PART VI SUMMARY OF THE RISK MANAGEMENT PLAN

This is a summary of the risk management plan (RMP) for lumasiran. The RMP details important risks of lumasiran, how these risks can be minimized, and how more information will be obtained about lumasiran's risks and uncertainties (ie, missing information).

Lumasiran's Summary of Product Characteristics (SmPC) and its Package Leaflet (PL) give essential information to healthcare professionals and patients on how lumasiran should be used.

This summary of the RMP for lumasiran should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of lumasiran's RMP.

I THE MEDICINE AND WHAT IT IS USED FOR

Lumasiran is authorized for treatment of Primary Hyperoxaluria 1 (PH1) in patients of all age groups. It contains lumasiran as the active substance, and it is given by injection under the skin (subcutaneously (SC)).

Further information about the evaluation of lumasiran's benefits can be found in lumasiran's EPAR, including in its plain-language summary, available on the European Medicines Agency website under the medicine's webpage:
https://www.ema.europa.eu/en/medicines/human/EPAR/oxlumo.

II RISKS ASSOCIATED WITH THE MEDICINE AND ACTIVITIES TO MINIMIZE OR FURTHER CHARACTERIZE THE RISKS

Important risks of lumasiran, together with measures to minimize such risks and the proposed studies for learning more about lumasiran's risks are outlined below.

Measures to minimize the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the PL and SmPC addressed to patients and healthcare professionals.
- Important advice on the medicine's packaging.
- The medicine's legal status; the way a medicine is supplied to the patient (eg, with or without prescription) can help to minimize its risks.

Together, these measures constitute *routine risk minimization measures*.

In addition to these measures, information about adverse reactions is collected continuously and regularly analyzed, including in the Periodic Safety Update Report assessment, so that immediate actions can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of lumasiran is not yet available, it is listed under "missing information" (see Section II.A below).

II.A List of Important Risks and Missing Information

Important risks of lumasiran are risks that need special risk management activities to further investigate or minimize the risk so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of lumasiran. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (eg, on the long-term use of the medicine).

List of Important Risks and Missing Information	
Important identified risks	• None
Important potential risks	• Hepatic effects
Missing information	• Longer-term safety (>1 year) • Use in patients with hepatic impairment • Use in patients with severe renal impairment or ESRD, including patients on dialysis • Use in pregnant or lactating women and effects on pregnancy outcomes • Use in patients <2 years of age • Immunogenicity

Abbreviations: ESRD=end stage renal disease

II.B Summary of Important Risks

Important Identified Risk: None

Important Potential Risk: Hepatic effects	
Evidence for linking the risk to the medicine	Lumasiran is directed for delivery to the liver, therefore adverse hepatic effects are possible. Minor and reversible changes were noted in the non-clinical (animal) studies. The relevance of these nonclinical findings to humans remains unclear. No clinically significant liver events or abnormal liver function tests indicative of hepatotoxicity (liver toxicity) have been observed, however, given the relatively small size of the safety database, potential effect of lumasiran on the liver has not been characterized. Therefore, hepatic effects are included as an important potential risk to ensure further characterization of this potential safety concern.
Risk factors and risk groups	Unknown

Important Potential Risk: Hepatic effects	
Risk minimization measures	Routine risk minimization measures: • Not applicable Additional risk minimization measures: • Not applicable
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Hepatic effects will be evaluated as part of the ongoing studies, Study 002, Study 003, Study 004, and Study 005, and the observational Post Authorization Safety Study (PASS) (ALN-GO1-007).

Missing Information: Longer-term safety (>1 year)	
Risk minimization measures	Routine risk minimization measures: • A summary of the safety profile of lumasiran in the clinical development program is provided in the Undesirable effects section (Section 4.8) of the SmPC.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Long-term safety will be evaluated as part of the ongoing studies, Study 002, Study 003, Study 004, and Study 005, and the observational PASS (ALN-GO1-007).

Missing Information: Use in patients with hepatic impairment	
Risk minimization measures	Routine risk minimization measures: • Information on the absence of data in patients with hepatic impairment is included in the Posology and method of administration section (Section 4.2) and Pharmacokinetic properties section (Section 5.2) of the SmPC. • Information that caution is required when treating patients with moderate or severe hepatic impairment is included in the Posology and method of administration section (Section 4.2) and Pharmacokinetic properties section (Section 5.2) of the SmPC. • In the Special Warnings and Precautions for Use section (Section 4.4) of the SmPC it is also included that patients with moderate or severe hepatic impairment should be monitored for potential decreased efficacy.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Use in patients with hepatic impairment will be evaluated as part of the observational PASS (ALN-GO1-007).

Missing Information: Use in patients with severe renal impairment or ESRD, including patients on dialysis	
Risk minimization measures	Routine risk minimization measures: • Information on the limited data in patients with severe renal impairment, ESRD or patients on dialysis is included in the Posology and method of administration section (Section 4.2) and Pharmacokinetic properties section (Section 5.2) of the SmPC. • The following information is also included in the Special Warnings and Precautions for Use section (Section 4.4) of the SmPC: Treatment with lumasiran increases plasma glycolate levels, which may increase the risk of metabolic acidosis or worsening of pre-existing metabolic acidosis in patients with severe renal impairment or ESRD. These patients should therefore be monitored for signs and symptoms of metabolic acidosis.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Evaluation of data from the ongoing Study 005 and the observational PASS (ALN-GO1-007).

Abbreviations: ESRD=end stage renal disease

Missing Information: Use in pregnant or lactating women and effects on pregnancy outcomes	
Risk minimization measures	Routine risk minimization measures: • Information on the lack of clinical data in pregnant women and in lactating women is included in the Fertility, pregnancy and lactation section (Section 4.6) of the SmPC, with a cross-reference to nonclinical data on embryo-fetal development, lactation, and fertility in the Preclinical safety data section (Section 5.3) of the SmPC. Routine risk minimization activities recommending specific clinical measures to address the risk: • Advice is provided to evaluate the benefits and risks of treatment with lumasiran during pregnancy and breastfeeding for the mother and infant, and the mother's clinical need for lumasiran in the Fertility, pregnancy and lactation section (Section 4.6) of the SmPC and Section 2 of the Package Leaflet.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Use in pregnancy or lactation and effects on pregnancy outcomes will be evaluated as part of the observational PASS (ALN-GO1-007).

Missing Information: Use in patients <2 years of age	
Risk minimization measures	Routine risk communication: • Information on safety profile in pediatric population is provided in Section 4.8 and Section 5.2 of the SmPC. Information on limited data in children younger than 1 year of age is included in the Posology section (Section 4.2) and the Pharmacokinetic properties section (Section 5.2) of the SmPC. Routine risk minimization activities recommending specific clinical measures to address the risk: • None.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Use in patients <2 years of age will be evaluated as part of ongoing studies, Study 004, Study 005, and the observational PASS (ALN-GO1-007).

Missing Information: Immunogenicity	
Risk minimization measures	Routine risk minimization measures: • Information on immunogenicity is provided in Section 4.8 of the SmPC. Routine risk minimization activities recommending specific clinical measures to address the risk: • None.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Anti-drug antibodies will continue to be collected and evaluated every 6 months to the end of study in the ongoing clinical studies, including in patients <6 years of age in Study 004 and Study 005. Immunogenicity will also be evaluated as part of the planned observational PASS (ALN-GO1-007).

II.C Post-Authorization Development Plan

II.C.1 Studies Which Are Conditions of the Marketing Authorization

There are no studies that are conditions of the marketing authorization or specific obligations.

II.C.2 Other Studies in Post-Authorization Development Plan

Additional PV activities include monitoring of safety in the ongoing studies: Study 002, Study 003, Study 004, and Study 005, in addition to a prospective observational PASS (ALN-GO1-007).

- Study 002:

Study 002 is an ongoing Phase 2 OLE study to evaluate the long-term safety, PK, and PD of lumasiran in adult and pediatric (≥6 years of age) patients with PH1 who completed Study 001B. Patients receive lumasiran for up to 54 months.

- Study 003:

Study 003 is an ongoing Phase 3, randomized, double-blind, placebo-controlled study with extension period designed to evaluate the efficacy and safety of lumasiran in adults and pediatric (≥6 years of age) patients with PH1. The 6-month double-blind period of the study was completed 06 November 2019. In the ongoing extension period, patients receive lumasiran for up to 54 months.

- Study 004:

Study 004 is an ongoing Phase 3 single-arm study in infants and children with PH1 aged ≥1 day to <6 years. Patients receive weight-based loading doses followed by maintenance doses for up to 60 months.

- Study 005:

Study 005 is an ongoing Phase 3 single-arm study to evaluate lumasiran in adult and pediatric patients of all ages with PH1 who have advanced disease with or without hemodialysis. Patients will receive a weight-based loading dose followed by a maintenance dose for up to 60 months.

- ALN-GO1-007: Observational PASS

The Sponsor is conducting a prospective observational longitudinal study (ALN-GO1-007), to characterize the longer-term safety and effectiveness of lumasiran in a real-world cohort of PH1 patients of all ages. The study will also collect and evaluate information on pregnancy complications, birth outcomes, breast feeding and infant outcomes in women exposed to lumasiran during pregnancy.