APPLICATION NUMBER: 210922Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS
DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 210922

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 New Drug Application (NDA) proposed for submission under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Onpattro (patisiran) injection.

We also refer to the meeting between representatives of your firm and the FDA on November 13, 2017. The purpose of the meeting was to discuss the content and format of a planned NDA for patisiran for the treatment of adult patients with hereditary transthyretin-mediated amyloidosis with polyneuropathy.

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 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
Deputy Director
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes
MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: Pre-NDA

Meeting Date and Time: November 13, 2017
Meeting Location: White Oak Building 22, Room 1309

Application Number: NDA 210922
Product Name: Onpattro (patisiran)
Indication: Treatment of adult patients with hereditary transthyretin-mediated amyloidosis with polyneuropathy
Sponsor/Applicant Name: Alnylam Pharmaceuticals, Inc.

FDA ATTENDEES

Office of Drug Evaluation I
Robert Temple, MD, Deputy Director
Naomi Lowy, MD, Associate Director for Regulatory Science

Division of Neurology Products
Billy Dunn, MD, Director
Eric Bastings, MD, Deputy Director
Nick Kozauer, MD, Clinical Team Leader
Rainer Paine, MD, PhD, Clinical Reviewer
David Hawver, PhD, Nonclinical Reviewer
Heather Bullock, RN, Regulatory Project Manager
Annie Nguyen, RPh, Regulatory Project Manager

Office of Product Quality
Mariappan Chelliah, PhD, Chemistry Reviewer
Martha Heimann, PhD, CMC Lead for Neurology Products
Wendy Wilson-Lee, PhD, Branch Chief
Dahlia Woody, MS, PMP, Regulatory Business Process Manager

Office of Clinical Pharmacology
Bilal AbuAsal, PhD, Clinical Pharmacology Reviewer

Reference ID: 4192902
SPONSOR ATTENDEES

Alnylam Pharmaceuticals

Andrew Slugg, MS, MBA, Vice President, Regulatory Affairs
Holly Maier, PhD, Associate Director, Regulatory Affairs
Saraswathy (Sara) Nochur, PhD, Senior Vice President, Regulatory Affairs
Jared Gollob, MD, Vice President, Clinical Development
Pushkal Garg, MD, Chief Medical Officer, Senior Vice President, Clinical Development
Sunita Goyal, MD, Senior Director, Clinical Development
Jihong Chen, PhD, Director, Biostatistics
Andrew Strahs, PhD, Senior Director, Biometrics
Marianne Sweetser, MD, PhD, Senior Director, Global Patient Safety & Risk Management
Akshay Vaishnaw, Executive Vice President, Research & Development
John Berk, MD, Associate Professor of Medicine, Boston University Associate Clinical Director, Amyloid Treatment and Research Program
Scott Solomon, MD, Professor of Medicine, Harvard Medical School Director Cardiac Imaging Core Laboratory and the Clinical Trials Endpoints Center at Brigham and Women’s Hospital
Teji Singh, Senior Medical Director Clinical Development Sanofi Genzyme, Development Partner
Cone (Sarah) Conant, Associate Director, Regulatory Affairs Sanofi Genzyme, Development Partner

1.0 BACKGROUND

Alnylam Pharmaceuticals is developing patisiran (ALN-TTR02), an RNAi therapeutic, for the treatment of adults with hereditary transthyretin (TTR)-mediated amyloidosis with polyneuropathy, also called familial amyloidotic polyneuropathy (FAP). The sponsor states that patisiran is a small interfering ribonucleic acid encapsulated in a lipid nanoparticle intravenous formulation for target delivery to the liver.

The Agency has granted orphan drug designation for the treatment of TTR-FAP and fast track designation for the treatment of TTR-FAP for patisiran on June 14, 2012, and October 31, 2013, respectively.
On March 14, 2013, a pre-IND meeting was held to obtain agreement that the overall CMC, nonclinical plan, and the preliminary clinical data support inclusion of U.S. sites and initiation of dosing with respect to the ongoing Phase 2 study.

IND 117395 was submitted on April 29, 2013, along with a request for Breakthrough Therapy Designation. On May 29, 2013, the sponsor was informed that they may proceed with its clinical investigation. On August 7, 2013, the Agency denied the Breakthrough Therapy Designation request because the preliminary evidence submitted did not indicate that patisiran may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints.

On September 23, 2013, an End-of-Phase 2 meeting was held to discuss the overall development plan for patisiran and the design of the proposed Phase 3 clinical protocol. On October 8, 2015, a Type C guidance meeting was held to discuss the proposal for an interim analysis of an ongoing Phase 3 study, APOLLO, to support accelerated approval of patisiran.

On September 29, 2017, the sponsor submitted requests for rolling review and Breakthrough Therapy Designation. Rolling review was granted on October 19, 2017. Breakthrough Therapy Designation was granted on November 17, 2017.

The sponsor has requested this Pre-NDA meeting to seek Agency feedback on the timing, content, and format of elements of a rolling NDA submission to support the review of patisiran as a treatment for adults with TTR-FAP.

FDA sent Preliminary Comments to Alnylam on November 8, 2017.

2. DISCUSSION

2.1. General

Discussion:

There were a number of general topics of discussion regarding the applicant’s planned NDA, as follows:

- The Division asked the sponsor to comment on the generalizability of the results of the APOLLO study results to the large (>120) number of different genetic mutations that are associated with hATTR amyloidosis. The sponsor replied that 39 different genetic mutations were represented in the APOLLO study. The Division stated that the planned NDA submission should include mutation subset analyses in order to support the generalizability of the efficacy results to a broader population of patients with mutations that were not represented in the trial. The Division also indicated that the application should include a justification of any mechanistic basis that could support the drug’s effectiveness in other genetic forms of the disease.
In response to a question from the Division about the proposed dose of patisiran, the sponsor replied that its data suggests that there is no expected greater benefit with higher doses (based on pharmacodynamic analyses) along with a higher likelihood of adverse events.

The Division asked about the sponsor’s plans with respect to the opening of any expanded access protocols. The sponsor replied that it is prepared to submit expanded access protocols.

In response to a question from the sponsor, the Division stated that although there are no obvious issues that would lead to the need for an advisory committee meeting, any such determination could only be made during the review period.

The sponsor offered to hold a review orientation meeting once the NDA submission is complete. The Division agreed to this proposal.

The sponsor stated that it will provide the previously requested information about clinical inspection sites in early December. The Agency noted that clinical site inspections would be planned once this information is submitted.

There was discussion about the difficulty of quantitatively measuring amyloid change in patients with transthyretin amyloidosis. The sponsor noted that in serial leg skin biopsies of patisiran-treated subjects, there were decreases in amyloid levels and improvement in intraepidermal nerve fiber density.

The Division asked about the potential for the drug to cause decreased vitamin A levels and risk visual impairment. The sponsor replied that all subjects were given vitamin A supplements and received retinograms. According to the sponsor, there were no signs of vitamin A deficiency or vision change.

The sponsor confirmed that the clinical trial formulation of patisiran will be the same as the to-be-marketed formulation.

**Question 1:**

Does the Agency agree that the overall data package is adequate to support review of an NDA for patisiran-LNP as a treatment of adults with hATTR amyloidosis with polyneuropathy?
FDA Response to Question 1:
The overall data package appears adequate to support the filing of your planned NDA. However, a final decision regarding filability is a matter for review at the time of NDA submission.

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.

Discussion:
No discussion.

Question 2:
Does the Agency agree with the proposed plan for the format and content of the eCTD including the proposed rolling NDA submission?

FDA Response to Question 2:
The proposed plan for the content of the eCTD submission appears acceptable. As you have already been notified on October 19, 2017, a rolling review has been granted for your planned application.

From a technical standpoint (not content related), the structure and eCTD format for the planned NDA is generally acceptable. However, additional nodes should not created beyond what is in the specifications, as it is likely that the information would not display properly. Section 3.2.A.3 cannot have extra nodes. The section can be separated with bookmarks in a single document, or seven separate documents can be submitted using leaf titles to distinguish the contents. In section 3.2.P.4.6, leaf titles can be used to distinguish between two novel excipients. Forms like the 356h should be placed in section 1.1. There is no specific section for a request for priority review; this can be placed in section 1.12.4.

Also, please see additional comments below:

- For ease of review, all pdf documents more than 5 pages long should have a table of contents (TOC), proper and clear bookmarks, and hyperlinks (including the Briefing Package, which was not bookmarked). For more information on submitting pdf files, please refer to the PDF Specifications located here: http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163565.pdf
- Make sure leaf titles of documents are clear and indicative of the content.
- The cover letter and form should state “presubmission to rolling submission – part 1 of XXX” (depending on how many parts before the final submission). The final submission completing the application should be coded as “original-application” to start the respective review clock. The cover letter and form of the final submission should state "original application – part XXX of XXX of rolling submission”.
- Please note that Study Tagging Files (STF) files are required for submissions to the FDA when providing study information in 5 with the exception of module 5.2 Tabular Listing,
5.4 Literature References and 5.3.6 if the Periodic Report is a single PDF document. Each study should have an STF and all components regarding that study should be properly file tagged and placed under the study’s STF, including case report forms (crfs). Case Report Forms need to be referenced in the appropriate study’s STF to which they belong, organized by site as per the specifications, and tagged as “case report form”. Subject Data Listings (16.4) should be file tagged as “data-listing-dataset”. For documents with no specific file tags, “study-report-body” or “legacy-clinical-study-report” file tag can be applied. Please refer to The eCTD Backbone File Specification for Study Tagging Files 2.6.1 (PDF - 149KB) (6/3/2008) - http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf

From a Product Quality perspective, we have the following comments (previously sent to you by e-mail on October 27, 2017):

- With respect to Table 11: NDA Submission Content Plan: Administrative (Module 1) you state that “All facilities will have a DUNS number at the time of final component of the NDA submission, FEI for each facility will be either available or will be filed before NDA approval.” To facilitate review of the rolling submission, and planning for inspections, we recommend that you include DUNS and FEI numbers with the CMC section of the NDA. The information will be required when you submit the final component of the NDA. For a domestic facility, you may contact the local FDA District Office to obtain an FEI, for foreign facilities the firm may send an e-mail to fdaforeignoeirequests@fda.hhs.gov.

- With respect to Table 12: NDA Submission Content Plan: Quality
  - Include your acceptance specification for PEG\textsubscript{2000}-C-DMG, analytical procedures and supporting validation data in 3.2.P.4.6.
  - If the specification for DLin-MC3-DMA is contained in 3.2.A.3, we recommend that you include a link to the specification in 3.2.P.4.6.
  - 3.2.A.1 Facilities and Equipment is only applicable to biotechnology derived products. We recommend that you include information regarding the Ajinomoto Althea facility and equipment in Module 3.2.P.3.

Discussion:
No discussion.

2.2. Nonclinical

Question 3:

Does the Agency agree with the Sponsor's planned approach for inclusion of nonclinical datasets?

FDA Response to Question 3:
Your planned approach for inclusion of nonclinical datasets is acceptable.
Discussion:
No discussion.

2.3. Clinical

Question 4:
Can the Agency confirm that the proposed plans for the content and location of efficacy and safety data meet the requirements for an Integrated Summary of Efficacy and an Integrated Summary of Safety?

FDA Response to Question 4:
We generally agree with your proposal.

You state your intention not to include Study 002 in the ISE and ISS because it was a short-term, 2-dose study that explored different patisiran doses and dosing frequencies and did not include clinical efficacy endpoints other than serum TTR levels. We agree that Study 002 can be omitted from the Integrated Summary of Efficacy. However, you should include a summary of safety findings from Study 002 in the Integrated Summary of Safety.

We agree with your plan to split a small ISS and ISE between Module 2 and Module 5, as described in the Guidance for Industry, Integrated Summaries of Effectiveness and Safety: Location Within the Common Technical Document.

Refer to Attachment 2 for further information about the submission of clinical safety data.

Discussion:
In a response to the Division’s preliminary meeting comments, the sponsor indicated that “all adverse events (AEs) were coded to the primary MedDRA System Organ Class (SOC) with the exception of AEs with a dictionary-derived preferred term (AEDECOD) of INFUSION RELATED REACTION. This AE dictionary-derived term was coded for analysis purposes to a secondary MedDRA SOC of IMMUNE SYSTEM DISORDERS per sponsor coding convention, instead of being coded to the primary MedDRA SOC of INJURY, POISONING AND PROCEDURAL COMPLICATIONS. In this case, the coding present in the AE SDTM dataset (in the variables AESOC and AEBODSYS) only reflects the selected alternative coding path used for analysis, not the primary coding path.”

The Division responded that this approach would be acceptable but that there should not be events coded to the Preferred Term “Infusion Related Reaction” because this term does not provide information on what type of reaction occurred. More descriptive coding (e.g., local site injection pain, flushing, etc.) should be used. The sponsor replied that application will also include the more specific preferred terms that would describe the reported infusion related reactions.

Reference ID: 4192902
Question 5:

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

**FDA Response to Question 5:**
The proposed plan to provide the safety update report to the Agency in late-March 2018, approximately 3 months after the NDA filing in late-December 2017, appears acceptable. Note that the safety update report must be submitted in the same format as the integrated summary in CFR 314.50 (d)(5)(vi)(a). In addition, the report must include the case report forms for each patient who died during a clinical study or who did not complete the study because of an adverse event.

**Discussion:**
No discussion.

Question 6:

Does the Agency agree that the positive results of the pivotal Phase 3 APOLLO trial (ALN-TTR02-004) support granting of Priority Review of this NDA for the proposed indication?

**FDA Response to Question 6:**
Review designation decisions are made at the time of NDA filing.

**Discussion:**
No discussion.

2.4. Post-meeting comments

- We refer to our June 20, 2017, correspondence wherein we notified you that your proposed proprietary name was conditionally acceptable. We remind you that a request for a proprietary name review of Onpattro should be submitted with the NDA submission.

3.0 ADDITIONAL INFORMATION

**DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION**

- The content of a complete application was discussed. The application will be complete at time of submission and there will be no late submissions.

- All applications are expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities included or referenced in the application.
A preliminary discussion was held on the need for a REMS, other risk management actions and, where applicable, the development of a Formal Communication Plan.

Major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission. You stated you intend to submit a complete application and therefore, there are no agreements for late submission of application components.

**PREA REQUIREMENTS**

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable. Because this drug product for this indication has an orphan drug designation, you are exempt from these requirements. Please include a statement that confirms this finding, along with a reference to this communication, as part of the pediatric section (1.9 for eCTD submissions) of your application. If there are any changes to your development plans that would cause your application to trigger PREA, your exempt status would change.

**PRESCRIBING INFORMATION**

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

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products.
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential.
- Regulations and related guidance documents.
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of important format items from labeling regulations and guidances.
- FDA’s established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.
The application should include a review and summary of the available published literature regarding drug use in pregnant and lactating women, a review and summary of reports from your pharmacovigilance database, and an interim or final report of an ongoing or closed pregnancy registry (if applicable), which should be located in Module 1. Refer to the draft guidance for industry – *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format* ([http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425398.pdf](http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425398.pdf)).

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

**SUBMISSION FORMAT REQUIREMENTS**

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

**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.”

<table>
<thead>
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<th>Site Name</th>
<th>Site Address</th>
<th>Federal Establishment Indicator (FEI) or Registration Number (CFN)</th>
<th>Drug Master File Number (if applicable)</th>
<th>Manufacturing Step(s) or Type of Testing [Establishment function]</th>
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</thead>
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<tr>
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<tr>
<td>2.</td>
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</tbody>
</table>

Corresponding names and titles of onsite contact:

<table>
<thead>
<tr>
<th>Site Name</th>
<th>Site Address</th>
<th>Onsite Contact (Person, Title)</th>
<th>Phone and Fax number</th>
<th>Email address</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
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<td>2.</td>
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</tbody>
</table>

**OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS**

The Office of Scientific Investigations (OSI) requests that the following items be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA field investigators who conduct those inspections (Item I and II). This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

The dataset that is requested in Item III below is for use in a clinical site selection model that is being piloted in CDER. Electronic submission of the site level dataset is voluntary and is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. This request also provides instructions for where OSI requested items should be placed within an eCTD submission (Attachment 1, Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format).
I. Request for general study related information and comprehensive clinical investigator information (if items are provided elsewhere in submission, describe location or provide link to requested information).

1. Please include the following information in a tabular format in the original NDA for each of the completed pivotal clinical trials:
   a. Site number
   b. Principal investigator
   c. Site Location: Address (e.g., Street, City, State, Country) and contact information (i.e., phone, fax, email)
   d. Location of Principal Investigator: Address (e.g., Street, City, State, and Country) and contact information (i.e., phone, fax, email). If the Applicant is aware of changes to a clinical investigator’s site address or contact information since the time of the clinical investigator’s participation in the study, we request that this updated information also be provided.

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

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

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

5. For each pivotal trial provide original protocol and all amendments ((or identify the location and/or provide a link if provided elsewhere in the submission).
II. Request for Subject Level Data Listings by Site

1. For each pivotal trial: Site-specific individual subject data listings (hereafter referred to as “line listings”). For each site, provide line listings for:
   a. Listing for each subject consented/enrolled; for subjects who were not randomized to treatment and/or treated with study therapy, include reason not randomized and/or treated
   b. Subject listing for treatment assignment (randomization)
   c. Listing of subjects that discontinued from study treatment and subjects that discontinued from the study completely (i.e., withdrew consent) with date and reason discontinued
   d. Listing of per protocol subjects/ non-per protocol subjects and reason not per protocol
   e. By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)
   f. By subject listing, of AEs, SAEs, deaths and dates
   g. By subject listing of protocol violations and/or deviations reported in the NDA, including a description of the deviation/violation
   h. By subject listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint.
   i. By subject listing of concomitant medications (as appropriate to the pivotal clinical trials)
   j. By subject listing, of testing (e.g., laboratory, ECG) performed for safety monitoring

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

OSI is piloting a risk based model for site selection. Voluntary electronic submission of site level datasets is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. If you wish to voluntarily provide a dataset, please refer to the draft Guidance for Industry Providing Submissions in Electronic Format – Summary Level Clinical Site Data for CDER’s Inspection Planning” (available at the following link http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf ) for the structure and format of this data set.

Attachment 1

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

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

<table>
<thead>
<tr>
<th>DSI Pre-NDA Request Item¹</th>
<th>STF File Tag</th>
<th>Used For</th>
<th>Allowable File Formats</th>
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</thead>
<tbody>
<tr>
<td>I</td>
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<td>Data listings, by study</td>
<td>.pdf</td>
</tr>
<tr>
<td>I</td>
<td>annotated-crf</td>
<td>Sample annotated case report form, by study</td>
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</tr>
<tr>
<td>II</td>
<td>data-listing-dataset</td>
<td>Data listings, by study (Line listings, by site)</td>
<td>.pdf</td>
</tr>
<tr>
<td>III</td>
<td>data-listing-dataset</td>
<td>Site-level datasets, across studies</td>
<td>.xpt</td>
</tr>
</tbody>
</table>

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

¹ Please see the OSI Pre-NDA/BLA Request document for a full description of requested data files
C. It is recommended, but not required, that a Reviewer’s Guide in PDF format be included. If this Guide is included, it should be included in the BIMO STF. The leaf title should be “BIMO Reviewer Guide.” The guide should contain a description of the BIMO elements being submitted with hyperlinks to those elements in Module 5.

References:

eCTD Backbone Specification for Study Tagging Files v. 2.6.1  

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

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

Attachment 2
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)


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 as well as the alternative MedDRA coding paths.

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](https://www.fda.gov).  
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.

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

/s/

ERIC P BASTINGS
12/08/2017
Dear Dr. Nochur:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for ALN-TTR02 solution for injection.

We also refer to the meeting between representatives of your firm and the FDA on September 23, 2013. The purpose of the meeting was to discuss further development of ALN-TTR02 for the treatment of transthyretin-mediated amyloidosis in patients with symptomatic polyneuropathy.

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, by phone or email at (301) 796-2899 or fannie.choy@fda.hhs.gov.

Sincerely,

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

Enclosure:
Meeting Minutes
MEMORANDUM OF MEETING MINUTES

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

Meeting Date and Time: September 23, 2013 at 3:00 p.m. EST
Meeting Location: FDA White Oak Campus, Building 22, Rm. 1311

Application Number: IND 117395
Product Name: ALN-TTR02 Solution for Injection
Indication: Treatment of ATTR in patients with symptomatic polyneuropathy
Sponsor/Applicant Name: Alnylam Pharmaceuticals, Inc.

Meeting Chair: Eric Bastings, M.D.
Meeting Recorder: Fannie Choy, R.Ph.

FDA ATTENDEES

Center for Drug Evaluation and Research
Robert Temple, MD, Deputy Director for Clinical Science

Office of Drug Evaluation I
Ellis Unger, MD, Director

Division of Neurology Products
Eric Bastings, MD, Acting Director
Billy Dunn, MD, Acting Deputy Director
Ronald Farkas, MD, PhD, Clinical Team Leader
Devanand Jillapalli, MD, Medical Officer
Lois Freed, PhD, Supervisory Pharmacologist
David Hawver, PhD, Nonclinical Reviewer
Fannie Choy, RPh, Regulatory Project Manager
Margaret Lim, Pharmacy Student
Vanita Spagnolo, Pharmacy Student

Office of New Drug Quality Assessment
Martha Heimann, PhD, Neurology CMC Lead
Monica Cooper, PhD, Quality Reviewer
John Duan, PhD, Biopharmaceutics Reviewer

Division of Biometrics I
Kun Jin, PhD, Biometrics Team Leader
**SPONSOR ATTENDEES**

**Alnylam Pharmaceuticals**  
Akshay Vaishnaw, M.D., Ph.D., CMO, Clinical Research  
Jared Gollob, M.D., Vice President, Clinical Research  
Garvin Warner, Ph.D., Vice President, Preclinical Development  
Jessica Sutherland, Ph.D., Associate Director, Toxicology  
Lubomir Nechev, Ph.D., Vice President, Process Chemistry  
Brian Bettencourt, Ph.D., Associate Director, Biometrics  
Andrew Strahs, Ph.D., Sr. Director, Biometrics  
Saraswathy (Sara) Nochur, Ph.D., Sr. Vice President, Regulatory Affairs & QA  
Lauri Binné, Ph.D., Sr. Manager, Regulatory Affairs  

(Consultant to Alnylam)

**Genzyme (Alnylam partner for Asia)**  
Pamela Williamson, Senior. VP, Regulatory Affairs
1.0 BACKGROUND

Alnylam Pharmaceuticals is developing ALN-TTR02 for the treatment of transthyretin-mediated amyloidosis (ATTR) patients with symptomatic polyneuropathy (FAP). The sponsor states that ALN-TTR02 is a small interfering ribonucleic acid (siRNA), ALN-18328, encapsulated in a lipid nanoparticle intravenous formulation for target delivery to the liver.

The sponsor has requested the end of phase 2 (EOP2) meeting to discuss the overall development plan to support a New Drug Application (NDA). The purpose of the meeting is to seek concurrence from the Agency on the adequacy of the CMC and nonclinical aspects of the program, and on the design of the proposed Phase 3 clinical protocol.

ALN-TTR02 has received orphan drug designation for the treatment of FAP.

2.0 DISCUSSION

2.1 CHEMISTRY, MANUFACTURING AND CONTROLS

Question 1:

Does the Agency agree that the proposed CMC plan for the drug substance ALN 18328 including:

a) Characterization of ALN-18328, including impurities characterization (Section 3.1.2 and Section 3.1.3);

b) Release specifications (Section 3.1.4.1); and

c) Plan for Phase 3 and commercialization (Section 3.1.5);

is adequate to support an NDA for ALN-TTR02?

FDA Preliminary Response to Question 1:

1a) The drug substance characterization you have proposed appears to be adequate. However, a more detailed evaluation of the data during the NDA review cycle may prompt additional questions.

1b) We are not commenting on your proposed acceptance criteria in the drug substance regulatory specification, as these will be evaluated during the review cycle when the data are analyzed. We recognize that you are controlling individual impurities However, individual impurities should also be specified for release and stability testing of the drug substance. In your specification tables for the , it is not completely clear which relative retention time (RRT) is associated with which molecular mass and impurity class. Please better clarify these in the NDA submission.
1c) Your plan for Phase 3 and commercialization using [b][4] as the drug substance manufacturer appears adequate.

**Meeting Discussion:**
The sponsor agreed.

**Question 2:**

Does the Agency agree that the proposed CMC plan for the drug product ALN-TTR02 Solution for Injection, including:

a) Characterization of ALN-TTR02, (see question (iii) below for the in vitro release test) (Section 3.2.3);

b) Specifications (Section 3.2.6.2);

c) Scale-up, manufacturing validation and stability plan (Section 3.2.10);

is adequate to support an NDA?

**FDA Preliminary Response to Question 2:**

2a) The adequacy of the in vitro release test is deferred to Question #3 (Biopharmaceutics). Per the draft FDA guidance, “Liposome Drug Products” (2002), the quantity of lipid in the formulation should be expressed as the molar ratio and percentage by weight of the lipid to the drug substance as well as on the milligram per milliliter and per vial basis (please include this information in the components and composition section of your NDA submission). Regarding the proposed characterization of the drug product, please refer to the draft FDA guidance, “Liposome Drug Products” (2002) and provide justification in the NDA for your inclusion or exclusion of the recommended physicochemical tests. Provide the complete particle size distribution profile for the drug product (in addition to the D10, D50, D90, average, and polydispersity values). Provide characterization of the liposome nanoparticles (LNP) with and without active at the molecular level, manufactured using your intended commercial process. Shape and aspect ratio, hydrodynamic size, surface area, surface charge/zeta potential, physical stability, and aggregation/agglomeration should also be considered for characterization of nano-sized materials. Discuss the general adequacy of your analytical methods to measure nano-sized materials (system suitability, preparation of standards, potential interactions with filters, etc.) and the adequacy of your primary packaging (surface interactions, leachables, etc.).

2b) Per ICH Q6A, identification solely by a single chromatographic retention time is not regarded as being specific. We recommend that melting temperature (T_m) and mass spectrometry tests be added to your identification tests to confirm the correct molecular mass and sequence of the API in the drug product. Individual degradation products should be specified. Forced degradation studies should be performed to determine the potential degradation products from the siRNA and the lipids. Provide a limit for “area
% outside lipid peaks,” as this attribute determines the total degradation products related to the lipids. With respect to metal impurities, you note that “specifications will be set at the time of the NDA based on the EMA draft guideline on Specification Limits for Residues of Metal Catalysts (2007).” Please also consider the recommendations of the draft guidances, ICH Q3D and USP <232>.

2c) Your approach to scale-up, manufacturing, and stability for Phase 3 and commercialization of the drug product appears adequate.

**Meeting Discussion:**

With respect to the FDA Preliminary Response to Question 2b, the sponsor stated that three identity tests are currently included for the drug product – ID by single strand retention time, ID by duplex retention time, and lipid identity by retention time. Addition of T_m or MS would pose practical difficulties due to the presence of the lipid excipients in the drug product, which interfere with standard tests for siRNA. The sponsor will continue their efforts to explore additional analytical techniques (including LC-MS methods). Either a new method will be included or a justification for non-inclusion will be provided in the NDA.

The Division encouraged the sponsor to continue to explore additional identity methods, as HPLC retention time is not considered specific. If no other method is found suitable, the sponsor should provide convincing evidence (i.e., data) in the NDA that the combination of single strand retention time and duplex retention time specifically identifies their siRNA drug substance.

The sponsor agreed to all other parts of FDA’s Preliminary Response to Question 2.

**Question 3:**

Does the Agency agree with this proposal to incorporate in vitro release assay as a characterization method for ALN-TTR02 and not for inclusion as part of drug product specifications?

**FDA Preliminary Response to Question 3:**

No, we do not agree. As previously indicated in our comments for your IND submission dated 4/29/2013, the release of the active ingredient from the encapsulated form is an important quality attribute regarding the timing of the release, the amount being released, and the conditions of the release. It is not only related to safety, but also to the effectiveness of the drug product. Therefore, an in vitro release assay and its acceptance criteria should be included in the drug product specifications.
For the development of the in vitro release method and setting the acceptance criteria of your proposed product, please follow the advice/guidelines that we previously gave you for your IND.

**Meeting Discussion:**
The sponsor agreed.

### 2.2 NONCLINICAL

**Question 4:**

Is the totality of the Sponsor’s nonclinical program including:

a) The nonclinical pharmacology (Section 4.1), general toxicology (Section 4.3) and ADME studies conducted (Section 4.2) and planned (Section 4.2.3) with ALN-TTR02;

b) The plan as outlined for reproductive toxicology studies (Section 4.3.4.1); and

c) The plan for carcinogenicity assessment (Section 4.3.4.1); adequate to support an NDA?

**FDA Preliminary Response to Question 4:**

A final decision on the adequacy of your proposed nonclinical program to support an NDA will be a matter of review. However, we note that you are not planning to conduct a fertility and early embryonic development study, an embryo-fetal development study in rabbit, or a 2-year carcinogenicity study in rat. Since ALN-TTR02 contains novel excipients, these studies would also be needed. The studies in rat (fertility, carcinogenicity) could be conducted using the available rat surrogate. We acknowledge that the development of anti-PEG antibodies in the 6-month toxicity study in rat resulted in marked decreases in plasma exposure to the siRNA over the 6-month period. Plasma exposures to the excipients also decreased but to a much lesser extent. These data suggest that a 2-year study may be feasible, at least to assess the carcinogenic potential of the novel excipients. If you continue to believe that a meaningful 2-year study cannot be conducted in rat, you should provide additional justification (with supportive data) for that position.

**Meeting Discussion:**
The sponsor will conduct a fertility study in rats. The sponsor believes that an embryo-fetal development (EFD) study in rabbit is unnecessary because the effect of Vitamin A deficiency on the developing organism is well understood. The Division stated that there is concern regarding unexpected developmental toxicity, in part, because of the novel lipid excipients in the ALN-TTR02 formulation. Therefore, an EFD study in rabbit will be required to support an NDA unless the sponsor provides compelling justification (with supportive data) that such a study is not feasible or would not provide useful information.
Regarding the carcinogenicity studies, the Division agreed that a two-year IV carcinogenicity study of ALN-TTR02 in rat may not be feasible but recommended that the sponsor investigate the feasibility of using an alternative route (e.g., subcutaneous administration).

Question 5:

Does the Agency concur that no separate toxicology studies are required for the novel excipients DLin-MC3-DMA and PEG2000-C-DMG?

**FDA Preliminary Response to Question 5:**

We agree that separate toxicology studies for the novel excipients DLin-MC3-DMA and PEG2000-C-DMG are not needed.

**Meeting Discussion:**

None.

### 2.3 CLINICAL

Question 6:

Does the Agency concur that the proposed ALN TTR02 Phase 3 study including:

a) Single pivotal study
b) Randomized, placebo-controlled Phase 3 design;

b) Patient population;
c) Dose and regimen;
d) Primary and other key endpoints;
e) Study duration;
f) Criteria for enrollment into open-label extension study;
g) Sample size;
h) Statistical analyses, including interim analysis; and

i) Safety assessments

is appropriate for this serious and life-threatening orphan disease?

**FDA Preliminary Response to Question 6:**

a) *Single pivotal study:* The ability of a single phase 3 trial to support approval would depend on the persuasiveness of the efficacy findings. See also the additional responses to question 6 below.

b) i) *Randomized, placebo-controlled design:* We agree.

ii) *Patient population:* We agree.
c) **Dose and Regimen:** The dose and regimen appear reasonable based on the TTR reductions and safety results of study ALN-TTR02, and the nonclinical findings.

d) **Primary and other key endpoints:** 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 clearly 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). Statistically robust results on both such endpoints might then support full approval if other aspects of the phase 3 study met the criteria for single-study NDA approval described in *Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products*.1 We remain open to the possibility of Subpart H approval on the basis of a persuasive effect on a surrogate endpoint like mNIS+7 and input from an Advisory Committee regarding whether such an effect is reasonably likely to predict clinical benefit. A reasonable approach might be to design this study to achieve a convincing result on the surrogate designed to support Subpart H filing, and to continue the same placebo-controlled study during NDA review as a 'study already underway' to verify and describe the clinical benefit of the drug, as described in the regulations.

Alternatively, the directly clinically meaningful endpoint might be chosen as the sole primary endpoint, with mNIS+7 as secondary endpoint, but in the context of the evidence needed to support single-study approval, it is not clear that this would be much different from declaring the endpoints co-primary, as consistent results among independent measures of efficacy would be expected for approval.

mBMI, which is calculated from albumin level combined with BMI (itself based on height and weight), is proposed as a secondary endpoint intended to measure nutritional status. However, we are concerned that mBMI may not accurately reflect nutritional status in the presence of drugs like ALN-TTR02 that affect serum proteins like TTR, or more generally in complex underlying diseases like TTR-FAP. While we understand that other measures of nutritional status would also not be validated in the use you propose, methods that measure body composition more precisely, like DXA scanning, appear likely to be more robust and interpretable.

e) **Study duration:** The study duration appears reasonable based on your sample-size assumptions.

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f) **Criteria for enrollment into open-label extension study:**

You propose to evaluate study subjects at 9 months, and to enable those patients with evidence of rapid disease progression (≥ 24 point increase in mNIS+7 from baseline) to discontinue study drug if they choose and to receive local standard of care treatment, which could include either tafamidis or diflunisal. You estimate that fewer than 5% of patients will meet the definition of rapid disease progression at 9 months. We agree with the general approach of allowing patients that have reached some threshold of progression to discontinue study drug, and that specifying a 9-month period of treatment may increase confidence that the drug was given for a long enough period of time to demonstrate efficacy if present. We also agree that the 24 point threshold is acceptable given that it is estimated that the placebo group of the proposed phase 3 study is expected to progress by that amount over the 18-month period of the entire study. However, you have not provided enough detail for us to comment about the acceptability of your statistical analysis plan regarding the handling of patients that discontinue due to rapid progression or for other reasons.

g) **Sample size:** The sample size appears reasonable based on the assumptions of your sample size calculation.

h) **Statistical analysis, including interim analysis:**

You need to submit a detailed Statistical Analysis Plan. You need to provide details on the imputation procedure and also provide a justification for the appropriateness of this procedure for your data. You also need to provide details on your sensitivity analyses, and on your multiplicity adjustment procedure. From your brief description, it seems to be problematic. The Hochberg procedure is generally applied to all relevant endpoints, not families of endpoints. Your procedure, as we understand, is unlikely to control the type I error.

i) **Safety Assessments:** i) Cardiac involvement can occur in TTR-FAP, particularly in non-V30M patients. Other treatments of TTR-FAP (i.e., liver transplantation) have led to unexpected worsening of cardiac function. While we do not believe that there is a specific reason to predict similar effects from ALN-TTR02, we recommend more intensive cardiac safety monitoring. We note, for example, that ECG is not performed between baseline and month 9, and that echocardiogram is only performed at baseline and month 18. ii) Nyctalopia is the earliest and most common symptom of vitamin A deficiency, and should be specifically monitored for.

**Clinical Pharmacology Comments**

- The dose and regimen for the proposed study are acceptable.
- An effort should be made to obtain a plasma sample when a serious adverse event occurs.
Meeting Discussion:

Clinical:
The sponsor proposed to show statistical significance for mNIS+7 as the primary endpoint, and a trend in Norfolk QOL-DN as the first secondary endpoint. Citing cross-sectional natural history data from V30M and non-V30M TTR-FAP patients, the sponsor argued that NIS, the main component of mNIS+7, correlates with disease severity (FAP stage) and polyneuropathy disability score, and thus the proposed primary endpoint is a clinically relevant measure in FAP. The Agency reiterated its position that mNIS+7 does not directly measure treatment benefit (i.e., how a patient feels or functions), and stated that for conventional approval it is necessary to show statistical significance on mNIS+7 and QOL-DN. The Agency stated that QOL-DN need not be co-primary but could be key secondary endpoint, and that mNIS+7 and QOL-DN could be tested in a sequential manner. The Agency also noted that for a single study approval, it would be important to show that data from other secondary clinical endpoints were supportive.

If statistical significance was demonstrated on mNIS+7 but not on QOL-DN, the Agency noted that it remained open to considering Subpart H approval provided the rest of the data in the package was consistent and strongly supportive. Importantly, an effect on the mNIS+7 should be statistically very persuasive, i.e., a p-value of 0.05 is not persuasive enough.

The Agency asked the sponsor to consider ranking clinically meaningful secondary endpoints high in the statistical testing hierarchy. The Agency also noted that even if ALN-TTR02 does not have an effect on serum albumin levels, other factors potentially affecting mBMI could confound a treatment effect on mBMI.

There was a brief discussion on handling of patients that discontinue ALN-TTR02 due to rapid progression but will stay on study and return for their 18-month visit efficacy assessment. The Agency noted that if these patients begin taking tafamidis or diflunisal between discontinuation and the 18-month visit, study interpretation may become difficult. The sponsor stated that the Statistical Analysis Plan (SAP) will include multiple sensitivity analyses including the use of last observation carried forward. The Agency asked the sponsor to submit the SAP as soon as possible and not wait till database lock.

The Agency noted that even if there were animal data and published literature indicating that alternate pathways for Vitamin A transport exist, it was important to monitor for this potential safety issue. In this regard, the Agency stated that the sponsor should provide strong justification that the proposed tests (including visual acuity and visual fields) will adequately assess early signs of night blindness. The sponsor agreed to provide additional information to support the proposed testing.

The Agency agreed to the sponsor's plan to submit the protocol to the IND and send in an amendment shortly reflecting the above noted changes regarding secondary endpoints,
additional time points for ECG evaluations, and justification for the proposed tests for night blindness.

**Statistical:**
There was a discussion on the hierarchical testing proposed for the two families of secondary endpoints. The Agency did not accept the sponsor’s proposal. The Agency stated that we could accept a partitioning of the remaining type I error, but emphasized that if only one of the two tests in a family produced a statistically significant result, the alpha remaining for the next family could be no higher than 0.025. It was recommended that the sponsor consider individual secondary endpoints and incorporate them in order of importance and ability to achieve the endpoint and propose to test them sequentially in a hierarchical manner, rather than in families. The sponsor agreed to consider this advice and to describe the details in the statistical analysis plan (SAP). The Agency encouraged the sponsor to send in the SAP well before database lock.

**Question 7:**

Given the small population of ATTR patients, and the serious morbidity and mortality associated with this disease, is the overall program of completed and planned clinical studies adequate to support an NDA for ATTR FAP, a serious and life-threatening orphan disease?

**FDA Preliminary Response to Question 7:**

See response to Question 6 regarding efficacy evidence to support an NDA for ALN-TTR02.

You anticipate that > 200 FAP patients will have been exposed to the commercial dose of ALN-TTR02 for 6 months, > 150 for 18 months and > 50 patients for ≥ 2 years at the time of NDA filing. This exposure is likely to be adequate to support an NDA for FAP.

**Meeting Discussion:**

There was no discussion.

**Question 8:**

ALN-TTR02 has been granted orphan designation # 12-3711. Alnylam requests exemption from the FDASIA requirement to submit an initial Pediatric Study Plan, as 21 U.S.C. 355c (PREA) does not apply to products granted orphan designation under section 526.
**FDA Preliminary Response to Question 8:**

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

Because this drug product for this indication has an orphan drug designation, you are exempt from these requirements. If there are any changes to your development plans that would cause your application to trigger PREA, your exempt status would change.

**Meeting Discussion:**

There was no discussion.

3.0 **ADDITIONAL COMMENTS**

3.1 **DATA STANDARDS FOR STUDIES**

CDER strongly encourages IND sponsors to consider the implementation and use of data standards for the submission of applications for investigational new drugs and product registration. Such implementation should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. CDER has produced a web page that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers. The web page may be found at: [http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm](http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm)

3.2 **PROSPECTIVE SUICIDALITY ASSESSMENTS IN CLINICAL PROTOCOLS**

Treatment-emergent suicidality (suicidal ideation and behavior) has been identified in recent years as a concern for a number of drugs and drug classes. FDA-conducted meta-analyses of clinical trial data for both antiepileptic drugs and antidepressants have demonstrated that these drug classes increase the risk of suicidal thoughts and behavior. Spontaneous reports have led to concerns about the risk for suicidality with other drugs as well. These drugs include isotretinoin and other tretinoins, beta blockers, reserpine, smoking cessation drugs, and drugs for weight loss.
Given the heightened concern regarding the potential for treatment-emergent suicidality with certain drugs, particularly those products with central nervous system activity, the Division of Neurology (DNP) has made the determination that prospective assessments for suicidality should be included in clinical trials involving all drugs for neurological indications. There are two primary reasons for this new requirement pertaining to prospective suicidality assessments. First, such prospective assessments will ensure the collection of more timely, complete, and reliable data pertaining to suicidality than have been collected in the past. This will allow assessment of the risk for suicidality with a given drug and, when the data are collected in a systematic and uniform fashion, will allow for additional analyses to be conducted in the future aggregating findings and comparing findings across drugs and drug classes. Second, such prospective assessments will help ensure that patients who are experiencing suicidal thoughts or behavior are properly recognized and adequately managed. This is important whether or not a particular product is known or suspected to be associated with treatment-emergent suicidality.

All clinical protocols for products developed in DNP for any indication should therefore include a prospective assessment for suicidality. These assessments must 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. It is reasonable to omit such assessments from these trials. An acceptable instrument should map to the Columbia Classification Algorithm for Suicide Assessment (C-CASA), directly classifying events of interest into one of 11 categories of suicidal ideation and behavior. The Columbia Suicide Severity Rating Scale (C-SSRS) is an example of an acceptable instrument.

You must obtain DNP's prior approval for any alternative assessment instrument that you wish to use. A request to use an alternative prospective suicidality assessment instrument should include a justification for the use of this instrument, including an explanation of how the alternative instrument would map to the Columbia Classification Algorithm for Suicide Assessment (C-CASA). As discussed above, the ability of an assessment instrument to map to a common scale is important for any analyses conducted in the future.

This new policy is applicable to all new protocols submitted to DNP and to ongoing protocols in which you have an IND residing within DNP. For ongoing protocols, amendments must be submitted to incorporate this assessment. For newly submitted protocols drafted prior to you becoming aware of this new policy, the lack of a prospective assessment for suicidality will not constitute a reason for placing your IND on clinical hold. As with ongoing protocols, an amendment should be submitted to incorporate such assessments. In the future, however, the absence of a plan for prospective suicidality assessments may constitute a reason for placing an IND on clinical hold.
It is reasonable to omit prospective assessments for suicidality, or consider alternative assessments, in trials involving patients with impairment that is so substantial as to interfere with such assessment.

A sponsor considering the omission or alteration of standard suicidality assessments from a particular clinical protocol should discuss this omission with DNP to gain prior agreement. In certain instances, alternative instruments may permit the assessment of suicidality.


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 HANDOUTS

Sponsor submitted slides titled “End of Phase 2 Meeting with FDA ALN-TTR02 / Alnylam Pharmaceuticals, Inc. / 23 September 2013”

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

/s/

ERIC P BASTINGS
10/22/2013
Alnylam Pharmaceuticals, Inc.
Attention: Saraswathy V. Nochur, Ph.D.
Vice President, Regulatory Affairs and Quality Assurance
300 Third Street
Cambridge, MA  02142

Dear Dr. Nochur:

Please refer to your Pre-Investigational New Drug Application (PIND) file for ALN-TTR02.

We also refer to the meeting between representatives of your firm and the FDA on March 14, 2013. The purpose of the meeting was to discuss the development of ALN-TTR02 for the treatment of transthyretin mediated amyloidosis.

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, by phone or email at (301) 796-2899 or fannie.choy@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Russell G. Katz, M.D.
Director
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes
MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: Pre-IND meeting
Meeting Date and Time: March 14, 2013 3:00 P.M. EST
Meeting Location: FDA White Oak Campus, Building 22, Rm. 1311
Application Number: PIND 117395
Product Name: ALN-TTR02 Solution for Injection
Indication: Treatment of TTR-mediated familial amyloidotic polyneuropathy
Sponsor/Applicant Name: Alnylam Pharmaceuticals, Inc.
Meeting Chair: Russell G. Katz, M.D.

FDA ATTENDEES

Division of Neurology Products
Russell Katz, MD, Director
Eric Bastings, MD, Deputy Director
Ronald Farkas, MD, PhD, Clinical Team Leader
Devanand Jillapalli, MD, Clinical Reviewer
Lois Freed, PhD, Supervisory Pharmacologist
David Hawver, PhD, Nonclinical Reviewer
Fannie Choy, RPh, Regulatory Project Manager

Office of New Drug Quality Assessment
Martha Heimann, PhD, Neurology CMC Lead

Office of Clinical Pharmacology
Angela Men, MD, PhD, Clinical Pharmacology Team Leader
Bei Yu, PhD, Clinical Pharmacology Reviewer

Rare Diseases Program
Larissa Lapteva, MD, Medical Officer

Office of Orphan Products Development
Erica McNeilly, RPh, Health Science Administrator
SPONSOR ATTENDEES

Alnylam Pharmaceuticals
Akshay Vaishnaw, MD, PhD, CMO, Clinical Research
Jared Gollob, MD, Vice President, Clinical Research
Garvin Warner, PhD, Vice President, Preclinical Development
Saraswathy (Sara) Nochur, PhD, Sr. Vice President, Regulatory Affairs & QA
Lauri Binné, PhD, Sr. Manager, Regulatory Affairs
Brian Bettencourt, PhD, Associate Director, Biostatistics

Alnylam Consultant

Genzyme
Pamela Williamson, SVP Regulatory
1.0 BACKGROUND

Alnylam Pharmaceuticals has requested the pre-IND meeting to discuss the development of ALN-TTR02 for the treatment of TTR-mediated familial amyloidotic polyneuropathy (FAP).

The sponsor states that ALN-TTR02 is a small interfering ribonucleic acid (siRNA), ALN-18328, encapsulated in a lipid nanoparticle intravenous formulation to target delivery to the liver.

The purpose of this meeting is to introduce the novel RNAi therapeutic, and to obtain agreement that the overall CMC, nonclinical plan, and the preliminary clinical data support inclusion of U.S. sites and initiation of dosing with respect to the ongoing Phase 2 study.

2.0 DISCUSSION

2.1 CLINICAL

Question 1:

ALN-TTR02 has been evaluated in a Phase 1 randomized, single-blind, placebo-controlled, single ascending dose study in healthy volunteers in the UK. The study design is summarized in Section 5.1.1 and results suggest a favorable risk/benefit profile, supportive of further clinical evaluation. The Phase 2 protocol that is currently enrolling patients in Portugal, Sweden and France is included in Appendix A. In this ongoing multi-dose ALN-TTR02-002 study, 12 patients have been dosed to date with no adverse effects, including 8 who have received 2 doses each, and 3 patients who have been dosed at the highest dose of 0.3 mg/kg (Section 5.1.2).

Does the Agency concur that the proposed Phase 2 protocol is acceptable for patient accrual in the US?

FDA Preliminary Response to Question 1:

You ask this question in the context of the ongoing ALN-TTR02-002 study in which 27 patients are planned for enrollment (Amendment #2) and who receive 2 doses 3 or 4 weeks apart (highest dose 0.3 mg/kg), with plans to have “optional cohorts” to evaluate two dosing regimens and premedication/infusion rate regimens, and a follow up period of up to 208 days. This protocol also notes your plans for an open-label extension study for enrolled subjects to receive additional, long-term dosing. It is not clear to us how many patients you intend to enroll in the US, into which study (ALN-TTR02-002 and/or open-label extension study), and the proposed duration of treatment (i.e., number
of doses) in the open-label extension. Please clarify why subjects enrolled in Study ALN-TTR02-002 are followed up for 208 days.

**Meeting Discussion:**

The sponsor clarified that 2-3 patients in the US are planned for enrollment in the ongoing ALN-TTR02-002 Study, and these same 2-3 patients in the US will be enrolled in the open-label extension study in which 0.3 mg/kg (IV infusion over 70 minutes) will be administered every 3-4 weeks for 2 years. The sponsor stated that signed reports from chronic-treatment non-clinical studies will be submitted with the open-label extension protocol.

The Division stated that the proposed cohort size (3 per cohort) should be increased to adequately assess the safety at a given dose. The sponsor stated that the 0.3 mg/kg dose is intended to take forward for development, and about 18 subjects would be exposed to this dose.

The sponsor clarified that the reason for follow-up of patients in Study ALN-TTR02-002 for 208 days is to allow for passage of at least 5 half-lives.

There was also a brief discussion on whether higher dose(s) could be used to achieve even greater reductions in serum TTR. The sponsor stated that TTR levels with the 0.3mg/kg dose are expected to steadily decrease with the first few doses, stabilizing by approximately the 3rd dose. Further, the sponsor stated that they do not believe that meaningfully greater reductions can be achieved with higher doses than the 0.3 mg/kg dose and with an acceptable risk/benefit profile.

**Question 2:**

ATTR is a serious and life-threatening orphan disease with a high unmet medical need as outlined in Section 2.1. We therefore plan to submit a fast track designation request for ALN-TTR02 concurrent with the IND application.

Given the nature of ATTR and the pharmacological potential of ALN-TTR02 to be disease-modifying via the substantial suppression of the pathogenic amyloidogenic protein, does the Agency concur that ALN-TTR02 would be suitable for fast track consideration upon submission of the application?

**FDA Preliminary Response to Question 2:**

Please submit a request for fast-track designation for our review. You may refer to the following guidance for additional details: Guidance for Industry: Fast Track Drug Development Programs — Designation, Development, and Application Review.
Meeting Discussion:
The sponsor stated their intention to request fast-track designation.

2.2 NONCLINICAL

Question 3:
The nonclinical program has been conducted in consideration of ICH Safety Guidelines and in accordance with 21 CFR 312.23(a)(8). A summary of the results from the 2-dose and 4-dose nonclinical toxicology studies with ALN-TTR02 in the rat, and the 4-dose study in NHP are included in Section 4.4.1. These study results are supportive of the proposed dosing and duration in the Phase 2 study. Further, long-term in-life data in the GLP rat and monkey chronic toxicology studies (Section 4.4.1.4), indicate no ALN-TTR02-related clinical signs of toxicity up to doses of 0.3 mg/kg in the rat and 1.0 mg/kg in the monkey.

Does the Agency agree that these nonclinical data support the Phase 2 study in the US?

FDA Preliminary Response to Question 3:
On face, the completed nonclinical studies appear sufficient to support the proposed initial Phase 2 trial. A signed and dated pathology report will need to be provided for each pivotal toxicity study, even if the study report is provided in draft form.

Regarding the open-label extension, the duration of the toxicity studies is typically expected to be similar to or greater than that proposed for humans, up to 6- and 9-months in rodent and non-rodent, respectively. However, in certain cases, it is possible for dosing in humans to exceed the duration of the pivotal nonclinical studies, e.g., if previous human experience warrants such a strategy in the absence of adequate nonclinical data. If the IND is submitted before completion of the chronic toxicity studies, you should submit the following data from those studies:

- all available in-life data for both chronic toxicity studies.
- all available information (in-life and terminal studies) for the one high-dose female that died following the second dose in the 39-week study in monkey study.

You should also address the apparently greater toxicity observed in the 39-week monkey study compared to the 4-week monkey study at the same high dose (3 mg/kg). The overall adequacy of the data will be a matter of review.

A full battery of reproductive and developmental toxicity studies (cf. ICH M3(R2)) in rat, using the rat surrogate TTR siRNA LNP formulation, and an embryo-fetal
development toxicity study in rabbit, using the clinical formulation, will be needed to support your NDA, unless submission post-approval is warranted.

Meeting Discussion:
The Division confirmed that the sponsor’s plan to submit study reports for the chronic toxicity studies (rat and monkey) with the clinical protocol for the open-label extension study is acceptable.

2.3 CHEMISTRY, MANUFACTURING AND CONTROLS

Question 4:
Appropriate raw material specifications, process controls, analytical methods, release specifications and other manufacturing and quality aspects are in compliance with current Good Manufacturing Practices (cGMP). Release of the drug product is suitable for Phase 2 human testing. An overview of the CMC, including cGMP manufacture, process controls, characterization, impurities and specifications, as well as available batch analysis data and stability information for the drug substance ALN-18328 (Section 3.1), and for drug product ALN-TTR02 (Section 3.1) are included, and support the proposed Phase 2 study.

Does the Agency agree that the CMC information for the drug substance and drug product are adequate to support the proposed Phase 2 study in the US?

FDA Preliminary Response to Question 4:
Based on the information outlined in the briefing package, the CMC appears adequate; however, this will be a review issue based on evaluation of the information provided in the IND submission.

Meeting Discussion:
There was no further discussion during the meeting.

3.0 ADDITIONAL COMMENTS

3.1 CLINICAL PHARMACOLOGY

1. In Study ALN-TTR02-001, the mean serum TTR reduction was similar (15-20% reduction) for 10 ug/kg and 50 ug/kg, and it dropped to 80-90% for doses at 150 ug/kg and 300 ug/kg. To fully characterize the PK-PD (dose/concentration-response) correlation in the Phase 2 study (Study ALN-TTR02-002), we recommend you add one more dose level between 50 ug/kg and 150 ug/kg, e.g., 100 ug/kg.
**Meeting Discussion:**

The sponsor presented updated PK-PD data in primate and humans, and indicated that non-human primate accurately predicts pharmacology in humans, and that TTR reduction with the 0.1 mg/kg dose would be anticipated to be similar to the 0.15 mg/kg dose already evaluated in humans. Per this claim, the Division questioned why 0.1 mg/kg was not selected. The sponsor explained that due to lower inter-subject variability of the TTR reduction at higher doses in primate and human, a dose level of 0.15 mg/kg but not 0.1 mg/kg was selected in the ongoing Phase 2 study. This explanation was acceptable to the Division.

2. In the Phase 2 study (Study ALN-TTR02-002), plasma PK sampling at Day 3 and Day 4 (72 hr and 96 hr post infusion) should be added to evaluate the PK profile of the drug.

**Meeting Discussion:**

The sponsor indicated that based on Phase 1 data AUC and Cmax were dose-proportional and there was no difference in the AUC with or without these two data points. Additionally, 2 sampling points would cause inconvenience for the enrolled patients to visit sites during the study. Not adding PK samples at Day 3 and Day 4 is acceptable for the Division.

3. Immunogenicity of the product should be proposed and evaluated in the proposed study.

**Meeting Discussion:**

The Division questioned the sponsor’s plan to only assess anti-PEG antibody but not anti-siRNA in the current Phase 2 study. The sponsor claimed that because siRNA is cleared very fast, there is very little siRNA (<1%) in the system after the drug administration. The sponsor will submit a justification when they submit an IND.

4. The induction effect of ALN-18328 on cytochrome P450 isozymes and potential effect on major transporters should be determined during early drug development.

**Meeting Discussion:**

These studies are planned and will be submitted with the Phase 3 protocol by the sponsor.
3.2 **DATA STANDARDS FOR STUDIES**

CDER strongly encourages IND sponsors to consider the implementation and use of data standards for the submission of applications for investigational new drugs and product registration. Such implementation should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. CDER has produced a web page that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers. The web page may be found at:


3.3 **PROSPECTIVE SUICIDALITY ASSESSMENTS IN CLINICAL PROTOCOLS**

Treatment-emergent suicidality (suicidal ideation and behavior) has been identified in recent years as a concern for a number of drugs and drug classes. FDA-conducted meta-analyses of clinical trial data for both antiepileptic drugs and antidepressants have demonstrated that these drug classes increase the risk of suicidal thoughts and behavior. Spontaneous reports have led to concerns about the risk for suicidality with other drugs as well. These drugs include isotretinoin and other tretinoins, beta blockers, reserpine, smoking cessation drugs, and drugs for weight loss.

Given the heightened concern regarding the potential for treatment-emergent suicidality with certain drugs, particularly those products with central nervous system activity, the Division of Neurology (DNP) has made the determination that prospective assessments for suicidality should be included in clinical trials involving all drugs for neurological indications. There are two primary reasons for this new requirement pertaining to prospective suicidality assessments. First, such prospective assessments will ensure the collection of more timely, complete, and reliable data pertaining to suicidality than have been collected in the past. This will allow assessment of the risk for suicidality with a given drug and, when the data are collected in a systematic and uniform fashion, will allow for additional analyses to be conducted in the future aggregating findings and comparing findings across drugs and drug classes. Second, such prospective assessments will help ensure that patients who are experiencing suicidal thoughts or behavior are properly recognized and adequately managed. This is important whether or not a particular product is known or suspected to be associated with treatment-emergent suicidality.

All clinical protocols for products developed in DNP for any indication should therefore include a prospective assessment for suicidality. These assessments must 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. It is reasonable to omit
such assessments from these trials. An acceptable instrument should map to the Columbia Classification Algorithm for Suicide Assessment (C-CASA), directly classifying events of interest into one of 11 categories of suicidal ideation and behavior. The Columbia Suicide Severity Rating Scale (C-SSRS) is an example of an acceptable instrument.

You must obtain DNP's prior approval for any alternative assessment instrument that you wish to use. A request to use an alternative prospective suicidality assessment instrument should include a justification for the use of this instrument, including an explanation of how the alternative instrument would map to the Columbia Classification Algorithm for Suicide Assessment (C-CASA). As discussed above, the ability of an assessment instrument to map to a common scale is important for any analyses conducted in the future.

This new policy is applicable to all new protocols submitted to DNP and to ongoing protocols in which you have an IND residing within DNP. For ongoing protocols, amendments must be submitted to incorporate this assessment. For newly submitted protocols drafted prior to you becoming aware of this new policy, the lack of a prospective assessment for suicidality will not constitute a reason for placing your IND on clinical hold. As with ongoing protocols, an amendment should be submitted to incorporate such assessments. In the future, however, the absence of a plan for prospective suicidality assessments may constitute a reason for placing an IND on clinical hold.

It is reasonable to omit prospective assessments for suicidality, or consider alternative assessments, in trials involving patients with impairment that is so substantial as to interfere with such assessment.

A sponsor considering the omission or alteration of standard suicidality assessments from a particular clinical protocol should discuss this omission with DNP to gain prior agreement. In certain instances, alternative instruments may permit the assessment of suicidality.

Further details pertaining to the prospective assessment of the occurrence of suicidality in clinical trials can be found in the following Draft Guidance for Industry: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM225130.pdf

Meeting Discussion:

The sponsor questioned the need for assessment of suicidality for a number of reasons including that ALN-TTR02 does not cross the blood-brain barrier, had no evidence of CNS pathology in nonclinical studies, is intended for a disease affecting the peripheral nervous system, is for a small study population, and pain and anxiety/depression will be assessed in the open-label extension study.
The Division stated that its policy generally required suicidality assessment in every product. The Division also stated that it is more difficult to exclude the potential for suicidality if some drug crosses the blood-brain barrier than if, based on data, no drug crosses the blood-brain barrier (although the drug might still have an effect on suicidality that is independent of its presence in the brain). The Division asked the Sponsor to submit for consideration a proposal to omit the assessment of suicidality.

3.4 **Other Meeting Discussion:**

The Division stated that given the relatively small number of subjects with TTR FAP, the sponsor explore the possibility of enrolling the 27 subjects (from ALN-TTR02-002 study) into the placebo-controlled efficacy study rather than rolling them into an open-label extension. The sponsor expressed reservations about this proposal considering the expected structural changes induced by ALN-TTR02 and the consequent difficulties it might impose in study interpretation.

The Division asked the sponsor for their plans to monitor for vitamin A deficiency and to a lesser extent thyroid function in the long-term placebo-controlled and open-label studies. The sponsor stated that patients will be monitored and assessments will include ophthalmological examinations.

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 HANDOUTS**

- Sponsor submitted slides: Pre-IND Meeting with FDA, ALN-TTR02, Alnylam Pharmaceuticals, Inc., 14 March 2013

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

RUSSELL G KATZ
04/12/2013