Dear Mr. Rigourd:

Please refer to the rolling submission of your planned New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for givosiran.

We also refer to your February 26, 2019, correspondence, received February 26, 2019, requesting a meeting to discuss the content of the final (clinical) component of your rolling NDA submission.

Our preliminary responses to your meeting questions are enclosed.

You should provide to me a hardcopy or electronic version of any materials (i.e., slides or handouts) to be presented and/or discussed at the meeting.

In accordance with 21 CFR 10.65(e) and FDA policy, you may not electronically record the discussion at this meeting. The official record of this meeting will be the FDA-generated minutes.

If you have any questions, call me at (240) 402-4622.

Sincerely,

[See appended electronic signature page]

Jennifer J. Lee, PharmD
Senior Regulatory Health Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

ENCLOSURE:
Preliminary Meeting Comments
PRELIMINARY MEETING COMMENTS

Meeting Type: B
Meeting Category: Pre-NDA

Meeting Date and Time: Thursday, May 2, 2019; 11:00 AM – 12:00 PM (ET)
Meeting Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1313
Silver Spring, Maryland 20903

Application Number: NDA 212194
Product Name: givosiran
Proposed Indication: Acute hepatic porphyria (AHP)
Sponsor/Applicant Name: Alnylam Pharmaceuticals, Inc.

Introduction:

This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for Thursday, May 2, 2019, between Alnylam Pharmaceuticals, Inc. and the Division of Hematology Products. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda and/or changing the format of the meeting (e.g., from face to face to teleconference). Contact the Regulatory Project Manager (RPM) if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, as we may not be prepared to discuss or reach agreement on such changes at the meeting.

1.0 BACKGROUND

Givosiran is a synthetic double stranded oligonucleotide comprised of small interfering RNA that is proposed to inhibit synthesis of liver aminolevulinic acid synthase 1, leading to the downstream reduction of neurotoxic heme intermediates, ALA and PBG. This product is currently in development by Alnylam Pharmaceuticals, Inc. for the treatment of AHP in adults.

On May 23, 2017, givosiran was granted breakthrough therapy designation for the prophylaxis of attacks in patients with AHP and granted rolling submission review of portions of their planned...
NDA on August 8, 2018. The nonclinical and product quality modules of the NDA were submitted on November 15, 2018, and January 22, 2019, respectively. The final component of the NDA is expected to be submitted in June 2019.

On February 26, 2019, the Sponsor requested a pre-NDA meeting to discuss the content of the final component of the rolling NDA submission.

2.0 DISCUSSION

2.1. Clinical

**Question 1:** Does the Agency agree that the proposed clinical data package is adequate to support the review of an NDA of givosiran for the proposed indication: "for the treatment of acute hepatic porphyria (AHP) in adults"?

**FDA Response to Question 1:** Yes. The proposed data package appears to be adequate to support review of an NDA for givosiran for the treatment of AHP. The acceptability of the data to support the proposed indication will be a review issue.

**Question 2:** Does the Agency agree with the Sponsor’s proposed content and format of the Clinical Section (Part 3) of the rolling NDA submission?

**FDA Response to Question 2:** The proposed content and format of Part 3 of the rolling NDA submission appear acceptable.

2.2. Regulatory

**Question 3a:** Does the Agency agree with the proposed content and timing for the safety update report required under 21 CFR 314.50 (d)(5)(vi)(b)?

**FDA Response to Question 3a:** Ideally a Safety Update Report consisting of six-month follow-up information should be submitted as part of the NDA review process. In the meeting background package, you propose to submit four-month follow-up data in the Safety Update Report. The adequacy of the follow-up data that you intend to submit to support a benefit-risk assessment for givosiran for the proposed AHP indication will be a review issue.

**Question 3b:** Does the Agency agree with the proposed content and timing for the BIMO information?

**FDA Response to Question 3b:** The proposed content and timing of the BIMO information to be submitted is acceptable.

**Question 3c:** Does the Agency agree to an Applicant Orientation Meeting, and can the Agency provide any additional recommendations to facilitate the NDA review process?
**FDA Response to Question 3c:** Yes. An Applicant Orientation Meeting (AOM) would be desirable. In addition, a technical walkthrough after the AOM would assist in the review of the application.

**Question 3d:** Based on the proposed NDA, and data from the ENVISION study, does the Agency anticipate the need for an Advisory Committee meeting?

**FDA Response to Question 3d:** This question is premature. Determination on need for an Advisory Committee Meeting will be made after the application is filed.

**Question 3e:** Based on the proposed NDA and with Breakthrough Therapy Designation granted to givosiran, does the Agency anticipate conducting an expedited review of the application?

**FDA Response to Question 3e:** You should request Priority review of the application with the submission of Part 3 of the NDA and include any rationale to support the request. Refer to the Guidance for Industry, Expedited Programs for Serious Conditions – Drugs and Biologics, (available at https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf) for information regarding the qualifying criteria for priority review designation. The adequacy of the data to support granting Priority Review of the application will be a review issue.

**Additional Clinical Pharmacology Comments:**

**Recommendations regarding the labeling:**

We recommend that the content and format of information found in the Clinical Pharmacology section (Section 12) of labeling submitted to support this application be consistent with FDA Guidance for Industry, Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products – Content and Format (available at https://go.usa.gov/xn4qB). Consider strategies to enhance clarity, readability, and comprehension of this information for health care providers through the use of text attributes, tables, and figures as outlined in the above guidance.

**Address the following questions in the Summary of Clinical Pharmacology:**

1. What is the basis for selecting the doses and dosing regimen used in the registration trials to support your marketing application? Identify individuals who required dose modifications and provide time to the first dose modification and reasons for the dose modifications in support of the proposed dose and administration.

2. What are the exposure-response relationships for efficacy, safety, and biomarkers?

3. How do extrinsic (e.g., other drugs) and intrinsic factors (such as sex, race, body weight, organ dysfunctions, and disease) influence the exposure, efficacy, or safety of your drug? What dose modifications are recommended?
4. What is the impact of immunogenicity on exposure, efficacy and safety?

*Apply the following advice in preparing the clinical pharmacology sections of the original submission:*

1. Submit bioanalytical methods and validation reports for all clinical pharmacology and biopharmaceutics trials.

2. Provide final study report for each clinical pharmacology trial. Present the pharmacokinetic parameter data as geometric mean with coefficient of variation (and mean ± standard deviation) and median with range as appropriate.

3. Provide complete datasets for clinical pharmacology and biopharmaceutics trials. The subjects’ unique ID number in the pharmacokinetic datasets should be consistent with the numbers used in the clinical datasets.
   - Provide all concentration-time and derived pharmacokinetic parameter datasets as SAS transport files (*.xpt). A description of each data item should be provided in a define.pdf file. Any concentrations or subjects that have been excluded from the analysis should be flagged and maintained in the datasets.
   - Identify individual subjects with dose modifications; the time to the first dose reduction, interruption or discontinuation; the reasons for dose modifications in the datasets.

4. Submit the following for the population pharmacokinetic analysis reports:
   - Standard model diagnostic plots.
   - Individual plots for a representative number of subjects. Each individual plot should include observed concentrations, the individual prediction line and the population prediction line.
   - Model parameter names and units in tables.
   - Summary of the report describing the clinical application of modeling results.

Refer to the following pharmacometric data and models submission guidelines [http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm180482.htm](http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm180482.htm).

5. Submit the following information and data to support the population pharmacokinetic analysis:
   - SAS transport files (*.xpt) for all datasets used for model development and validation.
• A description of each data item provided in a Define.pdf file. Any concentrations or subjects that have been excluded from the analysis should be flagged and maintained in the datasets.

• Model codes or control streams and output listings for all major model building steps, e.g., base structural model, covariates models, final model, and validation model. Submitted these files as ASCII text files with *.txt extension (e.g., myfile_ctl.txt, myfile_out.txt).


3.0 OTHER IMPORTANT MEETING INFORMATION

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

As stated in our February 28, 2019, communication granting this meeting, if, at the time of submission, the application that is the subject of this meeting is for a new molecular entity or an original biologic, the application will be subject to “the Program” under PDUFA VI. Therefore, at this meeting be prepared to discuss and reach agreement with FDA on the content of a complete application, including preliminary discussions on the need for risk evaluation and mitigation strategies (REMS) or other risk management actions and, where applicable, the development of a Formal Communication Plan. You and FDA may also reach agreement on submission of a limited number of minor application components to be submitted not later than 30 days after the submission of the original application. These submissions must be of a type that would not be expected to materially impact the ability of the review team to begin its review. All major components of the application are expected to be included in the original application and are not subject to agreement for late submission.

Discussions and agreements will be summarized at the conclusion of the meeting and reflected in FDA’s meeting minutes. If you decide to cancel this meeting and do not have agreement with FDA on the content of a complete application or late submission of any minor application components, your application is expected to be complete at the time of original submission. In addition, we remind you that the application is expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities.

Information on the Program is available at https://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/default.htm.
PREA REQUIREMENTS

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

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

PRESCRIBING INFORMATION

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

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

Pursuant to the PLLR, you should include the following information with your application to support the changes in the Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of labeling. The application should include a review and summary of the available published literature regarding the drug’s use in pregnant and lactating women and the effects of the drug on male and female fertility (include search parameters and a copy of each reference publication), a cumulative review and summary of relevant cases reported in your
pharmacovigilance database (from the time of product development to present), a summary of drug utilization rates amongst females of reproductive potential (e.g., aged 15 to 44 years) calculated cumulatively since initial approval, and an interim report of an ongoing pregnancy registry or a final report on a closed pregnancy registry. If you believe the information is not applicable, provide justification. Otherwise, this information should be located in Module 1. Refer to the draft guidance for industry – Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425398.pdf).

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

**MANUFACTURING FACILITIES**

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

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

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

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

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

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


**ONCOLOGY PILOT PROJECTS**

The FDA Oncology Center of Excellence (OCE) is conducting two pilot projects, the Real-Time Oncology Review (RTOR) and the Assessment Aid. RTOR is a pilot review process allowing interactive engagement with the applicant so that review and analysis of data may commence prior to full supplemental NDA/BLA submission. Assessment Aid is a voluntary submission from the applicant to facilitate FDA’s assessment of the NDA/BLA application (original or supplemental). An applicant can communicate interest in participating in these pilot programs to the FDA review division by sending a notification to the Regulatory Project Manager when the top-line results of a pivotal trial are available or at the pre-sNDA/sBLA meeting. Those applicants who do not wish to participate in the pilot programs will follow the usual submission process with no impact on review timelines or benefit-risk decisions. More information on these
pilot programs, including eligibility criteria and timelines, can be found at the following FDA websites:

- RTOR: https://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/OCE/ucm612927.htm. In general, the data submission should be fully CDISC-compliant to facilitate efficient review.

- AssessmentAid: https://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/OCE/ucm612923.htm
This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

JENNIFER J LEE
04/26/2019 08:51:36 AM
IND 126094

Alnylam Pharmaceuticals, Inc.
Attention: Samuel Rigourd, PharmD
Senior Director, Regulatory Affairs
300 Third Street
Cambridge, MA  02142

Dear Dr. Rigourd:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for givosiran (ALN–AS1).

We also refer to the meeting between representatives of your firm and the FDA on June 14, 2017. The purpose of the meeting was to discuss the suitability of the nonclinical and clinical development program for givosiran to support a New Drug Application (NDA) for the treatment of adults with acute hepatic porphyria (AHP).

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

If you have any questions, call Quyen Tran, Regulatory Project Manager, at (301) 796-2771.

Sincerely,

[See appended electronic signature page]

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

Enclosure:
Meeting Minutes

Reference ID: 4112947
MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: Pre-Phase 3 and Initial Breakthrough Therapy
Meeting Date and Time: June 14, 2017, 3:00 p.m. – 4:00 p.m. EDT
Meeting Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1309
Silver Spring, MD 20993

Application Number: 126094
Product Name: Givosiran (ALN-AS1)
Indication: Acute hepatic porphyria (AHP)
Sponsor Name: Alnylam Pharmaceuticals, Inc.

Meeting Chair: Kathy Robie Suh, MD, PhD
Meeting Recorder: Quyen Tran, PharmD

FDA ATTENDEES

Office of Hematology and Oncology Products (OHOP)/Division of Hematology Products
Albert Deisseroth, MD, PhD, Supervisory Associate Division Director
Kathy Robie Suh, MD, PhD, Clinical Team Leader
Andrew Dmytrijuk, MD, Clinical Reviewer
Andrea Baines, MD, PhD, Clinical Reviewer
Theresa Carioti, MPH, Chief, Project Management Staff
Quyen Tran, PharmD, Regulatory Project Manager

OHOP/Division of Hematology, Oncology, Toxicology
Christopher Sheth, PhD, Supervisory Pharmacologist
Natalie Simpson, PhD, Toxicologist

Office of Biostatistics/Division of Biometrics V
Yuan Li Shen, DrPh, Statistical Team Leader

Office of Clinical Pharmacology (OCP)
CDR Hobart Rogers, PharmD, PhD, Genomics and Targeted Therapy Reviewer

OCP/Division of Clinical Pharmacology V
Bahru Habtemariam, PharmD, Clinical Pharmacology Team Leader

Reference ID: 4112947
1.0 BACKGROUND

Givosiran (ALN–AS1) is being developed for the treatment of acute hepatic porphyria (AHP) (b) (4). Givosiran is a small interfering ribonucleic acid (siRNA) that targets aminoleuvulinic acid synthase 1 (ALAS1), a mitochondrial enzyme involved in the rate limiting step of heme biosynthesis. Currently, the only specific treatment of AHP is the administration of intravenous hemin; Panhematin® is the only commercially available heme therapy in the United States.

The purpose of the requested meeting is to seek FDA advice and agreement on the suitability of the nonclinical and clinical development program to support an NDA for givosiran for the treatment of AHP. The Sponsor has evaluated the safety and efficacy of givosiran in in vitro HepG2 cell lines and in vivo mice, rats and cynomolgus monkeys. Givosiran received orphan designation for the treatment of AHP on August 29, 2016. Givosiran was granted breakthrough therapy designation for the prophylaxis of attacks in patients with AHP on May 23, 2017.

FDA sent Preliminary Comments to Alnylam Pharmaceuticals, Inc. on June 6, 2017.

2.0 DISCUSSION

Question 1:
Does the Agency agree that the Sponsor’s overall nonclinical program is adequate to support an NDA application for the use of givosiran to treat patients with AHP?
**FDA Response to Question 1:**
Yes, we agree.

**Discussion:**
There was no discussion.

**Question 2:**
Based on available in vitro, preclinical and clinical information from givosiran, the Sponsor proposes not to conduct a thorough QT/QTc, hepatic impairment, renal impairment or radiolabel PK studies with givosiran. Does the Agency agree with the Sponsor’s approach?

**FDA Response to Question 2:**
No.

We agree that a radiolabeled PK study (mass balance study) may not be appropriate in human due to long residence time of radiolabeled givosiran or its metabolites in the liver. Your proposed mass balance study in rats with radiolabeled givosiran and human excretion data from Phase 1 study with non-radiolabeled givosiran appear reasonable to understand the mass balance of givosiran in human.

The need for dedicated hepatic and renal impairment studies will depend on the following:

a. Finding of the rat mass balance study and human excretion study

b. Enrollment and evaluation of adequate number of patients with varying degree of renal and hepatic impairment (mild, moderate, and severe) in the planned Phase 3 trial

From the information provided in your briefing material, it appears that the QTc data collected from the Phase 1 study (ALN-AS1-001) is not adequate to inform any potential QTc effects because the ECG collection appears to have been done only prior to start of treatment and at completion of treatment period and none at/near T\(_{\text{max}}\). You will need to address the requirement to study the potential of your product to prolong the QT interval.

Also, we note that the schedule of assessments table (Table 1) in the protocol concept for Study ALN-AS1-003 seems to suggest that triplicate 12-lead ECGs will be also assessed at but the footnote text is not in conformity with this information. Please correct the information appropriately.

**Discussion:**
The Sponsor plans to include patients with mild and moderate renal impairment and mild hepatic impairment in the planned Phase 3 trial. The Sponsor is concerned that the comorbidities and the small size of these subpopulations will make data interpretation difficult.
The Agency advised the Sponsor to optimize the PK and QTc sampling schedule. The Sponsor will provide the updated PK and QTc sampling schedule.

**Question 3:**
Does the Agency agree with the Sponsor’s proposed strategy to evaluate whether a dedicated clinical drug-drug interaction (DDI) study is warranted for CYP3A4 substrates?

**FDA Response to Question 3:**
No.

**Discussion:**
The Agency agrees with the Sponsor’s proposed DDI plan as outlined in slide 12.

**Question 4:**
Does the Agency agree that results from Phase 1 as well as PK/PD analyses support the proposed SC dosing regimen of givisorian 2.5 mg/kg monthly to be evaluated in the Phase 3 study?

**FDA Response to Question 4:**
The proposed dosing regimen appears acceptable in terms of achieving reduction of PD biomarkers such as urinary ALAS1 mRNA and ALA levels.

**Discussion:**
There was no discussion.

**Question 5:**
Does the Agency agree with the Sponsor’s Phase 3 study design, specifically:

a. Does the Agency agree with the Sponsor’s choice of comparator?
b. Does the Agency agree with the proposed study inclusion and exclusion criteria?
c. Does the Agency agree with the study primary and secondary endpoints?
d. Does the Agency agree with the proposed randomization and stratification scheme?
e. Does the Agency agree with the plan for exemption from expedited reporting for protocol-specified endpoints and disease-related events as outlined?

**FDA Response to Question 5:**

a. Yes.

b. You will need to submit the study report for Study No. AS1-GLP15-018 (5001380) “A 39-Week Subcutaneous Injection Toxicity and Toxicokinetic Study in the Juvenile Cynomolgus Monkey with a 13-Week Recovery Period” as soon as possible and prior to initiation of your Phase 3 clinical study which would enroll patients aged 12 years and older. Also, unless there are specific safety concerns, your study should enroll patients with varying degrees of renal or hepatic impairment.
c. The proposed primary endpoint is acceptable. However, you should consider including improvement in Patient Reported Outcomes (PRO) in patients with AHP who are treated with givosiran as a key endpoint due to the importance of pain and quality of life (QOL) in this disease setting. Please also consider additional clinical comments below regarding the development of PRO to support the proposed indication for givosiran.

d. Yes.

e. No. The Agency agrees that porphyria attacks requiring hospitalization, urgent healthcare visits or home hemin administration, and the exploratory endpoint of all porphyria attacks, including those at home not requiring hemin administration, are expected events that are to be collected as efficacy parameters and will not be reported as adverse events or serious adverse events. Other adverse events and serious adverse events should still be captured and reported.

Discussion:
There was no discussion.

Question 6:
Does the Agency agree with the Sponsor’s statistical considerations, specifically:

a. Does the Agency agree with the primary analysis method for the primary efficacy endpoint?

b. Does the Agency agree with the proposed use of hierarchical testing to control the overall type I error for the testing of primary and key secondary endpoints?

FDA Response to Question 6:

a. The proposed negative binomial model for the primary efficacy endpoint analysis appears to be reasonable. However, please submit the proposed software (e.g., example code) of such analyses for further evaluation.

The number of patients not being evaluated for the primary and key secondary endpoints should be kept to a minimum. Too much missing data (or early study dropout) will undermine the reliability and confidence of the results. The reasons for missing assessments should be collected. Sensitivity analyses (e.g., recurring time to event analyses) should be performed to examine the potential impact of missing data. For further advice, see the National Academies of Sciences report on The Prevention and Treatment of Missing Data in Clinical Trials. An electronic version of the document can be found from the National Academies Press at http://www.nap.edu/catalog.php?record_id=12955. A special report of the document can be found at http://www.nejm.org/doi/full/10.1056/NEJMsr1203730.

b. The proposed hierarchical testing procedure appears to be reasonable. However, this will depend on agreement with secondary efficacy endpoints, details of the definitions and analysis strategy of secondary endpoints, and the proposed order of testing.
Discussion:
There was no discussion.

Question 7:
The Sponsor intends to seek an indication for the treatment of AHP, therefore:

a. Does the Agency agree with the Sponsor’s overall program of completed and planned clinical studies?

b. 

FDA Response to Question 7:
a. The adequacy of the proposed clinical program to support the indication will be a review issue.

b. No.

You should note that generally, two adequate and well-controlled studies are needed for a new indication. The adequacy of a single study to support approval of a new indication will be determined by its ability to support the efficacy claim based on strength of the results. Internal consistency across study subsets, evidence of an effect on multiple endpoints, and statistically very persuasive efficacy results will be considered in the evaluation. The Sponsor should also refer to the “Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drugs and Biological Products, May 1998” at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072008.pdf. We encourage additional discussion regarding the registration pathway as the development plan for givosiran progresses.

Discussion:

Question 8:
Given the seriousness of the condition, the preliminary data from givosiran indicating a potentially meaningful advantage over available therapy and the demonstration of benefit on clinical endpoints likely to predict long term clinical benefit in a confirmatory clinical trial, the
Sponsor would like to discuss with the FDA the potential for accelerated approval for givosiran for the treatment of AIP. The Sponsor believes the proposed data package for givosiran based on Phase 1 and Phase 1/2 data meets the FDA criteria for accelerated approval. Does the Agency agree?

**FDA Response to Question 8:**
This question is premature.

**Additional Statistical Comment:**

a. We are unable to replicate the sample size calculation results. It is expected that the statistical analysis method used for the primary efficacy endpoint analysis will be used for the sample size calculation. Please provide more details (e.g., programming code) to demonstrate the sample size calculation results.

**Additional Clinical Comments:**

a. **Health-Related Quality of Life Measurement**

   - We recommend you prioritize analyses of collected PRO data by the most important patient-reported symptoms and functional impacts (i.e., physical function) that are responsive to treatment. We also recommend separate measurement of treatment-related symptoms using an unbiased selection set of symptom concepts from an item library such as the PRO-CTCAE.

b. **Pain Measurement**

   - Pain measurement may be challenging in your trial context given patients may have chronic background pain complicated by acute episodes. It is unclear whether you intend to measure pain palliation, or time to pain worsening or pain consistent with an episode of acute hepatic porphyria. We have provided general considerations for both measurement of pain palliation and time to pain appearance or progression below.

c. **Pain Palliation**

   - Pain palliation resulting from treatment of the underlying disease can provide direct evidence of treatment benefit when combined with evidence of disease control. Please refer to the manuscript providing trial design considerations coauthored by FDA on this topic (Basch et al., Pain palliation measurement in cancer clinical trials. Cancer 2014; 120: 761-7).

   - The Brief Pain Inventory – Short Form (BPI-SF) Item 3 (“pain at its worst in the last 24 hours”) is a well-documented measurement of pain and appears reasonable to use for assessment of pain intensity. You should propose an appropriate threshold that would constitute a clinically meaningful change (both improvement and
d. Time to Pain Progression
   • There is currently no standard endpoint definition for time to pain progression. Please provide your rationale for the definition you select. Clearly pre-specify the endpoint definition and include pain medication within the definition for your primary statistically tested hypothesis. To strengthen PRO pain results, include a patient-reported analgesic log to document analgesic use. Given the uncertainty regarding optimal endpoint definition, pre-specify several sensitivity analyses to include differing change thresholds as well as confirmation versus unconfirmed pain progression events.

e. Patient-Reported Analgesic Log
   • Provide a detailed daily patient log of pain medications for analgesic use and changes to prescribed analgesic (medication name [generic name], dose, unit, and route of administration).

Additional General Comments Regarding Measurement of Patient-Reported Outcomes:

f. Trial Design Advice
   • Optimize the frequency and timing of assessments. Increased assessments early in therapy is important to capture acute toxicity and tolerability and can maximize the amount of data available in both the investigational and control arms, particularly for patients who withdraw early.
   • Prospectively put in place procedures for minimizing missing data, including obtaining PRO data from patients at time of early withdrawal, and include these procedures in the protocol. Reasons for missing PRO data at the overall score- and item-level should be documented and included in the analysis dataset.
   • Where feasible, analyze measures of disease-related symptoms, symptomatic adverse events, and physical function as distinct concepts.
   • Provide a pre-specified plan for the analysis of PRO data including the threshold for and interpretation of a meaningful change in score(s). Any deviation from the instrument’s scoring manual should be noted and a rationale provided.
   • Carefully record the use of concomitant medications that may affect the interpretation of the concept(s) being measured (e.g., use of concomitant pain medications when measuring pain).

g. Labeling Considerations
   • Inclusion of PRO data in the product label will depend on the adequacy of submitted data, the strengths and limitations of the instrument within the given context of use, and the design and conduct of the trial.
   • If a claim of superiority in a particular PRO concept is sought, pre-specify the PRO hypothesis and test it within the statistical hierarchy of hypothesis testing in the
clinical trial. Control the overall type I error rate for testing hypotheses based on primary and all secondary endpoints. Prospectively define the statistical analysis methods, especially procedures for handling missing values. Provide justification in advance for the endpoint definition, including what constitutes meaningful change, for FDA review and comment.

- PRO findings without a prospectively specified statistical analysis plan are considered descriptive. FDA will review these data as part of the totality of submitted information, and will evaluate and consider whether inclusion of descriptive PRO data in labeling is appropriate on a case-by-case basis, taking into consideration any factors that may affect the interpretability and reliability of the findings.

**Discussion:**
The Sponsor proposed to submit a package for accelerated approval including a total of [b (4)] patients. The Agency expressed extreme reservations about the likelihood that this would be an adequate database to support an approval. The Agency agreed wholeheartedly there is an unmet medical need in this population and is committed to working with the sponsor to get available therapy to patients as quickly as possible. The Agency encouraged the Sponsor to consider aggressively pursuing the planned Phase 3 study (recruitment of study sites, initiation, enrollment, etc.) and possibly consider whether an interim analysis might be appropriate for the study. The Agency will make itself available for discussions as needed to advance the development program.

3.0 OTHER IMPORTANT MEETING INFORMATION

**PREA REQUIREMENTS**

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

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

**DATA STANDARDS FOR STUDIES**

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

On December 17, 2014, FDA issued final guidance, Providing Electronic Submissions in Electronic Format--- Standardized Study Data (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292334.pdf). This guidance describes the submission types, the standardized study data requirements, and when standardized study data will be required. Further, it describes the availability of implementation support in the form of a technical specifications document, Study Data Technical Conformance Guide (Conformance Guide) (See http://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM384744.pdf), as well as email access to the eData Team (cder-edata@fda.hhs.gov) for specific questions related to study data standards. Standardized study data will be required in marketing application submissions for clinical and nonclinical studies that start on or after December 17, 2016. Standardized study data will be required in commercial IND application submissions for clinical and nonclinical studies that start on or after December 17, 2017. CDER has produced a Study Data Standards Resources web page that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers.

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

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

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

Reference ID: 4112947
LABORATORY TEST UNITS FOR CLINICAL TRIALS

CDER strongly encourages IND sponsors to identify the laboratory test units that will be reported in clinical trials that support applications for investigational new drugs and product registration. Although Système International (SI) units may be the standard reporting mechanism globally, dual reporting of a reasonable subset of laboratory tests in U.S. conventional units and SI units might be necessary to minimize conversion needs during review. Identification of units to be used for laboratory tests in clinical trials and solicitation of input from the review divisions should occur as early as possible in the development process. For more information, please see the FDA website entitled, Study Data Standards Resources and the CDER/CBER Position on Use of SI Units for Lab Tests website found at http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/ucm372553.htm.

SUBMISSION FORMAT REQUIREMENTS

The Electronic Common Technical Document (eCTD) is CDER and CBER’s standard format for electronic regulatory submissions. 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.

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 Item</th>
<th>STF File Tag</th>
<th>Used For</th>
<th>Allowable File Formats</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>data-listing-dataset</td>
<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>
<td>.pdf</td>
</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:

- [m5]
  - datasets
    - bimo
      - site-level

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.

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1 Please see the OSI Pre-NDA/BLA Request document for a full description of requested data files
References:

eCTD Backbone Specification for Study Tagging Files v. 2.6.1

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

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

**PATIENT-FOCUSED ENDPOINTS**

An important component of patient-focused drug development is describing the patient’s perspective of treatment benefit in labeling based on data from patient-focused outcome measures [e.g., patient-reported outcome (PRO) measures]. Therefore, early in product development, we encourage sponsors to consider incorporating well-defined and reliable patient-focused outcome measures as key efficacy endpoints in clinical trials, when appropriate, and to discuss those measures with the Agency in advance of confirmatory trials. For additional information, refer to FDA’s guidance for industry Patient-Reported Outcome Measures: Use in Medical Product Development to Support Claims, available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM193282.pdf.

**NEW PROTOCOLS AND CHANGES TO PROTOCOLS**

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

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

We recommend you consider requesting a meeting to facilitate discussion of multiple and/or complex issues.
4.0 ISSUES REQUIRING FURTHER DISCUSSION

No issues requiring further discussion.

5.0 ACTION ITEMS

No action items identified during the meeting.

6.0 ATTACHMENTS AND HANDOUTS

A presentation containing the Sponsor’s response to the FDA’s meeting preliminary comments is appended.
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

KATHY M ROBIE SUH
06/19/2017
Section I: Provide the following information to determine if the BTDR can be denied without Medical Policy Council (MPC) review.

1. Briefly describe the indication for which the product is intended (Describe clearly and concisely since the wording will be used in the designation decision letter):

   The proposed indication for ALN-AS1 is for the prophylaxis of attacks in patients with acute hepatic porphyria.

2. Are the data supporting the BTDR from trials/IND(s) which are on Clinical Hold? □YES □NO

   If 2 above is checked “Yes,” the BTDR can be denied without MPC review. Skip to number 5 for clearance and sign-off. If checked “No”, proceed with below:

3. Consideration of Breakthrough Therapy Criteria:

   a. Is the condition serious/life-threatening1)? □YES □NO

      If 3a is checked “No,” the BTDR can be denied without MPC review. Skip to number 5 for clearance and sign-off. If checked “Yes”, proceed with below:

   b. Are the clinical data used to support preliminary clinical evidence that the drug may demonstrate substantial improvement over existing therapies on 1 or more clinically significant endpoints adequate and sufficiently complete to permit a substantive review?

      □ YES the BTDR is adequate and sufficiently complete to permit a substantive review

      □ Undetermined

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NO, the BTDR is inadequate and not sufficiently complete to permit a substantive review; therefore the request must be denied because (check one or more below):

i. Only animal/nonclinical data submitted as evidence

ii. Insufficient clinical data provided to evaluate the BTDR (e.g. only high-level summary of data provided, insufficient information about the protocol[s])

iii. Uncontrolled clinical trial not interpretable because endpoints are not well-defined and the natural history of the disease is not relentlessly progressive (e.g. multiple sclerosis, depression)

iv. Endpoint does not assess or is not plausibly related to a serious aspect of the disease (e.g., alopecia in cancer patients, erythema chronicum migrans in Lyme disease)

v. No or minimal clinically meaningful improvement as compared to available therapy\(^2\) historical experience (e.g., <5% improvement in FEV1 in cystic fibrosis, best available therapy changed by recent approval)

4. Provide below a brief description of the deficiencies for each box checked above in Section 3b:

If 3b is checked “No”, BTDR can be denied without MPC review. Skip to number 5 for clearance and sign-off (Note: The Division always has the option of taking the request to the MPC for review if the MPC’s input is desired. If this is the case, proceed with BTDR review and complete Section II). If MPC review is not required, email Miranda Raggio and Sandy Benton as soon as this determination is made so that the BTDR can be removed from the MPC calendar.

If 3b is checked “Yes” or “Undetermined”, proceed with BTDR review and complete Section II, as MPC review is required.

5. Clearance and Sign-Off (no MPC review)

Deny Breakthrough Therapy Designation

Reviewer Signature: {See appended electronic signature page}

Team Leader Signature: {See appended electronic signature page}

Division Director Signature: {See appended electronic signature page}

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Section II: If the BTDR cannot be denied without MPC review in accordance with numbers 1-3 above, or if the Division is recommending that the BTDR be granted, provide the following additional information needed by the MPC to evaluate the BTDR.

6. A brief description of the drug, the drug’s mechanism of action (if known), the drug’s relation to existing therapy(ies), and any relevant regulatory history. Consider the following in your response.

Acute hepatic porphyria (AHP) is a rare disease with a prevalence of 5-10 cases/100,000 people in the US and affects primarily females (age range 15-45 years). AHP occurs as a result of an autosomal dominant mutation that leads to deficiency of aminolevulinic acid dehydratase and porphobilinogen deaminase which are enzymes in the heme biosynthesis pathway. The rate limiting step in heme synthesis is the enzyme aminolevulinic acid synthase 1 (ALAS1) which is controlled by feedback repression via the end-product heme. ALAS1 is induced in response to a decrease in the endogenous heme pool in the liver which can occur with stressors such as: fasting, hormonal alterations or cytochrome P450 inducing drugs. The induction of ALAS1 results in increased production and accumulation of toxic heme intermediates delta aminolevulinic acid (ALA) and porphobilinogen (PBG) in the plasma.

and urine. Clinically, the accumulation of toxic heme intermediates results in acute attacks characterized by severe abdominal pain, muscle weakness, seizures, psychiatric dysfunction, irreversible neurologic damage and increased risk of hepatic malignancy. (Bissell, 2015)

Management of AHP attacks often requires hospitalization. Patients are initially treated with supportive care, intravenous fluid administration, carbohydrate loading, analgesics, antiemetics and removal of known precipitating factors. Panhematin® (Hemin for Injection, approved for marketing in 1983) is an intravenously administered iron containing metalloporphyrin ALAS1 inhibitor that is derived from processed red blood cells. Panhematin is indicated for the amelioration of recurrent attacks of acute intermittent porphyria (AIP) temporally related to the menstrual cycle in susceptible women. The recommended Panhematin dose is 3-4 mg/kg infused over 15 minutes in a large vein or central venous catheter once daily for a period of 3-5 days. Prior to administration of Panhematin the drug must be filtered in order to remove particulates. Symptoms generally improve in patients after 2-5 days of hematin treatment accompanied by a decrease in ALA and PBG production. Panhematin is not typically stocked in hospital pharmacies and must be ordered from the manufacturer which can delay therapy. Liver transplants, when available, can also be considered for this disease. (Lichtman, 2003)

ALN-AS1 (Givosiran) is a small interfering RNA (siRNA) that inhibits aminolevulinic acid synthase 1 (ALAS1) synthesis in the liver. Inhibition of ALAS1 reduces the downstream synthesis of ALA and PBG. Currently there are no approved therapies that are indicated for the prophylaxis of AHP attacks. ALN-AS1 (Givosiran) is being developed for the prophylaxis of acute hepatic porphyria attacks and may meet an unmet medical need. Panhematin has been used off label as a twice weekly infusion. Frequent administrations of Panhematin may lead to thrombotic complications of superficial veins, iron overload and end organ damage due to hemosiderosis. (Pischik, 2015)

7. Information related to endpoints used in the available clinical data:

a. Describe the endpoints considered by the sponsor as supporting the BTDR and any other endpoints the sponsor plans to use in later trials. Specify if the endpoints are primary or secondary, and if they are surrogates.

The sponsor submitted data from study ALN-AS1-001 titled, “A Phase 1, Single-Ascending Dose, Multiple-Ascending Dose, and Multi-Dose Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics Study of Subcutaneously Administered ALN-AS1 in Patients with Acute Intermittent Porphyria (AIP)”. The primary efficacy endpoints for this study were pharmacokinetic and pharmacodynamic endpoints including reduction in serum and urinary aminolevulinic acid (ALA) and porphobilinogen (PBG) levels. Important exploratory endpoints included evaluation of the frequency, duration, and severity of porphyria attacks, change in the frequency of hematin and pain medication administration and the number and duration of hospitalizations.

b. Describe the endpoint(s) that are accepted by the Division as clinically significant (outcome measures) for patients with the disease. Consider the following in your response:

A clinically significant change in the in the frequency of porphyria attacks and a decrease in the number of hospitalizations would allow assessment of the benefit of ALN-AS1 (Givosiran) and support regular approval of the drug for the treatment of patients with acute hepatic porphyria.

c. Describe any other biomarkers that the Division would consider likely to predict a clinical benefit for the proposed indication even if not yet a basis for accelerated approval.

Secondary efficacy endpoints that would support an assessment of the benefit of givosiran would be significant changes in serum/urinary ALA and PBG levels compared to baseline.

8. A brief description of available therapies, if any, including a table of the available Rx names, endpoint(s)
used to establish efficacy, the magnitude of the treatment effects (including hazard ratio, if applicable), and the specific intended population. Consider the following in your response:

As described in the response to question 6, management of acute hepatic porphyria (AHP) attacks often requires hospitalization. Patients are initially treated with supportive care, intravenous fluid administration, carbohydrate loading, analgesics, antiemetics and removal of known precipitating factors. Panhematin® (Hemin for Injection, approved for marketing in 1983) is an intravenously administered iron containing metalloporphyrin ALAS1 inhibitor that is indicated for the amelioration of recurrent attacks of acute intermittent porphyria (AIP) temporally related to the menstrual cycle in susceptible women. There are no other therapies that are used to treat AHP.

9. A brief description of any drugs being studied for the same indication, or very similar indication, that requested breakthrough therapy designation.

No other drugs are being studied for the proposed indication, i.e., treatment of acute hepatic porphyria (AHP).

10. Information related to the preliminary clinical evidence:

a. Table of clinical trials supporting the BTDR (only include trials which were relevant to the designation determination decision), including study ID, phase, trial design, trial endpoints, treatment group(s), number of subjects enrolled in support of specific breakthrough indication, hazard ratio (if applicable), and trial results.

The sponsor submitted data from the ongoing study ALN-AS1-001 titled, “A Phase 1, Single-Ascending Dose, Multiple-Ascending Dose, And Multi-Dose Safety, Tolerability, Pharmacokinetics, And Pharmacodynamics Study Of Subcutaneously Administered ALN-AS1 In Patients With Acute Intermittent Porphyria (AIP)” (original protocol submitted to IND 126094 August 13, 2015). Briefly, study ALN-AS1-001 is a first-in-human-study of ALN-AS1 (Givosiran) in patients with AHP or patients who are asymptomatic high excreters (ASHE) of aminolevulinic acid (ALA) and porphobilinogen (PBG). The objectives of this study are to evaluate the safety and tolerability, pharmacokinetics and pharmacodynamics of ALN-AS1 administration to patients with AIP who are ASHE of ALA and PBG and in patients with AHP who experience recurrent attacks. Study ALN-AS1-001 is a phase 1, multicenter, randomized, single-blind (Parts A and B) and open label (Part C), placebo-controlled, three part study. Up to 72 adult patients, age 18-65 years, with AHP who are ASHE (Parts A and B) or those who have symptomatic AHP (Part C) will be enrolled. The key enrollment criteria are as follows.

- Diagnosis of AHP defined as a genetic test showing documentation of a mutation of porphobilinogen deaminase (PBGD) PBGD (Parts A, B and C).
- PBG level >4 mmol/mL serum creatinine (Cr) (Parts A and B). Patients who have experienced an acute porphyria attack within 6 months of planned study enrollment are excluded from parts A and B.
- AHP attack (defined as intense abdominal or back pain requiring hospitalization, hematin use, treatment consisting of increased carbohydrate intake and/or pain medication use) at least 2 times during the 6 months before enrollment (Part C).
- Patient on a scheduled regimen of hematin to prevent porphyria attacks at the time of enrollment and has experienced at least 1 porphyria attack (requiring unscheduled hematin or opiate use) during the 6 months before enrollment (Part C).

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3 Biweekly reports of all BTDRs, including the sponsor, drug, and indication, are generated and sent to all CPMSs.
4 Trial design information should include whether the trial is single arm or multi-arm, single dose or multi-dose, randomized or non-randomized, crossover, blinded or unblinded, active comparator or placebo, and single center or multicenter.
Patients are monitored in Parts A, B and C of the study for 42 days following the dose of study drug for safety by a Safety Review Committee (SRC) consisting of the principal investigator (PI), sponsor’s Medical Monitor and the Study Medical Monitor. ALA and PBG are monitored every 2 weeks for 8 weeks and then once every 4 weeks until the end of the study. In Parts A and B patients are randomized 3:1 to either ALN-AS1 or placebo treatment. The ALN-AS1 starting dose is 0.035 mg/kg in this Phase 1 study. In Part A patients will receive a single dose of study drug and in parts B and C of the study multiple doses of study drug are administered (two doses in part B and up to four doses in part C). The reviewer’s table below summarizes the key study data that is submitted to support the sponsor’s Breakthrough Therapy Designation Request for ALN-AS1 (Givosiran). Notably, in Part C the mean annualized AHP attack rate for patients in cohorts 1, 2 and 3 was 14 attacks/year (range 0-50 attacks/year).

Table 1. Study ALN-AS1-001 Summary

<table>
<thead>
<tr>
<th>Study ID</th>
<th>Phase</th>
<th>Trial Design</th>
<th>Trial Primary Efficacy Endpoints</th>
<th>Treatment Groups</th>
<th>Number of Patients Enrolled To Date</th>
<th>Key Trial Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALN-AS1-001</td>
<td>1</td>
<td>Phase 1, randomized (3:1 [givosiran: placebo]) single-blind single ascending dose and multiple ascending dose and double-blind multiple-dose safety, tolerability, pharmacokinetic and pharmacodynamic study.</td>
<td>Pharmacokinetics of ALN-AS1 and pharmacodynamic effects of ALN-AS1 on serum and urinary ALA and PBG levels</td>
<td>Part A (single ascending dose): 0.035-2.5 mg/kg administered SC as a single dose. Part B (multiple ascending dose): 0.35-1.0 mg/kg administered SC in two doses 28 days apart. Part C (multiple dose): Cohort 1: 2.5 mg/kg administered SC every three months for two doses. Cohort 2: 2.5 mg/kg administered SC once monthly for four doses. Cohort 3: 5.0 mg/kg administered</td>
<td>Part A: 15 patients treated with givosiran and 5 patients treated with placebo Part B: 6 patients treated with givosiran and 2 patients treated with placebo Part C: 9 patients treated with givosiran and 3 patients treated with placebo</td>
<td>Parts A and B: dose dependent reductions in serum/urinary ALA and PBG relative to baseline. Part B: Reduction from baseline of in mean urinary ALA (84% reduction compared to baseline) and mean urinary PBG (93% reduction compared to baseline) observed in the 1.0 mg/kg dose group, i.e., the highest dose tested in part B. ALA and PBG reduction in both dose were sustained for...</td>
</tr>
</tbody>
</table>
The reviewer’s table below summarizes the frequency of adverse events (AEs) and serious AEs (SAEs) reported in study ALN-AS1-001. AEs reported in ≥ 4 patients in the study included abdominal pain (n=6 patients), nausea (n=5 patients), nasopharyngitis (n=5 patients) and abdominal pain (n=4 patients). SAEs were reported in 4 patients of which one was fatal (n=2 abdominal pain, n=1 constipation and n=1 fatal hemorrhagic pancreatitis (Patient # (b) (6) ). The case of hemorrhagic pancreatitis is summarized below.

### Table 2. Summary of Safety in Study ALN-AS1-001

<table>
<thead>
<tr>
<th></th>
<th>Part A</th>
<th>Part B</th>
<th>Part C</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Givosiran (n=15)</td>
<td>Placebo (n=5)</td>
<td>Givosiran (n=6)</td>
</tr>
<tr>
<td><strong>Adverse Events</strong></td>
<td>n, %</td>
<td>n, %</td>
<td>n, %</td>
</tr>
<tr>
<td></td>
<td>11, 73</td>
<td>5, 100</td>
<td>6, 100</td>
</tr>
<tr>
<td><strong>Serious Adverse Events</strong></td>
<td>2, 13</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>Premature Treatment Discontinuations</strong></td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Reviewer’s table derived from sponsor’s Breakthrough Therapy Request Designation submission pages 24 and 25

- **Patient # (b) (6):** This patient was a female age 6 years with acute hepatic porphyria (AHP) who had monthly AHP attacks associated with her menstrual cycle. Her past medical history includes obesity, hypertension, hypothyroidism, depression, anxiety and central venous catheter placement for Panhematin infusion. The patient required near constant opioid treatment for pain and hematin for porphyria attacks. The patient was treated with givosiran 5mg/kg every 4 weeks. The patient had received 3 doses of study drug prior to the SAE. No serum or urinary ALA or PBG levels were reported by the sponsor prior to or during therapy with givosiran. Sixteen days after the first dose of study drug the patient was febrile and had a blood culture positive staphylococcal infection which was related to an infected central venous catheter. The
infection was treated with vancomycin and the patient’s central venous catheter was removed. Three days prior to the SAE (hemorrhagic pancreatitis) the patient complained of worsening abdominal pain associated with nausea and vomiting. The patient was diagnosed with pancreatitis (serum lipase 1242 U/L). The patient’s serum total bilirubin was 1.6 and elevated serum alanine aminotransferase (AST 258 U/L) and alanine aminotransferase (ALT 132 U/L). An abdominal ultrasound was reported to show poor gallbladder emptying and pancreatic duct dilation of 4 mm but did not show gallstones. The patient had an autopsy which confirmed hemorrhagic pancreatitis, however the patient had a transthoracic echocardiogram at the time of the autopsy which confirmed a pulmonary embolism.

Generally, trial ALN-AS1-001 can be considered a small trial (n=30 patients enrolled to date out of 70 patients that are planned to be enrolled). However, acute hepatic porphyria (AHP) is a rare disease with a prevalence of 5-10 cases/100,000 people in the US. The overall mean decrease in annualized AHP attack rate in givosiran cohorts 1, 2 and 3 (n=9 patients) of 68% compared to the placebo treated cohort (n=3 patients) of 8% can be considered preliminary clinical evidence of a substantial improvement over available therapies. Sustained decreases in the neurotoxic intermediates aminolevulinic acid (ALA) and porphobilinogen (PBG) in patients with AHP attacks or who are high excreters of ALA and PBG supports the assessment of a clinical benefit givosiran therapy for the treatment of patients with AHP. One fatal event was reported (hemorrhagic pancreatitis and pulmonary embolism) which occurred after the patient’s third dose of study drug suggesting that givosiran may not have been related to these SAEs. Overall however, givosiran appears to be generally well tolerated.

11. Division’s recommendation and rationale (pre-MPC review):

GRANT:

Provide brief summary of rationale for granting:

During acute hepatic porphyria (AHP) attacks there is an accumulation of toxic heme intermediates aminolevulinic acid (ALA) and porphobilinogen (PBG) that results in acute attacks characterized by neurovisceral damage. ALN-AS1 (Givosiran) is a small interfering RNA (siRNA) that inhibits aminolevulinic acid synthase 1 (ALAS1) synthesis in the liver and subsequently reduces the downstream synthesis of the neurotoxic intermediates ALA and PBG. Currently, there are no approved therapies that are indicated for the prophylaxis of AHP attacks. ALN-AS1 (Givosiran) is being developed for the prophylaxis of acute hepatic porphyria attacks and may meet an unmet medical need. In study ALN-AS1-001 the overall mean decrease in annualized AHP attack rate in ALN-AS1 (Givosiran) treated cohorts (n=9 patients) was 68% compared to the placebo treated cohort (n=3 patients) which was 8% and can be considered preliminary clinical evidence of a substantial improvement over available therapies.

Note, if the substantial improvement is not obvious, or is based on surrogate/pharmacodynamic endpoint data rather than clinical data, explain further.

DENY:

Provide brief summary of rationale for denial:

Note that not looking as promising as other IND drugs is not a reason for denial; the relevant comparison is with available (generally FDA-approved) therapy. If the Division does not accept the biomarker/endpoint used as a basis for traditional approval or accelerated approval or as a basis for providing early clinical evidence of a substantial improvement over available therapy, explain why:

12. Division’s next steps and sponsor’s plan for future development:
a. If recommendation is to grant the request, explain next steps and how the Division would advise the sponsor (for example, plans for phase 3, considerations for manufacturing and companion diagnostics, considerations for accelerated approval, recommending expanded access program):

The Division of Hematology Products (DHP) recommends that the sponsor complete trial ALN-AS1-001 to further establish the recommended phase 2 dose of ALN-AS1 (Givosiran) and continue to define the safety profile of the drug. The sponsor is encouraged to further explore the safety and efficacy of givosiran in adequate and well controlled phase 3 trials in order to support an evaluation of the risks and benefits of givosiran for the treatment patients with acute hepatic porphyria (AHP).

b. If recommendation is to deny the request and the treatment looks promising, explain how the Division would advise the sponsor regarding subsequent development, including what would be needed for the Division to reconsider a breakthrough therapy designation:

13. List references, if any:


14. Is the Division requesting a virtual MPC meeting via email in lieu of a face-to-face meeting? YES ❌ NO ❌

15. Clearance and Sign-Off (after MPC review):

Grant Breakthrough Therapy Designation ❌
Deny Breakthrough Therapy Designation ❌

Reviewer Signature: Andrew Dmytriuk, M.D. {See appended electronic signature page}
Team Leader Signature: Kathy Robie-Suh, M.D., Ph.D. {See appended electronic signature page}
Division Director Signature: Ann Farrell, M.D. {See appended electronic signature page}

Revised 1/15/16/M. Raggio
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ANDREW DMYTRIUK  
05/19/2017

KATHY M ROBIE SUH  
05/19/2017

ANN T FARRELL  
05/19/2017