CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214103Orig1s000

OTHER REVIEW(S)

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	November 16, 2020
Requesting Office or Division:	Division of Cardiology and Nephrology (DCN)
Application Type and Number:	NDA 214103
Product Name and Strength:	Oxlumo (lumasiran) injection, 94.5 mg/0.5 mL
Applicant/Sponsor Name:	Alnylam Pharmaceuticals, Inc. (Alnylam)
OSE RCM #:	2020-73-1
DMEPA Safety Evaluator:	Mariette Aidoo, PharmD, MPH
DMEPA Team Leader:	Hina Mehta, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised carton labeling received on November 4, 2020 for Oxlumo. We reviewed the revised carton labeling for Oxlumo (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

The Applicant implemented all of our recommendations and we have no additional recommendations at this time.

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[a] Aidoo, M. Label and Labeling Review for Oxlumo (NDA 214103). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 AUG 18. RCM No.: 2020-73.

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/s/

MARIETTE A AIDOO
11/16/2020 11:43:12 AM

HINA S MEHTA
11/17/2020 02:28:53 PM

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: November 3, 2020

To: Brian Proctor, RAC, Regulatory Project Manager
Division of Regulatory Operations for Cardiology, Hematology, Endocrinology, and Nephrology (DRO-CHEN)

Michael Monteleone, MS, Associate Director for Labeling
Division of Cardiology and Nephrology (DCN)
Michael Monteleone, MS, Associate Director for Labeling, DCN

From: Puja Shah, Pharm.D., RAC, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: James Dvorsky, Pharm.D., RAC, CPH, Team Leader, OPDP

Subject: OPDP Labeling Comments for OXLUMO (lumasiran) injection, for subcutaneous use

NDA: 214103

On May 19, 2020, DRO-CHEN sent a labeling review consult request to OPDP for the original NDA for OXLUMO (lumasiran) injection, for subcutaneous use. The labeling review consult included a request to review the proposed product labeling (PI) and carton and container labeling.

Labeling: On August 31, 2020, OPDP provided comments on the proposed labeling based on the draft labeling received by electronic mail from DRO-CHEN (Brian Proctor) on August 27, 2020. OPDP's review of the PI was uploaded in DARRTS and a courtesy copy emailed to DRO-CHEN (Brian Proctor).

Carton and Container Labeling: On October 28, 2020, OPDP reviewed the attached proposed carton and container labeling accessed on DCN's SharePoint, and we did not have any comments. Our review was emailed to DRO-CHEN (Brian Proctor) on October 28, 2020.

Thank you for your consult. If you have any questions, please contact Puja Shah at (240) 402-5040 or puja.shah@fda.hhs.gov.

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/s/

PUJA J SHAH
11/03/2020 09:46:12 AM

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: August 31, 2020

To: Brian Proctor, RAC, Regulatory Project Manager
Division of Regulatory Operations for Cardiology, Hematology, Endocrinology, and Nephrology (DRO-CHEN)

Michael Monteleone, MS, Associate Director for Labeling
Division of Cardiology and Nephrology (DCN)
Michael Monteleone, MS, Associate Director for Labeling, DCN

From: Puja Shah, Pharm.D., RAC, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: James Dvorsky, Pharm.D., RAC, CPH, Team Leader, OPDP

Subject: OPDP Labeling Comments for OXLUMO (lumasiran) injection, for subcutaneous use

NDA: 214103

In response to DRO-CHEN's consult request dated August 19, 2020, OPDP has reviewed the proposed product labeling (PI) for the original NDA for OXLUMO (lumasiran) injection, for subcutaneous use.

Labeling: OPDP's comments on the proposed labeling are based on the draft labeling received by electronic mail from DRO-CHEN (Brian Proctor) on August 27, 2020, and are provided below.

Thank you for your consult. If you have any questions, please contact Puja Shah at (240) 402-5040 or puja.shah@fda.hhs.gov.

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/s/

PUJA J SHAH
08/31/2020 05:00:58 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Pediatric and Maternal Health
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-2200
FAX 301-796-9744

Division of Pediatric and Maternal Health Review

Date: 8/26/20 **Date consulted:** 8/10/20

From: Miriam Dinatale, DO, Team Leader, Maternal Health
Division of Pediatric and Maternal Health

Through: Lynne P. Yao, MD, OND, Division Director
Division of Pediatric and Maternal Health

To: Division of Cardiovascular and Nephrology (DCN)

Drug: Oxlumo **(**lumasiran)

NDA: 214103

Applicant: Alnylam Pharmaceuticals Inc

Subject: Pregnancy and Lactation Labeling Recommendations

Indication: Treatment of primary hyperoxaluria type 1 (PH1) in adult and pediatric patients

Materials Reviewed:

- Applicant's submitted background package and proposed labeling for NDA 214103
- DPMH consult request dated 8/10/20, DARRTS Reference ID 4654242

Consult Question: "Please provide comments on proposed pregnancy and lactation labeling language."

INTRODUCTION AND BACKGROUND

On April 3, 2020, Alnylam Pharmaceuticals Inc submitted a new molecular entity (NME) new drug application (NDA) for Oxlumo **(**lumasiran) for the treatment of primary hyperoxaluria type 1 (PH1) in adult and pediatric patients On August 10, 2020, DCN consulted DPMH to assist with the Pregnancy and Lactation subsections of labeling.

Regulatory History

- February 8, 2016: Lumasiran received Orphan Drug Designation (ODD) for the treatment of PH1.
- February 23, 2018: Lumasiran received Breakthrough Therapy Designation for the treatment of PH1.
- December 20, 2019: Lumasiran received Rare Pediatric Disease Designation.

Lumasiran Drug Characteristics[1]

Drug class	Lumasiran is double-stranded small interfering ribonucleic acid (RNA)
Mechanism of action	Lumasiran reduces levels of glucolate oxidase (GO) enzyme by targeting hydroxyacid oxidase 1 (HAO1) messenger RNA in hepatocytes through RNA interference. Decreased GO enzyme levels reduce the amount of available glyoxylate, a substrate for oxalate production
Dose and administration	Subcutaneous injection; loading and maintenance doses vary based on weight. For body weight of 20kg and above loading dose is 3mg/kg monthly for three doses and then 3mg/kg once every three months.
Molecular weight	17,285.76 Daltons
Half-life	5.2 hours
Plasma protein binding	85%
Contraindications	None
Warnings and precautions	None
Adverse reactions	Injection site reaction

REVIEW

PREGNANCY

Primary hyperoxaluria type 1 (PH1) and Pregnancy[2,3,4]

- **Description:** PAH is a rare, progressive, serious and life-threatening autosomal recessive inborn error of metabolism, which results in increased endogenous hepatic production of oxalate and leads to progressive damage to the kidney leading to renal impairment and end-stage renal disease (ESRD) if left untreated.

[1] Applicant's proposed labeling for Oxlumo (lumasiran)
[2] National Center for Advancing Translational Sciences. https://rarediseases.info.nih.gov/diseases/2835/primary-hyperoxaluria-type-1#:~:text=Primary%20hyperoxaluria%20type%201%20(PH1,the%20kidneys%20and%20urinary%20tract. Accessed 8/13/2020
[3] U.S. National Library of Medicine- Genetics Home Reference. https://ghr nlm nih.gov/condition/primary-hyperoxaluria#genes. Accessed 8/13/2020
[4] Norby S and Milliner D. Outcomes and complications of pregnancy in women with primary hyperoxaluria. Am J Kidney Disease. 2004; 43(2): 277-85.

- **Types of PH**
    - In PH1, kidney stones appear anytime from childhood to early adulthood and ESRD can develop at any age.
    - PH type 2 is similar to type 1, but ESRD develops later in life.
    - In PH type 3, affected individuals develop kidney stones in early childhood, but signs and symptoms of PH type 3 are unclear.
- **Incidence:** PH1 affects 1 in 58,000 worldwide. Type 1 is the most common form and affects 80% of cases. Types 2 and 3 account for 10% of cases.
- **Incidence in Pregnant Women:** 40 pregnancies in patients with PH were reported between 1961 and 1998. Of the 40 pregnancies, there were 26 pregnancies in 11 patients with PH1 and 14 pregnancies in five patients with PH2.
    - Of the 40 pregnancies, 30 of the pregnancies were carried to term and 33 infants were born.
    - There were four miscarriages, four preterm births and two elective abortions.
    - There were no maternal complications in 20 of the pregnancies.
    - In the remaining pregnancies, the following maternal complications were observed: hypertension, urinary tract infection and urolithiasis.
    - One PH1 patient developed preeclampsia and had a stillborn infant. Another PH1 patient developed hyperemesis gravidarum with a decline in renal function.
    - All PH1 patients eventually required renal replacement therapy (ie. dialysis or renal transplantation) at an average of 17.5 years after their first pregnancy. No PH2 patients required renal replacement therapy.
- **Symptoms of PH1:** include recurrent kidney stones, hematuria and urinary tract infections. As the disease progresses, excess oxalate causes systemic oxalosis and effects tissues in the bones, heart, eyes and skin. Without treatment, death occurs due to ESRD and complications from oxalosis.
- **Treatments:** There are no approved therapies for PH1. Current treatment options include high fluid intake, vitamin B6, calcium-oxalate crystallization inhibitors (citrate, pyrophosphate, and magnesium), management of kidney stones and, in some cases, dialysis. Liver and/or kidney transplantation may also be needed for severe cases.

Nonclinical Experience

In an embryofetal development study in pregnant rats, lumasiran was administered subcutaneously at doses of 3, 10, and 30 mg/kg/day during organogenesis (gestational days 6-17). Administration of lumasiran resulted in no effects on embryo-fetal survival or fetal body weights. No lumasiran-related fetal malformations were observed. An increased incidence of skeletal variations (bipartite ossification of the sternebrae and misshapen cervical arches) was observed at 30 mg/kg/day in rats, which is 45 times the maximum recommended human dose (MRHD) for women of 3 mg/kg/month normalized to 0.1 mg/kg/day, based on body surface area. In an embryo-fetal development study in female rabbits, lumasiran was administered subcutaneously at doses of 3, 10, and 30 mg/kg/day during organogenesis (gestational days 7-19).

There were decreases in maternal food consumption and decreases in maternal body weight gains at ≥3 mg/kg/day. There were no lumasiran-related fetal findings identified at doses up to 30 mg/kg/day (90 times the normalized MRHD based on body surface area).

In a postnatal development study, lumasiran administered subcutaneously to pregnant female rats on gestational days 7, 13, 19 and on lactation days 6, 12, and 18 through weaning at doses up to 50 mg/kg did not produce maternal toxicity or developmental effects in the offspring

The reader is referred to the Pharmacology/Toxicology review by Philip Gatti, Ph.D., for further details.

Pharmacovigilance (PV) Database
There have been no confirmed pregnancies during the lumasiran clinical development program.

DPMH review of literature
DPMH conducted a search of published literature search for "lumasiran" and "pregnancy" and "congenital defects/congenital anomalies/teratogenicity/prematurity/stillbirth/spontaneous abortion/miscarriage" and did not identify any publications.

Lumasiran is not referenced in Micromedex,[5] REPROTOX,[6] or Teris.[7]

Reviewer's comment: Overall, the applicant performed an adequate summary of their clinical trial database regarding lumasiran use during pregnancy. This is an NME; therefore, the applicant did not conduct a review of published literature. The reader is referred to the Discussion and Conclusions section at the end of this review for DPMH's opinion of the data, submission, and recommendations.

LACTATION
Nonclinical Experience
No animal lactation studies have been performed.

Pharmacovigilance Database
There are no reports of lactation in the clinical studies.

DPMH Review of Literature
DPMH conducted a search in PubMed and Embase using the search terms "lumasiran" AND "lactation/breastfeeding" did not identify any articles.

Lumasiran is not referenced in ReproTox, TERIS, LactMed, or Thomas Hale's Book (*Medications and Mothers' Milk*[8]*).*

Reviewer's comment: Overall, the applicant performed an adequate summary of their clinical trial database regarding lumasiran use during lactation. This is an NME; therefore, the applicant did not conduct a review of published literature. The reader is referred to the Discussion and Conclusions section at the end of this review for DPMH's opinion of the data, submission, and recommendations.

[5] https://www.micromedexsolutions.com, accessed 8/13/20.
[6] Truven Health Analytics information. Reprotox, accessed 8/13/20.
[7] Truven Health Analytics information. Teris, accessed 8/13/20.
[8] Hale TW. Hale's medications and mother's milk. 2019. Springer Publishing Co. NY, New York.

FEMALES AND MALES OF REPRODUCTIVE POTENTIAL

Nonclinical Experience

Administration of lumasiran by weekly subcutaneous doses of 0, 5, 15, and 50 mg/kg in male and female rats prior to and during mating and continuing in females once on Day 6 of presumed gestation resulted in no adverse effects upon the male or female fertility endpoints evaluated.

The reader is referred to the the Pharmacology/Toxicology review by Philip Gatti, Ph.D., for further details.

Review of Pharmacovigilance Database

The applicant did not report any cases of infertility in clinical trials conducted for lumasiran.

DPMH review of literature:

DPMH conducted a search of published literature using the search terms "lumasiran" AND "fertility/infertility/reproduction/sperm" and did not identify any relevant publications.

Lumasiran is not listed in Micromedex, REPROTOX, or Teris.

Reviewer's comment: Overall, the applicant performed an adequate literature summary of their clinical trial database regarding lumasiran use in females and males of reproductive potential. This is an NME; therefore, the applicant did not conduct a review of published literature. The reader is referred to the Discussion and Conclusions section at the end of this review for DPMH's opinion of the data, submission, and recommendations.

DISCUSSION AND CONCLUSIONS

Pregnancy

There are no human data regarding the use of lumasiran in pregnant women. In animal reproduction studies, there were no adverse effects on pregnancy or embryo-fetal development related to OXLUMO in doses 45 times (rats) and 90 times (rabbits) the MRHD in women.

Over a period of 37 years (1961 to 1998) there were a total of 26 pregnancies in 11 women with PH1. Given the overall rarity of this condition, a pregnancy registry would not be feasible for this population. However, since there are no human data with use of lumasiran in pregnant women, DPMH recommends issuing a post-marketing requirement to conduct a single-arm pregnancy safety study to collect information regarding the use of lumasiran in pregnant women.

Lactation

There is no information regarding the use of lumasiran in lactating animals or humans. There are no significant adverse effects associated with lumasiran. Additionally, based on the drug's characteristics (large molecular size, short-half), it is unlikely that lumasiran will accumulate in human milk. Therefore, DPMH recommends using the standard risk/benefit language in subsection 8.2 of lumasiran labeling.

Additionally, PH1 is a rare disease, and it would not be feasible to conduct a lactation study in this population.

Females and Males of Reproductive Potential

There are no data on lumasiran and the effects of fertility or contraception in humans. Animal data do not appear to affect fertility. (b) (4)

LABELING RECOMMENDATIONS

DPMH revised subsections 8.1 and 8.2 of labeling for compliance with the PLLR (see below). DPMH recommendations are below, and DPMH refers to the final NDA action for final labeling.

DPMH Proposed Pregnancy and Lactation Labeling

FULL PRESCRIBING INFORMATION
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy

Risk Summary

There are no available data with the use of OXLUMO in pregnant women to evaluate a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. No adverse effects on pregnancy or embryo-fetal development related to OXLUMO were observed in rats at 45 times and in rabbits at 90 times the maximum recommended human dose in women (see *Data*).

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

(b) (4)

Data

Animal Data

In an embryo-fetal development study in pregnant rats, lumasiran was administered subcutaneously at doses of 3, 10, and 30 mg/kg/day during organogenesis (gestational days 6-17). Administration of lumasiran resulted in no effects on embryo-fetal survival or fetal body weights and no lumasiran-related fetal malformations were observed. (b) (4)

30 mg/kg/day in rats (b) (4) is 45 times the maximum recommended human dose (MRHD) for women of 3 mg/kg/month normalized to 0.1 mg/kg/day, based on body surface area. In an embryo-fetal development study in female rabbits, lumasiran was administered subcutaneously at doses of 3, 10, and 30 mg/kg/day during organogenesis (gestational days 7-19).

There were decreases in maternal food consumption and decreases in maternal body weight gains at ≥3 mg/kg/day. There were no lumasiran-related fetal findings identified at doses up to 30 mg/kg/day (90 times the normalized MRHD based on body surface area).

In a postnatal development study, lumasiran administered subcutaneously to pregnant female rats on gestational days 7, 13, 19 and on lactation days 6, 12, and 18 through weaning at doses up to 50 mg/kg did not produce maternal toxicity or developmental effects in the offspring.

8.2 Lactation

Risk Summary

There are no data on the presence of OXLUMO in human milk, the effects on the breastfed child, or the effects of the drug on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clincal need for (b) (4) and any potential effects on the breastfed (b) (4) or from the underlying condition.

(b) (4)

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/s/

MIRIAM C DINATALE
08/26/2020 09:46:11 AM

LYNNE P YAO
08/26/2020 10:34:53 AM

LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	August 18, 2020
Requesting Office or Division:	Division of Cardiology and Nephrology (DCN)
Application Type and Number:	NDA 214103
Product Name, Dosage Form, and Strength:	Oxlumo (lumasiran) injection, 94.5 mg/0.5 mL
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Alnylam Pharmaceuticals, Inc. (Alnylam)
FDA Received Date:	April 03, 2020 and July 16, 2020
OSE RCM #:	2020-73
DMEPA Safety Evaluator:	Mariette Aidoo, PharmD, MPH
DMEPA Team Leader:	Hina Mehta, PharmD

1 REASON FOR REVIEW

As part of the New Drug Application (NDA) 214103 submission, this review evaluates the proposed Oxlumo (lumasiran) injection prescribing information (PI), container labels, and carton labeling to identify areas of vulnerability that could lead to medication errors.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B – N/A
Human Factors Study	C – N/A
ISMP Newsletters*	D – N/A
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Other	F
Labels and Labeling	G

N/A=not applicable for this review
*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Alnylam submitted a 505(b)(1) application to obtain marketing approval for Oxlumo (lumasiran) Injection. Oxlumo is proposed for the treatment of primary hyperoxaluria type I (PH1) in pediatric and adult patients. We performed a risk assessment of the proposed container labels, carton labeling, and PI, for Oxlumo (lumasiran) Injection to determine whether there are significant concerns in terms of safety, related to preventable medication errors.

We note Alnylam is being proposed as 94.5 mg/0.5 mL in single dose vials with dosing on mg/kg basis. Additionally, the administration instructions state "for volumes less than 0.3 mL, a sterile 0.3-mL syringe is recommended". As such, we sent an Information Request (IR) to Alnylam on July 10, 2020 (see Appendix F) asking them to provide information on the commercial availability of the 0.3 mL syringe, information on difficulties on the preparation and administration of the product in the clinical study, and a copy of the pharmacy manual if one was used. On July 17, 2020 Alnylam responded to our request and noted the following:

1. "The Applicant is recommending the use of the 0.3 mL syringe for small dosing volumes but is not considering it a requirement"

2. "In the United States, 0.3 mL insulin syringes are widely available in both inpatient and outpatient clinical practice settings. The 0.3 mL insulin syringes are equivalent to 30 unit insulin syringes (where 1 unit = 0.01 mL). Therefore in clinical setting where lumasiran will be administered, healthcare providers will readily have access to 0.3 mL insulin syringes. During the conduct of the study, the Applicant did not supply syringes to the study sites and the US sites had no known issues with sourcing the 0.3 mL insulin syringes. In addition, most healthcare professionals working in the field of pediatrics are routinely trained to use 0.1 mL insulin syringes (30 unit insulin syringes) to administer accurate doses with small injection volumes for pediatric patients."

In addition, we discussed these concerns with the clinical team. In an email response dated July 10, 2020 clinical stated they were not concerned as providers in most pediatric centers are accustomed to drawing small volumes from vials for little babies and children. They also stated they were no reported issues drawing up the small doses in the clinical studies. We note the 0.3 mL insulin syringe was used in the clinical study as needed.

Given that the product will be administered by healthcare professionals, we find Alnylam's proposal to recommend the 0.3 mL syringe for small doses acceptable. We have identified areas of the proposed PI and carton labeling that could be revised to improve clarity and readability of important information. For the Division, we note the PI needs clarity on route and ideal vs. actual body weight dosing in addition to clarity on use of syringes. For the Applicant, we recommend changes to the carton labeling to improve readability and prominence of important information. We find the container acceptable from a medication error perspective. We provide recommendations for the Division in Section 4.1 and the Applicant in Section 4.2 below and advise they be implemented prior to approval of NDA 214103.

4 CONCLUSION & RECOMMENDATIONS

DMEPA concludes that the proposed Oxlumo PI and carton labeling can be improved to increase clarity of important information to promote the safe use of the product. We provide specific recommendations for the Division in Section 4.1 and recommendations for Alnylam in Section 4.2 below.

4.1 RECOMMENDATIONS FOR DIVISION OF CARDIOLOGY AND NEPHROLOGY (DCN)

A. Prescribing Information

1. Dosage and Administration Section
   a. Consider including the route of administration "subcutaneously" within the leading dosage statement in Section 2.1. For example, revise the statement to read "The recommended dosing regimen of OXLUMO consists loading doses followed by maintenance doses administered subcutaneously as shown in Table 1."

b. In reviewing the proposed PI, Alnylam states in section 2.1: "Dosing is based on body weight." Consider revising this statement in Section 2.1 by directly specifying the use of ideal, actual or adjusted body weight for dosing regimens.
c. In pediatric patients, small volumes for administration can result in medication errors when measured incorrectly.
In Section 2.2 (Administration Instructions), we recommend adding this statement to bullet point # 4: 'If using an insulin syringe, each short line on the 0.3 mL insulin syringe equals 0.01 mL (1 unit).'

2. Dosage Forms and Strength
   a. There is inconsistency in the description of the strength between the carton and container labels and the PI. The strength should be expressed with that amount that is in the single dose vial. We recommend deleting all occurrences of 189 mg/mL and ensure that strength is only denoted as 94.5 mg/0.5 mL.

4.2 RECOMMENDATIONS FOR ALNYLAM PHARMACEUTICALS, INC. (ALNYLAM)

We recommend the following be implemented prior to approval of this NDA:

A. Carton Labeling

1. We recommend revising "Subcutaneous use" to read "For Subcutaneous Injection by Healthcare Professional Only" to help alert patients and healthcare providers that the patient should take the product to their healthcare provider for administration.
2. For the side panel labeling, please revise "Each mL of solution contains…" to read: "Each 0.5 mL of solution contains 94.5 mg lumasiran (as 100 mg lumasiran sodium) per vial."

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Oxlumo received on April 3, 2020 from Alnylam Pharmaceuticals, Inc. (Alnylam).

<table>
<tr><th colspan="2">Table 2. Relevant Product Information for Oxlumo</th></tr>
<tr><td>Initial Approval Date</td><td>N/A</td></tr>
<tr><td>Active Ingredient</td><td>lumasiran</td></tr>
<tr><td>Indication</td><td>Treatment of primary hyperoxaluria type 1 (PH1) in adult and pediatric patients</td></tr>
<tr><td>Route of Administration</td><td>subcutaneous</td></tr>
<tr><td>Dosage Form</td><td>injection</td></tr>
<tr><td>Strength</td><td>94.5 mg/0.5 mL</td></tr>
<tr><td>Dose and Frequency</td><td>The recommended dose of OXLUMO by subcutaneous injection is based on body weight.
<table>
<tr><th>Body Weight</th><th>Loading Dose</th><th>Maintenance Dose (begin 1 month after the last loading dose)</th></tr>
<tr><td>less than 10 kg</td><td>6 mg/kg once monthly for 3 doses</td><td>3 mg/kg once monthly</td></tr>
<tr><td>10 kg to less than 20 kg</td><td>6 mg/kg once monthly for 3 doses</td><td>6 mg/kg once every 3 months (quarterly)</td></tr>
<tr><td>20 kg and above</td><td>3 mg/kg once monthly for 3 doses</td><td>3 mg/kg once every 3 months (quarterly)</td></tr>
</table></td></tr>
<tr><td>How Supplied</td><td>2 mL single-dose vials containing 0.5 mL total drug in vial.</td></tr>
<tr><td>Storage</td><td>Store at 2°C to (b)(4)°C (36°F to (b)(4)°F).</td></tr>
<tr><td>Container Closure</td><td>Single-use glass vial</td></tr>
</table>

APPENDIX F. INFORMATION REQUESTS

On July 10, 2020 we sent the following information request (IR) to Alnylam:

We refer to your NDA 214103 for lumasiran submitted on April 3, 2020 which proposes a 94.5 mg/0.5 mL injection in single dose vial for subcutaneous administration. We note your proposed lumasiran vial is intended for administration of a variable, weight-based lumasiran dose via a syringe (potentially a 0.3 mL graduated syringe as proposed in the Prescribing Information) by a healthcare provider in the clinical setting. We are concerned that the 0.3 mL graduated syringe may not be readily available on the US market. Please provide information regarding the commercial availability of the 0.3 mL syringe. In addition, please provide information or difficulties on the preparation and administration of the product, in particular the size of the syringe, used in the clinical study. If a pharmacy manual was used you could provide us a copy of that document. Finally, please submit five (5) intent-to-market samples and associated packaging and labeling to assist in completion of our review.

On July 17, 2020, we received the following response[a] from Alnylam:

The Applicant acknowledges the concerns regarding the accessibility and usability of the 0.3 mL syringe. The recommended instructions for the dosing and administration of lumasiran reflect the
procedure used in the clinical trials and, given the weight-based dosing and the potential for small dosing volumes in pediatric patients, 0.3 mL insulin syringes are appropriate for this use. The Applicant is recommending the use of the 0.3 mL syringe for small dosing volumes (volumes <0.3 mL) but is not considering it a requirement; see Draft Prescribing Information Section 2.2 Administration instructions, "For volumes less than 0.3 mL, a sterile 0.3-mL syringe is recommended."

Commercial Availability of 0.3 mL Syringes

In the United States, 0.3 mL insulin syringes are widely available in both the inpatient and outpatient clinical practice settings. The 0.3 mL insulin syringes are equivalent to 30 unit insulin syringes (where 1 unit = 0.01 mL). Therefore, in clinical settings where lumasiran will be administered, healthcare providers will readily have access to 0.3 mL insulin syringes. During the conduct of the study, the Applicant did not supply syringes to the study sites and the US sites
had no known issues with sourcing the 0.3 mL insulin syringes.

In addition, most healthcare professionals working in the field of pediatrics are routinely trained
to use 0.3 mL insulin syringes (30 unit insulin syringes) to administer accurate doses with small

[a] Response to Information Request. Cambridge (MA): Alnylam; 2020 Jul 17. Available from: IR \\cdsesub1\evsprod\nda214103\0021\m1\us\111-information-amendment\responses-to-clinical-ir-received-on-10jul2020.pdf

injection volumes for pediatric patients. Thus, 0.3 mL insulin syringes are widely available in clinical practice for pediatric patients and can be considered for this application.

Preparation and Administration using 0.3 mL Syringes

During the conduct of Study 004, patients as young as full term neonates were recruited as participants and the sites were recommended to use 0.3 mL insulin syringes for doses <0.3 mL (refer to ALN-GO1-004 Pharmacy Manual), which are marked with units and not milliliters. However, there were no protocol deviations or issues that occurred on study related to the preparation or administration of doses using the 0.3 mL insulin syringe.

The Applicant considered the potential issues with dosing accuracy and ease of preparation for small dosing volumes when developing the protocol for Study 004. Given the concentration of lumasiran at 94.5 mg/0.5 mL (equivalent to 189 mg/mL) and the lowest anticipated weight of neonates (2.4 kg), the lowest anticipated dose volumes for loading and maintenance doses were 0.08 mL and 0.04 mL, respectively (of note, the lowest dose administered in Study 004 was 0.11mL).

To evaluate the dose accuracy encompassing and exceeding the expected range of dose volumes expected in the clinic, an in vitro study was conducted using common, commercially available 0.3 mL insulin syringes and 1 mL syringes, as well as to assess the applicability of using dilution methods (Report No. PD-00242 *Evaluation of Low Volume Dose Preparation of Lumasiran at Clinical Sites Using GalNAc siRNA at 189 mg/mL*). It was determined that the use of a 0.3 mL insulin syringe was preferred over the dilution method due to minimization of manipulation of the product and therefore the minimization of potential error, and that, while both options were appropriate, a 0.3 mL insulin syringe was more accurate than a 1 mL syringe, specifically at volumes < 0.3 mL.

Therefore, the Applicant recommends the use of a 0.3 mL insulin syringe for dosing volumes 0.3 mL but considers the use of 1 mL syringes appropriate as well.

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[b] along with postmarket medication error data, we reviewed the following Oxlumo labels and labeling submitted by Alnylam Pharmaceuticals, Inc. (Alnylam).

- Container label received on April 3, 2020
- Carton labeling received on April 3, 2020
- Prescribing Information (Image not shown) received on April 3, 2020 and July 16, 2020, available from \\cdsesub1\evsprod\nda214103\0020\m1\us\114-labeling\draft\labeling\oxlumo-lumasiran-us-prescribing-information-pdf.pdf

G.2 Label and Labeling Images

(b) (4)

1 Page(s) of Draft Labeling has been Withheld in Full as B4 (CCI/TS) immediately following this page

[b] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

MARIETTE A AIDOO
08/18/2020 03:03:30 PM

HINA S MEHTA
08/18/2020 05:54:25 PM

Interdisciplinary Review Team for Cardiac Safety Studies

QT Study Review

Submission	NDA-214103
Submission Number	006
Submission Date	4/3/2020
Date Consult Received	4/10/2020
Drug Name	Lumasiran
Indication	Treatment of primary hyperoxaluria type 1 in adult and pediatric patients
Therapeutic dose	Body-weight based dosing which includes loading and maintenance doses (See Section 3.1)
Clinical Division	DCN

Note: Any text in the review with a light background should be inferred as copied from the sponsor's document.

This review responds to your consult dated 4/10/2020 regarding the sponsor's QT evaluation. We reviewed the following materials:

- Previous IRT review dated 04/10/2018 under IND-128941 in DARRTS (link);
- Sponsor's clinical study protocol # ALN-GO1-001 (SN0006 / SDN006; link);
- Sponsor's clinical study report # ALN-GO1-001 (SN0006 / SDN006; link);
- Sponsor's QT assessment report # ALN-GO1-001 (SN0006 / SDN006; link);
- Sponsor's proposed product label (SN0006 / SDN006; link); and
- Highlights of clinical pharmacology and cardiac safety (SN0007 / SDN008; link).

1 SUMMARY

No significant QTc prolongation effect of lumasiran was detected in this QT assessment.

The effect of lumasiran was evaluated in clinical study # ALN-GO1-001. This was a phase-1/2, single-blind, placebo-controlled, single- (Part-A) and multiple-ascending (Part-B) dose study evaluating the safety, tolerability, pharmacokinetic, and pharmacodynamics of lumasiran following subcutaneously administration in healthy adult subjects (Part-A) and patients with primary hyperoxaluria type-1 (Part-B). The highest dose evaluated was 6 mg/kg in healthy subjects (Part-A), which is expected to cover the supra-therapeutic exposures as the sponsor claims that the intrinsic or extrinsic factor are not expected to meaningfully increase systemic exposure to lumasiran. (section 3.1). Lumasiran has a low drug interaction potential as a victim drug and the exposures are not expected to increase in subjects with hepatic impairment (mild) or renal impairment (mild to moderate). (b) (4) the pharmacokinetics of lumasiran

has not been studied patients with hepatic impairment (moderate to severe) or renal impairment (severe, end-stage renal disease, or those on dialysis).

The data from Part-A of the study were analyzed using exposure response analysis as the primary analysis, which did not suggest that lumasiran is associated with significant QTc prolonging effect (refer to section 4.5) – see Table 1 for overall results.

Table 1: The Point Estimates and the 90% CIs (FDA Analysis)

ECG Parameter	Treatment	Concentration (ng/mL)	ΔΔQTcF (msec)	90% CI (msec)
QTc	Lumasiran 6.0 mg/kg	994.5	-1.4	(-7.3 to 4.5)

For further details on the FDA analysis please see section 4.

The reviewer's analysis did not suggest the presence of significant negative QT measurement bias (section 4.2.2). The findings of this analysis are further supported by the available by time analysis (section 4.3) and categorical analysis (section 4.4).

1.1 RESPONSES TO QUESTIONS POSED BY SPONSOR

Not applicable.

1.2 COMMENTS TO THE REVIEW DIVISION

Not applicable.

2 RECOMMENDATIONS

2.1 ADDITIONAL STUDIES

Not applicable.

2.2 PROPOSED LABEL

Below are proposed edits to the label submitted to SDN006 (link) from the IRT. Our changes are highlighted (addition, ~~deletion~~). Please note that this is a suggestion only and that we defer final labeling decisions to the Division.

12.2 Pharmacodynamics

Cardiac Electrophysiology

(b) (4)

-At the recommended dose, <TRADENAME> does not prolong the QT interval to any clinically relevant extent.

We propose to use labeling language for this product consistent with the "Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products – Content and Format" guidance.

3 SPONSOR'S SUBMISSION

3.1 OVERVIEW

3.1.1 Clinical

Alnylam Pharmaceuticals Inc. is developing lumasiran for the treatment of primary hyperoxaluria type-1 in pediatric and adult patients. Lumasiran (ALN-GO1, Oxlumo; MW: 17286 Da, sodium salt) is a hydroxy-acid oxidase-1 (HAO1)-directed double-stranded small interfering ribonucleic acid (synthesized siRNA covalently linked to a ligand containing three GalNAc residues). The sponsor claims that lumasiran reduces levels of glycolate oxidase enzyme by targeting the HAO1 messenger ribonucleic acid in hepatocytes through RNA interference. The product is formulated as a sterile solution for injection containing 189 mg/mL lumasiran (in water for injection; a single-dose glass vial) subcutaneous administration. The proposed dose is body-weight based and includes loading doses (3 mg/kg for ≥ 20 kg or 6 mg/kg for < 20 kg; once a month for 3 doses) followed by maintenance doses (3 mg/kg every 3 months for ≥ 20 kg; 6 mg/kg every 3 months for < 20 kg and ≥ 10 kg; and 3 mg/kg every month for < 10 kg). The maximum proposed therapeutic dose is 6 mg/kg (subcutaneous administration).

The peak concentrations of 1020 ± 340 ng/mL (Tmax: ~4 h; half-life ~1.5 to 9 h) are expected at steady-state with the anticipated therapeutic dose (6 mg/kg). Minimal accumulation is expected at steady-state with the proposed maximum therapeutic dose (3 to 6 mg/kg once monthly; Cmax Racc: ~1.2). The maximum tolerated dose was not identified during the development.

The sponsor describes that lumasiran is metabolized by endo- and exonucleases (not a substrate of the CYP450 enzymes) and highlights that it has a low drug interaction potential as a victim drug. No formal clinical drug interaction studies have been conducted by the sponsor. No clinical studies were conducted by the sponsor to evaluate the effect of hepatic impairment (moderate to severe) or renal impairment (severe) on the pharmacokinetics of lumasiran. The sponsor claims that the intrinsic or extrinsic factor are not expected to increase systemic exposure to lumasiran meaningfully. (b) (4) The sponsor indicates that the pharmacokinetics and pharmacodynamics of lumasiran were similar in adult and pediatric patients. Further, the sponsor highlights that the lumasiran Cmax was higher in < 1 year old and the range of observed values overlapped with the range for the ≥ 6 years age group.

Previously, the IRT reviewed the sponsor's proposal not to conduct a thorough QT study and suggested that Study # ALN-GO1-001 may have adequate information to serve as a substitute for a thorough QT study and provided guidance on data modeling and submission (Dt: 04/10/2018). Study # ALN-GO1-001 is a phase-1/2, single-blind, placebo-controlled, single- (Part-A, healthy subjects; 0.3, 1.0, 3.0, and 6.0 mg/kg) and multiple-ascending (Part-B, patients) dose study evaluating the safety, tolerability, pharmacokinetic, and pharmacodynamics of lumasiran following subcutaneously administration in healthy adult subjects, and patients with primary hyperoxaluria type-1. The peak concentrations

associated with the highest dose studied (mean Cmax: 1020 ng/mL with 6 mg/kg single dose) is expected to cover the therapeutic exposures in pediatric population.

3.1.2 Nonclinical Safety Pharmacology Assessments

Refer to the sponsor's highlights of clinical pharmacology and clinical safety and the sponsor's QT assessment report.

An in vitro human ether-à-go-go-related gene (hERG) assay was not conducted given the physical chemical properties of lumasiran and targeted liver delivery with negligible distribution to the heart.

A repeat-dose GLP-compliant study was conducted to investigate the potential for CV and respiratory effects of lumasiran in conscious, telemeterized male monkeys (GO1-GLP15-014). On Days 1, 8, 15, and 22 of the dosing-phase, monkeys were administered SC injections of 0 (0.9% sodium chloride for injection), 10, or 100 mg/kg of lumasiran at a dose volume of 0.5 mL/kg in a parallel dosing design.

Repeat dosing was conducted to assess potential secondary CV or respiratory changes associated with pharmacologically mediated serum glycolate elevations. Four once-weekly doses of lumasiran at 10 and 100 mg/kg had no immediate or delayed effects on clinical observations, qualitative or quantitative electrocardiogram, hemodynamic parameters, respiration rate, or body temperature. Additionally, steady state elevations of serum glycolate following 4 once-weekly supratherapeutic doses of lumasiran demonstrated that there were no CV or respiratory functional effects as a result of this pharmacologically mediated increase. The no observed effect level (NOEL) for cardiovascular and respiratory effects was determined to be ≥100 mg/kg.

3.2 SPONSOR'S RESULTS

3.2.1 By-Time Analysis

The primary analysis for lumasiran was based on exposure response analysis, please see section 3.2.3 for additional details.

Sponsor provided mean ΔQTcF +/- SD for different time points.

Reviewer's comment: *Because of small sample size, results are not interpretable. FDA reviewer provided non-parametric descriptive statistics for ΔΔQTcF, ΔΔHR, ΔΔPR and ΔΔQRS to show the by-time trend. Please see section 4.3 for additional details.*

3.2.1.1 Assay Sensitivity

Not Applicable

3.2.1.1.1 QT Bias Assessment

No QT bias assessment was conducted by the sponsor.

Reviewer's comment: *FDA reviewer performed bias analysis. No significant bias was observed. Please see section 4.2.2 for additional details.*

3.2.2 Categorical Analysis

There were no significant outliers per the sponsor's analysis for QTc (i.e., > 500 msec or > 60 msec over baseline).

Reviewer's comment: *FDA reviewer could not locate categorical analysis of HR, PR and QRS in sponsor's report. FDA reviewer's categorical analysis results are similar to sponsor's results for QTcF and ΔQTcF. FDA reviewer also performed categorical analysis for HR, PR and QRS. Please see section 4.4 for details.*

3.2.3 Exposure-Response Analysis

The sponsor explored PK/PD relationship between concentration of lumasiran and ΔQTcF (change from baseline in QTcF) using linear regression analysis with PK/ECG data collected from both parts of the study for their analysis. The sponsor claims that the linear regression analysis indicated the absence of correlation between ΔQTcF and plasma lumasiran concentrations of up to 1420 ng/mL.

Reviewer's comment: The results of the reviewer's analysis agreed with the sponsor's conclusion. Please see Section 4.5 for additional details.

3.2.4 Safety Analysis

There were no deaths in the study and no SAEs were reported in Part A and four SAEs in lumasiran-treated patients in Part B. No subjects discontinued the study due to AEs and no cardiac-related TAEs were observed in the study.

Reviewer's comment: None of the events identified to be of clinical importance per the ICH E14 guidelines (i.e., seizure, significant ventricular arrhythmias or sudden cardiac death) occurred in this study.

4 REVIEWERS' ASSESSMENT

4.1 EVALUATION OF THE QT/RR CORRECTION METHOD

The sponsor used QTcF for the primary analysis, which is acceptable as no large increases or decreases in heart rate (i.e. |mean| < 10 bpm) were observed (see Section 4.3.2).

4.2 ECG ASSESSMENTS

4.2.1 Overall

Overall ECG acquisition and interpretation in this study appears acceptable. The sponsor provided fully automated ECG measurements for Part A (SAD) of this study.

4.2.2 QT Bias Assessment

QT bias assessment was conducted by evaluating the relationship between the difference between the sponsor provided QT measurements and the automated algorithm used by the ECG Warehouse and the mean of the two measurements (BA-slope). The resulting BA-slope by treatment (active/placebo/overall) is presented for QTcF (Table 2). This analysis does not suggest the presence of significant negative treatment bias.

Table 2: QTcF bias assessment by treatment

Part	Treatment	# of ECGs	mean (sd), msec	Slope [95% CI], msec per 100 msec
A	All	1724	6.11 (5.19)	2.32 [1.24 to 3.41]
	Lumasiran	1308	5.85 (5.52)	1.47 [0.18 to 2.77]
	Placebo	416	6.94 (3.86)	3.03 [0.47 to 5.59]

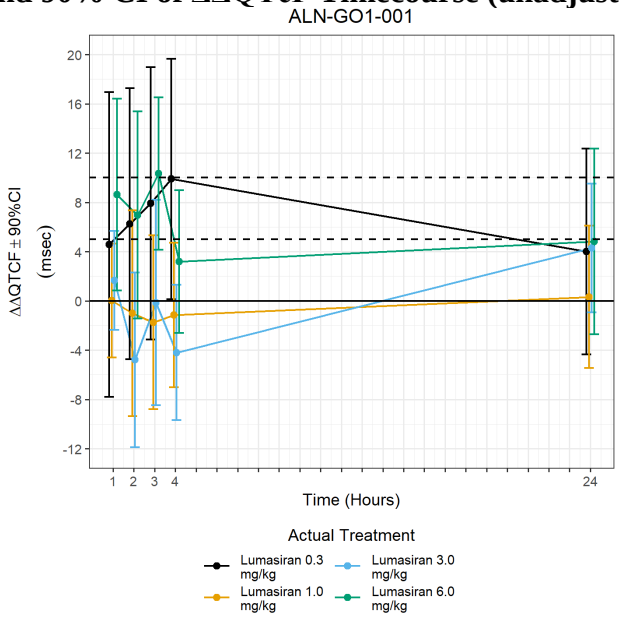
4.3 BY - TIME ANALYSIS

The analysis population used for by time analysis included all subjects with a baseline and at least one post-dose ECG. There were two parts in study ALN-G01-001 and FDA reviewer evaluated part A (SAD part) of this study. The statistical reviewer evaluated the ΔQTcF effect using nonparametric descriptive statistics. Because of small sample size, results are not interpretable.

4.3.1 QTc

Figure 1 displays the time profile of ΔΔQTcF for different treatment groups.

Figure 1: Median and 90% CI of ΔΔQTcF Timecourse (unadjusted CIs).



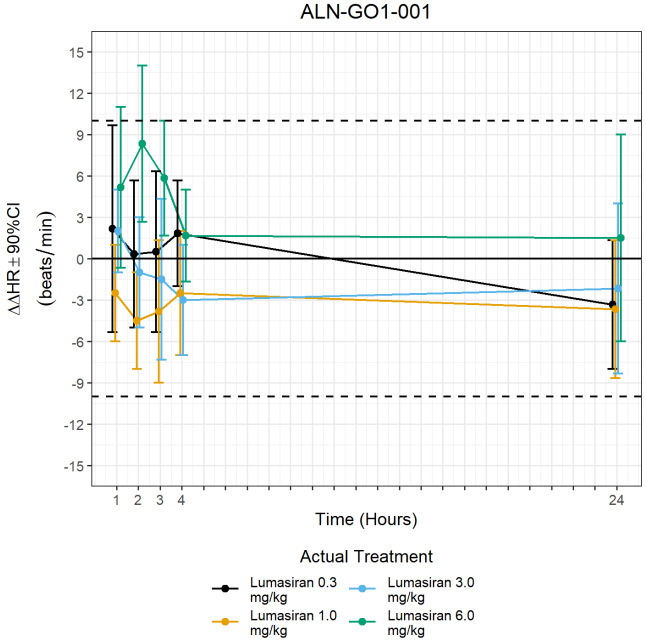
4.3.1.1 Assay sensitivity

Not Applicable.

4.3.2 HR

Figure 2 displays the time profile of ΔΔHR for different treatment groups.

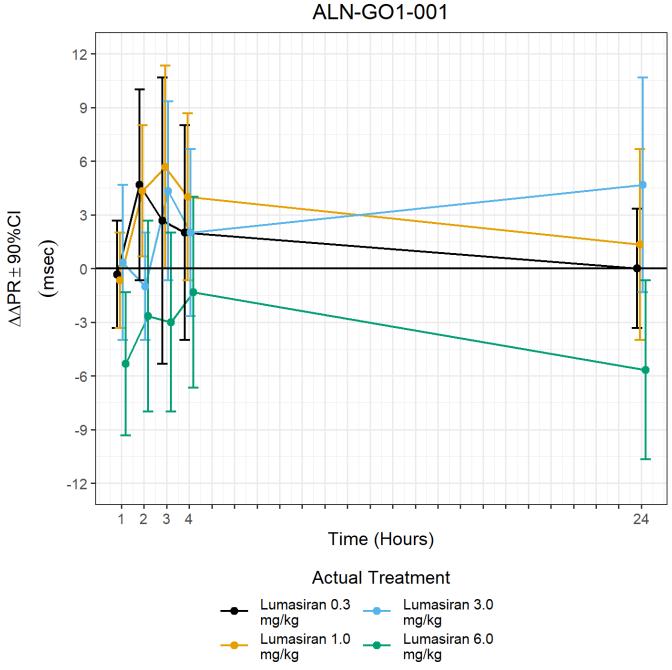
Figure 2: Median and 90% CI of ΔΔHR Timecourse



4.3.3 PR

Figure 3 displays the time profile of ΔΔPR for different treatment groups.

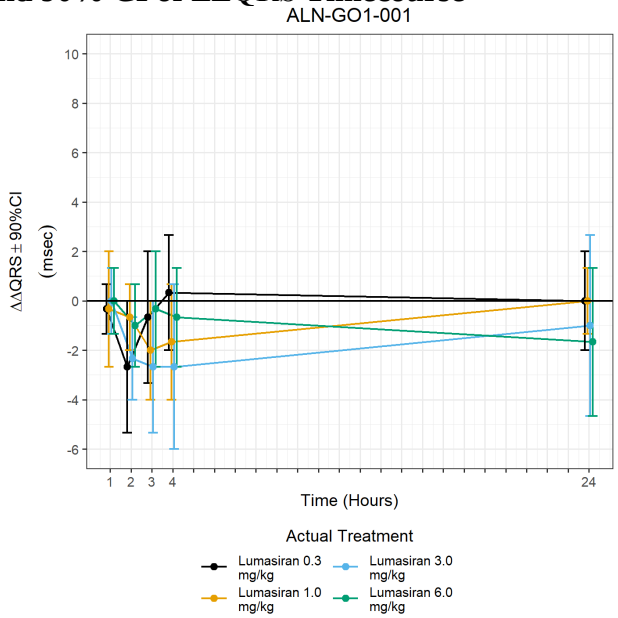
Figure 3: Median and 90% CI of ΔΔPR Timecourse



4.3.4 QRS

Figure 4 displays the time profile of ΔΔQRS for different treatment groups.

Figure 4: Median and 90% CI of ΔΔQRS Timecourse



4.4 CATEGORICAL ANALYSIS

Categorical analysis was performed for different ECG measurements either using absolute values, change from baseline or a combination of both. The analysis was conducted using the safety population and includes both scheduled and unscheduled ECGs. Categorical analysis was performed on part A (SAD part) of this study.

4.4.1 QTc

None of the subjects experienced QTcF greater than 450 msec or ΔQTcF greater than 30 msec in different dose levels of lumasiran.

4.4.2 HR

None of the subjects experienced HR less than 45 beats/min or greater than 100 beats/min in different dose levels of lumasiran.

4.4.3 PR

None of the subjects experienced PR greater than 220 msec in different dose levels of lumasiran.

4.4.4 QRS

None of the subjects experienced QRS greater than 120 msec in different dose levels of lumasiran.

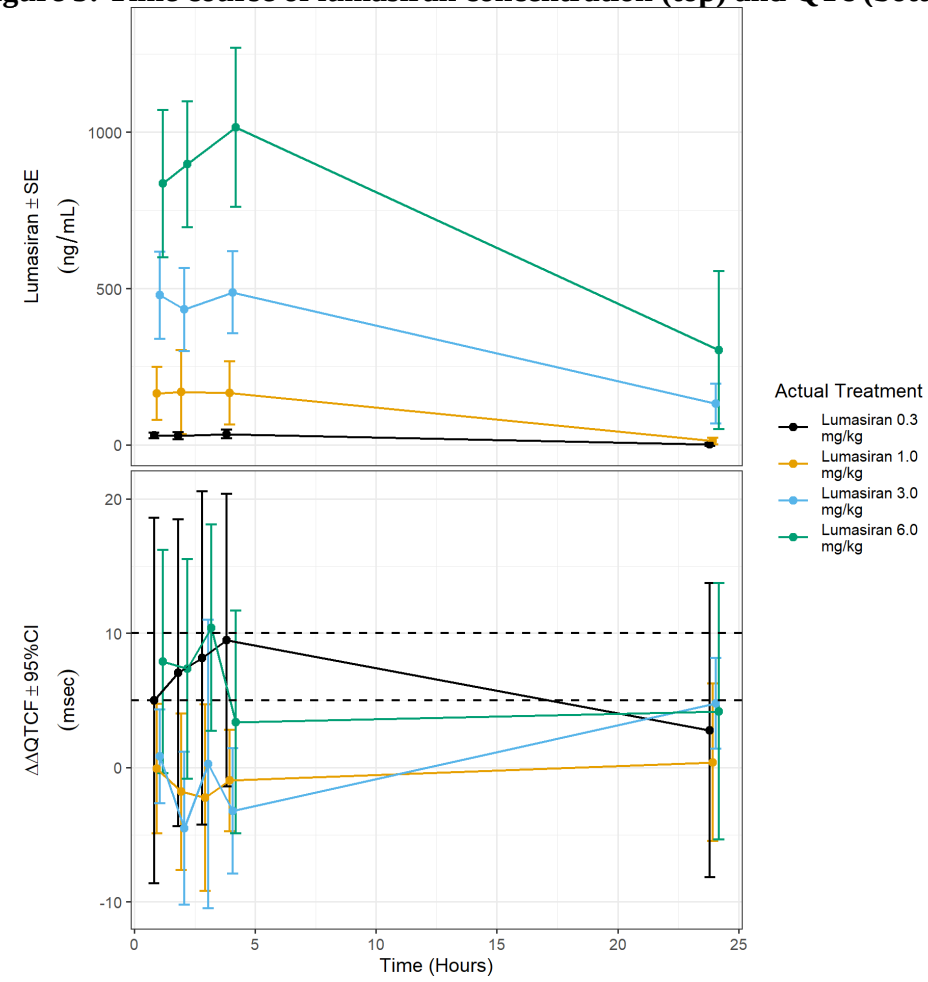
4.5 EXPOSURE-RESPONSE ANALYSIS

The objective of the clinical pharmacology analysis is to assess the relationship between ΔQTcF and concentration of lumasiran in healthy subjects using data from Part-A of the study. Exposure-response analysis was conducted using all subjects with baseline and at a least one post-baseline ECG with time-matched PK. The sponsor provided automated ECG

measurements for Part A (SAD) of this study. Prior to evaluating the relationship between concentration of lumasiran and QTc using a linear model, the three key assumptions of the model were evaluated using exploratory analysis: 1) absence of significant changes in heart rate (more than a 10 bpm increase or decrease in mean HR); 2) delay between concentration of lumasiran and ΔΔQTc and 3) presence of non-linear relationship.

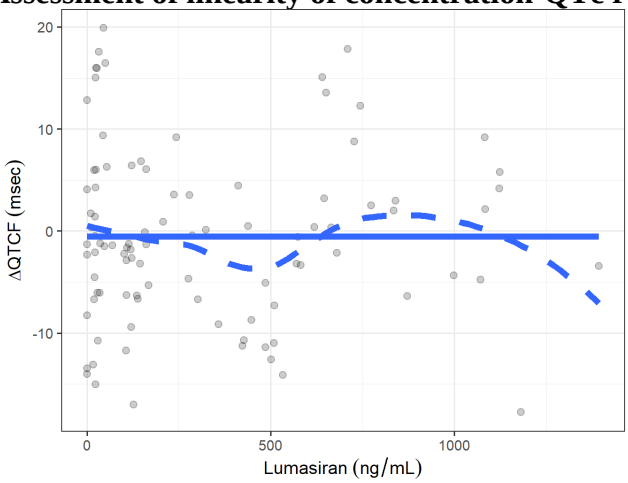
An evaluation of the time-course of lumasiran concentration and changes in ΔΔQTcF is shown in Figure 5. There was no apparent correlation between the time at maximum effect on ΔΔQTcF and peak concentrations of lumasiran indicating no significant hysteresis. Figure 2 shows the time-course of ΔΔHR, which shows an absence of significant ΔΔHR changes and the maximum change in heart rate is below 10 bpm (Sections 4.3.2 and 4.4.2).

Figure 5: Time course of lumasiran concentration (top) and QTc (bottom)



After confirming the absence of significant heart rate changes or delayed QTc changes, the relationship between lumasiran concentration and ΔQTcF was evaluated to determine if a linear model would be appropriate. Figure 6 shows the relationship between lumasiran concentration and ΔQTc and supports the use of a linear model.

Figure 6: Assessment of linearity of concentration-QTc relationship



Finally, the linear model was applied to the data and the goodness-of-fit plot is shown in Figure 7. Predictions from the concentration-QTc model are provide in Table 1.

Figure 7: Goodness-of-fit plot for QTc

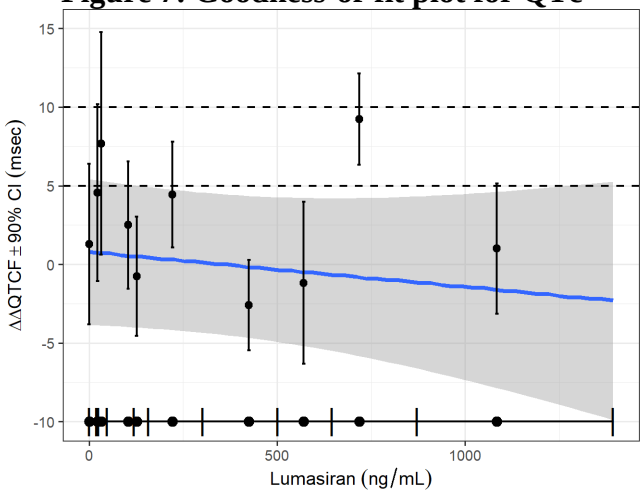


Table 3: Predictions from concentration-QTc model

Actual Treatment	Lumasiran (ng/mL)	ΔΔQTCF (msec)	90.0% CI (msec)
Lumasiran 0.3 mg/kg	34.8	0.7	(-3.9 to 5.3)
Lumasiran 1.0 mg/kg	164.5	0.4	(-4.1 to 4.9)
Lumasiran 3.0 mg/kg	495.4	-0.3	(-4.9 to 4.3)
Lumasiran 6.0 mg/kg	994.5	-1.4	(-7.3 to 4.5)

4.5.1.1 Assay sensitivity

Not applicable.

4.6 SAFETY ASSESSMENTS

See section 3.2.4. No additional safety analyses were conducted.

5 APPENDIX

5.1 EVALUATION OF CLINICAL QT ASSESSMENT PLAN

1. Product Information			
Generic Name	Lumasiran	Brand Name	Oxlumo
Drug class	siRNA		
Combination product	No		
Indication	Treatment of primary hyperoxaluria type 1 in adult and pediatric patients		
Therapeutic Dose	Body-weight based dosing which includes loading and maintenance doses (See Section 3.1)		
Maximum Tolerated Dose	Not established		
Dosage Form	Solution for Injection	Route of Administration	Subcutaneous

2. Clinical Cardiac Safety
Refer to the sponsor's highlights of clinical pharmacology and clinical safety.

3. QT Studies								
3.1 Primary Studies								
Protocol number / Population	**ECG Quality**		**Arms**		**Sample size**		**ECG & PK assessments**	
	Assessment	**Ok?**	**Arms**	**High dose covers?**	**No subjects**	**Ok?**	**Timing**	**Ok?**
Protocol number: ALN-GO1-001	Central read? Yes Blinded? Yes	Yes	Highest dose: 6 mg/kg (single dose)	Therapeutic (see Section 3.1.1)	32	Yes	Baseline: Pre-dose baseline	Yes

Population: Healthy subjects (Part-A) Design: Parallel	Replicates? Yes		Placebo: Yes Positive control: No				Timing: pre-dose, 1, 2, 3, 4, and 24 hours post-dose	
Part-A: Single Ascending Dose Study (in healthy subjects) Eligible healthy volunteers were admitted to the study center on Day -1 or the morning of Day 1 to determine continued study eligibility and for pre-dose assessments. Healthy volunteers were enrolled in 1 of 4 ascending dose cohorts (0.3, 1.0, 3.0, and 6.0 mg/kg). Each cohort comprised of 8 healthy volunteers randomized 3:1 to receive a single SC dose of lumasiran or placebo on Day 1. Healthy volunteers were discharged from the clinical study center on Day 2 after completing the 24-hour post-dose follow-up assessments. Safety, tolerability, PK, and PD assessments continued from Day 8 to Day 57 for post-dose follow-up, and healthy volunteers returned to the site every 28 days in the Safety and PD Follow-up Period. ECG: Screening, Day -1, Day 1: pre-dose, 1, 2, 3, 4, and 24 hours post-dose. PK: pre-dose, 0.5, 1, 2, 4, 6, 8, and 24 h post-dose.								
3.1 Secondary Studies								
Not applicable.								
3.3 Data pooling								
Data pooling?							No	
Did sponsor propose an assessment for heterogeneity?							N/A	
Is the data pooling appropriate?							N/A	
4. Analysis plan								

4.1 Study Objective related to QT	
What QTc effect size is the analysis trying to exclude?	10 ms (E14)
4.2 Dose Justification	
Not provided.	
4.3 QT correction method	
Is an HR increase or decrease greater than 10 bpm?	No
Primary method for QT correction	QTcF
4.4 Assay Sensitivity	
Assay sensitivity methods proposed by sponsor	☐ Moxifloxacin ☒ Exposure-margin ☐ QT bias assessment ☐ Not applicable ☒ Other
4.5 By Time Analysis	
4.5.1 Investigational drug	
Primary analysis	No
Did the sponsor use IUT or descriptive statistics?	Descriptive statistics
For IUT: Does the sponsor use MMRM to analyze longitudinal values that considers the correlation across time-points or use ANCOVA by time-point without considering correlation?	N/A

For IUT: Is the MMRM model specified correctly with regards to covariance structure, covariates, etc?	N/A
4.5.2 Positive control	
Primary analysis	N/A
Did the sponsor adjust for multiplicity?	Unknown
4.6 Concentration-QTc analysis	
4.6.1 Investigational drug	
5.Primary analysis	Yes
What is the dependent variable in the sponsor's model?	Single delta
White paper model?	No
Which concentration covariate(s) are included in the model?	Parent
Did the sponsor propose an assessment of delayed effects?	Unknown
Did the sponsor propose an assessment of linearity?	Unknown
Did the sponsor propose model selection criteria?	Unknown
What methods did the sponsor use for predicting the QT effect?	☒ Model-based confidence intervals ☐ Bootstrap-derived confidence intervals
4.6.2 Positive control	
Primary analysis	N/A
Same model as investigational drug	N/A
4.7 Categorical analysis	
QTc?	Yes

ΔQTc?	Yes
PR?	Unknown
QRS?	Unknown
HR?	Unknown
T-wave morphology?	Unknown

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/s/

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