CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214103Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

IND 128941

MEETING MINUTES

Alnylam Pharmaceuticals, Inc
Attention: Mugdha Sitole, PharmD
Associate Director, Regulatory Affairs
300 Third Street
Cambridge, MA 02142

Dear Dr. Sitole:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for lumasiran (ALN-GO1).

We also refer to the meeting between representatives of your firm and the FDA on February 24, 2020. The purpose of the meeting was to discuss your planned NDA filing.

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

If you have any questions, please call Brian Proctor, Regulatory Project Manager at (240) 402-3596.

Sincerely,

{See appended electronic signature page}

Aliza Thompson, MD, MS
Deputy Director
Division of Cardiology and Nephrology
Office of Cardiology, Hematology, Endocrinology and Nephrology
Center for Drug Evaluation and Research

Enclosure:

- Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: Pre-NDA

Meeting Date and Time: February 24, 2020 from 2 pm - 3 pm
Meeting Location: White Oak Building 22, Conference Room: 1315

Application Number: IND 128941
Product Name: lumasiran (ALN-GO1)
Indication: Treatment of primary hyperoxaluria type 1 (PH1)
Sponsor Name: Alnylam Pharmaceuticals, Inc

Meeting Chair: Aliza Thompson, MD, MS
Meeting Recorder: Brian Proctor, RAC

FDA ATTENDEES

Office of Drug Evaluation I

Ellis Unger, MD	Director

Office of Drug Evaluation I, Division of Cardiovascular and Renal Products

Norman Stockbridge, MD, PhD	Director
Aliza Thompson, MD, MS	Deputy Director
Kimberly Smith, MD	Clinical Team Leader
Kirtida Mistry, MD	Clinical Reviewer
Xuan Chi, PhD	Pharmacology Team Leader
Edward Fromm, RPh, RAC	Chief, Project Management Staff
Brian Proctor, RAC	Senior Regulatory Health Project Manager
Brian Cooney	Regulatory Health Project Manager

Office of Biostatistics, Division of Biometrics I

Jialu Zhang, PhD	Biometrics Team Leader
Ququan Liu, PhD	Biometrics Reviewer

Office of Clinical Pharmacology, Division of Clinical Pharmacology I

Sudharshan Hariharan, PhD	Clinical Pharmacology Team Leader
Li Wang, PhD	Clinical Pharmacology Reviewer

Office of Product Quality, Division of New Drug API

Mohan Sapru, PhD	CMC Lead
Theodore Carver, PhD	CMC Reviewer
Vidya Pai, PhD	CMC Reviewer
Kumar Janoria, PhD	CMC Reviewer

Office of Clinical Pharmacology, Genomics and Targeted Therapy Group
Katarzyna Drozda, PharmD, MS Clinical Pharmacology Reviewer

Office of Surveillance and Epidemiology, Division of Risk Management
Mona Patel DRISK Reviewer

Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis
Mariette Aidoo Reviewer

Office of Surveillance and Epidemiology, Division of Pharmacovigilance I
Christian Cao Reviewer

Office of Drug Evaluation IV, Division of Pediatric and Maternal Health
Shamir Tuchman, MD Medical Officer

SPONSOR ATTENDEES
Alnylam

Maged Darwish, PhD	Vice President, Regulatory CMC
Kenji Fujita, MD	Vice President, Clinical Research
John Gansner, MD, PhD	Director, Clinical Research
Varun Goel, PhD	Director, Clinical Pharmacology and Pharmacometrics
Bahru Habtemariam, PharmD	Sr. Director, Clinical Pharmacology
Jiandong Lu, PhD	Sr. Director, Data Sciences and Statistics
Tracy McGregor, MD, MSCI	Director, Clinical Research
Mugdha Sitole, PharmD	Associate Director, Regulatory Affairs
Andrew P. Slugg, MS, MBA	Senior Vice President, Regulatory Affairs
Nhu Debi Tran, PharmD	Senior Director, Regulatory Affairs
Jing-Tao Wu	Vice President, DMPK

1.0 BACKGROUND

Lumasiran (ALN-GO1) is a subcutaneously administered, synthetic, small interfering RNA (siRNA) designed to inhibit the mRNA of the hydroxyacid oxidase 1 (*HAO1*) gene, which encodes a hepatic enzyme that oxidizes glycolate to glyoxylate. Glyoxylate is then further metabolized to oxalate. Suppression of glycolate oxidase is expected to reduce oxalate production and stone formation. Alnylam Pharmaceuticals is developing lumasiran for the treatment of Primary Hyperoxaluria Type 1 (PH1) and was granted Breakthrough Therapy Designation for this indication on February 23, 2018.

Alnylam has completed enrollment in studies ALN-GO1-003 (ILLUMINATE-A) in patients ≥6 years of age and ALN-GO1-004 (ILLUMINATE-B) in patients <6 years of age. Both studies enrolled patients with PH1 and relatively preserved kidney function. Alnylam has requested this meeting to discuss the topline results from the 6-month,

placebo-controlled, double-blind phase of Study 003, the available data from open-label Study 004, and their planned NDA submission. Of note, the Agency previously provided written responses to questions on the format and content of an NDA submission on October 10, 2019.

The Agency issued preliminary responses on February 18, 2020. Alnylam used the appended slides to guide the meeting discussion.

2.0 DISCUSSION

2.1. Quality

Question 1: The Applicant is planning to include comparability protocols in the original NDA submission to (b) (4)

The protocols will include a detailed plan for the comparability assessment, the implementation of the change(s), and, a proposed reporting category for the change(s).

Does the agency agree with the applicant's proposed approach?

FDA Response to Question 1: We acknowledge your proposal to include a comparability protocol for (b) (4) with the original NDA submission. The comparability protocol should indicate that a supplement proposing the changes will be filed based on the appropriate post-approval change category. For additional information, see the FDA "Guidance for Industry: Changes to an Approved NDA or ANDA" (April 2004) and "Comparability Protocols for Human Drugs and Biologics: Chemistry, Manufacturing, and Controls Information" (Draft – Revision 1).

Alnylam's Response to Question 1: The applicant acknowledges the Agency's comment and confirms that as part of the comparability protocol included in the NDA, a detailed plan on the execution of the comparability assessment and acceptance criteria that will be achieved to assess the potential effects of CMC changes will be provided. Additionally, upon successful execution of the protocol, a reduced reporting category for the post approval supplement will be proposed in the protocol as stated in the "Guidance for Industry: Comparability Protocols for Human Drugs and Biologics: Chemistry, Manufacturing, and Controls Information" (Draft – April 2016) and in accordance to "Guidance for Industry: Changes to an Approved NDA or ANDA" (April 2004).

Discussion: No discussion occurred.

2.2. Clinical

Question 2: Does the Agency agree that the proposed clinical data package is adequate to support the review of an NDA of lumasiran for the treatment of PH1 in adult and pediatric patients?

FDA Response to Question 2: We agree that the proposed clinical data package appears to be adequate to support submission of an NDA. We note, however, that only 7 of 18 patients <6 years of age enrolled in study ALN-GO1-004 had been treated for 3 months and none had been treated for 6 months as of the data cutoff date for the NDA application. You note that "results from the pre-specified primary interim analysis with data from 16 patients through 6 months will be available in May 2020." Although we do not object to your proposal to provide the available data from study ALN-GO1-004 with the initial NDA submission and additional data during the review cycle, as noted in our Written Responses dated October 10, 2019, it is not clear that these data will be sufficient to support an indication in patients < 6 years of age. To facilitate timely access to your product, we may decide to limit our initial review of your application to the available data in patients ≥ 6 years of age.

Discussion: The Sponsor presented an overview of PH1, the mechanism of action of lumasiran, the design of the clinical development program, and the available data in patients with relatively preserved kidney function enrolled in studies ALN-GO1-003 (≥ 6 years of age) and ALN-GO1-004 (< 6 years of age)(Slides 4-18). The Sponsor noted that the proposed dosing regimens achieve similar exposures across the full range of weight categories, that efficacy and safety data in patients < 6 years of age are similar to older patients, and that there is a substantial burden of disease in infants and younger children with PH1 (Slides 20-22).

The Agency acknowledged that the available data through Month 3 do not raise concerns regarding PK, efficacy, or safety in patients <6 years of age but data beyond Month 3 are needed, for example, to confirm durability of the treatment effect after transition to quarterly dosing in certain weight bands. The Agency stated that it did not object to the sponsor's proposal to submit the available data with the initial NDA and provide additional datasets and a succinct summary of the findings with the safety update. The Agency reiterated, however, that the scope of the indication would be a review issue.

2.3. Regulatory

Question 3a: Does the Agency agree to the proposed Applicant Orientation Meeting?

FDA Response to Question 3a: We anticipate reviewing your application on an accelerated timeline. As such, it is not obvious to us that an Applicant Orientation Meeting one month after NDA submission will facilitate our review, but we are open to further discussions if you believe it would be helpful.

Alnylam's Response to Question 3a: We appreciate Agency's comment on reviewing the application on an accelerated timeline. We will not plan on an Applicant Orientation Meeting.

Discussion: No discussion occurred.

Question 3b: Can the Agency comment on which additional Review Divisions will be involved in the review of the NDA and provide any recommendations to facilitate an expedited NDA review process if lumasiran is granted Priority Review?

FDA Response to Question 3b: At this time, we anticipate also involving the Office of Biotechnology Products (OBP) to review the immunogenicity risk of lumasiran and the Office of Surveillance and Epidemiology to evaluate post-marketing pharmacovigilance activities.

With regard to facilitating review of your application, we do not have additional recommendations at this time.

Alnylam's Response to Question 3b: We thank the Agency for the response.

Discussion: No discussion occurred.

Post-meeting comment: Please include your risk management plan with the NDA submission.

Question 4: Based on the proposed NDA, and data from Study 003, does the Agency anticipate the need for an Advisory Committee meeting?

FDA Response to Question 4: We do not anticipate that one will be necessary; however, the need for such a meeting will be determined following NDA submission.

Alnylam's Response to Question 4: We acknowledge Agency's comments.

Discussion: No discussion occurred.

Additional Comments:

1. According to the meeting materials, each vial contains 94.5 mg of lumasiran in 0.5 mL. Given that individual doses range from 3 to 6 mg/kg, larger patients may require three or more vials to achieve one dose (e.g., a 70 kg patient would require 420 mg at a dose of 6 mg/kg). Developing a product strength that is incongruent with the dosage and administration of the product may lead to medication errors. Please address. For more information, please see the Guidance for Industry: Safety Considerations for Product Design to Minimize Medication Errors (2016), available at: https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm331810.pdf.

   Alnylam's Response to Additional Comment 1: Alnylam acknowledges the Agency's comment. Lumasiran's vial presentations have been designed to accommodate the full range of PH1 patients and recommended dosages administered on a mg/kg basis. This encompasses a population that varies from infants to adults, with a wide range of body weights. In the proposed dosing regimen, an infant with a weight of 5kg would receive an initial loading dose of 30mg (6 mg/kg); less than 1 vial. However, an adult patient with a weight of 70kg would receive loading and maintenance doses of 210mg (3 mg/kg); 3 vials. We appreciate the Agency's comment; however, given the wide variety of doses required for this very rare patient population, we believe we have developed a vial presentation that can be administered accurately and safely. Furthermore, the risk of medication errors will be mitigated because the prescribing information will include appropriate instructions for dosing and a recommendation that lumasiran be administered by a healthcare professional.

   Discussion: No discussion occurred.

2. According to the meeting materials, the primary endpoint for Study 003 was the percent change in 24-hour urinary oxalate excretion corrected for BSA from baseline to Month 6, and the primary analysis compared the difference in the average of LS means from Months 3 through 6. Please provide additional details regarding this analysis; specifically, please explain how you derived the estimated average treatment effect (Months 3 through 6) from the MMRM model. Please also provide the estimated treatment effect by month.

   Alnylam's Response to Additional Comment 2: The primary analysis was performed using a MMRM with restricted maximum likelihood approach. This model includes the percent change from baseline in 24-hour urinary oxalate (UOx) corrected for BSA at Months 3, 4, 5, and 6 as outcome variables and the following

variables: fixed effects of treatment arm (lumasiran vs. placebo), scheduled visits (Months 3, 4, 5 and 6) and baseline 24-hour UOx corrected for BSA as covariates; and patient as a random factor. An unstructured covariance structure is used to model the within-patient error and the Satterthwaite approximation is used to estimate the degrees of freedom. Additional details of the primary analysis can be found in the Statistical Analysis Plan (SAP) in section 7.1, which was submitted to the IND on 26-Mar-2019 (Serial #0030).

Therefore, the estimated average treatment effect (Month 3 through Month 6) corresponds to the coefficient estimate for the fixed effect of treatment arm. Estimated treatment effect by month is provided by the pre-specified sensitivity analysis 2 (see slide 31).

Discussion: The Sponsor explained that the primary endpoint is defined as the percent change from baseline in 24-hour urinary oxalate corrected for BSA to Month 6, averaged over Month 3 to Month 6, as pre-specified in the original SAP. The Sponsor further clarified that the primary analysis model considered only data from Month 3 to Month 6 as outcome variables of the MMRM model; hence, the treatment effect estimated from the fixed treatment factor in the model represented the treatment effect averaged over Month 3 to Month 6. The Sponsor agreed to include information on the model with the NDA submission. The Agency indicated that the MMRM model should include the interaction of treatment by visit.

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

LABORATORY TEST UNITS FOR CLINICAL TRIALS

CDER strongly encourages IND sponsors to identify the laboratory test units that will be reported in clinical trials that support applications for investigational new drugs and product registration. Although Système International (SI) units may be the standard reporting mechanism globally, dual reporting of a reasonable subset of laboratory tests in U.S. conventional units and SI units might be necessary to minimize conversion needs during review. Identification of units to be used for laboratory tests in clinical trials and solicitation of input from the review divisions should occur as early as possible in the development process. For more information, please see the FDA website entitled, Study Data Standards Resources and the CDER/CBER Position on Use of SI Units for Lab Tests website found at https://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM587505.pdf.

SUBMISSION FORMAT REQUIREMENTS

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

ABUSE POTENTIAL ASSESSMENT

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

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

None

5.0 ACTION ITEMS

None

6.0 ATTACHMENTS AND HANDOUTS

2020-02-24-Lumasiran Pre-NDA Meeting Slides for Presentation.pdf

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

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

/s/

ALIZA M THOMPSON
03/25/2020 07:59:38 AM

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 128941

MEETING MINUTES

Alnylam Pharmaceuticals, Inc
Attention: Mugdha Sitole, PharmD
Sr. Manager, Regulatory Affairs
300 Third Street
Cambridge, MA 02142

Dear Dr. Sitole:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for lumasiran (ALN-GO1).

We also refer to the meeting between representatives of your firm and the FDA on April 26, 2018. The purpose of the meeting to seek consensus with the Agency on the suitability of the planned nonclinical and clinical development program to support the submission of a New Drug Application (NDA) for lumasiran for the treatment of patients with Primary Hyperoxaluria Type 1 (PH1).

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, please call Brian Proctor, Regulatory Project Manager at (240) 402-3596.

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, M.D., Ph.D.
Director
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type:	B
Meeting Category:	End of Phase 2
Meeting Date and Time:	April 26, 2018 from 1 pm- 2 pm EST.
Meeting Location:	White Oak Building 22, Conference Room: 1311
Application Number:	IND 128941
Product Name:	lumasiran (ALN-GO1)
Indication:	Treatment of primary hyperoxaluria type 1 (PH1)
Sponsor Name:	Alnylam Pharmaceuticals, Inc
Meeting Chair:	Norman Stockbridge, MD, PhD
Meeting Recorder:	Brian Proctor

FDA ATTENDEES

Office of Drug Evaluation I

Ellis Unger, MD	Director
Robert Temple, MD	Deputy Director (Acting)

Office of Drug Evaluation I, Division of Cardiovascular and Renal Products

Norman Stockbridge, MD, PhD	Director
Aliza Thompson, MD	Clinical Team Leader
Kimberly Smith, MD	Clinical Reviewer
Thomas Papoian, PhD	Pharmacology Team Leader
Xuan Chi, PhD	Pharmacology Reviewer
Brian Proctor	Regulatory Health Project Manager

Office of Biostatistics, Division of Biometrics I

Steve Bai, PhD	Biometrics Reviewer

Office of Clinical Pharmacology, Division of Clinical Pharmacology I

Sudharshan Hariharan, PhD	Clinical Pharmacology Team Leader
Venkateswaran ChithambaramPillai, PhD	Clinical Pharmacology Reviewer

Office of Clinical Pharmacology, Genomics and Targeted Therapy Group

Hobart Rogers PharmD, PhD	Clinical Pharmacology Reviewer
Katarzyna Drozda, PharmD, MS	Clinical Pharmacology Reviewer

SPONSOR ATTENDEES

Alnylam Pharmaceuticals, Inc.

Pritesh Gandhi, PharmD	General Manager
David Erbe, PhD	Director, Research
Saraswathy (Sara) Nochur, PhD	Chief Regulatory Officer
Andrew P. Slugg, MS, MBA	Vice President, Regulatory Affairs
Mugdha Sitole, PharmD	Senior Manager, Regulatory Affairs
Tracy McGregor, MD, MSCI	Director, Clinical Research
Richard Riese, MD, PhD	Vice President, Clinical Research
Pushkal Garg, MD	Chief Medical Officer
Bahru Habtemariam, PharmD	Director, Clinical Pharmacology
Varun Goel, PhD	Director, Clinical Pharmacology and Pharmacometrics
Andrew Strahs, PhD Senior	Director, Biostatistics

External Consultant

(b) (4) MD (b) (4)

1.0 BACKGROUND

Lumasiran (ALN-GO1) is a subcutaneously administered, synthetic, small interfering RNA (siRNA) designed to inhibit the mRNA of the hyroxyacid oxidase 1 gene (HAO1), which encodes glycolate oxidase, a hepatic enzyme that oxidizes glycolate to glycoxylate. Glycoxylate is then further metabolized to oxalate. Suppression of glycolate oxidase is expected to reduce oxalate production. The drug substance is conjugated to a trivalentN-acetylgalactosamine ligand (GalNAc) to facilitate targeted delivery to the liver.

Alnylam Pharmaceuticals is developing lumasiran for the treatment of Primary Hyperoxaluria Type 1 and requested an End of Phase 2 meeting to discuss the preclinical and clinical development plan. Breakthrough Therapy Designation was granted on February 23, 2018, and this meeting also served as the initial Breakthrough Therapy meeting.

Preliminary responses to the submitted questions were provided to the sponsor, and are copied below, followed by any additional discussions that took place during the meeting. The sponsor used a slide presentation to guide the discussion at the meeting. Please refer to the attached slides.

2. DISCUSSION

2.1. Nonclinical

Question 1a: Does the Agency agree that the completed and planned nonclinical studies are adequate to support the submission and review of an NDA for lumasiran as a treatment of PH1 in adult and pediatric patients?

FDA Response to Question 1a: Yes, we agree. See our responses to Questions 1b and 1c below.
Discussion: *The sponsor accepted FDA's response; no discussion occurred.*

Question 1b: Does the Agency agree that given the absence of any significant adverse findings from both the pilot neonate-juvenile toxicity study (post-natal Day 4 at initiation of study, qWx5) and the 8-week repeat dose toxicity study (4-5 weeks of age at initiation of study, qWx9) in juvenile rats, and the observation that the PK/PD profiles in juveniles are similar to those observed in adult rats, no further nonclinical studies are required to support the dosing of pediatric patients below 6 years of age in the clinical development program and to support an NDA submission?

FDA Response to Question 1b: Yes, we agree, provided that the pilot neonate-juvenile study included a toxicokinetic evaluation and full histopathological evaluations of a standard battery of tissues.

Sponsor's Response to Question 1b: Sponsor confirms that the pilot neonate-juvenile study included a complete toxicokinetic evaluation and full histopathological evaluations of a standard battery of tissues.

Discussion: *The sponsor accepted FDA's response; no discussion occurred.*

Question 1c: Lumasiran specifically targets HAO1 mRNA. Based on a thorough review of the literature and existing data with lumasiran, the intended mechanism of action (suppression of HAO1 mRNA) does not raise a cause for concern regarding carcinogenic potential. The Sponsor is seeking agreement from the Agency that if required, completion of rodent carcinogenicity studies can be deferred to post approval.

Does the Agency agree with the Sponsor's proposal that, if required, rodent carcinogenicity studies can be completed post approval?

FDA Response to Question 1c: Standard rodent carcinogenicity studies are generally needed at the time of NDA submission. Given the apparent lack of significant findings in the chronic toxicity studies, high target specificity, and preliminary clinical evidence indicating that the product may demonstrate substantial improvement over available therapies for PH1, we agree that rodent carcinogenicity studies can be completed post-approval. We note, however, that toxicity findings indicative of potential carcinogenicity risk are not entirely absent and could result from the drug's intended mechanism of action on suppression of HAO1 mRNA and/or off-target or non-specific effects of siRNAs, particularly when given for prolonged periods of time. Therefore, pending review of a carcinogenicity assessment

document, carcinogenicity study protocols should be submitted for approval and studies initiated before NDA submission.

Sponsor's Response to Question 1c: Sponsor acknowledges Agency's comments and confirms that carcinogenicity assessment document (CAD) will be submitted once the registration study dose and dosing regimen have been confirmed. Dependent upon the outcome of the review of the CAD, carcinogenicity study protocols will be submitted for approval and studies initiated prior to NDA submission.

Discussion: *The sponsor accepted FDA's response; no discussion occurred.*

2.2. Clinical Pharmacology

Question 2: Based on available nonclinical and clinical information from the lumasiran development program, the Sponsor proposes not to conduct a dedicated thorough QTc study, additional in vitro and in vivo DDI studies, a human radiolabel PK study, or a dedicated hepatic impairment study.

Renal impairment is a natural part of the disease progression for PH1 patients and therefore, the Sponsor plans to study PH1 patients with varying degrees of renal impairment in the planned Study ALN-GO1-005. An additional renal impairment study in non-PH1 patients is not planned.

Does the Agency agree with the Sponsor's proposal?

FDA Response to Question 2: Yes, we agree with your proposal to not conduct any additional in vitro or in vivo DDI studies, a human radiolabel PK study, a dedicated hepatic impairment study or an additional renal impairment study in non-PH1 patients.

Regarding the need for a dedicated thorough QTc (TQT) study, Part A of Study ALN-GO1-001 may contain adequate information on the relationship between drug concentration and QT/QTc interval changes to substitute for a traditional TQT study (see ICH E14 Q&A (R3), Section 5.1). The following items are needed for us to determine whether a TQT study is needed. Please submit these items for our review:

a. Study report for Part A of Study ALN-GO1-001
b. Statistical analysis plan
c. Clinical study protocol
d. Investigator's Brochure
e. A completed Highlights of Clinical Pharmacology and Cardiac Safety Table
f. Annotated CRF
g. A data definition file which describes the contents of the electronic data sets
h. Electronic data sets as SAS.xpt transport files (in CDISC SDTM and ADAM format – if possible) and all the SAS codes used for the primary statistical and exposure-response analyses. Please make sure that the ECG raw data set includes at least the following: Subject ID, treatment, period, ECG date, ECG time (down to second),

nominal day, nominal time, replicate number, heart rate, intervals QT, RR, PR, QRS and QTc (including any corrected QT, e.g., QTcB, QTcF, QTcN, QTcI, along with the correction factors for QTcN and QTcI), Lead, and ECG ID (link to waveform files, if applicable).

i. Data set whose QT/QTc values are the average of the above replicates at each nominal time point
j. Narrative summaries and case report forms for any
    i. Deaths
    ii. Serious adverse events
    iii. Episodes of ventricular tachycardia or fibrillation
    iv. Episodes of syncope
    v. Episodes of seizure
    vi. Adverse events resulting in the subject discontinuing from the study
k. Submit all related ECG waveforms to the ECG warehouse (www.ecgwarehouse.com)

Sponsor's Response to Question 2: The data as requested will be provided. A timeline for this response will be provided to the Agency.

Discussion: *The sponsor accepted FDA's response; no discussion occurred.*

(b) (4)

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(b) (4)

Question 5: The Sponsor plans to evaluate the safety and efficacy of lumasiran in a broad population of PH1 patients. Planned Study ALN-GO1-004 will include those under 6 years of age with relatively intact renal function and (b) (4) By using clinical data available from Study ALN-GO1-001 and PK/PD modeling, the Sponsor has outlined a strategy to support selection of dose and dosing regimens for these studies. Does the agency agree with the study designs and proposal for dose selection for these studies?

FDA Response to Question 5: In study ALN-GO1-004, four patients with PH1 without evidence of systemic oxalosis aged 12 months to <6 years with an eGFR >45 mL/min/1.73m^2 or <12 months of age with normal renal function as assessed by serum creatinine will be treated with open-label lumasiran for 6 months; a minimum urinary oxalate excretion level will not required for study eligibility. Co-primary endpoints will be "safety and tolerability" and change in urinary oxalate: creatinine ratio from baseline to 6 months. Patients will be offered participation in an open-label extension (ALN-GO1-002). The study will be analyzed descriptively.

(b) (4)

We agree it is important to obtain data that speak to efficacy and safety in the proposed populations and that your overall dose selection strategy seems reasonable. We cannot, however, provide more specific feedback at this time. We recommend that you request a follow-up meeting to discuss these studies once we have reached alignment on the design of

(b) (4)

Additional Comment:
We remind you that the excipients in the formulation must be safe for use in pediatric patients beginning at birth. In addition, the concentration of the formulation must be adequate to provide accurate dosing in the youngest, lightest patients.

Sponsor's Response to Question 5: The Sponsor agrees with the Agency and plans to request another meeting to discuss study design and dosing for Studies ALN-GO1-004 and (b) (4). Agency's comment regarding formulation in the youngest, lightest patients will also be addressed at this meeting.

Discussion: *No discussion occurred.*

Question 6: The Sponsor intends to seek approval for lumasiran as a treatment of PH1 in adult and pediatric patients.

- Does the Agency agree that complete placebo-controlled efficacy and safety data from completion of Study ALN-GO1-001 Part A (healthy adult subjects), Part B (PH1 patients) (b) (4) is sufficient to support the submission and review of an NDA for lumasiran in PH1 patients who are at least 6 years old and have preserved renal function (eGFR >45 mL/min/1.73m^2)?

FDA Response: See our response to Question 3.

- Studies ALN-GO1-004 and (b) (4) are uncontrolled studies to demonstrate efficacy and safety of lumasiran in PH1 patients who are younger than 6 years of age and those with more impaired renal function, including those on dialysis. These studies will not be completed at the time of the initial NDA. Assuming that the Sponsor has adequate data from these two studies to inform the dose for these patients with critical unmet need at the time of the initial NDA submission, with a commitment to completing these studies post-approval, does the Agency agree that the safety database as proposed below is adequate to support review of the NDA for lumasiran for the treatment of adult and pediatric patients with PH1?

  FDA Response: At the time of NDA submission, you estimate that approximately 55 patients will have been exposed to lumasiran for ≥3 months, 49 for ≥6 months, 32 for ≥ 1 year, and 18 for ≥ 2 years. We acknowledge that the size of the safety database will be limited by the size of the affected population and agree that a safety database of this size and duration seems reasonable. See our response to Question 5 regarding the ability of these studies to support claims regarding efficacy.

  Discussion: *The sponsor accepted FDA's response; no discussion occurred.*

3.0 OTHER IMPORTANT MEETING LANGUAGE SECTIONS

PREA REQUIREMENTS

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

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

For additional guidance on the timing, content, and submission of the iPSP, including an iPSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and*

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

DATA STANDARDS FOR STUDIES

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

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

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

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

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

LABORATORY TEST UNITS FOR CLINICAL TRIALS

CDER strongly encourages IND sponsors to identify the laboratory test units that will be reported in clinical trials that support applications for investigational new drugs and product registration. Although Système International (SI) units may be the standard reporting mechanism globally, dual reporting of a reasonable subset of laboratory tests in U.S. conventional units and SI units might be necessary to minimize conversion needs during review. Identification of units to be used for laboratory tests in clinical trials and solicitation of input from the review divisions should occur as early as possible in the development process. For more information, please see the FDA website entitled, Study Data Standards Resources and the CDER/CBER Position on Use of SI Units for Lab Tests website found at https://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM587505.pdf.

SUBMISSION FORMAT REQUIREMENTS

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

ABUSE POTENTIAL ASSESSMENT

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

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM198650.pdf.

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 ATTACHMENTS AND HANDOUTS

Alnylam-Lumasiran FDA EOP2 Meeting-Slides-26Apr18.pdf

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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/

NORMAN L STOCKBRIDGE
05/21/2018

CDER Breakthrough Therapy Designation Determination Review Template

IND/NDA/BLA #	128941
Request Receipt Date	January 12, 2018
Product	ALN-GO1 (lumasiran)
Indication	Treatment of Primary Hyperoxaluria Type 1
Drug Class/Mechanism of Action	Reduction in mRNA for hydroxyacid oxidase-1 (HAO1) gene
Sponsor	Alnylam Pharmaceuticals, Inc.
ODE/Division	ODEI/Division of Cardiovascular and Renal Products
Breakthrough Therapy Request(BTDR) Goal Date (within 60 days of receipt)	March 12, 2018

Note: This document must be uploaded into CDER's electronic document archival system as a ***clinical review: REV-CLINICAL-24 (Breakthough Therapy Designation Determination) even if the review is attached to the MPC meeting minutes,*** *and will serve as the official primary Clinical Review for the Breakthrough Therapy Designation Request (BTDR)**.*** *Link this review to the incoming BTDR. Note: Signatory Authority is the Division Director.*

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 treatment of Primary Hyperoxaluria Type 1 (PH1).

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-threatening[1])? ☒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 adequeate and sufficiently complete to permit a substantive review?
      - ☒ YES the BTDR is adequate and sufficiently complete to permit a substantive review
      - ☐ Undetermined
      - ☐ 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):

[1] For a definition of serious and life threatening see Guidance for Industry: "Expedited Programs for Serious Conditions—Drugs and Biologics" http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf

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}

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.

Primary hyperoxaluria type 1 (PH1) is a rare, autosomal recessive disorder caused by a deficiency in liver peroxisomal enzyme alanine:glyoxalate-aminotransferase (AGT), an enzyme that catalyzes the conversion of glyoxylate to glycine in the liver. Absence of AGT results in overproduction of oxalate by the liver and deposition of calcium oxalate crystals in tissues. Initially, this leads to nephrolithiasis, nephrocalcinosis, and progressive renal failure. As GFR declines, reduced oxalate excretion by the kidney leads to higher oxalate levels and systemic oxalosis. Non-renal manifestations that occur after the loss of renal function include bone fractures, cutaneous ulcers, anemia, retinal deposits, peripheral neuropathy, synovitis, cardiomyopathy, and arrhythmias.

The prevalence of PH1 has been estimated at 1 to 3 cases per million. The age at symptom onset can range from infancy to adulthood with a median age at diagnosis of 5 to 6 years. Approximately half of patients present in late childhood or early adolescence. The clinical phenotype and disease severity is heterogeneous, even within a single

[2] For a definition of available therapy refer to Guidance for Industry: "Expedited Programs for Serious Conditions—Drugs and Biologics" http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf

family, and can range from severe oxalosis in an infant to occasional nephrolithiasis in an adult. The median age at diagnosis of ESRD is 24 years. The best available treatment option for patients with advanced chronic kidney disease is a combined liver and kidney transplant. There are no approved pharmacologic treatments for PH1, but some patients respond to supraphysiological doses of pyridoxine (vitamin B6), a cofactor for AGT. Other treatments include high fluid intake and potassium or sodium citrate.

ALN-GO1 is a subcutaneously administered, synthetic, small interfering RNA (siRNA) designed to inhibit the mRNA of the hyroxyacid oxidase 1 gene (HAO1), which encodes glycolate oxidase, a hepatic enzyme that oxidizes glycolate to glycoxylate. Glycoxylate is then further metabolized to oxalate. Suppression of glycolate oxidase is expected to reduce oxalate production. The drug substance is conjugated to an N-acetyl galactosamine ligand (GalNAc) to (b) (4).

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 has provided data on 24-hour urinary oxylate excretion, one of the study's secondary endpoints, in support of their request. The study's primary endpoint related to safety. Other secondary pharmacodynamic endpoints included 24-hour urinary glycolate excretion, plasma glycolate concentration, and creatinine clearance. Plasma oxalate concentration was an exploratory endpoint.

b. Describe the endpoint(s) that are accepted by the Division as clinically significant (outcome measures) for patients with the disease.

No drug has been approved for the treatment of PH1. We have indicated to sponsors that we may be willing to accept a substantial change in urinary oxalate in patients with high baseline levels as a surrogate endpoint in patients with PH1 and a prior history of kidney stones. We have indicated that further discussions are needed regarding the specific endpoint and what constitutes a "clinically meaningful" treatment effect (i.e., the magnitude of change and/or absolute level that would need to be achieved to result in a treatment benefit).

We have also encouraged sponsors to consider clinical events one might expect to see in these patients over a 2 to 3 year period of observation that might help define other clinical endpoints or surrogate endpoints that could be used to establish the efficacy for the treatment of PH1.

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.

We are not aware of other biomarkers that are likely to predict a clinical benefit in PH1. Plasma oxalate concentrations remain normal in patients with relatively preserved kidney function because oxalate is rapidly cleared by the kidneys.

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.

There are no approved pharmacologic treatments for PH1, but some patients respond to supraphysiological doses of pyridoxine (vitamin B6). Other treatments include high fluid intake and potassium or sodium citrate. The best available treatment option for patients with advanced chronic kidney disease is a combined liver and kidney transplant.

9. A brief description of any drugs being studied for the same indication, or very similar indication, that requested breakthrough therapy designation[3].

We are not aware of other drugs for PH1 that have requested breakthrough therapy designation.

10. Information related to the preliminary clinical evidence:

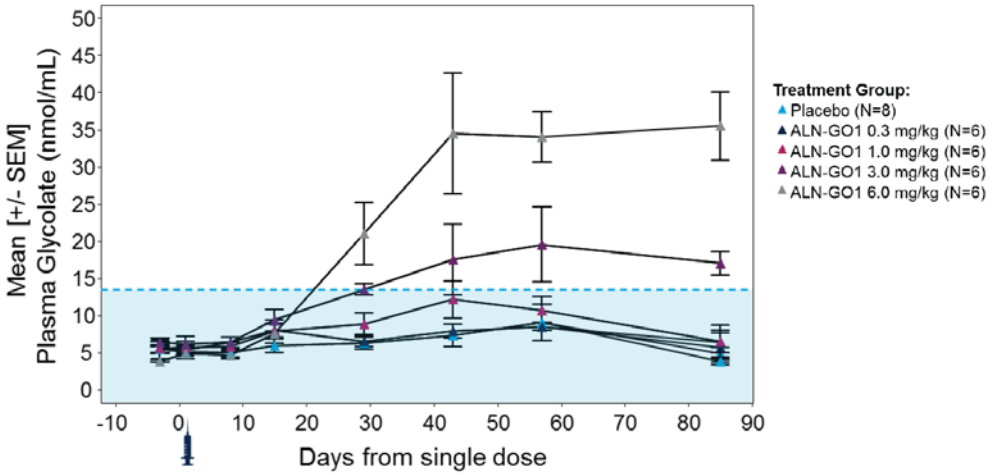
a. Table of clinical trials supporting the BTDR (only include trials which were relevant to the designation determination decision), including study ID, phase, trial design[4], trial endpoints, treatment group(s), number of subjects enrolled in support of specific breakthrough indication, hazard ratio (if applicable), and trial results.

The sponsor has an ongoing study (ALN-GO1-001), a randomized, single-blind (study subjects blinded), placebo-controlled, multicenter, phase 1/2 study to evaluate safety, tolerability, PK, and PD of ALN-GO1. The study includes two parts:

- Part A randomized a total of 32 healthy adult subjects in the United Kingdom 3:1 to a single ascending dose of ALN-GO1 0.3, 1.0, 3.0, or 6.0 mg/kg or placebo.
- Part B is ongoing and will enroll up to 24 adult and pediatric patients aged 6 to 64 years with PH1 and an eGFR ≥45 ml/min/1.73m^2 at up to 13 sites worldwide. Subjects will be randomized 3:1 to multiple ascending doses of lumasiran or placebo dosed on Days 1, 29, and 57. Subjects initially randomized to placebo will cross-over on Day 85 to receive three doses of study drug. The sponsor may also evaluate quarterly dosing (Day 1 and 85). After completion of Part B, subjects will have the option of enrolling in an open-label extension.

For Part A, plasma glycolate levels in healthy subjects increased in a dose-dependent manner starting around Day 15. A dose of 1 mg/kg was considered the lowest dose with a pharmacological effect and was well-tolerated, so this dose was selected as the starting dose for Part B.

Figure 1: Mean (±SEM) Plasma Glycolate Concentration after a Single Dose of Lumasiran or Placebo (Part A)



As of November 28, 2017, four patients have received lumasiran 1 mg/kg every 28 days for three doses including one patient who initially received placebo (Cohort 1). Three additional patients have received 3 mg/kg every 28

[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.

days for three doses, and one patient has received placebo and recently crossed over to start lumasiran (Cohort 2). All have been followed through at least Day 85.

The subjects were 6 to 19 years of age and had a baseline eGFR of 58 to 94 ml/min/1.73m^2. All subjects who received lumasiran had a reduction in 24-hour urinary oxalate levels (Figure 2, Figure 3). The mean percent reduction on Day 85 was 67% and 66% for Cohorts 1 and 2, respectively. According to the sponsor, the patient in Cohort 2 randomized to placebo did not have valid 24 hour urine collections for Days 29, 57, or 85, so they have excluded those data points.

Figure 2: 24-hour Urinary Oxalate Levels for Cohort 1

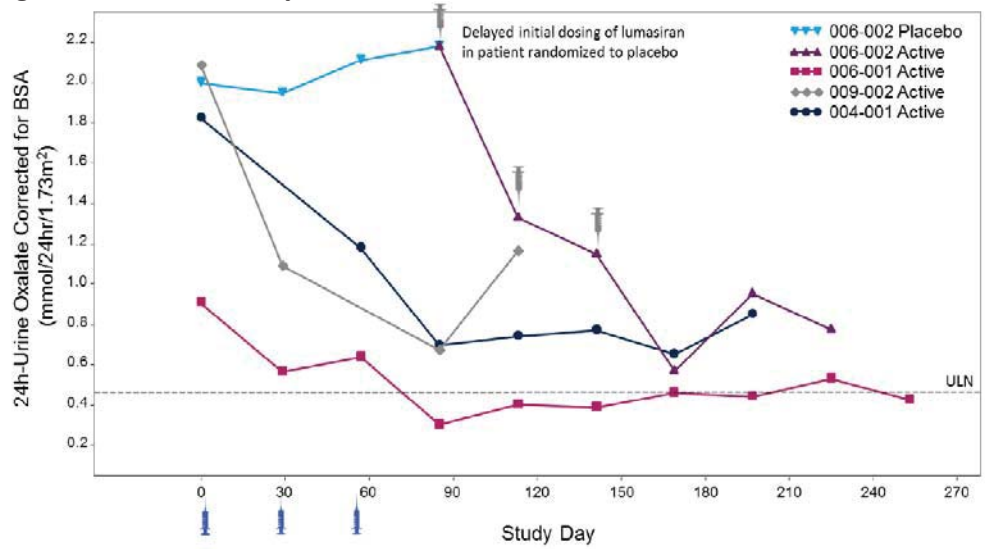
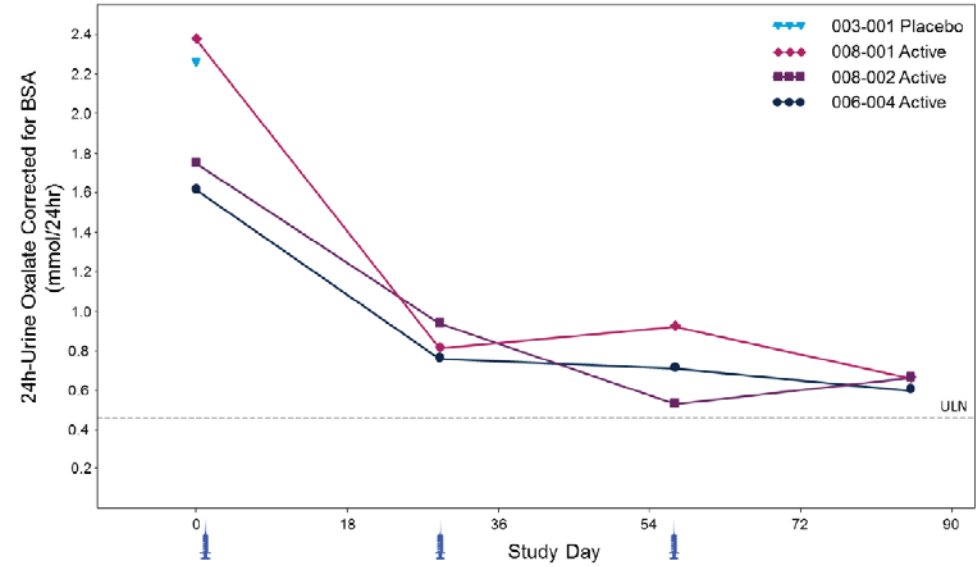
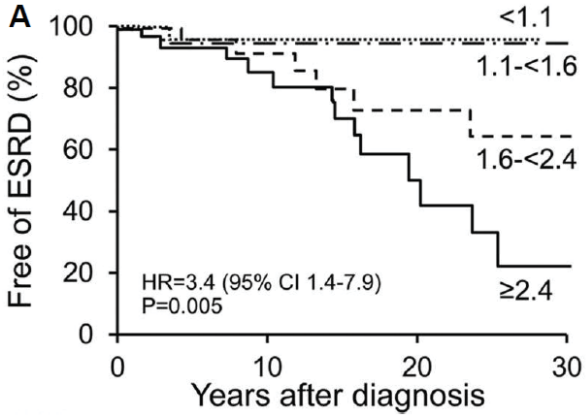


Figure 3: 24-hour Urinary Oxalate Levels for Cohort 2



All subjects achieved a 24-hour excretion below 0.67 mmol/24h/1.73m^2 (normal is ≤ 0.5 mmol/24h/1.73 m^2). The sponsor cites registry data indicating that patients with baseline urine oxalate values in the lowest quartile (<1.1) have a relatively low risk of ESRD, with a 20-year renal survival of 96% (Figure 4).

Figure 4: Rate of Progression to ESRD by Baseline Urinary Oxalate Excretion



b. Include any additional relevant information. Consider the following in your response:

With the exception of injection site pain, the adverse events seen to date appear to be common events in patients with PH1 (e.g., kidney stones, pyelonephritis).

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

☒ GRANT: Patients with PH1 treated with lumasiran in the sponsor's phase 2 study had marked and sustained reductions in levels of urinary oxalate. We believe this provides sufficient preliminary clinical evidence in this rare disease to support Breakthrough Therapy Designation.

☐ DENY:

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):

We will meet with the sponsor in the near term to begin discussions of the design of their phase 3 program. We are interested in exploring the enrollment of patients younger than 6 years of age and patients with reduced renal function and systemic oxalosis. In addition, given the limited experience with siRNA-based therapies, it will be important to ensure that product quality issues are adequately addressed.

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: {See appended electronic signature page}

Team Leader Signature: {See appended electronic signature page}
Division Director Signature: {See appended electronic signature page}

Revised 10/17/17/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/

KIMBERLY A SMITH
03/02/2018

ALIZA M THOMPSON
03/02/2018

NORMAN L STOCKBRIDGE
03/02/2018