CLINICAL STUDY REPORT SYNOPTIC
ALN-GO1-008 DATED 12 JUNE 2023

Protocol Title:	A Randomized, Double-blind, Placebo-controlled Study to Evaluate the Efficacy, Safety, Pharmacodynamics, and Pharmacokinetics of Lumasiran in Patients with Recurrent Calcium Oxalate Kidney Stone Disease and Elevated Urinary Oxalate Levels
Indication:	Recurrent Calcium Oxalate Kidney Stone Disease and Elevated Urinary Oxalate Levels
Development Phase:	Phase 2
Study Initiation Date:	27 January 2022 (first patient, first visit)
Study Completion Date:	01 November 2022 (study termination)
EudraCT Number:	2021-001519-10
IND Number:	128941
Sponsor:	Alnylam Pharmaceuticals, Inc. 300 Third Street Cambridge, MA 02142 USA Telephone: +1-617-551-8200
Sponsor's Responsible Medical Officer:	[redacted]

This study was conducted in accordance with the ethical principles of Good Clinical Practice, according to the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use including the archiving of essential documents.

SYNOPSIS

Name of Sponsor/Company: Alnylam Pharmaceuticals, Inc.

Name of Finished Product: Lumasiran (ALN-GO1)

Name of Active Ingredient: Lumasiran (ALN-GO1)

Title of Study: A Study to Evaluate Lumasiran in Adults with Recurrent Calcium Oxalate Kidney Stone Disease and Elevated Urinary Oxalate Levels

Study center(s): There were 35 clinical study centers activated worldwide

Publications (reference): None

Studied period (years):

Study initiation date: 27 January 2022 (first patient, first visit)

Study completion date: 01 November 2022 (study termination)

Phase of development: Phase 2

Objectives and Endpoints:

Objectives	Endpoints
Primary	
• To evaluate the effect of lumasiran on the percent change in urinary oxalate excretion	• Percent change in 24-hour urinary oxalate from baseline to Month 6 (average across Months 4 through 6)
Secondary	
• To evaluate the percentage of patients who achieve a ≥20% reduction in 24-hour urinary oxalate with lumasiran	• Percentage of patients who achieve a ≥20% reduction in 24-hour urinary oxalate from baseline to Month 6 (average across Months 4 through 6)
• To evaluate the effect of lumasiran on urinary calcium oxalate supersaturation	• Percent change in urinary calcium oxalate supersaturation from baseline to Month 6 (average across Months 4 through 6)
Exploratory	
• To evaluate the effect of lumasiran on absolute levels of urinary oxalate excretion	• Absolute change in 24-hour urinary oxalate from baseline to Month 6 (average across Months 4 through 6)
• To evaluate the effect of lumasiran on the occurrence of kidney stones	• Incidence rate of clinical and radiographic kidney stone events • Time to first kidney stone event

Objectives	Endpoints
• To evaluate additional pharmacodynamic (PD) parameters of plasma oxalate, plasma glycolate, and urinary glycolate	• Change from baseline in plasma oxalate • Change from baseline in plasma glycolate • Change from baseline in urinary glycolate
• To characterize the pharmacokinetics (PK) of lumasiran	• Plasma PK of lumasiran
• To assess for antidrug antibodies (ADA) against lumasiran	• ADA frequency and titer
• To evaluate the effect of lumasiran on maintaining 24-hour urinary oxalate ≤upper limit of normal (ULN) over time	• Percentage of patients with 24-hour urinary oxalate ≤ULN over time
• To evaluate the effect of lumasiran on maintaining a 25% reduction in urinary calcium oxalate supersaturation over time	• Percentage of patients having a 25% reduction in urinary calcium oxalate supersaturation over time
• To evaluate the effect of lumasiran on 24-hour urinary oxalate excretion after Month 6	• Change from baseline in 24-hour urinary oxalate excretion after Month 6
• To evaluate the effect of lumasiran on estimated glomerular filtration rate (eGFR)	• Change from baseline in eGFR
• To evaluate the effect of lumasiran on patient healthcare resource utilization	• Kidney stone event related hospitalizations, emergency room visits, unscheduled office visits, or procedures
Safety	
• To evaluate the safety and tolerability of lumasiran	• Frequency of adverse events (AEs)

Methodology:

This was a randomized, placebo-controlled, double-blind, multi-center, multinational, Phase 2 study to evaluate the efficacy, safety, PD, and PK of lumasiran administered subcutaneously (SC) in patients with recurrent calcium oxalate kidney stone disease and elevated urinary oxalate levels.

The study planned for up to 2 months of screening and 15 months of double-blind treatment (a 6-month Primary Analysis Period followed by a 9-month Treatment Extension Period). The screening window to determine patient eligibility extended from Day -60 to Day -1. During screening, patients provided at least two 24-hour urine collections to establish baseline urinary oxalate levels.

Consented patients meeting all eligibility criteria were randomized 1:1:1 to receive study drug: lumasiran 567 mg, lumasiran 284 mg, or placebo every 3 months during the primary analysis period. Stratification was determined by baseline urinary oxalate levels (≤ 1.25 × ULN vs >1.25

× ULN) from the mean of the first 2 valid 24-hour urine collections and the number of historical kidney stone events in the 12 months prior to screening (≤1 vs >1).

Study visits were planned as presented in Table 1 of the study protocol (refer to Appendix 16.1.1). During the study, and at the time of informed consent, patients were asked to adhere to a diet appropriate for kidney stone formers, including adequate calcium intake and avoidance of spinach and other foods high in oxalate.

The study was terminated early due to enrollment challenges. At the time of study termination, data were available for 2 randomized patients (1 patient received placebo and 1 patient received lumasiran 567 mg). This synoptic clinical study report describes the safety data for these 2 patients.

Number of patients:

Planned: 120 patients

Randomized: 2 patients

Dosed: 2 patients (1 lumasiran, 1 placebo)

Diagnosis and main criteria for inclusion:

To be eligible to participate in this study, patients must have been able to provide written informed consent, were at least 18 years of age or older with elevated urinary oxalate levels >ULN (ULN = 40 mg/24 hours) from 2 valid 24-hour urine collections obtained during screening, and had a clinical diagnosis of recurrent kidney stone disease defined as having at least 2 stone events, with a minimum of 1 stone event occurring within 5 years prior to screening. For this study, a historical kidney stone event was defined as a visible passage of a kidney stone, a procedural intervention for removal of an asymptomatic or symptomatic stone, or a new (≥1 mm) or enlarged (by ≥2 mm) kidney stone identified by computed tomography imaging.

Additional inclusion and exclusion criteria applied in the protocol, see Appendix 16.1.1.

Test product, dose and mode of administration, batch number:

Lumasiran is a small interfering RNA that is conjugated to a GalNAc targeting liver-expressed hydroxyacid oxidase *(HAO1)* messenger RNA, leading to the reduction of hepatic oxalate production.

Lumasiran was to be administered by subcutaneous (SC) injection on Day 1, Month 3, and Month 9 at a dose of 284 or 567 mg administered under the supervision of the Investigator at the study center or by a healthcare professional at the patient's home.

The batch number administered in this study for lumasiran was 75020-2.

Duration of treatment:

The planned estimated total time on study for each patient was up to 17 months, including up to 2 months of screening, a 6-month Primary Analysis Period and a 9-month Treatment Extension Period. The planned duration of treatment with study drug was up to Month 15.

Reference therapy, dose and mode of administration, batch number:

Placebo (sodium chloride 0.9% w/v for SC administration) was administered at the same dosing interval as lumasiran. Placebo was provided by the Sponsor. Placebo was packaged identically to lumasiran to maintain the blind.

The batch number for placebo administered in this study was 75020-1.

Criteria for evaluation:

Study assessments are described in Section 6 of the protocol (refer to Appendix 16.1.1).

Statistical Methods:

Planned analyses are described in the Statistical Analysis Plan, which was finalized in March 2022 (refer to Appendix 16.1.9). Due to the early termination of the study and limited available data, no formal analyses were conducted. Given the low number of patients in the study, data summaries were not deemed relevant and individual patient level listings were provided.

Efficacy:

No formal analysis of the primary and secondary endpoints was conducted due to the low number of enrolled patients.

Safety:

During this study, safety was evaluated through the surveillance and recording of AEs, use of concomitant medications, measurements of vital signs, weight and height, physical examinations, and clinical laboratory tests as described in Section 6 of the protocol (refer to Appendix 16.1.1).

Results Summary

Disposition:

Two patients were randomized in this study; among the 2 patients, 1 patient was randomized to lumasiran at the 567 mg dose and 1 patient was randomized to placebo (Listing 16.2.1.1). The primary reason for discontinuation of treatment was Study Terminated by Sponsor for both patients.

Patient eligibility criteria by enrollment status for all randomized patients is provided in Listing 16.2.2.1.

The patient who received lumasiran had a total of 1 dose on Day 1/Baseline and the patient who received placebo had a total of 2 doses; 1 dose on Day 1/Baseline and 1 dose at Month 3. For additional details on dosing, refer to Listing 16.2.5.1.

Demographics and Baseline Disease Characteristics:

Demographic characteristics by enrollment status are provided in Listing 16.2.4.1. The patient who received lumasiran was a white female, 52 years of age with a body mass index (BMI) of 36.1 kg/m^2. The patient who received placebo was a white male, 65 years of age with a BMI of 39 kg/m^2.

Baseline disease characteristics including the 24-hour urinary oxalate and glycolate, and plasma oxalate and glycolate are provided in Listing 16.2.4.2.

Medical history is presented in Listing 16.2.4.5. Demographic data, medical history, and concomitant medications were recorded from the Screening/Baseline period.

Protocol Deviations:

There were a total of 15 protocol deviations reported in this study (Listing 16.2.2.2). Five protocol deviations were reported for the patient who was administered placebo and 10 protocol deviations were reported for the patient who was administered lumasiran, including 1 major protocol deviation of incorrect stratification criteria selected at time of randomization (Listing 16.2.2.3). None of the protocol deviations affected the interpretation of available data as of the study termination.

Efficacy Results:

No formal analysis of the primary and secondary endpoints was conducted due to the low number of enrolled patients. Reference patient data listings 16.2.6.1 and 16.2.6.5 for additional details on urinary and plasma pharmacodynamic data for enrolled patients.

Safety Results:

There were a total of 2 AEs reported in the study; 1 transient event of dry cough was reported in the patient who was administered lumasiran and 1 event of new onset diabetes mellitus Type 2 occurred in the patient who was administered placebo (Listing 16.2.7.1) that was ongoing. Both AEs were moderate in severity and assessed by the investigator to be not related to study drug. No AE led to withdrawal from the study. There were no serious adverse events (SAEs), injection site reactions (ISRs), AEs of clinical interest, or deaths reported in this study.

Clinical laboratory assessments were collected for the 2 patients in this study and are presented in Listings 16.2.8.1.1 through 16.2.8.3.2. The patient who was administered lumasiran had aspartate aminotransferase (AST), alanine aminotransferase (ALT), and total bilirubin levels within the normal range. No elevations of ALT and/or AST >3x ULN, total bilirubin, or incidence of Hy's law were noted for either patient.

Vital signs are presented for each patient in Listing 16.2.9.1, and concomitant medications are included in Listing 16.2.9.2.

Conclusion:

The ALN-GO1-008 study was designed to evaluate the efficacy, safety, PD, and PK of SC lumasiran in patients with recurrent calcium oxalate kidney stone disease and elevated urinary oxalate levels, including the occurrence of kidney stones, the PD effect of lumasiran on plasma oxalate, plasma and urinary glycolate, and the characterization of plasma PK. The study terminated early due to enrollment challenges with a total of 2 patients randomized. There was no new information identified during this study that changed the current benefit-risk assessment of lumasiran.

Date of the report: 12 June 2023