CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

215515Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

IND 139086

MEETING MINUTES

Alnylam Pharmaceuticals, Inc.
Attention: David Hymes, M.S.
Regulatory Affairs
300 Third Street
Cambridge, MA 02142

Dear Mr. Hymes:

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

We also refer to the teleconference between representatives of your firm and the FDA on March 26, 2021. The purpose of the meeting was to discuss the content and format of a planned NDA submission for vutrisiran.

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

If you have any questions, contact Annie Nguyen, Regulatory Project Manager, by email at Anhtu.Nguyen@fda.hhs.gov or by phone at (240) 402-4460.

Sincerely,

{See appended electronic signature page}

Eric Bastings, MD
Director (Acting)
Division of Neurology 1
Office of Neuroscience
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 26, 2021, 11:00 am – 12:00 pm
Meeting Location: Teleconference

Application Number: IND 139086
Product Name: Vutrisiran
Indication: Treatment of the polyneuropathy of hereditary transthyretin-mediated amyloidosis in adults
Sponsor Name: Alnylam Pharmaceuticals
Regulatory Pathway: 505(b)(1) of the Federal Food, Drug, and Cosmetics Act

FDA ATTENDEES

Office of Neuroscience
Billy Dunn, MD, Director

Division of Neurology 1
Eric Bastings, MD, Director (Acting)
Teresa Buracchio, MD, Deputy Director
Laura Jawidzik, MD, Clinical Team Lead
Rainer Paine, MD, Clinical Reviewer
Annie Nguyen, RPh, Regulatory Project Manager
Sally Jo Yasuda, MS, PharmD, Safety Team Leader
Josephine Little, PharmD, Regulatory Project Manager
Justine Kankam, PharmD, Regulatory Project Manager

Office of Clinical Pharmacology
Bilal Abuasal, PhD, Clinical Pharmacology Team Leader
Yifei Zhang, PhD, Clinical Pharmacology Reviewer
Hobart Rogers, PharmD, PhD, Genomics and Targeted Therapy Reviewer

Office of Product Quality
Martha Heimann, PhD, CMC Lead for Neurology Products
Laura Wasil, PhD, Quality Microbiology Reviewer

Office of Biostatistics
Kun Jin, PhD, Team Leader, Division of Biometrics I
Tristan Massie, PhD, Statistical Reviewer

Controlled Substances Staff
Edward Hawkins, MD, CSS Reviewer

SPONSOR ATTENDEES

Alnylam Pharmaceuticals
Seth Arum, MD, Director, Global Patient Safety & Risk Management
Prajakta Badri, PhD, Director, Clinical Pharmacology
Rick Blakesley, PhD, Director, Biostatistics
Jihong Chen, PhD, Senior Director, Biostatistics
Maged Darwish, PhD, Vice President, Regulatory Affairs CMC
Rena Denoncourt, MBA, Vice President, Vutrisiran Program Leader
Bahru Habtemariam, PharmD, Senior Director, Clinical Pharmacology
David Hymes, MS, Contractor, Regulatory Affairs
Satyawan Jadhav, PhD, Principal Scientist, Clinical Pharmacology & Pharmacometrics
Rebecca Shilling, MD, Director, Clinical Research
Andrew P. Slugg, MS, MBA Senior Vice President, Regulatory Affairs
Caitlin Skenyon. PharmD, Manager, Regulatory Affairs
Ben Stevens, PhD, MPH, Director, Regulatory Affairs CMC
Jessica Sutherland, PhD, Senior Director, Toxicology
Marianne Sweetser, MD, PhD, Senior Distinguished Fellow
John Vest, MD, Vice President, Clinical Research

1.0 BACKGROUND

Alnylam Pharmaceuticals, Inc., (Alnylam) is developing vutrisiran for the treatment of the polyneuropathy of hereditary transthyretin (hATTR) amyloidosis. The sponsor states that vutrisiran is a long-acting, subcutaneously administered, synthetic ribonucleic acid interference (RNAi).

The Agency granted Orphan Drug Designation for vutrisiran on May 25, 2018, and Fast Track Designation on April 3, 2020.

FDA sent Preliminary Comments to Alnylam on March 16, 2021.

2.0 DISCUSSION

2.1. Chemistry, Manufacturing, and Controls

Question 1:

Does the Agency agree with the Applicant's plan to provide 12-month drug product stability data for the second and third primary batches within 30 days following the submission of the vutrisiran NDA as a minor amendment?

FDA Response to Question 1:

We note a minor discrepancy between Table 3 in the briefing package, which indicates that 18 months of stability data will be provided for primary lot ADASA01 and the Proposal for Submission Timelines and Justification, which states 12 months. We assume that 12 months data will be provided for lot ADASA01.

Your proposal to submit the NDA with nine months data for lots ADASL03 and ADATA01 and amend the NDA with 12 months data for these lots within the first 30 days is acceptable. However, we cannot guarantee review of any data submitted later than 30 days. Note that, per ICH Q1E Evaluation of Stability Data, extrapolation beyond real time may require statistical analyses. We recommend that any supporting statistical analyses be provided within the first 30 days.

Sponsor's response to preliminary comments

The Applicant appreciates the Agency's acceptance of our proposal to submit additional stability data within the first 30 days after NDA submission. The Applicant clarifies that 18-month data will be provided on the registration lot, ADASA01, in the initial NDA.

If not available at the time of the initial submission, 12-month data for the ADASL03 and ADATA01 lots will be provided within the first 30 days after NDA submission. A statistical analysis update will also be provided at the time of the stability update.

Discussion:

No discussion.

2.2. Clinical

Question 2a:

Does the Agency agree that the results from the pivotal Phase 3 HELIOS-A study and proposed clinical data package are adequate to support the review of an NDA of

vutrisiran for the treatment of the polyneuropathy of hereditary transthyretin-mediated amyloidosis in adults?

FDA Response to Question 2a:

On face, it appears that results of the phase 3 study HELIOS-A and proposed clinical data package presented in the briefing document have the potential to support the submission of an NDA for vutrisiran. A determination of whether the data will be adequate for filing will be made at the time of an NDA submission.

The number of patients with at least 1 year of safety data is not clear from the briefing document. Please clarify how many patients you will have with at least 1 year of safety data at the time of submission of the application.

Sponsor's response to preliminary comments

The Applicant appreciates the feedback on the proposed clinical data package.

The Applicant would also like to clarify that 74 patients will have at least 1 year of safety data in the initial application.

Discussion:

The Applicant clarified that they anticipate that about 100 patients will have 1-year safety data at the 120-day safety update.

Question 2b:

Does the Agency agree that the content of the NDA described below will constitute a complete application for the proposed indication?

FDA Response to Question 2b:

In regard to the content of your NDA, we have the following comments and requests:

1. The layout of Module 3 (Quality) for the application submission appears reasonable. However, see Guidance for Industry for the Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products, Section IV, for a description of the types of information and data that should be included in an application for an aseptically processed, sterile drug product to demonstrate the efficacy of the sterilization process. Additionally, Guidance for Industry Sterile Drug Products Produced by Aseptic Processing – Current Good Manufacturing Practice provides a description of the procedures and practices that will help enable the sterile drug manufacturing facility to meet CGMP requirements related to facility design, equipment

suitability, process validation, quality control, etc. for an aseptically processed, sterile drug product.

2. To facilitate the review of your NDA, please submit the datasets for the Phase 1 Study ALN-TTRSC02-001.

3. Please refer to the appendices at the end of this document, General Clinical Safety Requests and Clinical Pharmacology Summary Aid, when preparing for the NDA submission. Note that the General Clinical Safety Requests are common requests for safety analyses that you should consider for inclusion in your safety summary; however, the requests may not be applicable to all study populations. You should include the requests that are appropriate for your study population.

4. From a technical perspective, the eCTD structural content you have proposed is acceptable. For further guidance on acceptable submission format per Module, please follow https://www.fda.gov/media/71551/download .

Sponsor's response to preliminary comments

1. The Applicant will include the relevant information in Module 3 of the NDA in line with the above mentioned Guidances.

2. The Applicant will provide the SDTM datasets (SDTM v1.4/SDTM IG 3.2), define.xml, reviewer's guide, and annotated CRF for the Phase 1 Study (ALN-TTRSC02-001) in the NDA (located in 5.3.3.1). Non-CDISC format analysis datasets supporting the clinical study report can be made available upon request, within 30 days of the initial submission. The Applicant would like to confirm at the pre-NDA meeting that this is acceptable.

   Of note, the PK/PD data from this study will be included as part of the pooled PK/PD datasets (located in 5.3.4.2). The Phase 1 PK/PD data were used to develop quantitative models for Phase 3 dose selection.

3. The Applicant believes that the NDA submission components are consistent with the above-mentioned appendices where applicable to the study population. Importantly, the Summary of Clinical Pharmacology (SCP) and Summary of Biopharmaceutics (SBP) documents are written consistent with the latest Clinical Pharmacology Question Based Review template. As a result, the SCP and SBP documents address all the elements of the Clinical Pharmacology Review Aid relevant to vutrisiran.

4. The Applicant appreciates the confirmation that the eCTD content is acceptable from a technical perspective.

The Applicant would also like to discuss at the pre-NDA meeting our proposal for a formal Communication Plan. As mentioned in the briefing document, the Applicant is ready to actively work with the Division to support its review of this NDA. The proposed Communication Plan would include regular (e.g., bi-weekly or monthly), brief (e.g., 30 minute) teleconference meetings, with the assigned Regulatory Project Manager, relevant members of the Review Team, and other stakeholders such as members of the Office of Regulatory Affairs to:

- rapidly address any questions that arise during the review of our NDA and clarify any prior responses
- discuss the status of additional aspects, such as the need for and coordination of inspections, including pre-inspection record requests under section 704(a) of the FDCA.
- plan for timing and content of additional prearranged meetings, such as the mid- and late-cycle meeting

In addition, if the Agency would find it helpful to facilitate the review of this NDA the Applicant is receptive to an Applicant Orientation Meeting with the Agency approximately one month after submission.

Discussion:

The plan for submitting datasets for the Phase 1 Study ALN-TTRSC02-001 is acceptable.

The Applicant asked to discuss their proposal for a formal Communication Plan. The Agency did not find additional meetings beyond the PDUFA scheduled meetings necessary. Because the review process is ongoing, questions or issues are addressed as they arise.

The Agency will communicate with the Applicant regarding facility inspections to the extent possible. The Agency recommended that the Applicant keep in contact with contract facilities to ensure awareness of scheduled inspections or record requests under Section 704(a). Recommendations for facility inspections are generally made early in the review. A determination whether to request records under Section 704(a) in lieu of on-site inspection may require additional consultation within the Agency prior to the request.

The Agency agreed to an orientation meeting with the Applicant after the NDA has been submitted.

Question 2c:

Given that the HELIOS-B study in patients with ATTR amyloidosis with cardiomyopathy is still actively enrolling and remains blinded, does the Agency agree that a blinded listing of SAEs reported in HELIOS-B from the ARGUS database is not necessary for inclusion in the NDA of vutrisiran for the treatment of the polyneuropathy of hATTR amyloidosis?

FDA Response to Question 2c:

No, we do not agree. Please include the blinded listing of SAEs from the HELIOS-B study of hATTR-cardiomyopathy in the NDA submission.

Sponsor's response to preliminary comments:

The Applicant will provide the blinded SAE listings from HELIOS-B in Module 1.11.3 of the NDA.

Discussion:

No discussion.

Question 3:

Does the Agency agree that vutrisiran is not considered a drug with abuse potential and that no scheduling of vutrisiran under the Controlled Substances Act is warranted?

FDA Response to Question 3:

We agree. There is no need to include an assessment of the abuse potential of the drug, or a proposal for scheduling the drug in your NDA. The drug does not affect the CNS, it is not chemically or pharmacologically similar to other drugs with known abuse potential, and it does not produce psychoactive effects such as sedation, euphoria, and mood changes.

Sponsor's response to preliminary comments:

The Applicant appreciates the Agency's agreement that vutrisiran is not considered a drug with abuse potential and that an assessment of the abuse potential of vutrisiran and proposal for scheduling under the Controlled Substances Act is not needed in the NDA.

Discussion:

No discussion.

Question 4:

Does the Agency agree with the proposed content and timing for the BIMO information?

FDA Response to Question 4:

Yes, your proposed content and timing for the BIMO data submission is acceptable.

When submitting the BIMO data, please include details regarding the process for obtaining and scoring mNIS +7 data. Please specify whether raters used paper, an electronic tablet, or other source; how data was sent to a vendor for scoring (if applicable); and to which vendor (if applicable). Please specify the source available at clinical sites to verify mNIS +7 data.

Sponsor's response to preliminary comments:

The Applicant appreciates the agreement from the Agency that our proposed content and timing for the BIMO data submission is acceptable and will include the requested details regarding the process for obtaining and scoring mNIS+7 data in the BIMO package.

Discussion:

No discussion.

2.3. Regulatory

Question 5:

Does the Agency agree that vutrisiran qualifies for Priority Review?

FDA Response to Question 5:

Priority review decisions are made when the application is submitted. Provide your rationale for requesting a Priority Review Designation in your NDA submission, and we will review your request at that time.

Sponsor's response to preliminary comments:

The Applicant appreciates the feedback and will include a request for designation in the NDA submission.

Discussion:

No discussion.

Question 6:

Does the Agency agree with the proposed content and timing for the safety update report required under 21 CFR 314.50 (d)(5)(vi)(b)?

FDA Response to Question 6:

Yes. The proposed content and timing for the safety update report are reasonable.

Sponsor's response to preliminary comments:

The Applicant appreciates the agreement from the Agency regarding the proposed content and timing of the Safety Update Report.

Discussion:

No discussion.

3.0 ADDITIONAL INFORMATION

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

As stated in our January 22, 2021, communication granting this meeting, if, at the time of submission, the application that is the subject of this meeting is for a new molecular entity or an original biologic, the application will be subject to "the Program" under PDUFA VI. Therefore, at this meeting be prepared to discuss and reach agreement with FDA on the content of a complete application, including preliminary discussions on the need for risk evaluation and mitigation strategies (REMS) or other risk management actions and, where applicable, the development of a Formal Communication Plan. You and FDA may also reach agreement on submission of a limited number of minor application components to be submitted not later than 30 days after the submission of the original application. These submissions must be of a type that would not be expected to materially impact the ability of the review team to begin its review. All major components of the application are expected to be included in the original application and are not subject to agreement for late submission.

Discussions and agreements will be summarized at the conclusion of the meeting and reflected in FDA's meeting minutes. If you decide to cancel this meeting and do not have agreement with FDA on the content of a complete application or late submission of any minor application components, your application is expected to be complete at the time of original submission.

In addition, we remind you that the application is expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities.

Information on the Program is available at FDA.gov.[1]

PREA REQUIREMENTS

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

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

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57 including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the PLR Requirements for Prescribing Information[2] and Pregnancy and Lactation Labeling Final Rule[3] websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products.

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

- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential.

- Regulations and related guidance documents.

- A sample tool illustrating the format for Highlights and Contents, and

- The Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances.

- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

Pursuant to the PLLR, you should include the following information with your application to support the changes in the Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of labeling. The application should include a review and summary of the available published literature regarding the drug's use in pregnant and lactating women and the effects of the drug on male and female fertility (include search parameters and a copy of each reference publication), a cumulative review and summary of relevant cases reported in your pharmacovigilance database (from the time of product development to present), a summary of drug utilization rates amongst females of reproductive potential (e.g., aged 15 to 44 years) calculated cumulatively since initial approval, and an interim report of an ongoing pregnancy registry or a final report on a closed pregnancy registry. If you believe the information is not applicable, provide justification. Otherwise, this information should be located in Module 1. Refer to the draft guidance for industry *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format*.

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

DISCUSSION OF SAFETY ANALYSIS STRATEGY FOR THE ISS

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

optional; the issues can instead be addressed at the pre-NDA meeting.

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

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

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

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

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

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

SECURE EMAIL COMMUNICATIONS

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

MANUFACTURING FACILITIES

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and

specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
(1)				
(2)				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
(1)				
(2)				

To facilitate our facility assessment and inspectional process for your marketing application, we refer you to the instructional supplement for filling out Form FDA 356h[4] and the guidance for industry, *Identification of Manufacturing Establishments in Applications Submitted to CBER and CDER Questions and Answers*[5]. Submit all related manufacturing and testing facilities in eCTD Module 3, including those proposed for commercial production and those used for product and manufacturing process development.

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

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*.[6]

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

Appendix A. General Clinical Safety Requests

Datasets:

1. Each individual subject should be assigned a single unique subject identifier across the entire application (e.g., including open label extensions of the trials). Include the unique subject identifier in the ISS and individual studies' datasets.
2. Submit datasets for all Phase 1, Phase 2, Phase 3 studies (including open label extension studies), including the Phase 2 and 3 studies performed for indications other than the one proposed for this application.

For additional guidance refer to the FDA webpage on Study Data Standards Resources.

General Submission Contents:

1. Follow the requirements noted in 21CFR 314.50 (d)(5)(vi), Summary of Safety Information and the Guideline for the Format and Content of the Clinical and Statistical Sections of an Application
2. Provide an assessment of safety as per the FDA Guidance for Industry: Premarketing Risk Assessment
3. Include a copy of each clinical study protocol as well as each amended protocol. Provide a list of the inclusion and exclusion criteria for each of the studies, including those introduced as part of protocol amendments. Please submit all versions of the protocols (and Statistical Analysis Plan) and the date when changes were implemented. Please ensure that a Summary of Changes for each version is included.
4. In addition to the comprehensive analyses performed for the pivotal trials, the ISS should also comprehensively integrate safety analyses for all other study group pools for treatment-emergent adverse events (TEAEs), deaths, serious adverse events, discontinuations for TEAEs, TEAEs of special interest, subgroups, and vital sign/laboratory/ECG measurements.
5. Submit a table detailing all of the tables and figures featured in the clinical efficacy and safety sections of the application. The table should contain the following:
   a. Title of the table or figure in the application
   b. A hyperlink to the location of the table or figure with page number
   c. A hyperlink to the SAS code used to create the table or figure (including information regarding the datasets that were used)
6. Format the tables of the ISS according to examples in FDA's Reviewer Guidance – Conducting a Clinical Safety Review of a New Product Application and Preparing a Report on the Review.
7. Include active hyperlinks from the lists of references to the referenced article.
8. Provide DSMB meeting minutes (including any data/slides presented). For those meetings that were cancelled or meetings where no minutes were taken, please include a place holder for that meeting noting such and signed by a member of the

clinical team. Please also ensure that these packages come with a table of contents and are bookmarked by date.
9. Include information regarding important regulatory actions in other countries and foreign labeling (translated, if applicable).
10. Submit an annotated version of the pre-BLA meeting minutes that include hyperlinks, when applicable, to the analysis and/or documents requested.

Adverse events:

1. Follow the coding rules for MedDRA in the ICH-endorsed "MedDRA Term Selection: Points to Consider" document accessible at MedDRA
2. For each of the studies, the submitted datasets should contain both the verbatim terms and the MedDRA coding with all levels of the MedDRA hierarchy. For each adverse event, MedDRA coding should be provided for the primary MedDRA path.
3. Provide a summary table of the original AE coding dictionaries that were used in each of the trials.
4. The preparation of the adverse event dataset for the ISS should include MedDRA Preferred Terms from a single version of MedDRA.
5. Ensure that all adverse events are presented, and not only events deemed "drug-related."
6. Provide a table of treatment-emergent adverse events reported in ≥ 2% of subjects (after rounding) in any drug treated dose group (and greater than placebo) sorted by MedDRA SOC (in alphabetical order) and then by MedDRA Preferred Term.
7. Provide a table which summarizes the outcomes of all pregnancies. Provide a table which summarizes all known adverse events in subject offspring.

Narratives and Case Report Forms (CRFs):

1. Provide narratives and case report forms for deaths, adverse events leading to drug discontinuation, SAEs, pregnancies, and AEs of special interest. You should be prepared to supply any additional CRFs or narratives with a rapid turnaround upon request. Narratives should be integrated. For subjects who had more than one event requiring a narrative (whether in the same trial or in the core study and an extension) present a single narrative (rather than separate narratives for the various events).
2. Include a word file (and excel spreadsheet) that indicates those subjects for whom you submitted a case report form and/or narrative. This file should include an indicator for whether each item was submitted and the reason why it was submitted along with hyperlinks to the narrative and CRF.
3. Provide reports for any autopsies conducted during any of the studies.
4. Provide a line listing, narrative, and case report form for all subjects who fit the Hy's Law laboratory criteria.

5. Note that CRFs should include all clinical documents collected about the patient regardless of whether you label them “CRFs”, e.g., Medwatch/CIOMS forms, event fax coversheets, SAE or event worksheets, narrative worksheets, data queries, etc.
6. Provide a tabular listing of all subjects with all discontinuations, sorted by reason. The table should include columns for study number, treatment group, unique subject ID, primary reason for drug or study discontinuation. For reasons including Lost to follow-up, Other, Physician/investigator decision, Withdrew consent, and Patient decision, provide more specific information regarding the discontinuation. The Division may want to request selected narratives/CRFs from some of these patients, but they do not need to be submitted at the time of the initial NDA/BLA submission.
7. Narrative summaries should provide a complete synthesis of all available clinical data and an informed discussion of the case. The narratives should be comprehensive enough for the reader to come to a reasonable conclusion regarding the subject and the adverse event. The following items should be included (but not limited to):
    a) Patient age and gender
    b) Adverse event onset and stop dates (presented as relative Study Day number)
    c) Signs and symptoms related to the adverse event being discussed
    d) An assessment of the relationship of exposure duration to the development of the adverse event
    e) Pertinent medical history
    f) Concomitant medications with start dates relative to the adverse event
    g) Pertinent physical exam findings
    h) Any abnormal vital sign measurements
    i) Pertinent test results (e.g., lab data, ECG data, procedures, biopsy data, autopsy results)
    j) Discussion of the diagnosis as supported by available clinical data
    k) For events without a definitive diagnosis, a list of the differential diagnoses
    l) Treatment provided
    m) Re-challenge results (if performed)
    n) Outcomes and follow-up information

Laboratory and Vital Sign Measurements:

1. Refer to the following FDA webpage for the CDER position on use of SI units for lab tests:
   SI Units.
2. Provide the normal reference ranges for every laboratory value.
3. Clearly list the normal values, as well as the thresholds for analysis of outliers, for outlier analyses of laboratory data, vital signs, and ECG data.
4. When possible, use the latest version of the National Institutes of Health (NIH) Common Terminology Criteria for Adverse Events (CTCAE) for toxicity grades and shift analyses.

5. Report the number and percentage of subjects with at least one post-treatment vital sign measurement meeting any of these criteria:
    - Systolic Blood Pressure: <90 mmHg, >140 mmHg, >160 mmHg
    - Diastolic Blood Pressure: <50 mmHg, >90 mmHg, >100 mmHg
    - Pulse Rate: <60 bpm, >100 bpm
    - Body Weight: decrease of ≥7% from baseline and increase of ≥7% from baseline
    - Temperature: >38.0 °C, <36.0 °C
    - Respiratory rate: <12 breaths/min, > 20 breaths/min
6. Summarize the protocols for collecting ECG data. Summarize the frequency of post-treatment QTc >450 ms, >480 ms, and >500 ms.

Other requests:

1. Patient profiles
   Submit individual patient profiles containing all laboratory and other study results in a single place for each patient. Provide this information for patients who died, had a serious adverse event, discontinued from the trial due to an adverse event, or had a medically significant event for which a narrative is submitted. Include all the information recorded for that patient, including but not limited to:
    a) Age
    b) Sex
    c) Dates of screening, randomization and starting therapy
    d) Whether the patient completed or did not complete the study, with dates and reason for withdrawal
    e) Adverse events (reported term, preferred term, start and stop date [with relative study day], seriousness, outcome, whether it resolved or not and action taken with drug)
    f) Prior medications and concomitant medications with dates of start and end
    g) Vital signs and laboratories, sorted by date, with reference ranges *
    h) Autopsy reports for all deaths. (If an autopsy report is not available, explicitly state this.)
    i) Full reports for radiologic studies, ECG, MRI, pathology results, special studies and procedures with dates and reference ranges
    j) Provide relevant results obtained outside of clinical trial visits, including those obtained during hospitalization or emergency room visits, in each patient file. Also include baseline study results.
    k) For patients who had IND safety report(s), include dates when the initial and follow up safety reports were submitted.

   Create a PDF file for each patient and a table of contents with links to each assessment for each patient.

2. Please submit for Division comments an example narrative from a patient who had more than one serious adverse event and participated in the controlled and extension studies prior to submitting your NDA.
3. We request that you submit a sample integrated summary of safety datasets (with data definition file) for Division comments prior to submitting the NDA. This process could help to identify and resolve any potential issues of navigability or interpretability that could impact the review of your application.

Appendix B. CLINICAL PHARMACOLOGY SUMMARY AID

1. Goal

The goal of this Aid is to facilitate the creation of an optimal Clinical Pharmacology Summary that summarizes the relevant Clinical Pharmacology findings and focuses sponsor and reviewer on the critical review issues of a submission. To guide sponsors in creating the Clinical Pharmacology Summary in NDA and BLA submissions the Aid provides a generic questionnaire that covers the entire Clinical Pharmacology realm. The aggregate answers provided by sponsors generate the desired Clinical Pharmacology Summary in NDA and BLA submissions. Where needed instructions are added to the questions to clarify what the answers should address. The questions and instructions included in this guide are not intended to be either inclusive of all or exclusive of any questions that specific reviews will address. A special Section of the Clinical Pharmacology Summary should identify and discuss the critical findings and issues and indicate how the unresolved issues are addressed.

The Clinical Pharmacology Summary generated by sponsors is a **stand-alone document**, i.e. the answers to the questions including supporting evidence should be self-sufficient. Appropriate use of complementary tables and figures should be made. The sponsors' answers to the questions should be annotated with links to the detailed information in the study reports and the raw data located in SAS transport files.

2. Question Based Review

2.1 What are the *in vitro* and *in vivo* Clinical Pharmacology and Biopharmaceutics studies and the clinical studies with PK and/or PD information submitted in the NDA or BLA?

All performed Clinical Pharmacology studies (*in vitro* studies with human biomaterials and *in vivo* studies*)* and clinical studies with PK and/or PD information along with report numbers should be tabulated. Study titles, objectives, treatments (single or multiple doses, size of the dose/interval), demographics (sex, age, race/ethnicity, body weight, creatinine clearance) and numbers of study participants should be listed. Studies whose results support the label should be marked.

2.2 General Attributes of the Drug

2.2.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product?

Provide background information on the drug substance (description, chemical

name, molecular formula, molecular weight, structure), physical characteristics (Log D, solubility, pKa if applicable). Provide tabular information on the drug products, strengths, quantitative composition of ingredients and lot numbers for all formulations used in all *in vivo* studies and indicate corresponding study report numbers.

2.2.2 What are the proposed mechanism of action and therapeutic indications?

2.2.3 What are the proposed dosages and routes of administration?

2.2.4 What drugs (substances, products) indicated for the same indication are approved in the US?

2.3 General Clinical Pharmacology

2.3.1 What are the design features of the clinical pharmacology and biopharmaceutics studies and the clinical studies used to support dosing or claims?

Provide a tabular description of the designs, methodology and salient findings of the clinical pharmacology-, dose-ranging-, and pivotal studies and other clinical studies with PK and/or PD information in brief for each indication. Indicate duration of study, subjects' demographics, dose regimens, endpoints (clinical/biomarkers) and study report numbers.

2.3.2 What is the basis for selecting the response endpoints and how are they measured in clinical pharmacology studies?

Provide a rationale for the selected clinical endpoints and biomarkers. For biomarkers indicate relationship to effectiveness and safety endpoints.

2.3.3 Are the active moieties in plasma and clinically relevant tissues appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

Indicate circulating active moieties and their plasma and-tissue concentration range after therapeutic doses of the drug of interest. Provide evidence that sensitivity of the assay method(s) used is (are) sufficient to determine apparent terminal t1/2 and AUC.

2.4 Exposure-Response

2.4.1 Does the exposure-response relationship support evidence of effectiveness?

Describe briefly the method(s) used to determine the exposure-effectiveness relationship from randomized and well controlled trials (RCT) and other appropriate studies. Provide evidence that the exposure-response analysis

supports evidence of effectiveness: e.g. a significant slope in the E-R relationship or a clear separation in effectiveness at different drug levels and placebo.

Indicate whether the selected effectiveness endpoints are continuous, categorical or event driven variables. Indicate the number of pooled subjects studied and identify the trials they were enrolled in. Provide the results of the analysis of the dose- and/or concentration-effectiveness relationship. Indicate major covariates (e.g. age, body weight, sex, race/ethnicity, creatinine clearance, disease severity, genetic factors, hormonal status see also 2.6/2.7) impacting the exposure-effectiveness relationship. If not identifiable by commonly known covariates, evaluate different strategies, for example therapeutic drug monitoring, to maximize effectiveness for patients with a sub-therapeutic exposure.

Provide point estimate as well as a measure of the inter-subject variability for applicable. Indicate minimum and maximum effective dose- and concentration levels (major active moieties). Provide evidence that with the proposed regimens clinically meaningful effectiveness is maintained throughout the entire dose interval or alternatively provide evidence that maintenance of effectiveness during the entire dose interval is not important. Indicate the magnitude of the effect at peak and trough concentrations with the tested dose regimens. Indicate steady-state trough and peak plasma concentrations of the major active moieties with the proposed dose regimens. Indicate whether AUC, Cmax or Cmin is more correlated with effectiveness. Show the distribution of the effect size for each dose/concentration level tested.

Justify if an analysis of the exposure-effectiveness relationship was not done.

2.4.2 What are the characteristics of the exposure-response relationships for safety?

Describe briefly the method(s) used to determine the exposure-safety relationship. The analysis should focus on adverse events responsible for discontinuations and other drug related toxicities. Indicate whether the safety endpoints are continuous, categorical or event driven variables. Indicate the number of pooled subjects studied and identify the trials they were enrolled in. Provide the results of the analysis of the dose- and/or concentration-safety relationship. Indicate the major covariates (e.g. age, body weight, sex, race/ethnicity, creatinine clearance, disease severity, genetic factors, hormonal status) impacting the exposure-safety relationship. Provide point estimate as well as a measure of the inter-subject variability for relevant safety endpoints. Indicate magnitude and/or frequency of relevant adverse events at the tested dose/concentration levels. Indicate proportion of subjects with an excessive adverse response. Indicate whether AUC, Cmax or Cmin is more related to clinically relevant adverse effects. Add information on the maximum tolerated

single and multiple dose regimens and the corresponding plasma levels [mean (SD) Cmax and AUC] of the circulating major active moieties.

Justify if an analysis of the exposure-safety relationship was not done.

2.4.3 Does this drug prolong QT/QTc Interval?

Provide a brief description of the study design, regimens, population and data analysis used. Indicate whether plasma concentrations of the drug and the relevant metabolites and the positive control were measured. Give a rationale for the chosen supra-therapeutic dose regimen. Report the findings on the relationship between dose/concentration and QTc interval. Indicate point estimate and 95% confidence interval for the increase of the QTc- interval at the supra-therapeutic dose level. Discuss the relevance of the findings for safety. Provide support for the appropriateness of the selected supra-therapeutic dose, if applicable. Indicate whether the pharmacokinetics of the drug of interest at supra-therapeutic levels is different from that at therapeutic levels.

2.4.4 Is the dose and dosing regimen selected consistent with the known E-R relationship?

Provide information on the criteria used to select the dose regimen (doses, dose intervals) used in the RCTs. Indicate the therapeutic dose and/or concentration range for the drug and provide evidence that the proposed dose regimens are optimal given the effectiveness/safety profile of the drug.

2.5 What are the PK characteristics of the drug?

2.5.1 What are the single and multiple dose PK parameters of parent drug and relevant metabolites in healthy adults?

Briefly describe methods (two-stage and/or population approaches, compartment model dependent or-independent methods) in healthy subjects and in patients with the target disease used to determine the pharmacokinetic parameters of parent drug and relevant metabolites (pharmacologically active or impacting the exposure to parent drug or co-administered drugs). Provide mean, median (SD, CV%) pharmacokinetic parameters of parent drug and relevant metabolites after single doses and multiple doses at steady-state [Cmax, tmax, AUC, Cmax,ss, Cmin,ss, Cmax,ss/Cmin,ss, tmax,ss, AUC0-τ, CL/F, V/F and t1/2 (half-life determining accumulation factor), accumulation factor, fluctuation, time to steady-state]. Indicate how attainment of steady-state is determined. Provide evidence for attainment of steady-state.

2.5.2 How does the PK of the drug and its relevant metabolites in healthy adults compare to that in patients with the target disease?

Compare the pharmacokinetic parameters of the drug of interest and relevant metabolites in healthy subjects and patients with the target disease. Provide a

rationale for observed significant differences between healthy subjects and patients with the target disease.

2.5.3 What is the inter- and intra-subject variability of the PK parameters in volunteers and patients with the target disease?

Provide mean/median (SD, coefficient of variation, range within 5% to 95% confidence interval bracket for concentrations) about mean AUC, Cmax, Cmin, CL/F and t1/2 of the parent drug and relevant metabolites after single doses and at steady-state.

2.5.4 What are the characteristics of drug absorption?

Indicate absolute and relative bioavailability, lag time, tmax, tmax,ss, Cmax, Cmax,ss and extent of systemic absorption of parent drug and relevant metabolites in healthy subjects and patients with the target disease. Indicate mean (SD) for these parameters.

2.5.5 What are the characteristics of drug distribution?

Indicate mean (SD) V/F for the drug of interest in healthy subjects and patients with target disease. Provide mean (SD) blood/ plasma ratio for parent drug in healthy subjects. Briefly describe method and pH- and temperature conditions used for determining plasma protein binding for parent drug and relevant metabolites. Provide mean (SD) values of the plasma protein binding of the drug of interest and relevant metabolites measured over the therapeutic range in healthy subjects and patients with target disease and special populations.

2.5.6 Does the mass balance study suggest renal or hepatic as the major route of elimination?

Present total, renal and fecal recoveries as percent of the administered total radioactivity. Indicate the percentage of radioactivity excreted as unchanged parent drug in urine and feces and the percent of radioactivity excreted as metabolites in urine and feces.

2.5.7 What is the percentage of total radioactivity in plasma identified as parent drug and metabolites?

Provide identification for ≥ 90% of the circulating total radioactivity (AUC). If multiple small peaks are present whose individual radioactivity is too small to be assignable to individual metabolites provide an estimate for their contribution to circulating total radioactivity.

2.5.8 What are the characteristics of drug metabolism?

Present the metabolic scheme for the drug. Provide an estimate for the contribution of metabolism to the overall elimination of the drug of interest. Indicate mean (SD) values for the non-renal clearance in healthy subjects and patients with the target disease. Indicate whether active metabolites constitute major circulating moieties and if so how much they contribute to effectiveness

and/or whether they affect safety.

2.5.9 Is there evidence for excretion of parent drug and/or metabolites into bile?

If appropriate provide *in vitro* and/or *in vivo* evidence suggesting that parent drug and/or metabolites are excreted into bile (*in vitro*: parent drug and/or metabolites are substrates of BCRP, *in vivo*: recovery of unchanged parent drug in mass balance- and absolute bioavailability studies suggest excretion into bile)

2.5.10 Is there evidence for enterohepatic recirculation for parent and/or metabolites?

Indicate whether there are secondary peaks and humps in the plasma concentration profile correlating with food intake.

2.5.11 What are the characteristics of drug excretion in urine?

Provide an estimate of the contribution of renal excretion to the overall elimination of parent drug in healthy volunteers. Present mean values (SD) for the renal clearance (mL/min or mL/min/1.73m^2) in healthy subjects and in the target population. Using mean plasma protein binding and renal clearance values in healthy subjects estimate the respective contributions of glomerular filtration and net tubular secretion or re-absorption to renal clearance.

2.5.12 Based on PK parameters, what is the degree of the proportionality of the dose-concentration relationship?

Briefly describe the statistical methods used to determine the type of pharmacokinetics of the drug and its relevant metabolites (linearity, dose proportionality, non-linearity, time dependency) in healthy subjects and patients with the target disease. Identify the doses tested after single and multiple dose administrations of the drug of interest and the respective dose normalized mean (SD) Cmax and AUC values in healthy subjects and patients with the target disease. Indicate whether the kinetics of the drug is linear, dose proportionate or nonlinear within the therapeutic range. In case of nonlinear or time dependent pharmacokinetics provide information on the suspected mechanisms involved.

2.5.13 How do the PK parameters change with time following chronic dosing?

Indicate whether the mean ratio of AUC0-τ at steady-state to AUC after the first dose for the circulating major active moieties deviates statistically significantly from 1.0 in healthy subjects and patients with the target disease. Discuss the relevance of the findings and indicate whether an adjustment of the dose regimen is required. If the pharmacokinetics of the drug of interest changes with time provide a rationale for the underlying mechanism.

2.5.14 Is there evidence for a circadian rhythm of the PK?

Indicate whether Cmax and Cmin of the parent drug after the morning and evening dose differ significantly. Discuss the relevance of the findings and whether an adjustment of the dose regimen is required for the drug of interest. Provide a rationale for the underlying mechanism for the observed circadian rhythm of the pharmacokinetics of the drug of interest. Indicate whether the dose regimens in the pivotal studies were adjusted for circadian rhythm.

2.6 Intrinsic Factors

2.6.1 What are the major intrinsic factors responsible for the inter-subject variability in exposure (AUC, Cmax, Cmin) in patients with the target disease and how much of the variability is explained by the identified covariates?

Provide for all studies investigating the impact of the intrinsic factors (age, sex, body weight, ethnicity/race, renal and hepatic impairment) demographics and number of study subjects, and dose regimens. Provide summaries of the results and indicate intrinsic factors that impact significantly exposure and/or efficacy and safety of the drug of interest. Provide for each major identified covariate an estimate for its contribution to the inter-subject variability and indicate how much of the inter-subject variability is explained by the identified covariates.

Provide mean (SD) parameters for AUC, Cmax, clearance, volume of distribution and t1/2 for pairs studied (e.g. elderly vs. young, male vs. female, normal body weight vs. obese, race/ethnicity(x) vs. race/ethnicity (y), mild vs. severe target disease)

2.6.2 Based upon what is known about E-R relationships in the target population and their variability, what dosage regimen adjustments are recommended for each group?

Characterize the populations (age, sex, body weight, ethnicity/race) used to determine the impact of each intrinsic factor on variability in exposure and exposure-response. Indicate for each intrinsic factor whether a dose adjustment (change of dose or dose interval or both)) is required or not and provide a rationale for either scenario.

2.6.2.1 Severity of Disease State

2.6.2.2 Sex

2.6.2.3 Body Weight

2.6.2.4 Elderly

2.6.2.5 Pediatric Patients

If available provide mean (SD, range) pharmacokinetic parameters, biomarker activity, effectiveness and safety in the pediatric sub-populations (neonates (birth-1 month), infants (1 month- 2 years), children (2-12 years) and adolescents (12- < 16 years) and define the target disease. If no information is available in the pediatric population indicate age groups to be investigated in future studies. Provide a summary stating the rationale for the studies proposed and the endpoints and age groups selected. Include a hyperlink to the development plan of the drug of interest in children.

2.6.2.6 Race/Ethnicity

2.6.2.7 Renal Impairment

Characterize the demographics for each subgroup (normal renal function, mild, moderate and severe renal impairment, on and off dialysis). Indicate mean (SD, range) for creatinine clearance estimated by the Cockroft-Gaul- and MDRD equations for the stages of renal impairment investigated. Provide arithmetic mean (SD) AUC, Cmax and t1/2 of parent drug and relevant metabolites in the different sub-groups assessed by 2-stage or population PK approaches. Show regressions including 90% confidence intervals of AUC, Cmax and CL/F on Clcr for parent drug and relevant metabolites. If a population approach is used provide evidence supporting that statistical power was sufficient to determine impact of creatinine clearance.

Indicate mean (SD) for total and renal clearance of the drug in the different sub-groups and provide estimates of the contribution of glomerular filtration and net tubular secretion or re-absorption to the renal excretion of the drug of interest. Indicate whether plasma protein binding of the active moieties is significantly altered in renal impairment and whether the change in the unbound fraction is clinically relevant. Indicate whether a dose adjustment (dose or dose interval, or both) is required or not for each of the sub-groups of patients with impaired renal function and provide a rationale for either scenario.

2.6.2.8 Hepatic Impairment

Characterize the demographics for each subgroup (normal hepatic function, mild, moderate and severe hepatic impairment based on Child-Pugh scores). Provide information on arithmetic mean (SD) AUC, Cmax, tmax and t1/2 of parent drug and relevant metabolites in the different hepatic function sub-groups assessed by two-stage or population PK approaches. Show regressions including 90% confidence intervals of Cmax, AUC or CL/F on the Child-Pugh score for parent drug and relevant metabolites. Indicate whether plasma protein binding of the active moieties is significantly altered in hepatic impairment and whether the change in the unbound fraction is clinically relevant. Indicate whether a dose adjustment is required or not for each of the subgroups of patients with impaired hepatic function and provide a rationale for either scenario. If a population approach is used provide evidence supporting

that statistical power was sufficient to determine impact of Child-Pugh score.

2.6.2.9 What pregnancy and lactation use information is available?

2.6.3 Does genetic variation impact exposure and/or response?
Describe the studies in which DNA samples have been collected. If no DNA samples were collected state so. Include a table with links to the studies in which DNA was analyzed and genomic/genetic information is reported. In the description of these studies include demographics, purpose of DNA analysis (effectiveness, safety, drug metabolism, rule in-out of patients, etc.), rationale for the analysis, procedures for bio-specimen sample collection and DNA isolation, genotyping methods, genotyping results in individual subjects, statistical procedures, genotype-phenotype association analysis and results, interpretation of results, conclusions. If genomic polymorphism impacts either exposure and/or response indicate the measures to be taken to safeguard efficacy and safety of the drug in subjects with varying genotypes. Indicate the contribution of genetic factors to inter-subject variability.

2.6.4 Immunogenicity (NOT applicable to small molecule drugs)

2.6.4.1 What is the incidence (rate) of the formation of the anti-product antibodies (APA), including the rate of pre-existing antibodies, the rate of APA formation during and after the treatment, time profiles and adequacy of the sampling schedule?

2.6.4.2 Does the immunogenicity affect the PK and/or PD of the therapeutic protein?

2.6.4.3 Do the anti-product antibodies have neutralizing activity?

2.6.4.4 What is the impact of anti-product antibodies on clinical efficacy?

2.6.4.5 What is the impact of anti-product antibodies on clinical safety?
Provide information on the incidence of infusion-related reactions, hypersensitivity reactions, and cross-reactivity to endogenous counterparts.

2.7 Extrinsic Factors

2.7.1 Is there an in vitro basis to suspect in vivo drug-drug interactions?
Summarize the results of the in vitro studies performed with the drug of interest as substrate, inhibitor or inducer of relevant CYP and non-CYP enzymes and transporters. Give rationale for why based on the *in vitro* results an interaction study in humans is required or is not required

2.7.2 Is the drug a substrate of CYP enzymes?

Briefly describe the methods used (specific chemicals/antibodies, human recombinant CYP enzymes, human microsomes). Indicate incubate, initial rate conditions, concentration range tested relative to Km, controls etc. Provide a summary of the results of the *in vitro* studies investigating the drug of interest as a substrate of CYP 450 and non-CYP 450 enzymes. Provide for each of the relevant enzymes a mean estimate for the % contribution to the metabolism of the drug of interest. Discuss the relevance of the in vitro findings for the drug of interest as a substrate for deciding which drug-drug interactions should be or need not be performed in humans. For each situation provide supporting evidence.

2.7.3 Is the drug an inhibitor and/or an inducer of enzymes?

Briefly describe the methods used (type and source of liver tissue, concentration range tested for the drug of interest as substrate, inhibitor and inducer, experimental conditions, pre-incubation, probe substrates, positive/negative controls. Provide summary results of the *in vitro* studies with human liver tissues for the drug of interest as a potential inhibitor or inducer of enzymes. Indicate whether the drug is a reversible inhibitor (competitive, non-competitive or un-competitive) or an irreversible inhibitor (mechanism based) and supportive evidence. Provide mean (SD) values for Ki, IC_{50} and Vmax for each relevant enzyme and probe substrate. Indicate the anticipated maximum total and unbound concentration of the drug of interest as inhibitor ([I]). Provide the mean (SD) % activity relative to the positive control for the drug of interest as inducer. Discuss the relevance of the *in vitro* findings for the drug of interest as an inhibitor or inducer for deciding which drug-drug interactions should be or need not be performed *in vivo* in humans. If appropriate use the [I]/Ki ratio as a means to assess the likelihood of an *in vitro* result to be clinically relevant. For each situation provide supporting evidence.

2.7.4 Is the drug a substrate, an inhibitor and/or an inducer of transporter processes?

See 2.7.2.2 and 2.7.2.3. The instructions for the interactions of the drug of interest as substrate, inhibitor or inducer of transporters are analogous to those for enzymes.

2.7.5 Are there other metabolic/transporter pathways that may be important?

2.7.6 What extrinsic factors influence exposure and/or response, and what is the impact of any differences in exposure on effectiveness or safety responses?

Indicate extrinsic factors that impact significantly exposure and/or effectiveness and safety of the drug. Indicate extent of increase or decrease in exposure and/or response caused by extrinsic factors. State whether an adjustment of the dose is or is not required and provide supporting evidence for either case.

2.7.7 What are the drug-drug interactions?

Provide a list of the drug-drug interaction studies (PK or PD based mechanism) performed and give a rationale for conducting the listed studies. Indicate the suspected mechanism responsible for the interaction. For each of the *in vivo* studies performed provide a rationale for the design selected (single or multiple dose regimens, randomized/non-randomized cross-over or parallel design for perpetrator and/or victim).

a) Drug of interest is impacted by co-administered other drugs

Provide information on the demographics of populations, number of subjects, dose levels, and design of the studies performed in humans. Justify the magnitude of the equivalence interval selected if it is greater than the default interval. Report t1/2, point estimates and 90% confidence intervals of the geometric mean ratios of AUC and Cmax for the drug of interest in the presence and absence of each of the co-administered drugs. Provide a summary statement on the drug interaction liability of the drugs as victim. Indicate whether a dose adjustment is required or not. In either case provide a rationale. Define the required adjusted dose regimens.

b) Drug of interest impacts other co-administered drugs

Provide information on the demographics of populations, number of subjects, dose levels, and design of the studies performed in humans. Justify the magnitude of the equivalence interval selected if it is greater than the default interval. Provide a summary statement on the drug interaction liability of the drug as a perpetrator. Report t1/2, point estimates and 90% confidence intervals of the geometric mean ratios of AUC and Cmax for each of the co-administered drugs in the presence and absence of the drug of interest.

2.7.8 Does the label specify co-administration of another drug?

2.7.9 What other co-medications are likely to be administered to the target population?

2.7.10 Is there a known mechanistic basis for pharmacodynamic drug-drug interactions?

2.8 General Biopharmaceutics

For all *in vivo* studies performed in this section indicate study design, demographics and number of subjects enrolled, and type, composition, strength and lot number of the formulations used. Provide summary results with estimates for mean and inter-subject variability on AUC and Cmax after single and multiple dose administration and peak to trough fluctuation after

multiple dose administration.

IR Product

2.8.1 Based on the biopharmaceutic classification system principles, in what class is this drug and formulation? What solubility, permeability and dissolution data support this classification?

2.8.2 How is the proposed to-be-marketed formulation linked to the clinical service formulation?

2.8.2.1 What are the safety or effectiveness issues, if any, for BE studies that fail to meet the 90% CI using equivalence limits of 80-125%?

2.8.2.2 If the formulation does not meet the standard criteria for bioequivalence, what clinical pharmacology and/or safety and efficacy data support the approval of the to-be-marketed product?

2.8.3 What is the effect of food on the bioavailability of the drug when administered as solution or as drug product?
Indicate composition and calories of the food administered, and length of the pre-dose fasting period. State whether the impact of food is on the drug substance or the inactive ingredients of the formulation. Indicate the clinical relevance of findings. Indicate the temporal relationship between drug intake and food intake in the pivotal studies.

2.8.4 Was the bioequivalence of the different strengths of the to be marketed formulation tested? If so were the strengths bioequivalent or not?

2.8.5 If unapproved products or altered approved products were used as active controls, how is BE to the to be marketed product demonstrated? What is the link between the unapproved/altered and to be marketed products?

MR product (if an IR is already marketed)

2.8.6 What is the bioavailability of the MR product relative to the approved IR product? How does the plasma concentration time profile of the MR formulation compare to that of the IR formulation after single and multiple doses?
Indicate whether or not the pharmacokinetics of the drug of interest is linear, dose proportional or nonlinear after administration of the MR formulation. Summarize data on Cmax, AUC and Cmin of the IR and MR formulations after a single dose and multiple doses at steady-state. Provide information on the fluctuation factor at steady-state.

2.8.7 What is evidence that MR formulation *in vivo* consistently shows claimed MR characteristics?

2.8.8 What is evidence that MR formulation displays less variability in Cmax, AUC and Cmin than IR formulation?

2.8.9 Does the MR product show dose dumping *in vivo*?
Describe design, demographics and number of subjects participating in the studies performed to determine whether dose dumping occurs with the MR formulation when given in the fed state or when given together with alcohol. Present summaries of results.

2.8.10 Does ethanol *in vitro* have a dose-dumping effect on the MR product?
Provide the results of the *in vitro* dissolution testing of the various strengths of the ER product in pH 1.2, 4.5 and 6.8 media containing 0, 5, 10, 20 and 40% alcohol. Discuss any dose dumping observed. If an *in vivo* study was performed report the clinical relevance of the findings.

2.8.11 Are the MR and IR products marketed simultaneously?
If the intention is to market both the MR and IR products, indicate how patients are converted from the IR to the MR product and vice versa.

2.8.12 If the NDA is for an MR formulation of an approved IR product without supportive safety and effectiveness studies, what dosing regimen changes are necessary, if any, in the presence or absence of a PKPD relationship?

2.8.13 In the absence of effectiveness and safety data what data support the NDA for a MR formulation of an approved IR product?

2.9 Analytical Section

2.9.1 How are parent drug and relevant metabolites identified and what are the analytical methods used to measure them in plasma and other matrices?
List all assays used and briefly describe the individual methods.

2.9.2 Which metabolites have been selected for analysis and why?

2.9.3 For all moieties measured, is free, bound, or total measured?
Indicate whether free, bound or total (bound+unbound) concentrations of the drug of interest and relevant metabolites are measured and give a rationale for your selection.

2.9.4 What bioanalytical methods are used to assess concentrations of the

measured moieties?
Identify all studies that used a particular assay method. For each assay report indicate the corresponding assay validation report.

2.9.5 What is the range of the standard curve? How does it relate to the requirements for clinical studies? What curve fitting techniques were used?
For each method and analyte provide concentration range of calibration curve and indicate respective concentration range for relevant moieties with therapeutic regimens. Indicate fit type of the calibration curves.

2.9.5.1 What are the lower and upper limits of quantitation?
For each method and analyte indicate LLOD, LLOQ and ULOQ for undiluted and diluted samples.

2.9.5.2 What are the accuracy, precision, and selectivity at these limits?
For each method and analyte indicate inter-day and intra-day precision (CV%) and inter-day and intra-day accuracy (RE%).

2.9.5.3 What is the sample stability under conditions used in the study?
For all studies in which concentrations of the drug of interest and relevant metabolites were measured provide information on initiation date of study, date of last sample analyzed and total sample storage time. For each method and matrix provide information on the stability of the analytes, i.e. number of freeze-thaw cycles, benchtop stability at room temperature and stability during long term storage at ≤ –20° C.

2.9.5.4 What is the plan for the QC samples and for the reanalysis of the incurred samples?
For each study, method and analyte indicate precision (CV%) and accuracy (%RE) using the QC samples measured alongside samples with unknown concentrations. Indicate the concentrations of the QC and incurred samples used.

2.9.5.5 What evidence is available demonstrating that neither the assay of the drug on interest is impacted by co-administered other drugs and vice versa?

Applicable to therapeutic proteins only

2.9.5.6 What bioanalytical methods are used to assess therapeutic protein concentrations?
Briefly describe the methods and summarize the assay performance.

2.9.5.7 What bioanalytical methods are used to assess the formation of the anti-

product antibodies?
Briefly describe the methods and assay performance including sensitivity, specificity, precision, cut point, interference and matrix, etc.

2.9.5.8 What is the performance of the neutralizing assay(s)?

4.0 ISSUES REQUIRING FURTHER DISCUSSION

There were no issues identified requiring further discussion.

5.0 ACTION ITEMS

There were no action items identified during the meeting.

6.0 ATTACHMENTS AND HANDOUTS

See attached.

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

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

/s/

ERIC P BASTINGS
04/13/2021 04:34:00 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

PIND 139086

MEETING MINUTES

Alnylam Pharmaceuticals, Inc.
Attention: Andrew Slugg
Vice President, Regulatory Affairs
300 Third Street
Cambridge, MA 02142

Dear Mr. Slugg:

Please refer to your Pre-Investigational New Drug Application (PIND) file for ALN-TTRSC-02.

We also refer to the meeting between representatives of your firm and the FDA on July 17, 2018. The purpose of the meeting was to discuss your development program for ALN-TTRSC02.

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, contact Fannie Choy, Regulatory Project Manager, at (301) 796-2899 or fannie.choy@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Eric Bastings, M.D.
Deputy Director
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type:	B
Meeting Category:	End of Phase 2
Meeting Date and Time:	July 17, 2018, 11:00 a.m. – 12:00 p.m.
Meeting Location:	White Oak Building 22, Conference Room: 1315
Application Number:	PIND 139086
Product Name:	ALN-TTRSC02
Proposed Indication:	Treatment of hereditary transthyretin (hATTR) amyloidosis
Sponsor Name:	Alnylam Pharmaceuticals, Inc.
Meeting Chair:	Billy Dunn, M.D.
Meeting Recorder:	Fannie Choy, R.Ph.

FDA ATTENDEES

Office of Drug Evaluation I
Ellis Unger, MD, Director

Division of Neurology Products
Billy Dunn, MD, Director
Eric Bastings, MD, Deputy Director
Nick Kozauer, MD, Associate Director
Teresa Buracchio, MD, Clinical Team Leader
Rainer Paine, MD, PhD, Clinical Reviewer
Fannie Choy, RPh, Regulatory Project Manager

Office of Clinical Pharmacology
Kevin Krudys, PhD, Pharmacometrics Team Leader
Priya Brunsdon, PhD, Clinical Pharmacology Reviewer

Division of Cardiovascular and Renal Products
Preston Dunnmon, MD, MBA, Medical Officer
Karen Hicks, MD, Medical Team Leader (Acting)

Office of Biostatistics
Xiang Ling, PhD, Statistical Reviewer, DBI

Rare Diseases Program
Melanie Banks, MD, Medical Officer
Sandra Retzky, MD, Medical Officer

SPONSOR ATTENDEES

Alnylam Pharmaceuticals, Inc.
Andrew P. Slugg, MS, MBA, Vice President, Regulatory Affairs
Amjid Iqbal, Associate Director, Regulatory Affairs
Bahru Habtemariam, PharmD, Director, Clinical Pharmacology
Jihong Chen, PhD, Director, Biostatistics
John Vest, MD, Senior Director, Clinical Research
Pushkal Garg, MD, Chief Medical Officer, Clinical Research
Rena Denoncourt, MBA, Director, Program Lead
Richard Riese, MD, PhD, Vice President, Clinical Research
Sara Nochur, PhD, Chief Regulatory Officer

(b) (4) (via teleconference)

1.0 BACKGROUND

Alnylam Pharmaceuticals, Inc., (Alnylam) is developing ALN-TTRSC02 for the treatment of hereditary transthyretin (hATTR) amyloidosis. The sponsor states that ALN-TTRSC-02 is a synthetic ribonucleic acid interference (RNAi) for subcutaneous administration.

The sponsor has requested this meeting is to obtain the Division's feedback on its proposed development program for ALN-TTRSC02 and the adequacy of the proposed data package to support the submission of a New Drug Application.

Alnylam has completed a Phase 1, randomized, single-blind, placebo-controlled, single-ascending dose study (ALN-TTRSC02-001) in healthy subjects. The focus of this meeting is to discuss its planned study ALN-TTRSC02-002, titled "A Phase 3 Global, Open-label Study to Evaluate the Efficacy and Safety of ALN-TTRSC02 in Patients with Hereditary Transthyretin Amyloidosis (hATTR Amyloidosis)."

FDA sent Preliminary Comments to the sponsor on July 12, 2018.

2. DISCUSSION

2.1. Nonclinical

Question 1a:

Does the Agency agree that the completed and planned nonclinical studies are adequate to support the submission and review of an NDA for ALN-TTRSC02 as a treatment of hATTR amyloidosis in adults?

FDA Response to Question 1a:

Based on the information provided in the briefing document, the completed and planned nonclinical studies appear sufficient to support an NDA; however, the adequacy of your studies and the need for any additional nonclinical studies will be a matter of review.

Meeting Discussion: There was no meeting discussion.

Question 1b:

ALN-TTRSC02 specifically targets TTR mRNA. Based on existing data with ALN-TTRSC02, and absence of findings from other siRNA drug candidates that target TTR, the intended mechanism of action does not raise a cause for concern regarding carcinogenic potential. A 6-month carcinogenicity study in TgRAsH2 mice is planned and data will be available to be included in the NDA. Does the agency agree that submission of data from the 2-year rat carcinogenicity study can be deferred until after marketing approval of ALN-TTRSC02 is granted?

FDA Response to Question 1b:

Because of the seriousness of the indication, your proposal to conduct a 2-year carcinogenicity study in rat post approval is acceptable, provided the available data support such a strategy.

Meeting Discussion: There was no meeting discussion.

2.2. Clinical Pharmacology

Question 2a:

Based on the physiochemical properties of ALN-TTRSC02, as well as the nonclinical and clinical data to date, the Sponsor proposes not to conduct a thorough QT/QTc study and proposes routine electrocardiogram (ECG) monitoring in the Phase 3 clinical study in patients with hATTR amyloidosis. Does the agency agree?

FDA Response to Question 2a:

Study ALN-TTRSC02-001 appears to be adequate to characterize the potential for your drug to prolong the QTc and can potentially serve as an alternative to the TQT study. Whether these data exclude a 10-ms mean QTc effect at the highest clinical relevant exposure will be a review issue when the data are submitted.

1. When you submit your QT study report, please include the following items:

    a. Study report(s) for any other clinical studies of the effect of product administration on the QT interval that have been performed
    b. Study report
    c. Statistical analysis plan
    d. Clinical study protocol
    e. Investigator's Brochure
    f. A completed Highlights of Clinical Pharmacology and Cardiac Safety Table
    g. Annotated CRF
    h. A data definition file which describes the contents of the electronic data sets
    i. Electronic data sets as SAS.xpt transport files (in CDISC SDTM and ADAM format – if possible) and all the SAS codes used for the primary statistical and exposure-response analyses. Please make sure that the ECG raw data set includes at least the following: Subject ID, treatment, period, ECG date, ECG time (down to second), nominal day, nominal time, replicate number, heart rate, intervals QT, RR, PR, QRS and QTc (including any corrected QT, e.g., QTcB, QTcF, QTcN, QTcI, along with the correction factors for QTcN and QTcI), Lead, and ECG ID (link to waveform files, if applicable).
    j. Data set whose QT/QTc values are the average of the above replicates at each nominal time point
    k. Narrative summaries and case report forms for any
        i. Deaths
        ii. Serious adverse events
        iii. Episodes of ventricular tachycardia or fibrillation
        iv. Episodes of syncope
        v. Episodes of seizure
        vi. Adverse events resulting in the subject discontinuing from the study

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

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

Meeting Discussion: There was no meeting discussion.

Question 2b:

Based on the physiochemical properties of ALN-TTRSC02 and available data from ALN-TTRSC02 as well as nonclinical data from multiple products from the same siRNA-conjugate platform, the Sponsor proposes not to conduct further in vitro or in vivo drug interaction (DDI) studies. Does the Agency Agree?

FDA Response to Question 2b:

We agree that it is not necessary to conduct further in vitro or in vivo DDI studies.

Meeting Discussion: There was no meeting discussion.

Question 2c:

The Sponsor considers that available non-clinical absorption, distribution, metabolism and excretion (ADME) data and clinical plasma and urine pharmacokinetic (PK) data with ALN-TTRSC02 are adequate to characterize the fate of ALN-TTRSC02 and proposes not to conduct a radiolabeled human ADME study. Does the Agency agree?

FDA Response to Question 2c:

The proposal seems reasonable.

Meeting Discussion: There was no meeting discussion.

Question 2d:

The planned Phase 3 study will allow enrolment of patients with mild hepatic impairment and the influence of hepatic impairment on the pharmacokinetic (PK), pharmacodynamic (PD), and safety properties of ALN-TTRSC02 will be evaluated using a population PK/PD approach. Does the Agency agree?

FDA Response to Question 2d:

Based on the information provided in the meeting package, ALN-TTRSC02 may not be significantly impacted by organ function impairment. Therefore, we encourage you to allow enrollment of patients with moderate hepatic impairment in your proposed study. Utilizing a population PK/PD approach for the Phase 3 study to evaluate the impact of intrinsic/extrinsic factors on efficacy/safety seems reasonable. The adequacy of the data to support labeling will be a matter of review.

Meeting Discussion: There was no meeting discussion.

Question 2e:

The planned Phase 3 study will allow enrolment of patients with mild and moderate renal impairment and the influence of renal impairment on the PK, PD, and safety properties of ALN-TTRSC02 will be evaluated using population PK/PD approach. Does the Agency agree?

FDA Response to Question 2e:

The inclusion of patients with mild and moderate renal impairment and evaluation using a population PK/PD approach appears reasonable. The adequacy of the data to support labeling will be a matter of review.

Meeting Discussion: There was no meeting discussion.

2.3. Clinical

Question 3:

Does the Agency agree that results from Phase 1 study (ALN-TTRSC02-001) as well as pharmacokinetic/ pharmacodynamic analyses support the proposed ALN-TTRSC02 regimen of 25 mg quarterly for Phase 3 evaluation in Study ALN-TTRSC02-002?

FDA Response to Question 3:

We note that you are targeting a roughly 80% reduction in TTR, similar to what was observed in clinical trials with patisiran. However, your rationale for selecting the proposed dosing regimen and not evaluating other dosing regimens that may potentially lead to greater reductions in TTR is unclear. We recommend evaluating additional dosing regimens in Study ALN-TTRSC02-002 to allow for appropriate dose-response relationships to be evaluated. You should comment on your rationale for not evaluating additional doses or dosing intervals in your Phase 3 program.

Meeting Discussion: There was no meeting discussion.

Question 4a:

Does the Agency agree with the proposed study design for the single arm Phase 3 study ALN-TTRSC02-002 in patients with hATTR amyloidosis, in particular with regard to external control, the inclusion criteria for selection of the patient population, and study duration?

FDA Response to Question 4a:

We are willing to consider the use of an external control in your Phase 3 study for the evaluation of the effects of ALN-TTRSC02 on neuropathy in hereditary transthyretin-mediated amyloidosis (hATTR-PN). If there are approved therapies for hATTR-PN at the time that your study is

initiated, we strongly encourage you to include a concurrent active comparator to understand if ALN-TTRSC02 provides comparable benefit to available therapies.

(b) (4)

Although we understand your rationale based on benefit observed with patisiran after 9 months of treatment, the time required to demonstrate the benefit you expect to observe with ALN-TTRSC02 may be different than with patisiran. Therefore, we encourage you to conduct an 18 month study with an interim efficacy analysis at 9 months.

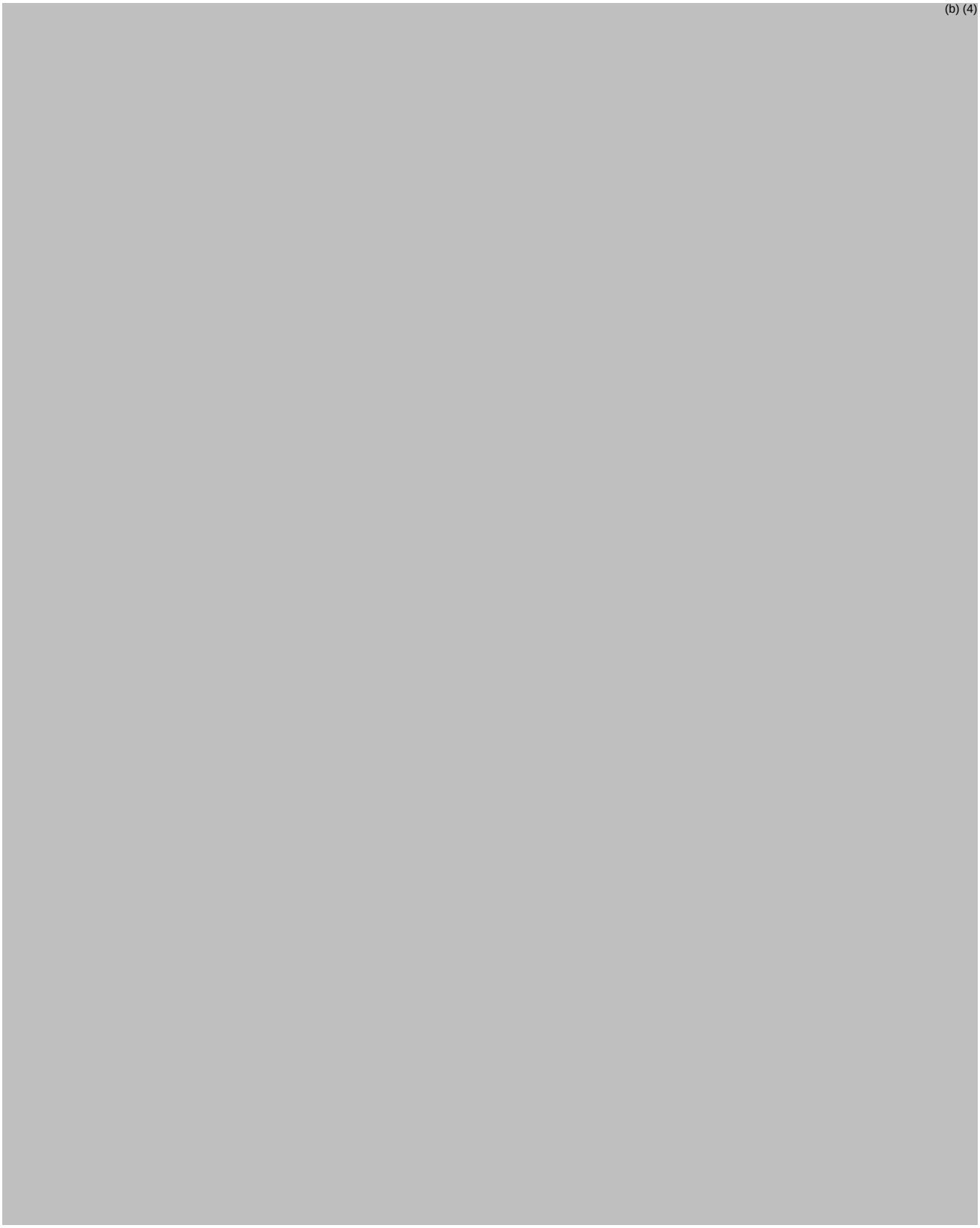
The inclusion criteria appear to be acceptable, on face. We note that there appears to be an error in Table 9 of the briefing document, which lists an inclusion criterion for ALN-TTRSC02 of "eGFR $\leq$30 mL/min/1.73m^2." Such subjects would have probable renal disease and should be excluded, as correctly stated in the submitted protocol concept sheet.

We also refer you to our response to Question 3 regarding the dosing regimen.

Meeting Discussion:

The sponsor presented a proposal for a revised Phase 3 trial design that included an active control group with patisiran. The study design maintained the co-primary endpoints of TTR reduction (evaluating non-inferiority to patisiran-LNP) and mNIS+7 (evaluating superiority to placebo from the patisiran-LNP Phase 3 APOLLO study), with a primary efficacy analysis after 9 months of treatment. The Division noted the importance of TTR reduction based on the mechanism of the drug, but indicated that clinical outcomes should be assessed as the primary endpoints for the study. The Division stated that TTR reduction would be most appropriate as a secondary endpoint, with adjustment for multiplicity. The Division strongly recommended the use of the Norfolk-QOL-DN and mNIS+7 as co-primary endpoints. The Division stated that it was open to the use of the placebo arm of the APOLLO study as an external control, with the expectation that there would be a large magnitude of effect with ALN-TTRSC02, comparable to the treatment effects that have been observed with patisiran. The Division clarified that the recommendation for the use of an active comparator was intended to provide a descriptive assessment of comparative efficacy and safety to patisiran, which would be important for future risk-benefit comparisons. An active comparator would also help deal with the subjectivity of some endpoint assessments. No formal statistical testing for the active comparator would be required.

(b) (4)



Question 4b:

Does the Agency agree with the selected co-primary and other key endpoints as proposed for the Phase 3 Study ALN-TTRSC02-002?

FDA Response to Question 4b:

The primary endpoint, mNIS+7, is composed of a clinical exam-based neuropathy impairment score (NIS) combined with electrophysiologic measures of small and large nerve fiber function (+7) such as nerve conduction studies (NCS), quantitative sensory testing (QST), and measurement of autonomic function (postural blood pressure). Many of the individual components of the score, such as nerve conduction studies, are biomarkers that do not, of themselves, represent direct clinical benefit. Other components of the score, such as motor and sensory function by neurological exam, also are not direct measures of clinical benefit, as differences detected by the physician might not be perceptible to the patient or result in improved function in daily activities. We recommend that you designate as co-primary endpoints mNIS+7 and Norfolk QOL-DN (or another clinically meaningful endpoint).

The TTR biomarker percent reduction would be appropriate as a secondary endpoint.

The statistical analysis plan should include an approach for control of the family-wise error rate for the co-primary endpoints and key secondary endpoints that are intended for inclusion in labeling.

For the derivation of the percent TTR reduction, explain why the steady-state periods are different for the two groups, i.e., between Months 6 to 9 for ALN-TTRSC02 group and Months 4 to 9 for patisiran-LNP group. The percent reduction of TTR between Months 6 to 9 may not be comparable to the percent reduction of TTR between Months 4 to 9.

Please discuss the subjectivity of the assessments of mNIS+7 and Norfolk QOL-DN (or other clinically meaningful endpoints) and the potential impact on the assessment with the knowledge that all patients will receive active treatment in an open-label trial.

Also, see response to Question 4a.

Meeting Discussion:
See meeting discussion under Question 4a.

Question 4c:

Does the agency agree with statistical considerations and sample size as proposed for Phase 3 Study ALN-TTRSC02-002?

FDA Response to Question 4c:

See response to Question 4a. We recommend that the analysis of TTR percent reduction adjusts for baseline values and key prognostic factors.

Meeting Discussion: There was no meeting discussion.

Question 5a:

Provided that the Phase 3 study as outlined in Question 4 meets its primary endpoints and the benefit/risk is positive in the target population, does the Agency agree that the clinical data package is adequate to support approval of ALN-TTRSC02 for the treatment of patients with hATTR amyloidosis?

FDA Response to Question 5a:

The acceptability of future studies to support drug approval depends on the study results, and cannot be determined prospectively.

Meeting Discussion: There was no meeting discussion.

Question 5b:

Does the Agency agree that co-primary efficacy endpoint data for ALN-TTRSC02 from the Phase 3 study ALN-TTRSC02-002 may be presented alongside external control data from the patisiran-LNP APOLLO study in the USPI at the time of the NDA?

FDA Response to Question 5b:

In general, the prescribing information would describe the results of the studies that are used to support approval. A discussion of the specific wording for inclusion in any eventual labeling is premature and would be a matter of review.

See the responses to Questions 4a and 4b.

Meeting Discussion: There was no meeting discussion.

Question 5c:

(b) (4)

FDA Response to Question 5c:

(b) (4)

Meeting Discussion: There was no meeting discussion.

Additional Comment (CMC)

You indicate in the briefing package that you received FDA's acceptance on the designation of GMP starting materials via an FDA Type B CMC meeting for (b) (4). Please note that the (b) (4). However, we remind you that you should provide the fate and purge data of all the impurities arising from (b) (4) to support designation of (b) (4) as a starting material.

Meeting Discussion: There was no meeting discussion.

3.0 ADDITIONAL COMMENTS

PROSPECTIVE ASSESSMENTS OF SUICIDAL IDEATION AND BEHAVIOR IN CLINICAL PROTOCOLS

Treatment-emergent suicidal ideation and behavior have been identified as a concern for a number of drugs and drug classes. For example, meta-analyses of clinical trial data for both antiepileptic drugs and antidepressants have demonstrated that these drugs increase the risk of suicidal ideation and behavior. Spontaneous reports have led to similar concerns with other drugs as well, e.g., isotretinoin and other tretinoins, beta blockers, reserpine, smoking cessation drugs, and drugs for weight loss. Because of these concerns, a prospective assessment for suicidal ideation and behavior should be included, when appropriate and feasible, in clinical trials involving all drugs and biological products for neurological indications. These assessments should generally be included in every clinical protocol, at every visit, and in every phase of development, with the exception of single-dose trials in healthy volunteers. These assessments should be conducted whether or not a particular product is known or suspected to be associated with treatment-emergent suicidal ideation and behavior. A sponsor considering the omission of the assessment of suicidal ideation and behavior from a particular clinical protocol should prospectively discuss this omission with the Division of Neurology Products.

PREA REQUIREMENTS

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

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End-of-Phase-2 (EOP2) meeting. In the absence of an EOP2 meeting, refer to the draft guidance below. The iPSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The iPSP should be submitted in PDF and Word format. Failure to include an Agreed iPSP with a marketing application could result in a refuse to file action.

For additional guidance on the timing, content, and submission of the iPSP, including an iPSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf. In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email Pedsdrugs@fda.hhs.gov. For further guidance on pediatric product development, please refer to: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm.

DATA STANDARDS FOR STUDIES

Under section 745A(a) of the FD&C Act, electronic submissions "shall be submitted in such electronic format as specified by [FDA]." FDA has determined that study data contained in electronic submissions (i.e., NDAs, BLAs, ANDAs and INDs) must be in a format that the Agency can process, review, and archive. Currently, the Agency can process, review, and archive electronic submissions of clinical and nonclinical study data that use the standards specified in the Data Standards Catalog (Catalog) (See http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm).

On December 17, 2014, FDA issued final guidance, *Providing Electronic Submissions in Electronic Format--- Standardized Study Data* (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292334.pdf). This guidance describes the submission types, the standardized study data requirements, and when standardized study data will be required. Further, it describes the

availability of implementation support in the form of a technical specifications document, Study Data Technical Conformance Guide (Conformance Guide) (See http://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM384744.pdf), as well as email access to the eData Team (cder-edata@fda.hhs.gov) for specific questions related to study data standards. Standardized study data will be required in marketing application submissions for clinical and nonclinical studies that start on or after December 17, 2016. Standardized study data will be required in commercial IND application submissions for clinical and nonclinical studies that start on or after December 17, 2017. CDER has produced a *Study Data Standards Resources* web page that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers.

Although the submission of study data in conformance to the standards listed in the FDA Data Standards Catalog will not be required in studies that start before December 17, 2016, CDER strongly encourages IND sponsors to use the FDA supported data standards for the submission of IND applications and marketing applications. The implementation of data standards should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. For clinical and nonclinical studies, IND sponsors should include a plan (e.g., in the IND) describing the submission of standardized study data to FDA. This study data standardization plan (see the Conformance Guide) will assist FDA in identifying potential data standardization issues early in the development program.

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

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

LABORATORY TEST UNITS FOR CLINICAL TRIALS

CDER strongly encourages IND sponsors to identify the laboratory test units that will be reported in clinical trials that support applications for investigational new drugs and product registration. Although Système International (SI) units may be the standard reporting mechanism globally, dual reporting of a reasonable subset of laboratory tests in U.S. conventional units and SI units might be necessary to minimize conversion needs during review. Identification of units to be used for laboratory tests in clinical trials and solicitation of input

from the review divisions should occur as early as possible in the development process. For more information, please see the FDA website entitled, Study Data Standards Resources and the CDER/CBER Position on Use of SI Units for Lab Tests website found at https://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM587505.pdf.

SUBMISSION FORMAT REQUIREMENTS

The Electronic Common Technical Document (eCTD) is CDER and CBER's standard format for electronic regulatory submissions. The following submission types: **NDA, ANDA, BLA, Master File** (except Type III) and **Commercial INDs** must be submitted in eCTD format. 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.

The FDA Electronic Submissions Gateway (ESG) is the central transmission point for sending information electronically to the FDA and enables the secure submission of regulatory information for review. Submissions less than 10 GB must be submitted via the ESG. For submissions that are greater than 10 GB, refer to the FDA technical specification *Specification for Transmitting Electronic Submissions using eCTD Specifications*. For additional information, see http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway.

SECURE EMAIL COMMUNICATIONS

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

ABUSE POTENTIAL ASSESSMENT

Drugs that affect the central nervous system, are chemically or pharmacologically similar to other drugs with known abuse potential, or produce psychoactive effects such as mood or cognitive changes (e.g., euphoria, hallucinations) need to be evaluated for their abuse potential and a proposal for scheduling will be required at the time of the NDA submission [21 CFR 314.50(d)(5)(vii)]. For information on the abuse potential evaluation and information required at the time of your NDA submission, see the Guidance for Industry, *Assessment of Abuse Potential of Drugs*, available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM198650.pdf.

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.

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

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

Please refer to the draft Guidance for Industry Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions (February 2018) and the associated Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications:

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

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

4.0 ISSUES REQUIRING FURTHER DISCUSSION

There were no issues requiring further discussion.

5.0 ACTION ITEMS

There were no action items identified during the meeting.

6.0 ATTACHMENTS AND HANDOUT

Alnylam submitted slides titled, "PIND 139086 ALN-TTRSC02 | Type B EOP2 Meeting | 17 July 2018."

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

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

/s/

ERIC P BASTINGS
08/10/2018