A. Menapace, MD, Global Safety Officer, Rare Blood Disorders

Todd Paporello, Global Head of Regulatory Affairs, Specialty Care

Dario De Angelis, MSc, Global Regulatory Affairs, Therapeutic Area Head, Rare Diseases and Rare Blood Disorders

Thomas Schönberg, Dipl. Ing., MS, Global Regulatory Lead, Global Regulatory Affairs Rare Blood Disorders

Amanda Meisel, PharmD, RPh, Regulatory Strategist, Global Regulatory Affairs Rare Blood Disorders

Jai Pandey, PhD, Global Device Regulatory Head for IVD/CDX and Digital

1.0 BACKGROUND

Fitusiran (also referred to as ALN-AT3SC) is a small interfering RNA therapy (RNAi) that interferes with antithrombin (AT) translation by binding and degrading messenger RNA-AT, thereby preventing AT synthesis. It is intended to lower antithrombin production to “rebalance hemostasis” in people with hemophilia A or B.

U.S. Food and Drug Administration

Silver Spring, MD 20993

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The Sponsor intends to submit an NDA for fitusiran for the following indication: routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adult and pediatric patients with hemophilia A or B, including patients with or without factor VIII or IX inhibitors.

Initial registration is planned in the adult and adolescent populations (≥ 12 years old). The proposed dosing regimen for fitusiran is 50 mg subcutaneous every other month initially to be adjusted to target an anti-thrombin (AT) level between 15-35% (AT-based dosing [AT-DR]).

During development, dosing of fitusiran was paused in all ongoing clinical studies due to reports of non-fatal vascular thrombotic events in patients on fitusiran in ongoing phase 3 studies receiving the 80 mg monthly regimen. The Sponsor correlated the risk of thrombosis with AT activity level and found patients with AT level $< 10\%$ had a greater risk for developing thrombotic events. They correlated bleeding events and identified a level of 25% would preserve efficacy. Considering the within subject variability of AT activity, the Sponsor proposed that targeting an AT level between 15% and 35% would increase the probability of identifying patients at risk for thrombotic events as well as those who may need a higher dose for bleeding control. Dosing in ongoing phase 2 studies continued with an AT level-based dosing.

The Sponsor has met with CDRH to discuss a companion diagnostic (CDx) for AT level testing, which is needed for the safe dosing of fitusiran. The Sponsor is engaging with the AT assay manufacturer and will collaborate on the companion diagnostic development plan. Per the Sponsor, the AT assay manufacturer, in collaboration with Sanofi, will submit a presubmission to CDRH to align on the CDx development plan before submitting the CDx regulatory submission for registration purposes.

The Sponsor has signed a Letter of Intent (LoI) (DATE: February 2, 2024) with the AT assay manufacturer, allowing them to present the development and submission plan for the CDx to CDRH. The Sponsor intends to submit the NDA in parallel with the CDRH consultation.

Fitusiran was granted:

- Orphan Drug Designation (ODD) on August 16, 2013, for the treatment of hemophilia A (ODD # 13-4028) and August 12, 2013, for the treatment of hemophilia B (ODD # 13-4029)
- Fast Track Designation (FTD) on December 23, 2020, for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in patients with hemophilia A or B with or without factor VIII or IX inhibitors.

- Breakthrough Therapy Designation (BTD) on December 6, 2023, for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in patients with hemophilia B with factor IX inhibitors.

The purpose of the meeting is to seek the Agency's concurrence regarding the Sponsor's plan to submit an NDA in March/April 2024. The objective of the meeting is to align with the Agency on:

- The clinical data package to support:
 - the filing and review of the planned NDA
 - the proposed indication in the label
- Planned NDA regulatory milestones.

FDA sent Preliminary Comments to Genzyme Corporation on March 15, 2024.

2.0 DISCUSSION

Question 1: Does the Agency agree that the proposed clinical data package is adequate to warrant filing and review of an initial NDA for the proposed indications?

FDA Revised Response to Question 1: The Sponsor plans to establish substantial evidence of efficacy based on two randomized active controlled studies (EFC14768 and EFC14769).

- Study EFC14768 (ALN-AT3SC-003) is a randomized controlled phase 3 study to evaluate the efficacy and safety of fitusiran compared with by-pass agent (BPA) on demand in patients with hemophilia A or B, with inhibitory antibodies to factor VIII or IX, currently treated with on demand BPA. Status: complete with 60 patients enrolled, *of whom 57 were randomized (38 fitusiran and 19 control) and 3 patients per request from the Chinese HA were assigned directly to the treatment arm; all participants in the active arm received fitusiran 80 mg QM.*
- Study EFC14769 (ALN-AT3SC-004) is a randomized controlled phase 3 study to evaluate the efficacy and safety of fitusiran compared with factor on-demand in patients with hemophilia A or B, without inhibitory antibodies to factor VIII or IX, not receiving prophylaxis. Status: complete with 120 enrolled, *80 fitusiran and 40 control. All participants in the active arm received fitusiran 80 mg QM except 1 who withdrew before first dose.*

The clinical package will also include data from study EFC15110 and study LTE 15174.

- EFC15110 (ALN-AT3SC-009) is an open-label, switching study to describe the efficacy and safety of fitusiran prophylaxis in patients with hemophilia A and B previously receiving factor or BPA prophylaxis. Status: Complete with 80 enrolled; 67 received 80 mg QM, and 2 received AT-DR with a starting dose of 50 mg Q2M.
- LTE15174 (ALN-AT3SC-005) is a phase 3, open-label, extension study of long-term safety, PK, PD, and exploratory clinical activity of fitusiran in patients who previously participated in ALN-AT3SC-003, ALN-AT3SC-004, or ALN-AT3SC-009. Status: ongoing, 281 enrolled. 180 received 80 mg QD, 166 switched to 50 mg Q2M.

EFC15110 and LTE15174 started before the AT-DR was implemented, but the patients already enrolled were switched to AT-DR during their study.

The demonstration of the efficacy of the revised AT-DR relies on the efficacy data from study LTE15174, integrating control data from the completed parent studies EFC14768, EFC14769 and EFC15110. The integrated study of efficacy (ISE) approach uses the AT-DR dosing from the LTE15174 study, compared to the pooled control arms from the parent studies. This approach, based on the ITT principle and maintaining the initial randomization, was suggested by the Agency during the September 2023 Type C Meeting.

Table removed.

Based on the Sponsor's analysis the topline efficacy of fitusiran prophylaxis with AT-DR in patients with hemophilia A or B with or without inhibitors met the prespecified primary efficacy endpoint with demonstration of superiority in bleed control with a statistically significant reduction of >70% in annualized bleeding rate (ABR) compared to on-demand treatment with CFC (clotting factor concentrates) or BPA (by-passing agents). These results were significant in the Hemophilia A and B with inhibitors cohort, and in the Hemophilia A and B without inhibitors cohort.

In Pool C overall, a 25% reduction in mean ABR compared to factor/BPA prophylaxis was observed; however, nominal statistical significance was not reached ($p=0.23$). When analyzed by presence or absence of inhibitors, in patients (HA and HB) with inhibitors, a 70% reduction in bleeds was observed in comparison to SOC prophylaxis ($p=0.0002$), and in patients (HA and HB) without inhibitors, a 25% reduction was observed but nominal statistical significance was not reached ($p=0.61$).

Safety

To support safety, the Sponsor's clinical package includes data derived from a total of 335 adult or adolescent patients with hemophilia A or B, with or without inhibitors, who

received at least one dose of fitusiran on a clinical study. Of these patients, 286 received the AT-DR, of which 64 received AT-DR only (“de novo”).

The Integrated Summary of Safety (ISS) focuses on the all fitusiran-treated pool, which presents data from adolescent and adult participants treated with fitusiran prophylaxis across all studies in the fitusiran program, including data from parent and extension studies from the ISE, to assess long term safety. The ISS includes patients exposed to any dose of fitusiran overall (“Pool B”) and by original dosing, by AT-DR dosing, and by de novo, fitusiran naïve, AT-DR dosing, as suggested and recommended by the Agency in the September 2023 Type C Meeting. The Agency provided feedback in October 2023 that the Sponsor’s ISS proposed data cutoff of June 14, 2023, and 120-day safety update cutoff of March 2024 were reasonable.

Whether or not the application is fileable will be determined based on an assessment made by all review disciplines after the application is received. This assessment will include your proposal for testing AT levels. Please clarify in the meeting your timing for having a CDx available for testing AT levels. If a CDx is essential for the safe and effective use of a drug, the lack of a CDx could jeopardize approval of the drug.

From a clinical perspective, the approaches described for the ISS and the ISE appear reasonable.

Meeting Discussion for Question 1: The Agency thanked the Sponsor for their responses to the preliminary responses. The FDA response to question 1 has been revised accordingly. The Agency revised their responses to Question 1 see the italicized text.

The Sponsor clarified that the patients enrolled from the Chinese Health Authority were not part of the randomization scheme. The Agency asked the Sponsor to address 1) how the data from the 3 non-randomized patients will be incorporated into the EFC14768 and 2) whether there are other non-randomized patients enrolled into trials EFC14768 and EFC14769.

The Sponsor provided their Figure 2 which shows the dosing regimens used in studies EFC14768, EFC14769, and EFC15110. The Sponsor clarified that the majority of the fitusiran dosing in trials EFC14768, EFC14769, and EFC15110 used the 80 mg QM dosing (only 2 individuals were switched to AT-DR regimen during study EFC15110). The Agency stated that the Clinical Study Reports (CSRs) and datasets from the studies to support efficacy of the original dosing 80 mg QM and the studies to support efficacy of the AT-DR dosing will need to clearly identify the patients and their respective dosing regimens and control groups. Because the Sponsor plans to market AT-DR dose, the CSRs and datasets to support safety likewise will need to be clearly identified as to dosing and concurrent controls. Any efficacy and safety analysis will need to be clear about the dosing regimen and not merely lump all fitusiran treated

patients together. This recommendation will be especially important for the integrated summary of efficacy and safety.

The Agency and Sponsor briefly discussed the concept of Substantial Evidence of Effectiveness and the Sponsor's trials.

Companion Diagnostics Discussion:

The Sponsor mentioned that they planned a pre-submission to CDRH around the time that the NDA is submitted to CDER. [REDACTED] (b) (4)

[REDACTED] The Agency reminded the Sponsor that they have suggested that fitusiran is a rebalancing agent and as such returns hemostasis to a more pro-coagulant position for patients with hemophilia. The proposed label has a dosing algorithm in order to avoid overcorrection of coagulation and resultant thrombosis. The dosing algorithm relies on the detection of AT levels at the lower end of detection, at levels less than 15%. Safe use of fitusiran will have to be accompanied by prescriber instructions on how to dose based on AT levels with a diagnostic that is fit-for-purpose and reliable at levels below 15%. Therefore, the Agency thinks that it will not be possible to recommend in product labeling AT assays that are not reliable. The Agency envisions significant safety problems with a potential launch of fitusiran without a reliable contemporaneous companion diagnostic device to measure AT levels. [REDACTED] (b) (4)

[REDACTED] The Agency notes in the case of entrectinib, the device was not necessary for dosing recommendations nor to ensure safe use. The [REDACTED] (b) (4)

[REDACTED] CDER agrees with CDRH that an approved device will be necessary for fitusiran.

Question 2: Based on the topline results, does the Agency agree that the clinical data supports the indications proposed in the label: routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adult and adolescent (≥ 12 years old) patients with hemophilia A or B with or without factor VIII or IX inhibitors?

FDA Response to Question 2: Whether clinical data supports the proposed indication is a review issue.

The overall risk-benefit analysis of fitusiran and the exact wording of any indication will be a review issue.

We have the following feedback.

In your topline results for Pool A, Pool B, and Pool C, you stated that “participants who did not dose in primary efficacy period (PEP) were excluded from the analysis.” We do not agree with excluding such participants from the primary analysis, which should be based on all randomized patients in the original studies.

For the major efficacy and safety studies, in addition to the study data, please provide the following with your application:

1. Executable SAS programs with adequate document(s) to allow FDA to derive the analysis datasets from the raw datasets you submitted.
2. SAS programs as well as format library files used for efficacy and safety data analysis. If the SAS programs use any SAS macros, please provide all necessary macro programs.
3. All study protocols, amendments, and all minutes as well as related materials for discussion during IND meetings.

Meeting Discussion for Question 2: The Sponsor acknowledged that the indication and the overall risk-benefit analysis of fitusiran will be review issues. The Sponsor also acknowledged the request for executable SAS programs for datasets, outputs, and format library files and confirmed that they will be provided for the major efficacy and safety studies in addition to the study data. In addition, the Sponsor confirmed that all study protocols, amendments, and all minutes as well as related materials for discussions during IND meetings will be submitted in the NDA.

In the response to the Agency’s preliminary comments, the Sponsor provided the following clarifications: All randomized participants were included in the primary analysis, per ITT principle, as recommended by the Agency in the September 2023 Type C meeting. Participants who did not receive fitusiran in the primary efficacy period (PEP) are not excluded from the primary analysis, and their bleeding data in PEP were imputed using multiple missing data strategies when conducting estimation and comparison using negative binomial model. However, they do not contribute to observed statistical data summaries during PEP. In tables 26-30 from the briefing package, footnote 1 “participants who did not dose in primary efficacy period (PEP) were excluded from the analysis” refers to the observed data summaries only. During the meeting, the Sponsor asked whether or not, given the information in the response, the Agency’s requests had been resolved.

The Agency stated that the Sponsor’s responses appeared reasonable. The Agency also indicated that they were still reviewing the Sponsor’s most recent SAP and would provide follow-up comments as needed.

Question 3: Does the Agency agree that an Advisory Committee is not required based on the data shared to date?

FDA Response to Question 3: The decision regarding the need for an Advisory Committee will be determined during the review process.

Meeting Discussion for Question 3: The Agency reiterated that the need for an Advisory Committee would be determined during the review process.

Question 4: Does the Agency plan on requesting an application orientation meeting?

FDA Response to Question 4: We believe an application orientation meeting will be helpful.

Meeting Discussion for Question 4: The Agency requested that the application orientation meeting (AOM) cover topics important to clinical, clinical pharmacology and statistics and highlighted the need to be clear about which patients received which dosing regimens so that the correct analyses could be performed by the Agency in an efficient manner. Other disciplines did not think they needed the AOM to highlight their review areas.

Additional Comments:

1. Substantial Evidence of Effectiveness

You state that you plan to establish substantial evidence of effectiveness of fitusiran for the routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adult and pediatric patients with hemophilia A or B, including patients with or without factor VIII or IX inhibitors using data from studies EFC14768 and EFC14769.

In addition, you will be submitting data from study EFC15110 and study LTE15174.

In your application, you should be very clear about how you are establishing substantial evidence of effectiveness and how the studies you are proposing to use to establish substantial evidence of effectiveness are adequate and well controlled. Based on the meeting package for the prior meeting along with the meeting package for the current meeting, it appears that you will be using studies EFC14768 and EFC14769 to show efficacy for fitusiran prophylaxis at the 80 mg QM dose for hemophilia A and B with or without inhibitors compared to on demand therapy.

You will then be using studies EFC15110 and LTE15174 to demonstrate the effectiveness of the AT-DR dose regimen for fitusiran prophylaxis for the hemophilia A and B with or without inhibitors compared to on demand therapy.

Because of the complexity of your development program, it will be important that you clearly lay out your argument supporting the efficacy of fitusiran and the AT-DR for each of the populations separately: Hemophilia A, Hemophilia A with inhibitors, Hemophilia B,

and Hemophilia B with inhibitors. You may wish to provide comparisons from each population to its own natural history.

Meeting Discussion for Substantial Evidence of Effectiveness: See meeting discussion from Question 1.

2. Liver Test Elevations

We note some instances of elevated liver enzymes in your summary safety data. Include a detailed analysis of liver test elevations, including a search involving your entire database for Hy's Law cases and narratives as outlined in the attachments to these preliminary meeting minutes.

Meeting Discussion for Liver Test Elevations:

The Agency provided the following comments:

1. Please refer to individual subjects using the unique subject identifier (USUBJID) consistently in all communications (original submission, response to IR, 120-day safety update, etc.). If a different SUBJECTID was used for the various EPOCHs (randomized phase vs OLE, for example, provide both the USUBJID and SUBJECTID in all case level narratives or summary tabulations).
2. The analysis data reviewer's guide should identify all acronyms used for study identifiers, provide treatment start and end dates and all definitions for custom baseline flags, DTYPES and BASETYPES, if adopted.
3. We previously provided advice on the content of case level narratives and 2 tables summarizing a) liver related laboratory test and b) evaluation testing for possible DILI. Please refer to the information request for the preferred format for submitted narratives.

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

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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 Information¹ and Pregnancy and Lactation Labeling Final Rule² 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.

¹ <https://www.fda.gov/drugs/laws-acts-and-rules/plr-requirements-prescribing-information>

² <https://www.fda.gov/drugs/labeling/pregnancy-and-lactation-labeling-drugs-final-rule>

- 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 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.).

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- 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)				

To facilitate our facility assessment and inspectional process for your marketing application, we refer you to the instructional supplement for filling out Form FDA 356h³ and the guidance for industry, *Identification of Manufacturing Establishments in Applications Submitted to CBER and CDER Questions and Answers*⁴. Submit all related manufacturing and testing facilities in eCTD Module 3, including those proposed for commercial production and those used for product and manufacturing process development.

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

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

- DILI Data Recommendations and Case level data reporting for subjects with suspected DILI

³ <https://www.fda.gov/media/84223/download>

⁴ <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/identification-manufacturing-establishments-applications-submitted-cber-and-cder-questions-and>

⁵ <https://www.fda.gov/media/85061/download>

- Sponsor's response to preliminary comments document.

5.0 ISSUES REQUIRING FURTHER DISCUSSION

No issues requiring further discussion.

6.0 ACTION ITEMS

No action items.

1 These recommendations apply to trials restricting enrollment to subjects with liver
2 enzymes no greater than 2-3x ULN at baseline.

3 1. **Case level data:** Subjects in the safety populations (i.e., those exposed to
4 investigational product [IP]) meeting any of the criteria below should be reported
5 using the attached case level data formatting document. Subjects should be
6 listed in a table with links to their case level data. The table should specify which
7 of the criteria below were met and the number days from IP start to liver injury
8 onset.

9 a. *Post-Day 0 ALT or AST $\geq 5x$ ULN*

10 b. *Post-Day 0 ALT or AST $\geq 3x$ ULN and any of the following:*

11 i. *TB $\geq 2x$ ULN*

12 ii. *INR ≥ 1.5*

13 iii. *Signs of liver failure (e.g., ascites, encephalopathy)*

14 c. *Post-Day 0 ALP $\geq 2x$ ULN*

15 d. *Liver related AEs leading to IP discontinuation*

16 2. **Study level data:** References are made to Section #3 below where formatting of
17 scatterplots, tables, and baseline versus maximum value plots are detailed.

18 a. *General recommendations for all studies and datasets*

19 i. *Completeness of Datasets (e.g., adlb, LB STDM)*

20 • Include all central and non-central (i.e., outside laboratory) lab results
21 related to liver safety. Such labs should include available ALT, AST,
22 ALP, GGT, TB, DB, INR, CK, and LDH values for all subjects.

23 • Lab data sets should include units (e.g., mg/dL, umol/L, U/L), upper
24 limits of normal (ULN), and multiples of ULN for all results.

25 ii. *Integrated Safety Summary (ISS):* We request scatterplots (hepatocellular
26 and cholestatic) and scatterplot summary tables for the ISS population,
27 grouping subjects by those never exposed to IP versus those ever
28 exposed, regardless of when such exposure may have occurred. See
29 Section #3 for output formatting.

30 iii. *Each pivotal study and studies used for safety assessment:* We request
31 scatterplots (hepatocellular and cholestatic), scatterplot summary tables
32 and baseline versus maximum value plots for each study during the
33 randomized control period (s). See Section #3 for output formatting. For
34 studies with more complex designs (e.g., cross-over, randomized drug
35 withdrawal) where controlled periods of IP arms versus comparator arms
36 is less clear, scatterplot and table structure may need to be customized
37 and worked out with the review division.

38 3. **Scatterplots, Comparison Tables, and Baseline versus Maximum Plots:**

a. *Hepatocellular DILI Scatterplot (eDISH) with Summary Table:* Each
subject is plotted based on their maximum post-first dose TB (y-axis) by
maximum post-first dose ALT or AST, whichever is higher (x-axis) (see
example **Figure 1**). Dashed lines represent TB and aminotransaminase

(AT) cut-offs of $\geq 2x$ ULN and $\geq 3x$ ULN, respectively. Subjects with TB values reaching $\geq 2x$ ULN within 30 days of the AT becoming $\geq 3x$ ULN are circled. Different arms of the study should be identified by different colors and/or shapes of markers.

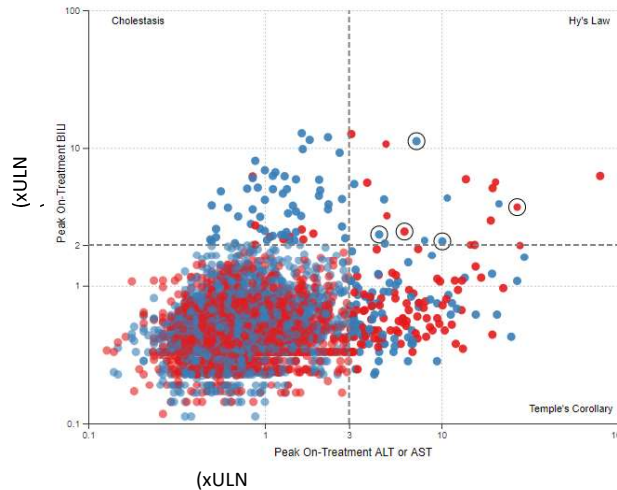


Figure 1: Hepatocellular Drug-Induced Liver Injury Case Screening Plot (eDISH). Circled subjects had TB $\geq 2x$ ULN within 30 days of ALT or AST becoming $\geq 3x$ ULN.

A table (**Table 1**) should provide summary counts of subjects in the three quadrants of interest from scatterplot.

39
40

Table 1. Number and percent of subjects in each of the three quadrants of interest (left upper, right upper [Hy's Law] and right lower [Temple's Corollary]) from Figure 1.

Quadrant	Active arm(s) (N=XXX) n (% of arm)	Comparator arm(s) (N=XXX) n (% of arm)
Right upper: Jaundice* with $\geq 3x$ ULN elevation in AST or ALT		
Left upper: Jaundice* without $\geq 3x$ ULN elevation in AST or ALT		
Right lower: Elevation in ALT or AST $>3x$ ULN without jaundice*		
Total		

41
42
43
44
45
46

N=total subjects in arm; n=number in each quadrant

*Jaundice = total bilirubin $\geq 2x$ ULN

We also recommend a table of subjects that are not plotted on the scatterplot including subject ID, study, and reason for exclusion (**Table 2**).

Table 2: Subjects excluded from scatterplot.

Subject ID	Study	Reason for exclusion from scatterplot

47

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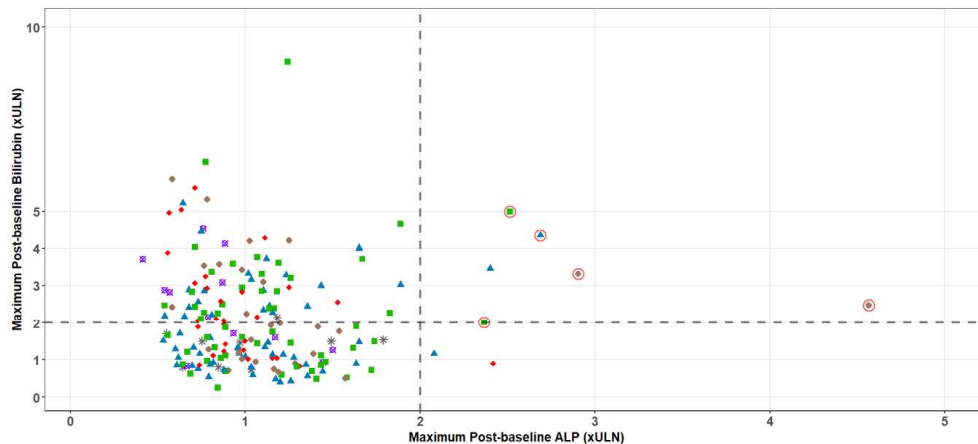
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b. *Cholestatic DILI Scatterplot with Summary Table:* This plot is similar to **Figure 1** above. However, peak AT (ALT or AST) is replaced by peak ALP along the x-axis. Each patient is plotted based on their maximum post-first dose TB (y-axis) and ALP (x-axis). Unlike the hepatocellular DILI plot, the cut-offs for both TB and ALP should be $\geq 2x$ ULN (**Figure 2**).



54

55

Figure 2: Example of cholestatic DILI Screening Plot

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57

A table (**Table 3**) should provide summary counts of subjects in the three quadrants of interest from the scatterplot.

58

59

60

Table 3. Number and percent of subjects in each of the three quadrants of interest (left upper, right upper, and right lower) from Figure 2.

Quadrant	Active arm(s) (N=XXX) n (% of arm)	Comparator arm(s) (N=XXX) n (% of arm)
Right upper: Jaundice* with $\geq 2x$ ULN elevation in ALP		
Left upper: Jaundice* without $\geq 2x$ ULN elevation in ALP		
Right lower: $\geq 2x$ ULN elevation in ALP without jaundice*		
Total		

61

*Jaundice = total bilirubin $\geq 2x$ ULN

62

63

As with the hepatocellular DILI scatterplot (eDISH), we recommend a Table for subjects excluded from the cholestatic DILI scatterplot (see **Table 2** above).

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c. *Comparison Table: Exposure adjusted rates of liver analyte elevations*
(Table 4)

Table 4. Liver Analyte Elevations at any Post-Randomization Visit, by Treatment Group

Liver Analyte Elevation	Active arm(s); N = __ Total Patient Exposure Years = __		Comparator arm(s); N = __ Total Patient Exposure Years = __		Risk Difference (95% CI)
	n (%)	Incidence rate per 100 patient exposure years	n (%)	Incidence rate per 100 patient exposure years	
ALT ≥ULN ≥3x ULN ≥5x ULN ≥10x ULN ≥20x ULN					
AST ≥ULN ≥3x ULN ≥5x ULN ≥10x ULN ≥20x ULN					
ALP ≥2x ULN ≥3x ULN					
TB ≥2x ULN ≥5x ULN ≥8x ULN					
DB ≥2x ULN ≥5x ULN					
GGT ≥2x ULN					
INR ≥1.5x ULN ≥3x ULN ≥5x ULN					

69 N = number of subjects

70
71
72
73

d. *Comparison Table: Exposure adjusted rates for liver analyte triggers*
(Table 5)

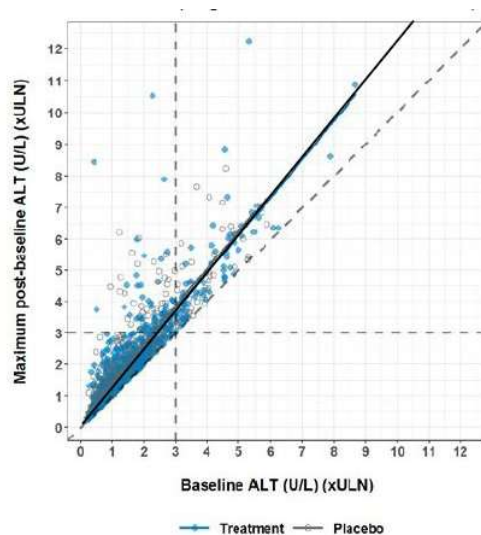
Table 5: Liver Analyte Triggers for Potential DILI by Treatment Group

Liver Analyte Triggers	Active arm(s) N = Total Patient Exposure Years =	Comparator arm(s) N = Total Patient Exposure Years =	Risk Difference (95% CI)

	n (%)	Incidence rate per 100 patient exposure years	n (%)	Incidence rate per 100 patient exposure years	
ALT ≥3x ULN or AST ≥3x ULN and TB ≥2x ULN					
ALT ≥5x ULN or AST ≥5x ULN ALT ≥8x ULN or AST ≥8x ULN ALT ≥3x ULN or AST ≥3x ULN					
ALP ≥2 ULN and TB ≥2 ULN GGT ≥2 ULN and TB ≥2 ULN					

74 N = number of subjects

75 e. *Baseline versus Maximum Value Plots*: Each subject is plotted using
 76 baseline in ULN (x-axis) by post-first dose maximum value (y-axis).
 77 Separate plots for ALT, AST, ALP, and TB should be made. See **Figure 3**
 78 for an example of an ALT baseline versus maximum plot.
 79



80
 81 **Figure 3:** Baseline ALT (xULN) versus maximum post-Day 0 ALT (xULN)
 82

83 4. **Technical guidance for datasets as they pertain to DILI:** We suggest perusal
 84 of the FDA Technical Specifications for Submitting Clinical Trial Data Sets for
 85 Treatment of Noncirrhotic Nonalcoholic Steatohepatitis (NASH), pages 27-33 for
 86 more information.¹ While the Guidance is for NASH, the section on lab and other
 87 datasets for DILI evaluation may be applicable to other target diseases.

88
 89
 90 Abbreviations:
 91 ALT: alanine aminotransferase

¹ <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/technical-specifications-submitting-clinical-trial-data-sets-treatment-noncirrhotic-nonalcoholic>

- 92 ALP: alkaline phosphatase
- 93 AST: aspartate aminotransferase
- 94 AT: aminotransferase (ALT and/or AST)
- 95 CK: creatine kinase
- 96 DB: direct bilirubin
- 97 GGT: gamma glutamyl transferase
- 98 INR: international normalized ratio
- 99 LDH: lactate dehydrogenase
- 100 TB: total bilirubin
- 101 ULN: upper limit of normal
- 102
- 103 Attachment: Reporting format for cases of potential DILI
- 104

Case level data reporting for subjects with suspected DILI

Cases should be listed in a table with columns for subject ID, study ID, treatment arm (if unblinded), latency (days from treatment start to liver injury onset) and criteria for notable liver injury (e.g., liver related adverse event term, ALT >5x ULN). If cases are unblinded, only subjects on IP (i.e., in the active arm) need to be reported. Each subject ID should be hot linked to a narrative, two tables, and a figure in the format outlined below.

1. Narratives: Subject narratives should follow a chronologic order of events giving both dates and study days. They should be written or edited by physicians or other medical personnel skilled in differential diagnosis and history writing. The narratives should include the following:
 - Age, sex, race/ethnicity, country where enrolled
 - Indication for investigational product (IP)
 - Blinding status: still blinded versus unblinded.
 - Medical history including medical illnesses, body mass index, alcohol intake history
 - Concomitant medications and herbal-dietary supplements with start and stop dates.
 - IP (or blinded treatment) dose and exposure by dates and study day including any interruptions and dose changes.
 - Treatment emergent, liver or DILI related symptoms, signs, and course (i.e., jaundice, pruritus, rash, eosinophilia abdominal pain, nausea, vomiting, fatigue, altered mental status, fever, liver transplant, death)
 - Details on clinical events that can lead to liver injury including surgeries, shock, heart failure, and sepsis.
 - Details on hospitalizations, tests, and treatments (e.g., antibiotics, endoscopies, surgeries, corticosteroids) for the liver injury.
 - Follow-up data including clinical course and laboratory values from both study site and non-study site locations (e.g., local emergency departments, clinics, hospitals).
 - Site investigator opinion on cause of liver injury
 - Hepatology Advisory Committee's (or equivalent independent review committee's) opinion on cause of liver injury, if available.
 - Evaluation testing for other causes of liver injury. Please send in tabular form embedded in or with the narrative (See **Table 1**). This list is not exhaustive nor implies that each item is necessary (e.g., liver histology), particularly if a firm non-DILI diagnosis is obvious. However, include whether each testing was or was not done as shown in **Table 1**.

Table 1: Line-item accounting of evaluation testing done and results.

Test	Test done after injury onset	Date, study day & result
Hepatitis A IgM antibody	{Yes//No}	
Hepatitis B surface antigen	{Yes//No}	
Hepatitis B anti-HB core IgM antibody	{Yes//No}	
Hepatitis B DNA	{Yes//No}	
Hepatitis C antibody	{Yes//No}	
Hepatitis C RNA	{Yes//No}	
Hepatitis E IgM antibody	{Yes//No}	
ANA (anti-nuclear antibody)	{Yes//No}	
ASMA (anti-smooth muscle antibody)	{Yes//No}	
Immunoglobulin G (IgG) level	{Yes//No}	
CMV (cytomegalovirus) antibody IgM	{Yes//No}	
EBV (Epstein Barr Virus) heterophile antibody	{Yes//No}	
EBV capsid antibody IgM	{Yes//No}	
EBV early antigen IgG	{Yes//No}	
Abdominal or liver ultrasound	{Yes//No}	
Abdominal computerized tomography scan	{Yes//No}	
Abdominal magnetic resonance imaging	{Yes//No}	
MRCP or MRC (magnetic resonance cholangiopancreatography or MR cholangiography)	{Yes//No}	
Cholangiogram (ERCP* or percutaneous)	{Yes//No}	
Liver histology	{Yes//No}	

*Endoscopic retrograde cholangiopancreatography

2. Liver Related Laboratory Data

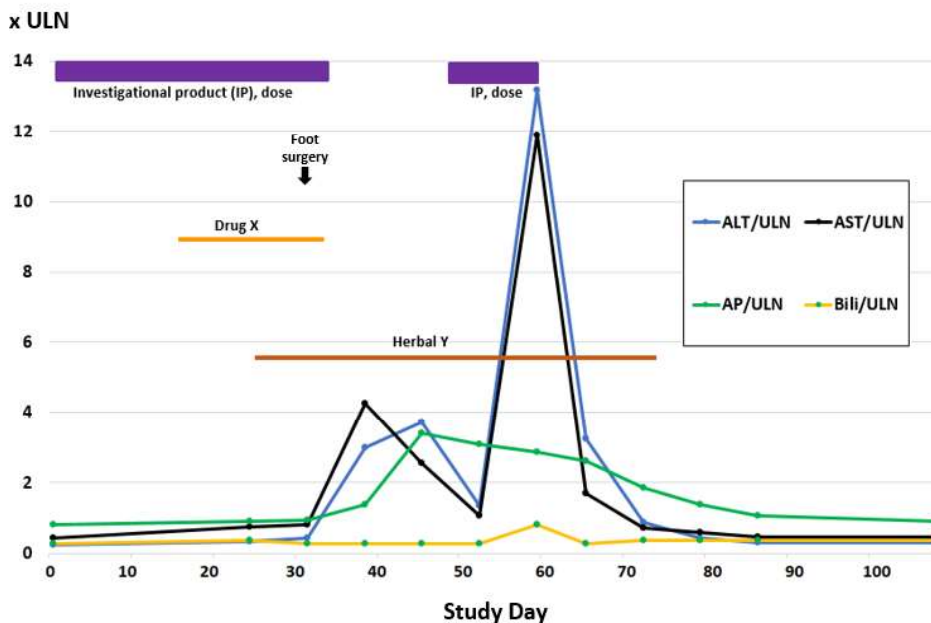
- a. Tabular: For each subject, provide all available values for the analytes by study date and day as shown in **Table 2**. The table should include values from central lab and non-study site locations (e.g., local emergency department, clinic, hospital). Please use the units outlined in **Table 2**. Please send in a separate Microsoft Excel spreadsheet file.

Table 2: Laboratory tests pertinent to liver injury course and evaluation by visit date and study day.

Visit Date	Study Day	ALT (U/L)	AST (U/L)	ALP (U/L)	GGT (U/L)	TB (mg/dL)	DB (mg/dL)	CPK (U/L)	LDH (U/L)	INR

- b. Line Graphic: For each subject, provide an ALT, AST, ALP, total bilirubin line graph of multiples of ULN over time with IP exposure including IP interruptions and dose changes. If the case is still blinded then substitute “blinded treatment” for IP. Please include values from non-study site locations (e.g., local emergency department, clinic, hospital). Please include on the graph pertinent events (e.g., surgeries) and new medications or herbal-dietary supplements started within six months prior to liver injury onset. (See **Figure 1** for example)

Figure 1: Example line graph of liver biochemistries in multiples of ULN by study day with IP and other pertinent exposures or events included.



Abbreviations:

ALP: alkaline phosphatase
ALT: alanine aminotransferase
AST: aspartate aminotransferase
CPK: creatinine phosphokinase
DB: direct bilirubin
DILI: drug-induced liver injury
GGT: gamma-glutamyl transferase
ID: identification
INR: international normalized ratio
IP: investigational product
LDH: lactate dehydrogenase
TB: total bilirubin
ULN: upper limit of normal

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This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

ANN T FARRELL
04/09/2024 09:58:48 AM



IND 125632

MEETING MINUTES

Alnylam Pharmaceuticals, Inc.
Attention: Lauren Melton, MSc, RAC
Director, Regulatory Affairs
300 Third Street
Cambridge, MA 02142

Dear Ms. Melton:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for fitusiran (ALN-AT3SC).

We also refer to the meeting between representatives of your firm and the FDA on May 10, 2016. The purpose of the End-of-Phase 2 meeting was to discuss the clinical development of fitusiran, a synthetic ribonucleic acid interference (RNAi) therapeutic targeting antithrombin, for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adult and adolescent patients (≥ 12 years old) with hemophilia A or B, including patients with inhibitory antibodies to exogenous factor VIII or factor IX substitution.

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 Alycia Anderson, Regulatory Project Manager, at (240) 402-4270.

Sincerely,

{See appended electronic signature page}

Nicole Gormley, MD
Acting 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**

MEMORANDUM OF MEETING MINUTES

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

Meeting Date and Time: May 10, 2016; 10:00 a.m. – 11:00 a.m. (ET)
Meeting Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1309
Silver Spring, Maryland 20903

Application Number: IND 125632
Product Name: fitusiran (ALN-AT3SC)
Indication: Routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adult and adolescent patients (≥ 12 years old) with hemophilia A or B, [REDACTED] (b) (4)

Sponsor/Applicant Name: Alnylam Pharmaceuticals, Inc.

Meeting Chair: Nicole Gormley, MD
Meeting Recorder: Alycia Anderson, CCRP

FDA ATTENDEES

Office of Hematology and Oncology Products/Division of Hematology Products

Ann T. Farrell, MD, Director
Edvardas Kaminskas, MD, Deputy Director
Nicole Gormley, MD, Acting Clinical Team Leader
Hyon-Zu Lee, PharmD, Clinical Reviewer
Lori Ehrlich, MD, Clinical Reviewer
Alycia Anderson, CCRP, Regulatory Project Manager

OHOP/Division of Hematology, Oncology, and Toxicology

Christopher Sheth, PhD, Pharmacology/Toxicology Team Leader
Ramadevi Gudi, PhD, Pharmacology/Toxicology Reviewer

Office of Clinical Pharmacology /Division of Clinical Pharmacology V

Bahru Habtemariam, PharmD, Acting Clinical Pharmacology Team Leader
Vicky Hsu, PhD, Clinical Pharmacology Reviewer

Office of Biostatistics/Division of Biometrics V

Yuan-Li Shen, DrPH, Biometrics Team Leader

Xin Gao, PhD, Biometrics Reviewer

SPONSOR ATTENDEES

Pushkal Garg, MD, Senior VP, Clinical Development

Benny Sorensen, MD, PhD Senior Director, Clinical Research

Sara Nochur, PhD, Senior VP, Regulatory Affairs

Lauren Melton, MSc, RAC Director, Regulatory Affairs

Akin Akinc, PhD, General Manager, Fitusiran

Chang-Heok Soh, PhD, Director, Biostatistics

Michael Placke, PhD, Senior VP, Drug Safety & Metabolism

Gabriel Robbie, PhD, VP, Drug Metabolism and Pharmacokinetics

Ali Seddighzadeh, MD, Senior Director, Clinical Drug Safety and Pharmacovigilance

Independent Hematologist attendee

(b) (4)

1.0 BACKGROUND

The drug product, fitusiran (ALN-AT3SC) injection (subcutaneous use), consists of the siRNA drug substance ALN-57213 (b) (4) and is intended for administration as a subcutaneous injection once monthly.

The purpose of this End-of-Phase 2 (EOP2) meeting is to discuss the clinical development of fitusiran, a synthetic ribonucleic acid interference (RNAi) therapeutic targeting antithrombin, for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adult and adolescent patients (≥ 12 years old) with hemophilia A or B, (b) (4)

FDA sent Preliminary Comments to Alnylam Pharmaceuticals, Inc. on May 4, 2016.

2. DISCUSSION

Preamble:

The Agency has concerns with your proposed development plan (see response to question 3). Your preliminary efficacy results suggest a median ABR of 4.3 or 2.2, which is higher than many currently available therapies in patients without inhibitors. The data you have presented thus far has been limited to patients without inhibitors. You may consider focusing your development of this product on patients with inhibitors or as an add-on therapy in a more severe patient population (i.e., those that have not achieved an adequate reduction in ABR, despite prophylaxis) as these populations may be able to derive significant benefit from a product that has an alternative mechanism of action, separate from factor replacement.

Question 1:

The completed and planned nonclinical toxicity studies, including studies to enable dosing of pediatric patients, developmental and reproductive toxicology studies and carcinogenicity assessment intended to support the registration of fitusiran, were addressed at the pre-IND meeting. The nonclinical program was conducted in consideration of principles set forth in ICH M3 (R2) and collectively, the completed and ongoing studies support full clinical development and potential future registration.

Does the Agency agree that the proposed modified nonclinical package is adequate to support registration of fitusiran?

FDA Response to Question 1:

The modified nonclinical package you have proposed in the EOP2 meeting package appears reasonable to support registration of fitusiran.

Discussion:

No discussion occurred.

Question 2:

Does the Agency agree that additional clinical pharmacology studies in healthy volunteers, special populations, or patients, are not required to support registration of fitusiran?

FDA Response to Question 2:

Your approach appears appropriate at this time. Whether additional studies are required will be a Biologics License Application (BLA) review issue.

Discussion:

No discussion occurred.

Question 3:

Given the mechanism of action of fitusiran is independent of the type of coagulation factor deficiency, each of the proposed Phase 3 clinical studies will include patients with hemophilia A and patients with hemophilia B. Further, given the age range of hemophilia patients and the known PK/PD characteristics of fitusiran, we propose to include adolescents >12 years in both pivotal studies.

Does the Agency agree with this approach for the proposed patient population in the two pivotal clinical studies?

FDA Response to Question 3:

No, we have the following concerns regarding the proposed trials:

- In patients without inhibitors, currently available prophylactic therapies with hemophilia A and B replacement factors have median ABRs as low as 0 and 1.4. According to the

submitted information, the median ABRs with fitusiran are 4.3 and 2.2 in patients without inhibitors. You have not provided justification for enrolling patients without inhibitors and switching them from factor prophylaxis to your product. Arm C of study ALN-AT3SC-004 is not appropriate at this stage of your development. Similarly for Arm C of study ALN-AT3SC-003, you have not provided any data as of yet regarding the use of fitusiran in patients with inhibitors. This will need to be reviewed by the Agency before Arm C would be allowed to proceed in this study.

- The Agency is concerned that the patients randomized to arm B (on-demand standard of care) in the ALN-AT3SC-003 and ALN-AT3SC-004 trials may not be appropriate for on-demand therapy, and may be better served by a prophylaxis strategy. What provisions will be in place to ensure that on-demand therapy is appropriate for the patients randomized to arm B?
- You have not provided any data in hemophilia A and B patients with inhibitors treated with fitusiran. You should provide summaries of the safety profile and ABR data of fitusiran in patients with hemophilia A and B with and without inhibitors at the proposed doses before proceeding with the phase 3 trials.

The Agency does agree with your proposal to include patients with hemophilia A and patients with hemophilia B and adolescents ≥ 12 years in the phase 3 trials.

Discussion:

The Sponsor presented additional preliminary data from their phase 1 trial, including preliminary data on patients with inhibitors (please see attached Sponsor slides). The Agency stated that it will be necessary for the Agency to review the sponsor's phase 1 data before consensus can be reached about the adequacy of the proposed phase 3 trials. The Agency reiterated their concerns regarding: the proposed dose (fixed-versus weight based dosing), dosing strategy (dose adjustments based on attainment of $> 75\%$ AT lowering), use in patients with inhibitors, the appropriateness of randomizing patients with a high ABRs to an on-demand therapy, and switching patients on prophylaxis to fitusiran. The Agency suggested that the Sponsor provide the Agency with additional clinical data (including data from the open-label extension trial) and other information to address these concerns. The Agency stated that they would be happy to have a future meeting with the Sponsor after this information has been received to further discuss their clinical development plan.

Question 4:

A detailed description and rationale for the fitusiran dose, dose regimen, and dose adjustment criteria for the Phase 3 studies (ALN-AT3SC-003 and ALN-AT3SC-004) are provided below.

Does the Agency agree with criteria for selection of the proposed dose, dosing regimen, and dose adjustments?

FDA Response to Question 4:

No, we do not agree. We have the following comments on the dose selection and the titration scheme proposed in the briefing package:

1. It appears that higher dose (e.g., 80 mg) would lead to 100% of patients achieving >75% of AT lowering. However, this recommendation is only based on efficacy data. We recommend you conduct integrated dose-response analyses in order to select fitusiran dose(s) that would lead to optimal risk: benefit.
2. Furthermore, the justification of a cutoff of >75% AT lowering is not clear. Based on the Figures 11 and 12 (Page 36) of the briefing package, one could target higher than 75% AT lowering to achieve a lower ABR.
3. The rationale of body weight tiered dosing based on 40 kg weight cutoff is not justified. It is unclear if there was an effect of body weight on PK of fitusiran which translated into difference in pharmacodynamics or efficacy between <40 and > 40 kg weight groups.
4. Based on the dose adjustment algorithm, you propose to increase the dose by 2-fold in patients < 40 kg (25 to 50 mg) and by 50% in patients > 40 kg (50 to 75 mg). Please provide a rationale for different dose adjustment criteria depending on body weight. Furthermore, please justify the criteria of increasing the dose on or after day 42 based on the residual AT activity.
5. Using clinical data, please evaluate appropriate dosing regimen (fixed or weight based dosing) that will result in consistent exposure for all patients

Discussion:

The Agency stated that the Sponsor should submit additional data to support their proposed dose (weight-based versus fixed dose) and dosing strategy.

Question 5:

Does the Agency concur that the design of the two proposed Phase 3 clinical studies is appropriate to support registration of fitusiran for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adult and adolescent patients (≥ 12 years old) with hemophilia A or B, (b) (4)

in particular:

5a: Does the Agency agree with the proposed study inclusion and exclusion criteria?

FDA Response to Question 5a:

No. See response to Question 3.

5b: Does the Agency agree with the proposed treatment duration and open label study design?

FDA Response to Question 5b:

Yes, the proposed treatment duration and open-label study design are acceptable.

5c: Does the Agency agree with the proposed randomization and stratification scheme?

FDA Response to Question 5c:

No. Randomization should also be stratified by hemophilia A vs. B. Additionally, please see response to question 3. The Agency does not agree that patients with a median ABR ≥ 20 are appropriate for on-demand therapy.

5d: Does the Agency agree with the primary and secondary endpoints?

FDA Response to Question 5d:

No. See response to question 3. If Arm C were to be included in either of the trials, the endpoints should be limited to the comparison of Arm A vs. Arm B, and should not be Arms A and C combined vs. Arm B.

We are unable to agree to the proposed secondary endpoint titled “HAEM-A-QoL” change because the briefing package contains inadequate information for our review. Please refer to the Appendix (b) (4)

for a list of items needed for FDA to review a Patient Reported Outcomes Instrument. Your briefing package, among other things, is missing a copy of the proposed instrument, the instructions for use, targeted claims, the endpoint model, the instrument’s conceptual framework, content validity documentation, assessment of other measurement properties, interpretation of scores, etc. (b) (4)
 please refer to the PRO guidance for the information needed for our review.

(b) (4)

Also, the proposed frequency of assessment for this instrument is inadequate (Day 1 and Month 7). Without the instrument, we cannot evaluate the proposed recall duration, but requiring patients to recall over a long period of time, compare their current state with an earlier period, or average their response over a period of time, are likely to undermine content validity.

For the other secondary endpoints (1st to the 4th in the list), please provide details of the definition and planned analysis methods. Whether or not these secondary endpoints are acceptable to the Agency will be a review issue.

Discussion:

No discussion occurred.

Question 6:

Does the Agency agree with the following statistical considerations proposed for the ALNAT3SC-003 Phase 3 study in hemophilia patients with inhibitors:

- Use of the efficacy evaluable population for primary analysis of the primary and secondary efficacy endpoints,

- **The definition of the efficacy period for analyses of the primary efficacy endpoint and the secondary efficacy endpoints on consumption of bypassing agents and annualized rate of subtypes of bleeding episodes,**
- **The primary analysis method for the primary efficacy endpoint,**
- **The use of hierarchical testing to control the overall type I error for the testing of primary and key secondary endpoints?**

FDA Response to Question 6:

No. The analysis of the primary and secondary efficacy endpoints should be based on the ITT population and should include all patients randomized to the treatment arms A and B regardless of receiving a dose of fitusiran and should include patients in Arms A and B who withdraw from the trial prior to Day 29.

Although the full pharmacodynamic effect of fitusiran is not expected until ~28 days following the first dose, the efficacy evaluation period for primary and all secondary endpoints should be from the time of randomization to Day 196.

The negative binomial regression model appears to be reasonable. Please submit the planned analysis program codes for further evaluation. However, the sample size calculation method is unclear. We expect that the sample size calculation method is the same as the one used for the primary efficacy analysis. If the sample size calculation is based on simulation with negative binomial regression model, please submit the simulation program code and results to the Agency for review.

The hierarchical testing procedure is acceptable for the testing of primary and key secondary endpoints. However, see comments on Question 5d for comments with regard to the secondary endpoints.

Please note that the number of patients who are randomized but have any missing assessments should be kept to a minimum. Too much missing data will undermine the reliability and confidence of the results. Sensitivity analyses should be performed to examine the potential impact of the missing data. For further advice on missing data, see the National Academies of Sciences report on *The Prevention and Treatment of Missing Data in Clinical Trials*. An electronic version of the document can be found from The National Academies Press at http://www.nap.edu/catalog.php?record_id=12955. A special report of the document can be found at <http://www.nejm.org/doi/full/10.1056/NEJMsr1203730>.

Discussion:

The Sponsor stated that they no longer plan to analyze Arms A+C versus Arm B, but instead plan to evaluate Arm A vs. Arm B. The Sponsor stated that given that fitusiran has a delayed onset of effect, they would like to use the efficacy evaluable population to conduct the primary analysis (or possibly a co-primary analysis, in which meeting statistical significance for both is required). The Agency stated that the primary analysis should be conducted on the ITT population, and that the efficacy evaluable population could be used for sensitivity

analyses. The Agency stated that they would be willing to discuss at a future time, possible ways to capture information regarding the efficacy of fitusiran at therapeutic levels after the onset period, but that the conversation was premature at this point and consensus could not be reached at this meeting. In a subsequent submission, the Sponsor will provide a detailed plan that will discuss their planned analyses, populations, and other statistical considerations.

Question 7:

Does the Agency agree with the following statistical considerations proposed for the ALNAT3SC-004 Phase 3 study in hemophilia patients without inhibitors:

- **Use of the efficacy evaluable population for primary analysis of the primary and secondary efficacy endpoints,**
- **The definition of the efficacy period for analyses of the primary efficacy endpoint and the secondary efficacy endpoints on consumption of bypassing agents and annualized rate of subtypes of bleeding episodes,**
- **The primary analysis method for the primary efficacy endpoint,**
- **The success criteria of $P \leq 0.05$ and estimated ABR ratio ≤ 0.5**
- **The use of hierarchical testing to control the overall type I error for the testing of primary and key secondary endpoints?**

FDA Response to Question 7:

No. See response to Question 6. Additionally, if “P” in your question stands for study-wise two-sided significance level, it is acceptable to the agency. However, the proposed estimated ABR ratio ≤ 0.5 as a success criterion is a review issue.

Discussion:

See discussion under Question 6.

Question 8:

Does the Agency agree with the proposed safety management plan to be implemented in the Phase 3 studies?

FDA Response to Question 8:

Yes. The proposed safety management plan appears acceptable. However, the full protocol should be submitted for review before final concurrence.

Discussion:

No discussion occurred.

Question 9:

Is the Sponsor's overall program of completed and planned clinical studies and the expected safety database adequate to support registration of fitusiran for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adult and adolescent patients (≥ 12 years old) with hemophilia A or B, with or without (b) (4)

FDA Response to Question 9:

No. For the ALNAT3SC-003 and ALNAT3SC-004 trials, the proposed numbers of hemophilia B patients (at least 5 and 20 patients, respectively) and patients who are 12-18 years of age (at least 5 and 8 patients, respectively) are not sufficient to assess the safety and efficacy for the proposed indications. Also see our responses to Question numbers 3, 5a, 5c, 5d, 6 and 7.

Additional Comments:

We support the inclusion of patient reported outcomes (PROs) in hematology clinical trials. The core patient-reported concepts we would like to see collected and analyzed include disease related symptoms, treatment related symptoms, and patient reported physical function. We are particularly interested in assessing pain (e.g., Brief Pain Inventory item #3), fatigue (e.g., Brief Fatigue Inventory item #3), anorexia (e.g., anorexia global item), and physical function (e.g., one of the PROMIS physical function measures).

(b) (4) PRO hypothesis should be tested in well controlled (e.g. randomized and double blind where feasible) clinical trials within the main statistical hierarchy of the clinical trial with a pre-specified analysis accounting for repeated measurements and potential confounding factors and procedures to control overall type 1 error. Justification for the interpretation of the PRO endpoint and what constitutes meaningful change should be provided. Careful attention should be paid to optimize the frequency and timing of assessments, particularly while on investigational therapy, in order to maximize the information obtained while taking the investigational drug.

PRO data will be carefully reviewed as part of the overall benefit-risk determination of a regulatory submission and should be collected diligently with this in mind. (b) (4)

We recommend that you select an instrument that is best supported by published data and most closely adheres to the principles laid out in the 2009 Guidance for Industry on *Patient Reported Outcome Measures* available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM193282.pdf>.

We understand that flexibility may be required with respect to strict adherence to some of the principles of the PRO guidance. We recommend that you communicate with us early regarding your selection of PRO endpoints.

Additional Comments: Device Constituent Part

1. In reference to Alnylam Pharmaceuticals plan to request a future meeting to focus on the CMC-Device development plans, we recommend that the meeting briefing document include at least the following information regarding the auto-injector:
 - Description of the device design and function including but not limited to:
 1. Information needed for subject safety
 2. Biocompatibility/sterility of the device
 3. Dose accuracy concerns that may lead to harm
 - List the essential performance requirements and identify the specifications you have established for the device constituent. These should include, but might not be limited to, the following:
 1. Injection depth
 2. Injection time
 3. Initiation of injection at correct depth
 4. User-Device Interaction forces (e.g., cap removal, activation, etc.)
 5. Injection Pathway Patency and Stability
 6. Visual and Audible feedback
 7. Volume delivery accuracy of the combination product
 - Evidence that the device intended for clinical study has met the established performance specifications.
 - Device risk analysis concluding that reasonably foreseeable hazards have been identified and mitigated.

These information requests are limited to the information needed to evaluate the device constituent prior to inclusion within a clinical study. Based on your responses there may be additional considerations for the clinical development. Additional information will be needed to support a marketing application, which includes the design control documentation, shelf life stability data, reliability data, etc.

2. It is recommended that the study success criteria for the phase 3 extension study should define specific quantitative measures for assessing drug delivery through the device constituent and incorporate this information into the description of the study endpoints. We also recommend you include in your study endpoints injection/device related adverse reactions. It is recommended that the clinically studied device be the device intended for commercialization.
3. Combination products under 21 CFR Part 3 are subject to 21 CFR Part 4 - Current Good Manufacturing Practice Requirements for Combination Products accessible at <https://www.federalregister.gov/articles/2013/01/22/2013-01068/current-good-manufacturing-practice-requirements-for-combination-products>.

3.0 OTHER IMPORTANT MEETING LANGUAGE

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>.

SUBMISSION FORMAT REQUIREMENTS

The Electronic Common Technical Document (eCTD) is CDER and CBER's standard format for electronic regulatory submissions. Beginning **May 5, 2017**, the following submission types: **NDA, ANDA, BLA** and **Master Files** must be submitted in eCTD format. **Commercial IND** submissions must be submitted in eCTD format beginning **May 5, 2018**. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit: <http://www.fda.gov/ectd>.

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).

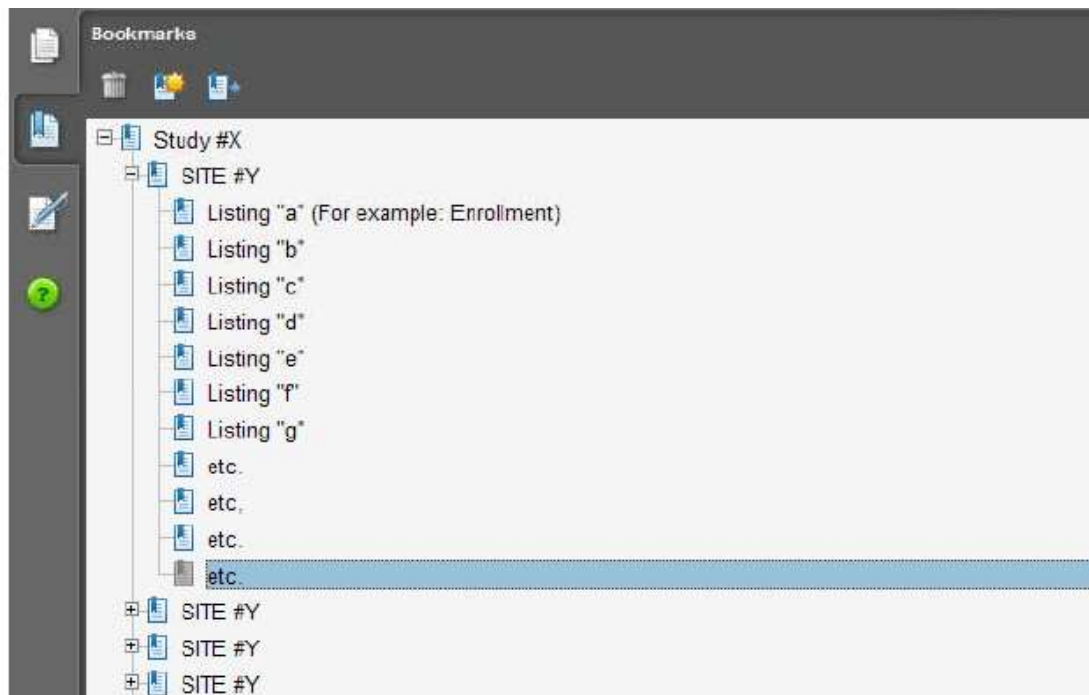
I. Request for general study related information and comprehensive clinical investigator information (if items are provided elsewhere in submission, describe location or provide link to requested information).

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 ¹	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.

¹ 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

NEW PROTOCOLS AND CHANGES TO PROTOCOLS

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

1. Study phase
2. Statement of whether the study is intended to support marketing and/or labeling changes
3. Study objectives (e.g., dose finding)
4. Population
5. A brief description of the study design (e.g., placebo or active controlled)
6. Specific concerns for which you anticipate the Division will have comments
7. For changes to protocols only, also include the following information:
 - A brief summary of the substantive change(s) to the protocol (e.g., changes to endpoint measures, dose, and/or population)
 - Other significant changes
 - Proposed implementation date

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

4.0 ISSUES REQUIRING FURTHER DISCUSSION

There are no issues requiring further discussion.

5.0 ACTION ITEMS

There are no action items.

6.0 ATTACHMENTS AND HANDOUTS

The Agency received slides from Alnylam Pharmaceuticals, Inc. on May 9, 2016 and they are attached.

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

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

/s/

NICOLE J GORMLEY
05/25/2016